



Clinical HIV/AIDS Care Guidelines for Resource-poor Settings

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Clinical HIV/AIDS Care Guidelines for Resource-poor Settings

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PREFACE TO THE SECOND EDITION

*The White Rabbit put on his spectacles.
‘Where shall I begin, please your
Majesty?’ he asked.
‘Begin at the beginning,’ the King said, very gravely,
‘and go on till you come to the end: then stop.’
(Lewis Carroll, 1865)*

More true than ever...

This second edition, I promised it years ago.

By the end of 2005 more than 40 million people are living with HIV/AIDS, the majority in resource-poor settings where MSF is working to reduce the suffering of the millions affected. Since the publication of the first edition of this guideline the world has seen many new developments in AIDS care, not in the least an increase in access to HAART, which has changed the face of AIDS in Africa and the rest of the developing world.

MSF and the Access Campaign have to be commended for their tireless efforts to increase access to HAART against all odds since 1999.

Although HAART increases survival and quality of life among people treated, still many patients succumb to opportunistic infections in Africa, Asia and South America because they present late, because they have no access to life-saving drugs, or because they develop complications despite HAART. Management of opportunistic infections is still very much part of the daily life of an MSF doctor or nurse in an AIDS care project. On top of that, a new disease entity, immune reconstitution inflammatory syndrome (IRIS), came to further complicate the clinical picture of AIDS care in resource-poor settings. And as the guidelines are problem-based, symptoms caused by HAART are part of the clinical management of HIV-patients and had to be dealt with in this second edition. Also the management of pathologies like Mycobacterium Avium Complex, Kaposi's sarcoma and Cytomegalovirus had to be reviewed in the light of a much better prognosis thanks to the availability of HAART.

The guidelines want to assist with the diagnosis and management of opportunistic infections, IRIS and side-effects of HAART, always taking into account different levels of expertise and the limitation of resources that we experience in the field every day.

I hope this second edition will contribute towards alleviating the suffering of patients and facilitating the task of health staff caring for them.

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MSF: David Wilson, Françoise Louis, Pierre Humblet, Line Arnould, Rony Zachariah, Elisabeth Szumilin, Alberto de Dios Romero, Christophe Michon, Arlene Chua and others.

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Others: Colette van Hees

Eva Vervecken and Tessa James for excellent editorial work.

Lut Lynen
ITM, Antwerp
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1 LIST OF ABBREVIATIONS

ABV	doxorubicin, bleomycin and vincristine
AFB	acid fast bacilli
AIDP	acute inflammatory demyelinating polyneuropathy
AIDS	acquired immune deficiency syndrome
ARV	antiretroviral
ART	antiretroviral treatment
AZT	zidovudine
BAL	broncho-alveolar lavage
BMI	body mass index
BV	bleomycin, vincristine
CBC	complete blood count
CDC	centre for disease control
CIDP	chronic inflammatory demyelinating polyneuropathy
CL	cutaneous leishmaniasis
CMV	cytomegalovirus
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CrAg	cryptococcal antigen
CSF	cerebrospinal fluid
CT	computed tomography
CVA	cerebrovascular accident
d4T	stavudine
DBS	dried blood spots
DC	developing countries
DRESS	drug rash, eosinophilia, systemic symptoms
DS	double strength
DSPN	distal, symmetrical polyneuropathy
EBV	Epstein-Barr virus
EFV	efavirenz
ELISA	enzyme-linked immunosorbent assay
EMB	ethambutol
ENT	ear nose throat
ESR	erythrocyte sedimentation rate
GBS	Guillain-Barré syndrome
GCS	Glasgow coma scale
GI	gastrointestinal
HAART	highly active antiretroviral therapy
Hb	haemoglobin
HHV8	(sexually transmitted) human herpes virus 8
HIV	human immunodeficiency virus
HSV	herpes simplex virus
HTLV-1	human T lymphotropic virus - 1

ICP	intracranial pressure
ICU	intensive care unit
IM	intra-muscular
IMAI	integrated management of adult and adolescents illnesses
INH	isoniazid
IPT	INH preventive therapy
IR	intrarectal
IRIS	immune reconstitution inflammatory syndrome
IU	international unit
IUATLD	International Union Against Tuberculosis and Lung Disease
IV	intravenous
IVDU	IV drug use
KCL	potassium chloride
KOH	potassium hydroxide
KS	Kaposi's sarcoma
LDH	lactate dehydrogenase
LIP	lymphoid interstitial pneumonitis
LN	lymph node
LP	lumbar puncture
MAC	<i>Mycobacterium avium</i> complex
MAI	mycobacterium avium intracellulare
MEDL	model essential drug list
MGIT	mycobacteria growth incubator tube
MM	mononeuropathy multiplex
MTCT	mother- to- child transmission
NaOCl	sodium hypochlorite
NHL	non-Hodgkin's lymphoma
NNRTI	non-nucleoside reverse transcriptase inhibitors
NRTI	nucleoside reverse transcriptase inhibitors
NSAID	non steroidal anti-inflammatory drugs
NVP	nevirapine
OC	oesophageal candidiasis
OD	once daily
OI	opportunistic infection
ORS	oral rehydration salts
PCP	<i>Pneumocystis carinii</i> pneumonia
PCR	polymerase chain reaction
PGL	persistent generalized lymphadenopathy
PI	protease inhibitors
PLHA	people living with HIV/AIDS
PML	progressive multifocal leukoencephalopathy
PMN	polymorphonuclears (white blood cells)
PMTCT	prevention of mother-to-child transmission
PRN	as needed
PO	per os
PP	progressive polyradiculopathy
PPD	purified protein derivate
PPE	papular pruritic eruption

PT	preventive therapy
PTB	pulmonary tuberculosis
PZA	pyrazinamide
RIF	rifampicin
RNA	ribonucleic acid
RPR	syphilis tests (rapid plasma reagin)
R/	treatment
RR	relative risk
RUQ	right upper quadrant
SC	subcutaneous
SCrAg	serum cryptococcal antigen
SS	single strength
STD	sexually transmitted disease
STI	sexually transmitted infection
TB	tuberculosis
TCA's	tricyclic antidepressants
TLC	total lymphocyte count
TPHA	treponema pallidum hemagglutination
TST	tuberculin skin test
ULN	upper limits of normal
UNAIDS	Joint United Nations Programme on HIV/AIDS
VCT	voluntary counselling and testing
VL	viral load
VL	visceral leishmaniasis
VDRL	syphilis test
WB	Western blot
WBC	white blood cell
WHO	World Health Organisation
ZN	Ziehl Neelsen



2 INTRODUCTION*

More than 40 million people are HIV-positive and will develop AIDS in the next decade.

90 % of those people are living in resource-poor countries. In some settings in Africa and Asia where MSF is working, AIDS is a public health problem of prime importance. It affects profoundly the functioning of health structures and the social and economic organisation of communities.

MSF medical practitioners are increasingly confronted with AIDS-related diseases. Prevention remains a priority of AIDS control programmes. However, for most people, HIV/AIDS is as much a disease that requires care and support, as it is an infection to avoid. It is no longer ethical to conduct research or prevention programs without the provision of HAART and treatment of opportunistic infections to the population served by the program.

For optimal health care for PLHA, the WHO proposes a strategy of "*comprehensive care across a continuum*".¹⁻³

Comprehensive care includes usually clinical management, nursing care, psychological and social support[†]. It should be provided through a network of services extending across a *continuum*, i.e. with interaction between home & community, the health centre and a referral hospital.

The medical competence for the care of PLHA is in many countries concentrated in the high level facilities. Few organisations play a medical role at the lower level of the health care pyramid, like smaller hospitals, health centres and home care. To guarantee good care at each level it is important that the flow between structures is organised in order to avoid unnecessary crowding at a higher level. MSF plays an important role in standardisation of care and training of staff at all levels.⁴ It was with this perspective that this guideline was written.

Given that in Africa most PLHA die of bacterial infections, including TB, early recognition and treatment of these diseases, and cotrimoxazole and INH prophylaxis will have an important impact on survival and improving the quality of life of PLHA and their family.

The purpose of this work is to develop and describe strategies to manage the health problems of AIDS patients at the different levels of care provision, in order to ensure a continuum of care.

For each level of care, a care strategy is proposed with the necessary equipment and drugs to respond to the health needs of PLHA.

* Adapted from first edition

† Others insist to offer legal advice and spiritual assistance as well. This depends of course on your objectives and resources.

A syndromic approach was used in producing this document, using algorithms that have been adapted from existing WHO guidelines (Guidelines for the clinical management of HIV infection in adults, WHO, 1991). Although flowcharts are not readily used during patient management, we decided to maintain the algorithms and adapted or simplified them. They may serve as a basis for training and may help to standardise patient care.

Different treatment options are described. For some symptoms the diagnostic tests and necessary equipment have been quite extensively described, because there is room for more accurate diagnosis of opportunistic infections in AIDS patients, especially at the referral level. It will be up to the different field teams to choose the level of care that is acceptable and affordable in their situation.

It is clear that these guidelines will have to be adapted to the prevailing situation in each setting. There is no gold standard. The necessary skills and the need for additional training will vary according to the pre-existing level of knowledge, attitude and practice.

The question of primary and secondary prevention of OI's and the follow-up of asymptomatic patients is addressed.

This document does not provide guidelines on how to manage the social problems such as orphans, unemployment, and stigmatisation. Every one involved in AIDS care should identify local partners that can help take care of AIDS patients. For MSF the content of the medical care is a priority.

This is not a guideline on antiretroviral therapy, but HAART has become an undeniable part of clinical management, and to the extent that HAART has an impact on symptoms and presentation of opportunistic infections, they are dealt with in this book.

The experience of different projects is generating very valuable information for MSF's medical expertise. In this regard all comments on this document are welcome, and should be sent to Line.Arnoald@brussels.msf.org and llynen@itg.be



3 METHODOLOGY

A syndromic approach has been used in the writing of these guidelines.

The first part of each chapter briefly describes the most important HIV-related problems (infections, malignancies, etc.) related to the syndrome (e.g. neurological syndrome). The different diagnostic and treatment issues are mentioned.

In the second part of most chapters **clinical algorithms** are developed for each level of care.

In most developing countries, diagnostic facilities are severely limited. Management decisions have to be based on clinical features and simple laboratory findings.

The diagnostic pathways are presented as flowchart algorithms (single or parallel). Further explanations about the treatment options or diagnostic tools are given in the annotations.

For some complex diagnostic problems (e.g. respiratory problems) a combination of linear algorithms is used.

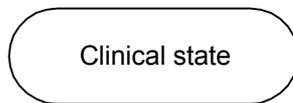
The flowchart algorithms that are proposed in these guidelines are based upon the "WHO guidelines for the clinical management of HIV infection in adults".⁵ The use of these guidelines is conditional on the knowledge of the patient's HIV status and WHO staging. For example, it is clear that *Pneumocystis carinii* cannot be a possible diagnosis if a patient is not immunosuppressed.

It is possible to identify those patients who are immunocompromised either by clinical evidence or by laboratory evidence. The diagnostic flowcharts mainly consider the differential diagnosis in patients with intermediate (stage 3) and late stage (stage 4) disease or patients with a known CD4 < 200. In this group of patients, opportunistic infections should be considered first because the probability is high.

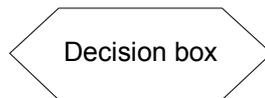
If the CD4 count is not known and there is no clinical evidence of immune deficiency, other diseases should be considered. These problems are not taken into account in this manual.

The algorithms contain three differently shaped boxes, which have the following functions:

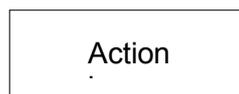
Clinical state or problem definition box: the box defines the clinical state or problem.



Decision box: the information necessary for taking some sort of decision.



Action box: indicates a therapeutic or diagnostic action.



Capital letters between brackets (A) within a box refer to annotations or comments printed on the following pages.

Each algorithm begins with a clinical box describing the symptom or problem. This box is followed by initial steps, after which a certain level of care has to be chosen according to the needs and according to what is available.

A careful history should be taken and a physical examination always carried out **before** an algorithm is applied.

A third part deals with the **palliative, symptomatic and terminal care** related to the syndrome. Before starting symptomatic treatment or palliative care, there must be certainty that all remediable causes are tackled. Therefore, a good interaction between the different levels of care (home care, health centre and hospital) is necessary. At each level of care, however, attention must be paid to involve family members or care-givers, and not to rely solely on drugs. Family members should receive counselling on how to deal with each problem.

Some chapters contain a fourth section describing the **laboratory examinations** in more depth.

The references of the second edition are all gathered at the end of the book. We added an index in this edition to facilitate the search for information. The lists of **drugs and diagnostic equipment** that are needed according to the level of care, which was presented at the end of each chapter in the first

edition is now summarized at the end of the book, in one table.

MSF mostly works at the health centre (level A) and district hospital (level B) level. However, more and more projects are developed that specifically target AIDS patients. In some of these projects an upgrading to certain aspects of level C (specialised AIDS care centres at university hospitals) has taken place. These algorithms will also be of particular interest to HIV clinics, which function as a second-line reference in district hospitals.

Each project will have to define which level of care (A, B, C) is appropriate in the different sites of the project area. If a home-care project receives referrals of terminally ill patients from a hospital, it will need support and input from medical professionals, and extra equipment and knowledge compared to home-care programmes run essentially by community health volunteers.

Depending on the possibilities available at each level in your situation, tasks, algorithms and referral patterns can be different from the ones proposed in this document.



4 DIAGNOSIS AND STAGING OF HIV/AIDS

4.1 Laboratory diagnosis of HIV Infection

Diagnosis of HIV is an important component of HIV/AIDS care. **A diagnosis of HIV should be based on a positive HIV test.**

The “3 Cs” advocated since 1985 remain the cornerstone of HIV testing of the individual. The UNAIDS/WHO policy Statement on HIV testing says that testing should be:

- **Confidential**
- Accompanied by **counselling**
- Only be conducted with informed **consent**

The rationale behind the “3Cs” is that it may reinforce preventive behaviour in sero-negative and sero-positive people.

If people know their serostatus, they can take measures to prevent the development of some opportunistic infections, to prevent further HIV transmission and prepare themselves and their families for the future.

The chance for behavioural change in someone who is tested by coercion is minimal. Behavioural change will only occur if testing is integrated into a comprehensive HIV/AIDS prevention and care package.

Guidelines for counselling with regard to HIV testing, infection and disease can be downloaded from the websites of UNAIDS (www.unaids.org) and the WHO (www.who.int).

Historically HIV testing is indeed performed after individual pretest counselling, client-initiated testing, where patients actively choose to be tested (“opt-in”). With the improved access to antiretroviral therapy, increasingly provider-initiated approaches to testing are promoted, where a patient is informed that routine testing is being done, but that he has a choice to “opt-out” of this systematic offer of testing.⁶

In the 2004 UNAIDS/WHO policy statement on HIV testing, besides VCT and testing for diagnostic reasons in patients who show signs of HIV infection or who have tuberculosis, they also consider routine HIV testing of asymptomatic patients in all health care settings where HIV is prevalent and antiretroviral therapy available, in antenatal clinics and in STD clinics.

For provider-initiated testing, whether for purposes of diagnosis or PMTCT patients retain the right to refuse testing (“opt-out”).

Rapid HIV tests should be used in order to be able to provide “same-day results” to patients, and appropriate post test counselling has to be in place for patients who test positive or negative.

It is very important that we understand the meaning of a positive and negative HIV test to give correct information to our patients. Especially in infants it can be complicated to diagnose HIV.

4.1.1 Diagnosis in adults

The gold standard for the diagnosis of HIV is detecting antibodies against HIV (serologic test). The classic strategy in the developed world is to screen a patient with an Elisa, and to confirm a positive Elisa with a Western blot confirmation assay. Many low-income countries cannot afford expensive confirmation tests in case of a positive Elisa test. The WHO has therefore recommended testing strategies based on a combination of screening tests that do not require expensive Western blot (WB) confirmation assays.

Several rapid serologic assays for HIV exist and allow for on-site testing, including confirmatory testing. Respass et al have reviewed the different test algorithms for the various testing strategies, the advantages and disadvantages of ELISA and of rapid test formats, and the characteristics and status of currently available rapid HIV tests.⁷

Currently, the procedure to diagnose HIV includes screening first with a **simple/rapid test** which is then confirmed by a **second rapid test**. In case of indeterminate results a third rapid test has to be done.

The testing strategy used will depend on: test objectives, HIV prevalence and the age of the individual.

Test objectives

1. Transfusion and transplant safety
2. Surveillance
3. Diagnostic

Prevalence of infection in the sample population

UNAIDS and WHO recommendations for HIV testing strategies according to test objectives and prevalence of infection in the sample population.⁸ (with adaptations according to Respass et al)⁷

Objective of testing	Prevalence of infection	Testing strategy
Transfusion and transplant safety	All prevalences	I
	>10%	I
Surveillance	≤10%	II
	Clinical signs of HIV infection	I
Diagnostic	>30%	I
	≤30%	II
Asymptomatic	>10%	II
	≤10%	II

For safe transfusion, testing strategy I (1 test) is sufficient to reject blood if it is positive. For surveillance in high prevalence settings (> 10%) one positive test result is enough. Except for the symptomatic patient in very high prevalence settings (>30%) at least two tests will be needed for the diagnosis of HIV (strategy II). In the case of a discordant result a third rapid test, or a Western blot confirmation assay if available, has to be performed.

In many situations where MSF is involved in clinical care for AIDS patients, the prevalence of HIV infection in the population is high and we are confronted with patients who meet WHO clinical stage 3 or 4 of HIV infection. In this situation, one simple positive screening test is sufficient to diagnose HIV (testing strategy I).

4.1.2 Diagnosis in children

For children <18 months it is impossible to use a serologic test, because of the persistence of maternal antibodies up to 18 months. The antibodies of the mother gradually decrease and are usually immeasurable by 7 up to 10 months of age, but can sometimes persist as long as 18 months: the antibody test can thus be positive until 18 months, whether the infant is infected or not. So the method of diagnosis is age-dependent as well.

The lack of appropriate diagnostic tests for early detection of HIV infection in

infants born to HIV-positive mothers is one of the bottle necks in scaling up access to ART to HIV-positive infants.

A panel of experts has been working on revised guidelines for antiretroviral treatment of HIV infection in infants and children in resource-limited settings and have addressed the problem of early diagnosis in infants, the presumptive diagnosis of severe HIV disease where definitive diagnosis is not available and also revised recommendations for clinical and immunological classification in infants and children with HIV.⁹

In their draft document they present flow charts for the HIV diagnosis in children, taking into account breastfeeding.

Children < 18 months

Definitive diagnosis of HIV infection in this group can only be made by virological testing. Virological tests that can be used for diagnosis in infants include assays to detect plasma HIV DNA, plasma HIV RNA, heat-denatured p24 antigen assays or viral cultures. HIV DNA PCR is the preferred method but technically demanding. The real time PCR is cheaper and easier to standardise. The heat-denatured p24Ag detection test (Schüpbach) is a reliable assay, but less sensitive than the HIV DNA/RNA assays. Whole blood is difficult to collect from young infants. Use of dry blood spots (DBS) can overcome this problem, because blood can be obtained using a heel-stick. DBS for HIV DNA and RNA testing has proved reliable.

It is recommended to perform the first virological testing after 6-8 weeks, at the first postnatal visit (by this time also children infected intrapartum or peripartum, will be positive on PCR). Reactive tests in duplicate (twice on the same specimen) confirm the diagnosis. Ideally a second sample should be tested, but for public health purposes, in symptomatic HIV-exposed children only one positive result is enough to confirm the diagnosis and to start antiretroviral therapy.

The heat-denatured p24 antigen testing can be used to diagnose HIV infection in infants 4-6 weeks old, but cannot be used to exclude it, because of a lower sensitivity than the DNA or RNA PCR assays.

At the age of 18 months HIV antibody testing should be done to confirm the diagnosis.

Negative virological testing should also be confirmed after 18 months by a negative antibody test.

Diagnosis of HIV in breastfeeding infants

As long as an infant or child receives breast feeding from an HIV-infected mother, there is a risk to acquire HIV through breast feeding.

WHO recommends that HIV virological testing should be performed at least 6 weeks after complete cessation of breast feeding. If the child is already between 9-18 months old, a HIV antibody test could be performed first. In case it is negative there is no need to do virological testing.

Diagnosis of HIV in infants who have received antiretrovirals as prophylaxis of MTCT

HIV DNA assays can be reliably done.

No data exist on the reliability of HIV RNA assays or p24 antigen testing in this group. It is recommended that in case of a negative HIV RNA test or p24 antigen test, this test is repeated 4 weeks after the completion of the prophylaxis.

Diagnosis in infants where the mother is on HAART

These infants are at low risk of acquiring infection, when not breastfed. Two virological tests are recommended when the infant is asymptomatic.

Children > 18 months:

At that age the same testing strategies as in adults can be used. A child is considered HIV + in case of a positive result by two different simple/rapid tests.

4.2 Presumptive diagnosis of HIV/AIDS

In the past, case definitions were developed for AIDS surveillance in countries with limited clinical and laboratory diagnostic facilities.^{10,11} These definitions took into account that in some situations no HIV tests were available. Due to the availability of rapid HIV tests, presumptive diagnosis is no longer justified in adults and children above 18 months of age.

The *diagnosis of AIDS* should be based on the combination of a positive HIV test and certain clinical signs or diagnoses.

The problem persists for children below 18 months. Very often PCR and p24Ag will **not** be **available**.

In situations where virological testing is not yet available it is necessary to make a presumptive diagnosis in infants who require the initiation of appropriate life-saving treatment. Based on expert opinion WHO has developed criteria to presumptively diagnose severe HIV disease in a child below the age of 18 months.^{9,12}

(adapted from WHO)

A presumptive diagnosis of severe HIV disease should be made if:

- Infant is confirmed HIV-antibody positive:
- Aged under 18 months; and
- Symptomatic with two or more of the following:
 - o Oral thrush
 - o Severe pneumonia
 - o Severe wasting/malnutrition
 - o Severe sepsis
- Other factors that support the diagnosis of severe HIV disease in an HIV-seropositive infant include:
 - o Recent HIV-related maternal death
 - o Advanced HIV disease in the mother
 - o CD4 < 25%

4.3 Staging of HIV infection according to WHO

Staging of HIV disease is well correlated with disease progression and mortality and is an important tool in the decision to start preventive therapy and antiretroviral therapy (ART). If possible, clinical staging will be combined with laboratory parameters like total lymphocyte count or CD4 count.

Although clinical stage alone, is not sensitive enough to determine whether a patient needs ART or cotrimoxazole, in many settings we are obliged to rely on clinical staging to take these decisions. Clinical staging may be the only

measure available for the monitoring of the effect of HAART in resource-limited settings.

In October 2005 WHO has published new interim guidelines on the clinical and immunological staging of HIV disease in adults and children.¹³

4.3.1 Clinical staging in adults

A list of clinical markers believed to have prognostic significance has been assembled, resulting in four prognostic categories.

Primary HIV infection

Asymptomatic

Acute retroviral syndrome

Clinical stage 1

1. Asymptomatic infection
2. Persistent generalised lymphadenopathy (PGL)

Clinical stage 2

3. Unexplained weight loss, <10% of presumed body weight
4. Papular pruritic eruptions
5. Seborrhoeic dermatitis
6. Angular cheilitis
7. Recurrent oral ulcerations (2 or > episodes in 6 months)
8. Herpes zoster (2 or > episodes in 6 months)
9. Recurrent upper respiratory tract infections (2 or > episodes in any 6 month period of sinusitis, bronchitis, otitis media, tracheitis, pharyngitis)
10. Fungal nail infections

Clinical stage 3

Conditions where a presumptive diagnosis can be made based on clinical signs or simple investigations

11. Unexplained severe weight loss, >10% of presumed body weight.
12. Unexplained chronic diarrhoea, >1 month
13. Unexplained prolonged fever (intermittent or constant for >1 month)
14. Oral candidiasis
15. Oral hairy leukoplakia
16. Pulmonary tuberculosis (current or in the last two years)
17. Severe presumed bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia)
18. Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis

Conditions where confirmatory diagnostic testing is necessary

19. Unexplained anaemia (< 8 g/dl) or neutropenia (< 500/mm³) and/or thrombocytopenia (<50,000/mm³) for more than 1 month

Clinical stage 4

Conditions where clinical diagnosis is accepted:

20. HIV wasting syndrome*
21. *Pneumocystis* pneumonia
22. Recurrent severe or radiological bacterial pneumonia (2 or > episodes within 1 year)
23. Chronic orolabial, genital, or anorectal Herpes simplex infection (of > 1 month duration) or visceral herpes simplex of any duration
24. Candidiasis of the oesophagus
25. Extrapulmonary tuberculosis (including lymphadenopathy)
26. Kaposi's sarcoma
27. CNS toxoplasmosis
28. HIV encephalopathy†

Conditions where confirmatory diagnostic testing is needed:

29. Extrapulmonary cryptococcosis including meningitis
30. Disseminated non-tuberculous mycobacteria infection
31. Progressive multifocal leukoencephalopathy (PML)
32. Candidiasis of trachea, bronchi, or lungs
33. Cryptosporidiosis (with diarrhoea > 1 month)
34. Isosporiasis (with diarrhoea > 1 month)
35. Cytomegalovirus infection (retinitis or of an organ other than liver, spleen, or lymph nodes)
36. Any disseminated endemic mycosis (e.g. Histoplasmosis, Cryptococcosis, Coccidiomycosis, Penicilliosis)
37. Recurrent non-typhoidal salmonella septicaemia (2 or > episodes in one year)
38. Lymphoma (Cerebral or B cell non-Hodgkin's)
39. Invasive cervical carcinoma
40. Visceral leishmaniasis,

* Weight loss of > 10% of BW, plus unexplained chronic diarrhoea (> 1 month) or unexplained prolonged or intermittent fever (> 1 month)

† HIV encephalopathy: clinical findings of disabling cognitive and/or motor dysfunction interfering with activities of daily living, progressing over weeks to months, in the absence of a concurrent illness or condition other than HIV infection which could explain the findings.

4.3.2 Immunological staging in adults

When CD4 testing is available the degree of immune deficiency can be determined. If this is not available, total lymphocytes can be used as an alternative marker.

CD4 and TLC levels in relation to severity of immunosuppression		
No significant immunosuppression	CD4 > 500/mm ³	
Mild immunosuppression	CD4 350-499/mm ³	
Advanced immunosuppression	CD4 200-349/mm ³	TLC < 1800
Severe immunosuppression	CD4 < 200/mm ³	TLC < 1500 [‡]

Studies have shown an association between total lymphocyte counts (TLC) and absolute CD4 counts.¹⁴⁻¹⁷ As TLC testing is more readily available, it has been suggested to use the TLC to decide when to start HAART.^{18,19} Once a patient's TLC is below 1200/ μ l, the likelihood that the CD4 count will be below 200/ μ l is higher than 90%. However, there is no TLC cut off value that has both a high specificity and sensitivity for detecting patients with a CD4 count below 200/ μ l.^{20,21} Some authors have found that higher TLC levels (< 1400 or 1500) have a better trade off between sensitivity and specificity.^{17,22,23} WHO has published guidelines for the start of HAART in resource-poor settings, in situations where CD4 count testing is not available.²⁴

Most studies show that clinical criteria are not sensitive enough.^{23,25} This is especially true for situations where a large percentage of patients are asymptomatic (eg. recruited from voluntary counselling and testing sites).

In settings where the majority of patients are in advanced disease (WHO stage 3 or 4) TLC does not add a lot to identify patients in need of HAART. In those settings when only looking at clinical criteria about 9 % of patients are wrongly identified to be in need of HAART.^{26,27} In order to avoid unnecessary treatment they identified subgroups of patients where a CD4 count should be targeted to (BMI > 22 or patients who have only weight loss as a stage 3 defining event).

In practice, more and more projects will have access to CD4 counting in the future. Therefore the decisions to start prophylaxis or ART will be dictated by the CD4 count combined with clinical staging.

N.B. The reference values used for lymphocytes and CD4 count are based on data available from the developed world. There are indications that Africans may have a physiologically higher lymphocyte count.²⁸ Even if normal ranges varied there are no data to suggest different trigger points for the initiation of prophylaxis and treatment (CD4 < 200 or CD4% < 15%).²⁹

[‡] WHO ART guidelines 2003 used the TLC < 1200. Some authors found that TLC < 1400 or 1500 provides a better trade off between sensitivity and specificity. We use here the 1500 cut off in agreement with what is proposed by the new interim guidelines for children above 5 years old.

4.3.3 Clinical staging in Children

Clinical stage 1

1. Asymptomatic
2. Persistent generalised lymphadenopathy (PGL)

Clinical stage 2

3. Hepatosplenomegaly
4. Papular pruritic eruptions
5. Seborrhoeic dermatitis
6. Fungal nail infections
7. Angular cheilitis
8. Lineal gingival erythema (LGE)
9. Extensive Human papilloma virus infection or Molluscum contagiosum infection (>5% body area)
10. Recurrent oral ulcerations (2 or >episodes in 6 months)
11. Parotid enlargement
12. Herpes zoster (2 or > episodes in 6 months)
13. Recurrent or chronic upper respiratory tract infections (otitis media, sinusitis 2 or > episodes in any 6 month period)

Clinical stage 3

Conditions where presumptive diagnosis is accepted

14. Unexplained moderate malnutrition not adequately responding to standard therapy
15. Unexplained persistent diarrhoea (>14 days)
16. Unexplained persistent fever (intermittent or constant, for longer than >1 month)
17. Oral candidiasis (outside neonatal period)
18. Oral hairy leukoplakia
19. Pulmonary tuberculosis
20. Severe recurrent presumed bacterial pneumonia (2 or > episodes in 6months)
21. Acute necrotizing ulcerative gingivitis/periodontitis

Conditions where confirmatory diagnostic testing is necessary

22. Lymphoid interstitial pneumonia (LIP)
23. Chronic HIV-associated lung disease, including bronchiectasis
24. Unexplained Anaemia (<8gm/dl), neutropenia (<1,000/mm³) or thrombocytopenia (<30,000/ mm³) for > 1 month

STAGE 4

Conditions where clinical diagnosis is accepted

25. Unexplained severe wasting or severe malnutrition
26. Pneumocystis pneumonia
27. Recurrent severe presumed bacterial infections (2 or > episodes within one year e.g. empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia)
28. Chronic orolabial or cutaneous Herpes simplex infection (of > 1 month duration)
29. Extrapulmonary tuberculosis
30. Kaposi's sarcoma
31. Oesophageal candidiasis
32. CNS Toxoplasmosis
33. HIV encephalopathy

Conditions where confirmatory diagnostic testing is needed

34. CMV retinitis or cytomegalovirus infection other than liver, spleen, or lymph node (onset at age >1 month)
35. Cryptococcal meningitis
36. Any disseminated endemic mycosis (e.g. extra-pulmonary cryptococcosis Histoplasmosis, Coccidiomycosis, Penicilliosis)
37. Cryptosporidiosis or Isosporiasis (with diarrhoea > 1 month)
38. Disseminated mycobacterial disease other than tuberculosis
39. Candida of tracheal, bronchi or lungs
40. Visceral herpes simplex infection
41. Acquired HIV associated rectal fistula
42. Cerebral or B cell non-Hodgkin Lymphoma
43. Progressive multifocal leukoencephalopathy (PML)
44. HIV-related cardiomyopathy or HIV-related nephropathy

4.3.4 Immunological staging in children

Also in children it is possible to assess the severity of immunosuppression with the level of CD4 count.⁹

The absolute CD4 count but also to a lesser extent the CD4% varies with age.

CD4 count in function of age and immune status in infants and children				
	<12 months	12 - 35 months	36 - 59 months	> 5 years
No significant immunosuppression	>35%	>30 %	>25%	>500/mm²
Mild immunosuppression	30-35%	25-30%	20-25%	350-499/mm³
Advanced immunosuppression	25-29%	20-24%	15-19%	200-349/mm³
Severe immunosuppression	<25%	<20%	<15%	<200/mm³

As in adults, the TLC significantly predicts mortality. Therefore in situations where CD4 count is not available the TLC may be used as an indicator for the need of HAART (see table).

Age-specific recommendations to initiate HAART				
Immunological marker	<12 months	12 - 35 months	36 - 59 months	> 5 years
CD4 %	25%	20%	15%	15%
CD4 count (cells/mm³)	1500	750	350	200
To be used only in absence of CD4 assays.				
TLC (cells/mm³)	4000	3000	2500	1500

4.4 CDC staging in adults and adolescents

When diagnostic capacity increases and CD4 count is available, clinicians may prefer the CDC clinical staging. This classification system is based on three ranges of CD4 counts and three clinical categories, giving 9 categories (see Table 2)

The CD4 category receives a number (1-3).

Category 1: CD4 > 500

Category 2: CD4 200-499

Category 3: CD4 < 200

The immunological classification of a patient is based on the patient's lowest CD4 count at any given time (nadir) and not on the most recent count.

The clinical category receives a letter (A-C).

HIV-infected individuals are assigned a letter based on their clinical symptoms. This then determines a patient's clinical staging (see Table 1).

Table 1: CDC CLINICAL CATEGORIES

Category A

- Asymptomatic HIV infection
- Persistent generalized lymphadenopathy
- Acute (primary) HIV infection with accompanying illness or history of acute HIV infection

Category B

Symptomatic conditions in an HIV-infected adolescent or adult that are not included among conditions listed in clinical category C and that meet at least one of the following criteria:

The conditions are attributed to HIV infection or are indicative of a defect in cell-mediated immunity;

The conditions are considered by physicians to have a clinical course or to require management that is complicated by HIV infection. Examples of condition in clinical category B include, but are not limited to:

- Bacillary angiomatosis
- Candidiasis oropharyngeal (thrush)
- Candidiasis vulvovaginal, persistent, frequent or poorly responsive to therapy
- Cervical dysplasia (moderate or severe)/cervical carcinoma in situ
- Constitutional symptoms, such as fever (38.5 °C) or diarrhoea lasting more than 1 month
- Hairy leukoplakia, oral
- Herpes zoster (shingles), involving at least two distinct episodes or more than one dermatome
- Idiopathic thrombocytopenic purpura
- Listeriosis
- Pelvic inflammatory disease, particularly if complicated by tubo-ovarian abscess
- Peripheral neuropathy

CDC CLINICAL CATEGORIES (continued)

Category C

Category C includes the clinical conditions listed in the AIDS surveillance case definition. For classification purposes, once a category C condition has occurred, the person will remain in category C.

- Candidiasis of bronchi, trachea, or lungs
- Candidiasis, oesophageal
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes)
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV-related
- Herpes simplex, chronic ulcer(s), >1 months duration; or bronchitis, pneumonitis, or oesophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1 months duration)
- Kaposi's sarcoma
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary of the brain
- Mycobacterium avium complex or M. kansasii, disseminated or extrapulmonary
- Mycobacterium tuberculosis, any site (pulmonary[§] or extrapulmonary)
- Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
- Pneumocystis carinii pneumonia
- Pneumonia, recurrent
- Progressive multifocal leukoencephalopathy
- Salmonella (nontyphoid) septicemia, recurrent
- Toxoplasmosis of the brain
- Wasting syndrome due to HIV (weight loss of >10% of body weight plus either unexplained chronic diarrhoea >1 month OR chronic weakness and unexplained prolonged fever >1 month)

[§] Pulmonary TB should be included in class C only in populations where the risk of tuberculosis is low. In developing countries the annual risk of infection is in many countries above 1% in the general population and in this setting it would be an error to consider all HIV patients with PTB in CDC stage C.

Table 2: CDC Revised Classifications System for HIV Infection and Expanded AIDS Surveillance Case Definition for Adolescents and Adults*

Immune Category	Clinical Category A	Clinical Category B	Clinical Category C
1. CD4 > 500	A1	B1	C1
2. CD4 200-499	A2	B2	C2
3. CD4 < 200	A3	B3	C3

*Modified from MMWR, Vol. 41, 1992 RR-17

 Any clinical category combined with an immune Category 3 is classified as AIDS and any immune category combined with the Clinical Category C is classified as AIDS.

4.5 CDC staging in children

N. No signs or symptoms considered to be the result of HIV infection or only one of the conditions listed in category A

A. Two or more of the conditions listed below but none of the conditions listed in categories B and C

Lymphadenopathy (≥ 0.5 cm at more than 2 sites; bilateral = 1 site)

Hepatomegaly

Splenomegaly

Dermatitis

Parotitis

Recurrent or persistent upper respiratory infection, sinusitis or otitis media

B. Symptomatic conditions other than listed in A or C that are **attributed to HIV**

Anemia (< 8 g/dl), neutropenia ($< 1,000/\text{mm}^3$), or thrombocytopenia ($< 100,000/\text{mm}^3$) persisting ≥ 30 days

Bacterial pneumonia (serious), meningitis or sepsis (single episode)

Candidiasis, oropharyngeal persisting (> 2 months) or recurrent in children > 6 months of age

Diarrhoea, recurrent or chronic

Persistent fever (lasting > 1 month)

Hepatitis

HSV stomatitis, recurrent (> 2 episodes within 1 year)

Zoster (at least 2 distinct episodes or more than 1 dermatoma)

Varicella, disseminated (complicated chickenpox)

CMV, HSV (pulmonary) or toxo infection, with onset before 1 month of age

Lymphoid interstitial pneumonia (LIP)

Nephropathy, Cardiomyopathy, nocardiosis

C. AIDS

Serious bacterial infections, multiple or recurrent at least 2 within a 2-year period, sepsis, pneumonia, meningitis, bone or joint infection, or deep abscess

Candidiasis, oesophageal or pulmonary

Cryptosporidiosis or isosporiasis with diarrhea > 1 month

Cryptococcosis, extrapulmonary

CMV (non liver, spleen or lymph nodes) or brain toxo onset > 1 month of age

Encephalopathy (progressive findings present for at least 2 months in absence of a concurrent illness)

- *Failure to attain or loss of developmental milestones or loss of intellectual ability*
- *Impaired brain growth or acquired microcephaly*
- *Acquired symmetric motor deficit :≥ 2 of : paresis, pathologic reflexes, ataxia or gait disturbance*

HSV mucocutaneous ulcer persisting > 1 month

Tuberculosis, disseminated or extrapulmonary

Mycobacterium, non tuberculosis, disseminated

Pneumocystis carinii pneumonia

Wasting syndrome

- persistent weight loss > 10% of baseline
 - downward crossing of at least 2 percentile lines (95th, 75th, 50th, 25th, 5th) on weight-for-age chart
 - < 5th percentile on weight-for-height chart on 2 consecutive measurements, ≥ 30 days apart
- + *chronic diarrhoea or persistent fever*



5 FOLLOW-UP OF ASYMPTOMATIC HIV-POSITIVE PATIENTS

Regular medical follow-up of asymptomatic patients will provide an opportunity for the health-care worker to address various questions with PLHA, such as the prevention of transmission, how to maintain good nutritional status, how to prevent health-care problems, and opportunistic infections. They need reassurance and correct information on HIV, their prognosis and the possible interventions that can be offered. The stage of the disease and the CD4 count will determine the need for prophylaxis, and the need for ARV.

Psychological support is also needed. The patient will have many questions and anxieties. It is important that in the post-test counselling the patient is informed as to who to see and where to go with questions. It also shows the patients that they are not abandoned, but will continue to be cared for, if they so desire. The concept that HIV infection has become a chronic disease in the era of HAART, not a lethal disease needs to be emphasized. And the patient needs to feel that he is an essential part of the management plan of his chronic disease. This takes away the common belief that nothing can be done to help HIV-infected patients.

The medical team should, together with other institutions, address social and financial problems. It is essential that PLHA are offered the opportunity to take part in peer support groups.^{30,31}

5.1 Initial check-up

5.1.1 Complete history

Medical history

- STD
- TBC
- Probable route of acquiring HIV infection - to identify risk behaviour.

Family history

- social situation
- marital status/sexual partner(s)
- children
- intention to have children
- any other PLHA in the family
- any tuberculosis in the family.

Economic situation

- income sources
- food security
- fixed costs.

Spiritual support

- religion
- traditional healers.

Present clinical situation

- current symptoms (see Table)
- staging following WHO clinical staging system (see chapter 4, page 23)

5.1.2 Physical examination

Perform a **complete** physical examination.

Look for indicator diseases like herpes zoster, oral candidiasis, wasting, etc.

Examine the genital area, and always give women a gynaecological examination.

5.1.3 Other possible tests

- *Complete blood count* (haemoglobin, WBC, platelets).
- *Lymphocytes* or *CD4* count.
- *ESR*: is usually elevated (>50) in HIV-positive patients. If more than 100, consider TB.
- *VDRL*, 6% false positives, confirm with *TPHA*. Relapse is common even with the recommended treatment. It is therefore important to perform follow-up *VDRL* at 6- 9 -12 months.
- If *hepatitis B serology* is possible and negative, start vaccination in those countries where hepatitis B vaccination is available. Risk factors for HIV and hepatitis B are the same, and in the US 70-80% of HIV patients have serologic markers for hepatitis B.
- *Hepatitis C serology* is recommended. Patients with chronic hepatitis have a higher risk for hepatotoxicity when started on HAART. The evolution of chronic hepatitis C is more rapid in HIV co-infected patients.
- Chest X-ray: It is useful in the initial check up because it serves as a comparison to later chest X-rays in case pulmonary problems appear. Sometimes, it allows for early detection of TB. Where *INH-prophylaxis* is possible, chest X-ray is necessary to exclude active TB, prior to starting the prophylaxis. (See chapter 6, page 47)
- *PPD skin testing* is not routinely recommended in MSF settings. Skin testing may be false positive due to BCG vaccination or false negative due to anergy. In developing countries there is a very high prevalence of *PPD* positivity. In this context, *INH prophylaxis* would be justified in all HIV-positive patients. However, because of the difficulty of excluding active TB,

and because of the weakness of TB programmes in most developing countries, large scale INH preventive therapy is difficult.

5.1.4 Health education

DO NOT TRY TO GIVE ALL INFORMATION DURING THE FIRST CONSULTATION

Information on HIV transmission

How to prevent the transmission of HIV to others

- Give information about how HIV is transmitted, about risk behaviour. Discuss points such as safe sex (condom use) and prevention of transmission.
- Give reassurance that they do not pose a risk for other family members in normal daily life.
- Body fluids that may transmit HIV through contact with abrasive skin are semen, vaginal secretions, and blood. Other risk fluids are peritoneal, pleural, pericardial, amniotic, CSF and synovial fluids, although contact with those fluids is less likely in household environment.
- Urine, stools, sputum, saliva, tears, vomit, and nasal secretion do not transmit HIV unless they are contaminated with blood.
- Care providers are advised to protect their hands whenever handling body fluids (including soiled bedding and clothes, or cleaning up vomit), or when coming into contact with open wounds. If gloves are not available plastic bags can be used instead.

Prevention of vertical transmission

Contraceptive use in women: if pregnancy is desired, discuss the risk of HIV in the offspring (30%) and discuss possible interventions to prevent this (according to the setting).³²

Prevention of transmission by exposure to blood

Needles, razor blades, and used condoms should be thrown away in such a way that their re-use is not possible. Do not share syringes or tattoo equipment.

For professionally-acquired exposure to blood, refer to the MSF guidelines.³³

Transfusion

HIV patients should know that they cannot give blood.

Hygiene

Good hygiene is necessary for everybody, not only HIV patients. The importance of good personal hygiene should be stressed.

Environment

Some professions bring about risks of opportunistic infection. Of particular relevance in situations where MSF works is the issue of health-care workers who are HIV-positive, and who are at risk of exposure to infections such as TB, enteropathogens, etc.

In developing countries where more than 60% of adult hospitalised patients can be HIV-positive, it is difficult to avoid contact with infectious patients. It is therefore recommended that cotrimoxazole and INH prophylaxis be offered to health workers wherever possible.

Wounds and skin lesions should be kept dry and clean. Contact with infectious people or places like hospitals should be avoided when possible, but in a way that ensures that stigmatisation is not increased.

Handwashing is the most effective way of preventing transmission of infections. Laundry, especially soiled bedding and clothes should be washed with hot water. Clothes stained with blood or body fluid stains should be washed with bleach solution (one part bleach (70%) to ten parts water).

Animals

Animals are a reservoir for *Salmonella*, *Cryptosporidium*, and *Campylobacter*. Avoid any contact with animal excrement; use gloves to clean up the environment around the house if necessary.

Nutritional advice

Water for consumption should be boiled or bottled water should be used instead.

Good nutrition means balanced food (cereals, fruits, vegetables, oil, meat/fish) prepared in a clean way. Avoid raw foods as much as possible. Meat and eggs should be thoroughly cooked. Fruit and vegetables should always be washed with clean water; vegetables should be cooked before eating.

When re-heating food, make sure it is very hot throughout. Do not reheat more than once.

Medical advice

Explain to patients that whenever they develop signs of infection they should contact the health service.

Nutrition

A balanced food intake is one of the most important ways to stay healthy. Malnutrition and malabsorption are major problems in AIDS patients. Patients

should be given an explanation about what to do when eating becomes a problem.^{34,35} For more in depth reading we refer to *HIV/AIDS:A guide For Nutrition, Care and Support*.³⁶

Loss of appetite:

- try to choose foods that the patient prefers
- try small, frequent meals
- allow them to eat whenever they feel like it, not at scheduled times
- physical exercise creates appetite
- ask family or friends to keep the patient company during a meal, even if it takes longer.

Sore mouth:

- choose soft foods that are easy to swallow
- avoid very hot or very cold food
- use a straw for drinking.

Nausea/vomiting:

- sit up to eat
- eat slowly and small amounts
- avoid greasy or spicy food
- in case of vomiting, try soup or bouillon, rather than solid foods.

Diarrhoea:

- continue to eat, even if eating seems to increase the diarrhoea
- avoid alcohol and coffee
- drink much more than usual, but remember that drinks do not replace food
- avoid high-fibre or bulky foods, such as fruit and vegetable peel and whole-grain cereals because they are hard to digest
- After the diarrhoea has stopped, the patient can take an extra meal every day, to make up for the weight loss.

In case of pain on swallowing, signs of dehydration, refusal of food and drinks, and inability to keep food down, patients should seek medical advice.

Regular physical exercise

- Favours digestion and appetite.
- Helps to maintain physical fitness.
- Improves emotional wellbeing.

Adequate rest

Emotional well-being

The medical care-provider has to take into account the emotional wellbeing of the patient. People who are sad and depressed will not take care of their physical wellbeing.

Important social and communication skills are required, but are often neglected because of time constraints. This is a mistake: patients will not feel understood and will stay away, even when they have medical problems. Therefore, it is difficult to imagine AIDS care without a multidisciplinary team that supports the medical care-provider.

It is essential to:

- listen carefully to the patient
- try to understand their feelings
- ask questions in an empathic way
- respect their feelings
- encourage patients when they express emotions
- offer care that helps to maintain self esteem and self confidence
- give correct information; do not give false hope
- help the family to deal with the emotions (the patient's and their own).

Patients should continue to do their daily routine work, and continue to attend the usual religious and community meetings.

Patients should participate in the decision making process when dealing with their health problems. This will help them to understand their medical problems and increase self-esteem. It is important for them to understand the natural evolution of HIV infection, and how it can be influenced by correct prevention of OI and by the timely initiation of HAART.

If patients are very sick already, families should be mobilised to take an active part in the care of the patient. They should be advised to learn certain techniques like massage and relaxation so that they can offer it to patients when they need it. They need to learn about the importance of good compliance to treatment and the need for regular follow-up.

Try to put the person in touch with community support groups. Groups will help the members to share their feelings and worries and to give each other support.

Some traditional practices or religious rituals can be helpful. Certain traditional healers, priests, monks or others can play a role in guiding the patient and the family through the process of shock, denial, anger, fear, sadness, hope and acceptance.

With the event of HAART, the emotional stress for people involved in care and support programmes for PLHA to deal constantly with terminal patients, has greatly decreased. AIDS is a disease that can be treated. It is important to convey this message of hope to the patient. However, even in the era of HAART a lot of problems still exist with stigmatisation, orphans and single parent families, poverty, loss of relatives and friends to AIDS. In most countries the number of new patients still exceeds the number of patients put on treatment. Psychological counselling for patients and health care workers dealing with this kind of social stigmatising diagnosis is therefore important.

5.2 Follow-up visits

After being informed about their test results, patients may need closer follow-up (weekly or monthly). Once a relationship has been established, and there has been an opportunity to explain most of the above advice, the interval may be extended to once every three months for asymptomatic patients.

Checklist for follow-up visits (from MSF guidelines for home care in Nairobi)

Patients will complain about the most disturbing symptoms at the time of presentation. It is important to review with your patient all systems in order to detect health problems early.

See checklist next page.

Blood tests at follow-up

- Complete blood count, including CD4 every 6 months.
- Other examinations only according to symptoms.

Check list

- Weight loss/appetite/weakness**
Diarrhoea, dysphagia, oral pain, etc?
- Fever**
<1 week: malaria, pneumonia, bacteremia
>1 week: TB, PCP, cryptococcosis, etc.
- Eyes**
Jaundice, anaemia, visual disturbance, etc?
- Oral cavity**
Oral thrush, ulcers, etc?
- Lymph nodes**
PGL (>1 month, >2 areas, <2 cm, not painful), infections (syphilis, wound infection, TB,...), lymphoma, Kaposi's sarcoma?
- Skin problems**
Itching? Duration? Relation to drug intake?

- Respiratory problems**
Duration of cough? Productive? Dyspnoea? Already taking TB treatment?
Already taking PCP prophylaxis?
- Gastrointestinal**
Dysphagia, diarrhoea, abdominal pain?
- Nervous system**
Central: headache, seizures, paralysis?
Peripheral: paraesthesias, numbness, neuropathy?
- Genital area**
Discharge, pruritis, lesions?
- Psychological**
Mood? Sleep disturbances?
- Clinical staging: (see staging)**
WHO 1-4? CDC A,B,C?
Lymphocytes/CD4
- Prevention of opportunistic infection?**
Clinical stage 2, 3 and 4, and all patients with a CD4<200 would benefit from cotrimoxazole prophylaxis.
- Drugs:** any new prescriptions, compliance, side effects, problems, etc?



6 PREVENTION OF OPPORTUNISTIC INFECTIONS

6.1 Introduction

In the Western world the incidence of opportunistic infections has dramatically decreased with the advent of HAART “The best and often only necessary prophylaxis for opportunistic infections is effective ART.”³⁷

The issue of prevention of opportunistic infections (OI) in developing countries is quite different from that in the Western world.³⁸ The spectrum of OI is different, as are the range of prevention options, the access to ART and the susceptibility of the infecting pathogen to antimicrobials. Due to poor general health infrastructures and non-access to ART, many AIDS patients in Africa do not survive long enough to develop CMV or MAC. Resources are also limited, and for the majority of patients CD4 counts that would enable us to follow-up the evolution of the disease are not available. Even if ART becomes more widely available, patients in developing countries are often only diagnosed with HIV when they present with AIDS-defining illnesses.^{39,40}

Important opportunistic infections for HIV-infected individuals in the developing world are:

- tuberculosis: widespread
- pneumococcal disease: widespread
- non-typhoid salmonellosis: particularly East and West Africa, Thailand, and Cambodia
- cryptococcosis: particularly East and South Africa, Thailand and Cambodia
- *Pneumocystis carinii* pneumonia: South Africa, and Asia
- penicilliosis: Thailand
- visceral leishmaniasis: Ethiopia, Sudan

Even within the developing countries incidences of different diseases vary and may have an influence on the need for prophylaxis. The estimated prevalence of these diseases might be biased by the available diagnostic facilities and resources. Cryptococcal meningitis is infrequent in West Africa, but it is the fourth most common reason for hospital admission in South Africa, and the first cause of death among hospitalised gold miners.⁴¹ In this population, TB was the first reason for hospitalisation, followed by bacterial pneumonia, indicating that INH, cotrimoxazole and fluconazole prophylaxis might possibly have a significant impact on hospital admission rates in this setting. MAC is considered very infrequent in West and East Africa, but a study from South

Africa showed a prevalence of MAC bacteremia of 10% in hospitalised patients with CD4 <100.^{42,43}

General measures to prevent infections are also important, such as avoiding unpasteurised dairy products, raw or undercooked eggs, meat, poultry, or fish as sources of salmonella infection, and undercooked meat as a source of toxoplasmosis. If no safe water supply is available, patients and family should be advised to boil drinking water to avoid diarrhoeal diseases such as cryptosporidiosis. Mouldy sugar cane or bamboo has been suggested as a possible source of *Penicillium marneffe* infection in Thailand.

Extensive reviews of prevention of OI in HIV patients in the industrialised world have been published, giving an exhaustive list of preventive measures.^{44,45} A slide presentation on exposure prevention based on the 2001 USPHS/IDSA Guidelines is available on the web.⁴⁶

Prevention of OI can be commenced as either **primary prophylaxis** (given to PLHA who have never had these infections) or **secondary prophylaxis** (given to PLHA who have had an episode of these illnesses to prevent recurrence). Lifelong primary and secondary prophylaxis has been advocated for most OI before the event of HAART. There is increasing evidence that it is safe to interrupt primary and secondary prophylaxis when immune restoration has occurred in a patient on HAART.

6.2 Cotrimoxazole

6.2.1 Rationale

In PLHA, cotrimoxazole is potentially useful for the prevention and treatment of a wide range of infections. These include PCP and toxoplasmosis, but also the most important causes of serious bacterial infections such as pneumonia, bacteraemia and bacterial enteritis: *Streptococcus pneumoniae*, *Salmonella* species, *Shigella* species, *Eschericia coli*, *Staphylococcus aureus* and *Haemophilus influenzae*. Cotrimoxazole is also active against *Plasmodium* species (malaria), *Isospora belli* (cause of diarrhoea) and *Nocardia asteroides* (respiratory and generalized infections).

6.2.2 Benefit of cotrimoxazole prophylaxis in developing countries

This has been proven in several studies. In a randomized trial conducted in Abidjan, Côte d'Ivoire, researchers compared the efficacy of daily double strength (DS) cotrimoxazole to placebo in PLHA in WHO clinical stages 2 and 3.⁴⁷ They found a significant reduction in severe events defined as either death or hospitalization.

The use of cotrimoxazole prophylaxis in a subgroup of PLHA with smear positive pulmonary TB was investigated during a second randomized study conducted in Abidjan. This showed more marked benefits with significant reductions in OIs and hospital admissions and a 50% reduction in mortality.⁴⁸ This finding of reduced mortality in TB patients who received cotrimoxazole prophylaxis under routine programme conditions was also reported in two studies in Malawi.^{49,50}

Moreover, the offer of a package of VCT and cotrimoxazole to TB patients has been shown to improve TB treatment outcomes in a district setting in Malawi.⁵¹

There is also an improvement of anthropometric indicators in HIV-positive adults who start on cotrimoxazole prophylaxis.⁵²

The main effect of cotrimoxazole prophylaxis in developing countries is not on PCP and toxoplasmosis but on other bacterial infections and on malaria.⁵³⁻⁵⁷ Even HIV-uninfected family members of HIV patients taking cotrimoxazole prophylaxis have a decrease in morbidity and mortality.⁵⁸

6.2.3 Target groups for cotrimoxazole prophylaxis

After the results of the two prevention trials from Côte d'Ivoire were published, UNAIDS formulated firm recommendations for the use of cotrimoxazole primary prevention in HIV-infected patients.⁵⁹

In the experience of the Côte d'Ivoire, the majority of HIV patients attending for medical reasons were in stage 2 and 3.⁴⁷ It was concluded that all HIV patients presenting with symptoms related to HIV should receive cotrimoxazole prophylaxis, and that all TB patients should be offered HIV testing and preventive treatment with cotrimoxazole, if HIV-positive. In most resource-poor settings CD4 counting is not yet available and the UNAIDS recommendation stating that all **symptomatic HIV patients** should receive cotrimoxazole prophylaxis is very practical.

The criteria for starting cotrimoxazole prophylaxis in **asymptomatic** patients have changed over time. UNAIDS/WHO guidelines propose CD4 < 500. Some countries used the threshold of CD4 200 (Thailand) others 350 (Cambodia). The question is: does the start of cotrimoxazole at CD4 > 200 have an impact on survival? Badri showed that, for the specific context in South Africa, if they applied the WHO/UNAIDS recommendations at a cut off

of CD4 500, 88 % of patients would need cotrimoxazole at the first visit. But, cotrimoxazole only had an impact on survival and on the occurrence of severe events in the group with CD4 < 200.⁶⁰ This is not necessarily the case in other countries. There are obviously several factors that have an impact on survival in other resource-poor countries, such as, access to health services and effective treatment, patient delays before presenting to the health service, prevalence of common pathogens with CD4 200-500 etc. It is worth emphasising that HIV-positive patients with active TB need to be offered cotrimoxazole preventive therapy whatever their CD4 count, even when there are no other signs of opportunistic infections.

Based on trial data from Zambia⁵⁷, WHO, UNAIDS and UNICEF have revised the recommendations for cotrimoxazole prophylaxis in **children**.⁶¹ Cotrimoxazole is recommended for all HIV exposed children (whether or not part of a PMTCT programme). PCP prophylaxis is also recommended for all children identified as HIV-infected with clinical signs or symptoms suggestive of HIV, regardless of the CD4 count. From the age of 18 months, when a definite serological diagnosis of HIV infection is made, prophylaxis is also given to asymptomatic children with CD4<15%.

Although one study from South Africa failed to show a reduction in the incidence of PCP in children, it had a marked effect on mortality, which decreased by 98.6%.⁶²

The recommendations are summarised in Table 3 and Table 4.

6.2.4 Discontinuation of cotrimoxazole prophylaxis

Discontinuation of cotrimoxazole for the prevention of PCP and toxoplasmosis is safe in patients responding to HAART, who have a sustained immune response with CD4>200 for more than 3 months.^{45,63,64}

Secondary prophylaxis or maintenance therapy was considered a lifelong necessity before the introduction of HAART.

Several small series and larger cohort data suggest that it is safe to interrupt secondary prophylaxis for PCP and toxoplasmosis after the start of HAART, when there is a sustained increase of CD4 >200.^{64,65} Restoration of prophylaxis is needed when ART is discontinued or when the CD4 count drops below 200 again, or in the absence of CD4 counts when the patient again becomes symptomatic. There remains some uncertainty about the safety to interrupt secondary prophylaxis in patients who had low CD4 nadirs (<50), especially when the patient is tolerating the drugs well. Patients who develop respiratory symptoms after discontinuation of PCP prophylaxis should always be investigated for recurrent PCP, even when the viral load is undetectable and the CD4 count is high.⁶⁶

Primary prophylaxis can be discontinued in children receiving HAART and having CD4>15% at two measurements, at least 3-6 months apart. In children, secondary prophylaxis with cotrimoxazole is never interrupted because there are no data to prove that it is safe.

Table 3: When to stop and when to start cotrimoxazole prophylaxis in adults?

A D U L T S	DOSE	WHEN TO START	WHEN TO STOP
			PRIMARY PROPHYLAXIS
	800 mg SMX/160 TMP (1 double strength) OD	Symptomatic HIV disease (WHO clinical stage 2, 3 or 4) or CD4 < 200/mm ³ or TLC < 1200/mm ³	Patient on HAART for at least 6 months and sustained level of CD4 >200/mm ³ †
		SECONDARY PROPHYLAXIS	
‡	1DS* OD	All patients after an event of PCP, Isospora belli, toxoplasmosis	Patient on HAART for at least 6 months with treatment success evidenced by a sustained CD4 count > 200/mm ³

* Double Strength tablet containing 800 mg sulphamethoxazole and 160 mg trimethoprim once daily (OD)

† If the CD4 count drops below 200 then cotrimoxazole prophylaxis should recommence until the CD4 count is again consistently above 200 for at least 6 months. If ART is stopped for more than a few weeks cotrimoxazole should be restarted.

‡ For pregnant women start only after the first trimester of pregnancy

Table 4: When to stop and when to start cotrimoxazole prophylaxis in children?

C H I L D R E N	DOSE	WHEN TO START	WHEN TO STOP
		6-8mg/kg	PRIMARY PROPHYLAXIS
	< 5 kg 2.5 ml OD (once daily)‡ 5-9 kg: 5 mL OD 10-14 kg: 1 tab (SS*) OD or 10 mL OD 15-24 kg: 1 tab OD or 15 mL OD >25 kg: 2 tab OD	All children born to an HIV-infected woman from 6 weeks of life on Child HIV-positive and symptomatic, regardless of CD4 count Child HIV-positive, asymptomatic but CD4 < 15%	When HIV-infection is ruled out and the child is not breastfed** At 18 months if HIV-negative After the start of HAART and sustained CD4 >15% for 6 months†
		SECONDARY PROPHYLAXIS	
	Same as above	All children who have been treated for PCP, toxoplasmosis, isosporiasis	No data available on the safety of discontinuation of cotrimoxazole for secondary prophylaxis in children → Lifelong

* Single Strength Tablet (SS) containing 400 mg sulphamethoxazole and 80 mg trimethoprim

** For a non-breastfed child <18 months: negative DNA or RNA virological testing
For a breastfed HIV exposed child < 18 months: negative DNA or RNA only reliable 6 weeks after cessation of breastfeeding
For a breastfed HIV exposed child > 18 months, negative HIV antibody testing 3 month after stopping breastfeeding

† If the CD4 percentage drops below 15 then cotrimoxazole prophylaxis should recommence until the CD4 percentage is again consistently above 15 for at least 6 months. If ART is stopped for more than a few weeks cotrimoxazole should be restarted. If ART is not available cotrimoxazole should be continued

‡ Or divided into two doses; every day or three days/week (consecutive or alternating).

6.2.5 Adverse reactions

Adverse reactions are common. Fortunately, the incidence of adverse reactions against cotrimoxazole seems to be lower in Africa and Asia than in Western countries.⁶⁷

The main side effects of cotrimoxazole are rash, bone marrow suppression and hepatitis. They are more likely to occur soon after initiation of cotrimoxazole. Minor rashes and itching are common and can usually be managed with careful observation while continuing cotrimoxazole. More severe rashes, including Stevens-Johnson syndrome and clinical hepatitis are possible and must lead to immediate cessation of cotrimoxazole. In fact, cotrimoxazole should be stopped in any patient well before this stage and at least as soon as there is any mucosal involvement (mouth or eye lesions).

Every effort should be made to continue prophylaxis with cotrimoxazole because it is more active against PCP than alternative regimens, and it is also protective against toxoplasmosis, bacterial respiratory infections and some enteric pathogens. Lower doses of cotrimoxazole, although better tolerated, are less effective than the recommended daily DS tablet. Moreover, the efficacy of lower doses of cotrimoxazole on other opportunistic infections, in particular toxoplasmosis, is not sure.⁶⁸

Side effect management

In cases of non-life-threatening adverse reactions, treatment should be stopped for two weeks, and the patient should then be re-challenged with cotrimoxazole in a gradually increasing dose (desensitisation).⁶⁹ Use for this purpose a cotrimoxazole suspension of 40 mg TMP + 200 mg SMX per 5 ml and give according to one of the following schedules:

1. Inpatient: Over 6 hours, give hourly doses (cotrimoxazole in mg): 0.004/0.02, 0.04/0.2, 0.4/2.0, 4.0/20, 40/200 and 160/800.
2. Outpatient: Give 1 ml daily for 3 days; 2 ml for 3 days and so forth until the dose can be administered as 1 SS daily and the next day 1 DS daily. Another example of desensitisation scheme is given in Table 5.
3. NEVER try desensitisation in a patient who had severe side effects (life-threatening hepatitis or Stevens-Johnson syndrome).

After desensitisation under surveillance, up to 70% of patients may again tolerate cotrimoxazole.⁴⁶

Alternative regimens

If desensitization fails, another regimen needs to be given. Which regimen depends on the CD4 count, the need to prevent toxoplasmosis and whether cotrimoxazole was being used as primary or as secondary prophylaxis.

WHO recommends dapsone 50 mg 2 x daily or 100 mg once daily (children 2mg/kg daily) as the first alternative for prevention of PCP. True cross-allergenicity between different sulphonamide antimicrobial agents is low, and SMX-TMP can safely be substituted for dapsone or sulphadoxine/pyrimethamine (Fansidar®), with 75% of patients tolerating these alternative sulphonamides.⁷⁰

When dapsone is combined with pyrimethamine it is also effective against toxoplasmosis (see chapter 14, page 243). In patients with CD4<100 and positive toxoplasma antibodies, pyrimethamine 50 mg weekly + folinic acid 25 mg weekly should be added. This regimen is much more expensive and complex than the cotrimoxazole preventive therapy.

Fansidar® 1-2 tablets weekly has primary preventive activity against PCP and toxoplasmosis.⁷⁰

Pentamidine aerosols 300 mg/ month are more difficult to administer, are less effective in preventing PCP, and have no effect on toxoplasmosis.

Table 5: Example of desensitisation scheme for cotrimoxazole	
1 ml cotrimoxazole suspension (40mg TMP/200mg SMX/5 ml) in 10 ml water	
day 1 :	1 ml solution
day 2 :	2 ml solution
day 3 :	4 ml solution
day 4 :	8 ml solution
Cotrimoxazole undiluted suspension	
day 5 :	0.6 ml
day 6 :	1.25 ml
day 7 :	2.5 ml
day 8 :	5 ml
day 9 :	10 ml
Cotrimoxazole tablets (80 mg TMP- 400 mg SMX)	
day 10:	1 co
day 11-17:	2 x 1 co/d
hereafter:	1 tablet cotrimoxazole DS/d

6.2.6 Unanswered questions regarding cotrimoxazole prophylaxis

Does the widespread use of cotrimoxazole prophylaxis have an impact on the development of resistance in bacterial pathogens to cotrimoxazole? This has been a concern since the UNAIDS recommendations on cotrimoxazole prophylaxis in Africa,^{49,71} and in several settings an increase in resistance to

cotrimoxazole has indeed been observed.^{54,72,73} Cotrimoxazole is still first-line therapy for a variety of childhood infections under the World Health Organization integrated management of Childhood Infections (IMCI) guidelines. Several African countries currently follow these guidelines and as resistance development could impair the effectiveness of the IMCI programme, this merits surveillance.

In vitro studies suggest that exposure to cotrimoxazole may lead to cross-resistance to sulphadoxine-pyrimethamine, now a first line anti-malarial drug in many African countries.^{74,75}

What will be the effect of cotrimoxazole prophylaxis in an area with high cotrimoxazole resistance? In several countries nontyphoidal salmonella species are resistant to cotrimoxazole (Thailand 40%, Malawi 73%).^{76,77} Shigella worldwide is resistant and pneumococcal resistance varies between 9 and > 50%.

Several studies have proven that cotrimoxazole prophylaxis is beneficial even in areas with high prevalence of cotrimoxazole resistance among bacterial isolates.^{57,78} In the trials in Côte d'Ivoire, 75% of pathogens cultured from patients taking cotrimoxazole prevention were resistant to cotrimoxazole, but the incidence of bacterial infection still decreased by 50% compared to the placebo group.⁷¹

6.2.7 Distribution of cotrimoxazole

Cotrimoxazole prophylaxis should be offered as an essential part of comprehensive care for PLHA. Cotrimoxazole can be given through community clinics and home-care projects. It could be integrated into counselling activities, with the regular follow-up of the PLHA by a counsellor at the same time as the cotrimoxazole prescription is renewed. When given free of charge and made available to patients the acceptability of its use is more than 90%.⁷⁹

Cotrimoxazole prevention is very effective and is **seriously** underused in developing countries.

6.3 Isoniazid (INH)

6.3.1 Rationale

HIV infection is the strongest known risk factor for the progression of latent TB infection to active TB. In countries with high TB prevalence, between 2.4% and 7.5% of HIV-infected adults may develop active TB each year. In those with a positive PPD test, the rate rises to between 3.4% and 10% per year with a lifetime risk of 50%.^{11,80} The mechanisms for this include reactivation of latent infection and/or re-infection with *Mycobacterium tuberculosis*,

characterised by a rapid progression of primary infection to active disease.⁸¹ Before the AIDS epidemic, preventive therapy for tuberculosis was never recommended in developing countries (poor cost-effectiveness, high rate of re-infection) except for breast-feeding infants of mothers with PTB, or children <5 years old living with infectious persons.

Preventive therapy as a public health strategy is now being reconsidered because of the high incidence of TB in HIV-positive patients in developing countries, and because active TB may accelerate the clinical course of HIV infection.^{82,83} In the pre-AIDS era, several placebo-controlled trials in the USA and Europe demonstrated the efficacy of INH prevention in PPD-positive persons, which is believed to be at least 60%.

Benefit of INH prevention

A review of randomised placebo controlled trials (Haiti, Kenya, Uganda, US) demonstrated that INH prevention reduced the incidence of TB in HIV-positive PPD-positive patients (approximately 70% reduction in risk, RR = 0.32), and delayed the onset of HIV-related disease and death (mortality reduced by 25%).^{84,84,85} It also reduces the incidence of tuberculosis in PPD-negative patients (RR 0.58; 95% CI 0.39 to 0.87), but in this group there is no effect on mortality. In a group with unknown PPD status, and in the absence of HAART, INH preventive therapy has no influence on mortality but significantly reduces the incidence of TB (45% reduction).⁸⁶

Duration of benefit

The duration of the efficacy of PT for tuberculosis depends on the regimen used. INH alone is effective for 18 months, while a three-month regimen with rifampicin and pyrazinamide or rifampicin and INH is effective for 3 years.⁸⁷ However, with the latter regimen there are reports of severe or fatal liver injury in non HIV-infected patients treated for latent TB, and compliance is not better with the short course prevention regimen.^{88,89}

The duration of benefit is in part related to the risk of **re-infection**. Some indication of this can be gained from studies of relapse following treatment for active TB. Studies to date appear to confirm re-infection as the major cause of relapse in PLHA living in high TB prevalence areas, providing further support for the suggestion that the efficacy of preventive therapy may not be long term.⁹⁰

WHO recommendations

In February 1998, at a joint meeting between the WHO global tuberculosis programme and UNAIDS, a policy statement was drawn up on preventive therapy against tuberculosis in people living with HIV.⁸⁰

Although preventive therapy has been shown to be effective in clinical trials, the feasibility of providing it in a programme setting in developing countries is less clear.

The following prerequisites were identified which should be in place before a

preventive therapy (PT) service is considered:

- adequate capacity for HIV counselling
- sufficiently trained health care staff
- linkage between HIV care and TB control services
- TB treatment services that have a high probability of curing cases of TB identified through the PT service (defaulter and failure rate <10%)

In settings meeting these standards, WHO and UNAIDS recommend to governments that:

1. *Preventive therapy against tuberculosis should be part of a package of care for people living with HIV/AIDS.*
2. *Preventive therapy should only be used in settings where it is possible to exclude active TB cases and to ensure appropriate monitoring and follow-up.*
3. *Information about tuberculosis, including preventive therapy, should be made available to people with HIV.*
4. *Preventive therapy should be provided from within settings that include established voluntary counselling and testing (VCT) services for HIV.*
5. *The priority for TB control programmes continues to be the detection and cure of infectious tuberculosis cases.*
6. *National authorities must regulate the procurement and supply of tuberculosis drugs in order to prevent the development of drug resistance.*

Delivery of preventive therapy requires **several steps**:

- (1) identification of HIV-positive subjects through VCT
- (2) screening to exclude active tuberculosis (with a chest X-ray)
- (3) screening to target those most likely to be infected with *M. tuberculosis*
- (4) provision of drugs
- (5) compliance to therapy

Screening for active TB

PT is inadequate treatment for active TB (constitutes monotherapy) and thus carries the risk of development of drug resistance. Active TB should therefore be excluded before PT is started.

WHO/UNAIDS advocated the use of a chest X-ray to exclude active TB, although it is recognised that most people with active TB will have symptoms. In Botswana, when nurses already do a symptom check, only 0.2% of TB cases were detected by chest X-ray.⁹¹ (see page 65, **Figure 1: TB preventive Therapy for Persons with HIV infection: an algorithm to screen for eligibility**)

In Malawi it was clearly demonstrated in an MSF project that uptake of INH was hampered because of the necessity to have a chest X-ray before INH could be started. In asymptomatic adults and children the chest X-ray detected TB in less than 1% of the patients.⁹²

Moreover, in stage 4 disease many patients will present with EPTB, which is not detected by a chest X-ray. This WHO recommendation to do a chest X-ray for the exclusion of active TB before the start of INH preventive therapy is questioned because of its low cost-effectiveness. Especially in resource-poor settings it is better to base the decision algorithm for the start of INH prophylaxis on (absence of) clinical symptoms alone (documented weight loss, cough, night sweats or fever, enlarged lymph nodes or hospitalised for HIV related symptoms).^{93,94}

Target those most likely to benefit from PT

PT is recommended for PPD-positive HIV-infected individuals who do not have active tuberculosis. In some settings it may not be feasible to perform PPD testing. Under these circumstances the following individuals may still be considered for preventive therapy if they are infected with HIV:

- those living in populations with a high prevalence of tuberculosis infection (estimated to be >30%);
- health care workers;
- household contacts of TB patients;
- prisoners;
- miners;
- other selected groups at high risk of acquisition or transmission of TB.
- HIV-positive mothers attending PMTCT programmes

Most of our target populations have a high prevalence of TB infection. Diagnostic possibilities are limited, making it difficult to exclude active TB in a symptomatic HIV patient. We recommend therefore that:

- INH prophylaxis should be given to all known HIV-infected persons, without performing a PPD skin test. Active TB has to be excluded before the start of the PT. In practice this means that only asymptomatic PLHA who are in WHO category 1 and 2 will be considered for PT.

In this group the diagnostic yield of a chest X-ray is very low, and therefore no longer recommended.

- IPT for **children** should only be provided in specialized centres with access to TST and the ability to exclude active TB in children. INH prophylaxis should not be given to symptomatic children because of the difficulty of excluding the diagnosis of TB in infants and children.

Either way, all individuals who are placed on INH should undergo systematic clinical screening each time they have a follow-up visit. In those who have symptoms suggestive of TB, INH should be stopped and the patient should be actively investigated for TB.

Choice of regimen

According to a recent review⁸⁴, the strongest evidence is for the use of INH alone. Trials using combination treatment report higher rates of adverse drug reactions. Isoniazid is the regimen recommended in developing countries.

Isoniazid may be given as a daily, self-administered therapy for 6 months at a dose of 5 mg/kg to a maximum of 300 mg. These individuals should be seen monthly and given a 1-month supply of medication at each visit. Compliance may be improved by giving an additional 2-week emergency buffer supply to be used if the individual has to defer his or her monthly review. Regimens other than isoniazid that have been investigated include rifampicin plus either isoniazid or pyrazinamide or both, given over two to four months. The trend in these studies was for isoniazid to be slightly more effective, perhaps related to the longer duration of therapy. In projects using ART, INH is easier to use than rifampicin and pyrazinamide because there is no drug interaction between INH, protease inhibitors and NNRTI. Rifampicin-containing regimens are not recommended, in order to eliminate the risk of promoting rifampicin resistance through inadequate screening procedures or misuse of the tablets.

Because of the high frequency of HIV-associated peripheral neuropathy, all PLHA on INH should receive pyridoxine 50 mg daily (children 25 mg daily)

Table 6: Dose of INH in TB Prophylaxis in HIV-infected children

Weight	Dosage of INH
5-10 kg	50 mg
11-20 kg	100 mg
21-30 kg	200 mg

Duration

Exactly how long isoniazid therapy should be given is unknown. Extrapolation from the use of isoniazid in HIV-negative individuals would suggest 9 months as an adequate period of time. Recent reviews of prophylaxis for opportunistic infections all recommend a 9-month regimen of INH to prevent tuberculosis.^{44,45} Similar conclusions were drawn from a review of the literature on INH prevention in immunocompetent persons.⁹⁵

Isoniazid resistance

There is concern that rates of isoniazid resistance could increase with expanded isoniazid preventive therapy programmes. No increase in isoniazid resistance was seen in the studies in PLHA who developed active TB despite isoniazid, but this may change when large-scale programmes are implemented. The efficacy of IPT is also dependent on the rate of isoniazid-resistant TB infection.

INH resistance development is associated with large numbers of bacilli (10^5 or 10^6) as mutations occur at these levels of bacillary load. When so many bacilli are present the patient also manifests clinical symptoms which can be picked up clinically. There is no evidence to date of mutations occurring with low bacillary load. Large scale use of INH prophylaxis (Alaska) is also not associated with the development of INH resistance.

Secondary prophylaxis

Long-term suppressive therapy for patients who successfully completed TB treatment is not considered necessary.⁴⁵ Also in MSF missions it is not recommended.

However, the TB incidence remains high among HIV patients on HAART with low CD4 counts when they live in communities with endemic tuberculosis.⁹⁶

Extended therapy (beyond 6-9 months of treatment) has shown to reduce the incidence of relapse, but showed no benefit in terms of survival.⁹⁷ A Haitian study⁹⁸ demonstrated that HIV-positive individuals had a ten-fold greater risk of recurrent TB than HIV-negative individuals after completion of a 6-month rifampicin-containing regimen. Half of the recurrences occurred after 18 months of post-treatment follow-up, and all cases of recurrent TB were in patients who had symptomatic HIV disease before the onset of TB (recurrence rate of 13.4 per 100 person-years). Post-treatment INH prophylaxis for one year reduced the incidence of recurrent TB in this group by 80%, but post-treatment INH prophylaxis did not prolong survival. However, a high recurrence rate of TB in HIV + individuals may have a number of consequences. Cure rates in recurrent TB are lower, five-drug re-treatment regimens are longer and more expensive, and it is also more difficult to achieve compliance.

In a cohort of South African gold miners, secondary prevention using INH 300 mg daily for an indefinite period reduced the incidence of TB by 55%. This difference was especially tangible in the group of patients with advanced disease and low CD4 counts.⁹⁹ Given the difficulties of combining HAART and TB treatment, this may be another point to be taken into account when considering INH secondary prevention in a group of patients eligible for HAART.

Conclusion on TB preventive therapy

In the short term, the delivery of PT will be limited by the number of sites where a sufficient number of people know their HIV status, or where there is sufficient demand for and capacity of VCT services. Programmes should continue to strengthen their curative services in addition to preventive measures, because finding and curing active TB is the most effective way of reducing new infections and TB-related mortality.¹⁰⁰ All projects that face difficulties in the control of tuberculosis (high defaulter rates, unregulated drug supply leading to incomplete TB treatment by private providers and national TB programmes, high treatment failure rate, etc.) **should not start INH preventive therapy on a routine basis.**

Projects that want to implement PT should have a close working relationship between HIV and TB services. The programmes should have qualified staff for counselling, a **high cure rate for TB and a low defaulter rate (less than 10%).**

One of the positive spin-offs of a TB preventive programme is the increase in detection rate of active TB during the screening procedure for eligibility for IPT.

HAART has significantly reduced the number of new cases of TB infection in the US, through immune restoration. Therefore, in patients eligible for HAART, the best prevention is to start with ART. In an environment where HIV/TB co-infection is very frequent, around 30% of patients develop TB-IRIS soon after the start of HAART. With the increased availability of HAART and the difficulties we encounter with drug interactions and TB IRIS, INH primary and secondary prevention will probably receive renewed attention.

6.4 Other preventive measures

6.4.1 Antifungals

Primary prophylaxis

In the industrialised world, most clinicians are reluctant to use azoles for primary prophylaxis because of the potential promotion of azole-resistant candida species, and the relatively low incidence of cryptococcal meningitis.^{44,101}

In some regions with an unusually high incidence of cryptococcal meningitis or *P. marneffei*, primary prophylaxis with fluconazole or itraconazole might be considered, given the price reductions in recent years, and the availability of generic fluconazole. In projects where a generic version is not available, timely initiation of ART is more cost-effective in preventing OI than primary prophylaxis with fluconazole. However, in projects where ART is not available or their use is rationed, fluconazole prophylaxis is justified.

Different dosing schemes have been proposed: 200 mg 3 x weekly, 400 mg weekly, 100 mg daily or 200 mg daily. One randomised study in the USA compared weekly versus daily fluconazole for the primary prevention of deep mycoses and found no difference in efficacy.¹⁰² Recently, a randomised trial from Thailand showed that fluconazole 400 mg once weekly significantly reduced the incidence of cryptococcal meningitis, and significantly increased survival.¹⁰³

Secondary prophylaxis

- *P. marneffei*: itraconazole 200 mg daily is effective in reducing the recurrence of *P. marneffei* in HIV patients who were successfully treated with amphotericin B.¹⁰⁴
- *Cryptococcus neoformans*: fluconazole 200 mg daily is the first choice¹⁰⁵, or amphotericin B, IV, once a week, or fluconazole 200 mg 3 x weekly.
- *Oral thrush/oesophageal candidiasis*: only in case of frequent and severe recurrent oesophageal candidiasis is secondary prophylaxis indicated: fluconazole 100-200 mg daily.

Discontinuation of antifungal prophylaxis

Several studies have shown that it is safe to interrupt secondary prophylaxis for cryptococcal meningitis in patients who are on HAART and who have a sustained CD4 > 100 for at least 6 months.^{106,107}

No studies were conducted for primary prophylaxis, but in analogy with other

Or it is probably safe to discontinue primary prophylaxis in patients who have a sustained CD4 > 100 for more than 3 months.

6.4.2 Vaccination

HIV-infected patients have a sub-optimal antibody response in comparison to healthy controls, especially when CD4 counts are < 100.¹⁰⁸ There are encouraging data that show that this response improves again after the administration of HAART. It seems wise, therefore, to defer vaccination until an increase in CD4 count has occurred.^{109,110}

In general, it is best to vaccinate as soon as possible, while the immune system is still good. In patients who have very low CD4 counts, it is wise to defer immunisation until ART-induced immune reconstitution has taken place. The only vaccines that are formally contra-indicated in symptomatic HIV patients (or patients with CD4<200) is yellow fever vaccine and BCG.¹¹¹

Childhood immunisation

Infant vaccinations should be given according to the regular vaccination scheme. All *asymptomatic* children should receive vaccinations as prescribed by the national immunisation schedule. Except for BCG, all regular vaccinations are recommended in HIV-positive *symptomatic* children. It is recommended that HIV-infected children be given an extra dose of measles vaccine at 6 months, followed by a second dose at 9 months.

Although measles and oral polio vaccine are live, attenuated vaccines, the benefits outweigh the risks of vaccine-associated complications, also in HIV-positive children. In countries where the wild-type polio virus has been eradicated, the inactivated polio vaccine should be used when available.¹¹²

23-valent pneumococcal vaccine

The 23-valent-pneumococcal vaccine is immunogenic in HIV-infected people.¹¹³ This vaccine, while effective in the US, had a negative effect on the incidence of pneumococcal disease in Kenya, and is therefore not recommended in Africa.¹¹⁴

Ongoing trials in the Gambia, Malawi and South Africa using newer-generation conjugate pneumococcal vaccines may show better results.

Hepatitis B vaccination

HIV-infected patients have a higher risk of hepatitis B because of common risk factors. Patients who are HIV-positive are more likely to develop chronic hepatitis. In the industrialised world, hepatitis B vaccination is recommended for certain risk groups, such as IV drug users, homosexuals, household contacts of hepatitis B carriers, health-care workers and sex workers who are HepBsAg and Ab negative (0 -1 month – 6 months).

In developing countries, although some EPI programmes include vaccination against hepatitis B, it is not routinely recommended in adult HIV patients, because very few countries have funds available to purchase the vaccine.

6.4.3 Malaria

A cross-sectional study from Malawi showed that HIV-positive pregnant women are more likely to have a malaria parasitaemia than HIV (-) women. The risk of clinical malaria (fever and positive blood smear) was also higher in HIV-positive adults in a Ugandan cohort and there was an inverse relation between malaria incidence and CD4 count.^{43,115} Viral load is significantly increased in patients with malaria.¹¹⁶ HIV-positive people should therefore take precautions to avoid mosquito bites when living in malaria endemic areas.

There are indications that placental malaria is more frequent in HIV-positive women. Co-infection with malaria and HIV during pregnancy increases the rate of MTCT. Preventing malaria during pregnancy might reduce the MTCT.¹¹⁷ A monthly dose of sulphadoxine/pyrimethamine during the second and third trimester of pregnancy seems to be safe and efficacious.¹¹⁸

However, some level of cross-resistance exists between cotrimoxazole and sulphadoxine/pyrimethamine. Therefore, if a patient develops malaria while on cotrimoxazole prophylaxis, he should be treated with another drug than sulphadoxine/pyrimethamine.

6.4.4 MAC

MAC prophylaxis is recommended in the US and Europe for patients who have CD4 < 50. Clarithromycin and azithromycin are better than rifabutin.

In developing countries this strategy has not been used because of the low incidence of MAC, except in Thailand, where national guidelines now prescribe MAC prophylaxis for patients (including children) with CD4 < 50. MAC is frequently associated with IRIS and can cause significant morbidity and complications soon after the start of HAART. This could be an additional reason to consider MAC prophylaxis. Azitromycin (1200 mg/week) has fewer interactions with HAART than clarithromycin, and is therefore preferred.

Primary prophylaxis can be interrupted when patients are treated with HAART and have a sustained increased CD4 > 100 during 3 months.¹¹⁹

Secondary prophylaxis can be interrupted when the patients have taken a macrolide antibiotic for at least 12 months, has a sustained CD4 > 100 for 6 months and no signs or symptoms suggestive of MAC.

6.4.5 Cytomegalovirus (CMV)

Primary prophylaxis with oral ganciclovir (1000 mg TID) reduces significantly the incidence of CMV disease in patients with CD4 < 50. However, due to the high cost price, the toxicity and the lack of survival advantage this is not used as a strategy in the US. Certainly in developing countries, where generic ART is far cheaper than ganciclovir, the priority is to start HAART in time, before the development of CMV disease. Some patients may develop CMV retinitis soon after the start of HAART. One strategy is to give 3-6 months prophylaxis to patients who have CMV viraemia when they start on HAART.³⁷

Treatment of CMV disease is not available in resource-poor settings.

However, in some countries ophthalmologists are using intraocular ganciclovir injections to stop progression of CMV retinitis. Especially in the era of HAART, this strategy should be evaluated, because it may prevent blindness in patients who have improved survival thanks to ART.

6.4.6 Mucocutaneous herpes simplex

Primary prophylaxis is not indicated. However, in case of frequent and severe recurrences of genital or mucocutaneous herpes secondary preventive doses of acyclovir (200 mg 3 x daily or 400 mg 2 x daily) can be given indefinitely or until immune recovery.

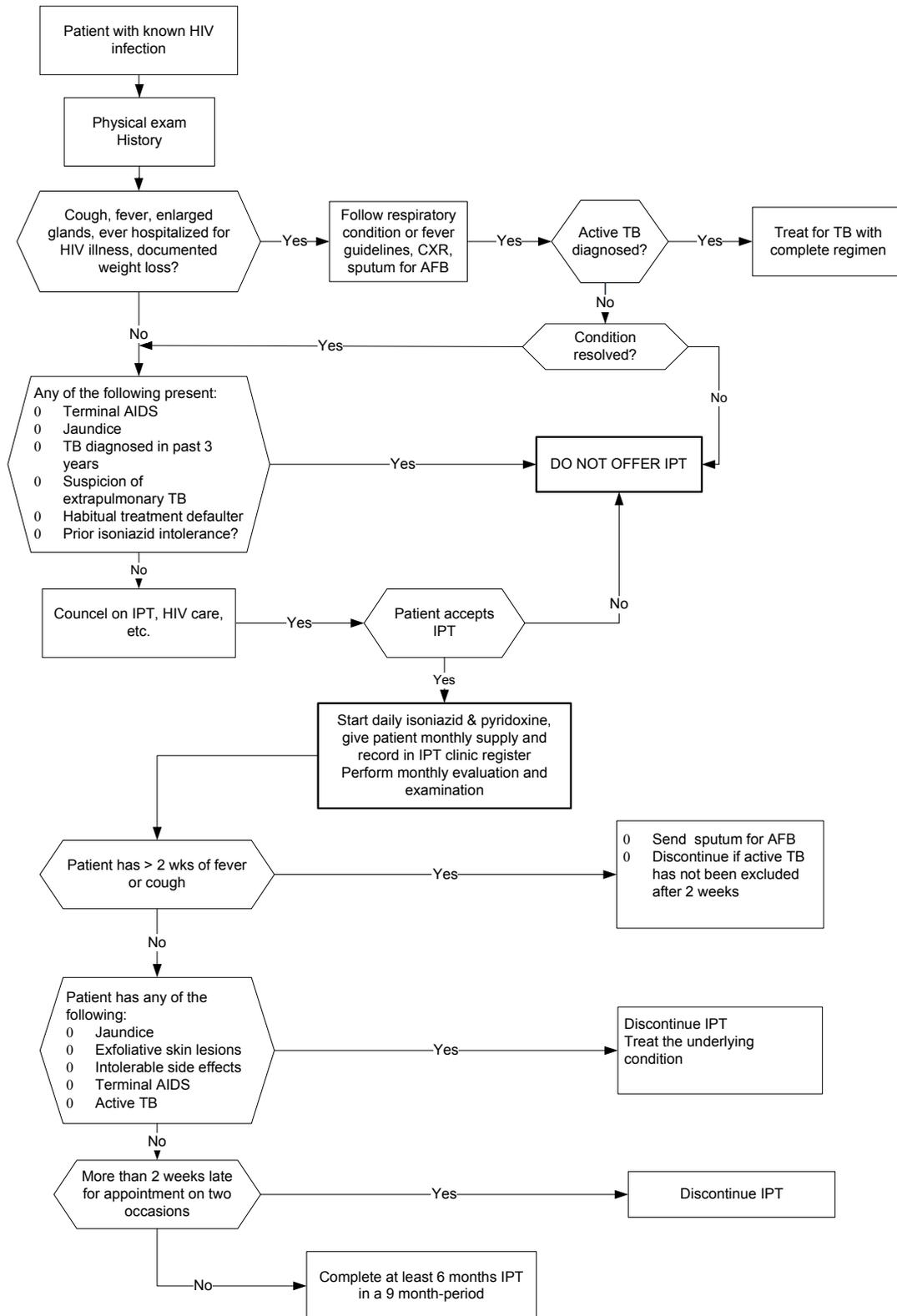
6.4.7 Helminthic infections

Treatment of helminthic infections with albendazole or mebendazole once a year has a positive effect on HIV progression because of decreased immune activation.¹²⁰

Table 7: Criteria for Starting, Discontinuing, and Restarting Opportunistic Infection Prophylaxis for HIV-positive Adults in resource-limited settings

Criteria to	Initiate Primary Prophylaxis	Discontinue Primary Prophylaxis	Restart Primary Prophylaxis	Initiate Secondary Prophylaxis	Discontinue Secondary Prophylaxis	Restart Secondary Prophylaxis
<i>Pneumocystis carinii</i> pneumonia	CD4 <200 Or WHO stage 2,3,4	CD4 >200 for ≥ 3 months	CD4 <200	Prior <i>Pneumocystis carinii</i> pneumonia	CD4 >200 during at least 3-6 months	CD4 <200
Toxoplasmosis	IgG antibody to Toxoplasma and CD4 < 100	CD4 >200 for ≥ 3 months	CD4 <100-200	Prior toxoplasmic encephalitis	CD4 > 200 ≥ 6 months and completed initial therapy and Asymptomatic for toxo	CD4 <200
Tuberculosis	As soon as the patient is diagnosed with HIV and active tuberculosis can be excluded and in an environment with a high risk of TB transmission	After 6-9 months of INH therapy	Not applicable	No consensus	No consensus	No consensus
Disseminated <i>Mycobacterium avium</i> Complex	CD4 < 50 Exclusion of MAC disease	CD4 >100 for 3 months	CD4 <50-100	Documented disseminated disease	CD4 >100 sustained (≥ 6 months) and completed 12 months of MAC therapy and asymptomatic for MAC	CD4 <100
Cryptococcosis	Stage 4 or CD4 < 100	CD4 > 100 after 6 months HAART	CD4 < 100	Documented disease	CD4 >100-200 sustained (≥ 6 months) and completed initial therapy and asymptomatic for cryptococcosis	CD4 <100-200
Cytomegalovirus Retinitis	None	Not applicable	Not applicable	Role for intra-ocular injections with ganciclovir in patients with evidence of CMV retinitis at the start of HAART?		
Herpes simplex	None	Not applicable	Not applicable	Severe recurrent disease		
Candida albicans	None	Not applicable	Not applicable	Severe recurrent OC		

Figure 1: TB preventive Therapy for Persons with HIV infection: an algorithm to screen for eligibility for IPT by nurses (adapted from Botswana National TB Control Programme and National AIDS Control Programme)





7 RESPIRATORY PROBLEMS

7.1 Introduction

Respiratory symptoms are among the most common complaints in AIDS patients. A cough lasting over >1 month is seen in at least one-third of patients some time during the progression of the disease. In the advanced stages of the disease, often more than one pathogen can be found. A study carried out in Thailand on 95 patients with respiratory symptoms found the five most frequent agents to be: *Mycobacterium tuberculosis* (37%); PCP (24%), *Cryptococcus neoformans* (15%), *S.pneumoniae* (6%), *Nocardia asteroides* (6%) and *Strongyloides stercoralis* (3%). Two pathogens were found to co-exist in 10% of patients.¹²¹

A study in an Ugandan hospital found as aetiology of lower respiratory infections in HIV adults mainly TB (62%) and PCP (16%). Pulmonary Kaposi's Sarcoma (0,45%) and pyogenic bacteria (0,35%) were uncommon.¹²²

Smoking is increasingly recognised as an important risk factor for bacterial pneumonia, PCP and TB in HIV patients.¹²³

Daily tobacco use appears to attenuate the immunological and virological responses to antiretroviral therapy. Appropriate counselling for stopping smoking is thus certainly advised for HIV patients.¹²³

7.2 Opportunistic infections

7.2.1 Tuberculosis

Epidemiology

TB is one of the most frequent respiratory problems in developing countries. WHO estimates that TB is the cause of death for 11% of all AIDS patients.¹²⁴

In Africa about 1/3 of deaths in HIV-positive patients are due to disseminated TB and in only 50% of these patients the diagnosis is made before death.¹²⁵⁻

¹²⁷ By the end of 2000, about 11.5 million HIV-infected people worldwide were co-infected with *M. tuberculosis*. 70% of co-infected people were in sub-Saharan Africa, 20% in South-East Asia and 4% in Latin America and the Caribbean.¹²⁸ In countries with high TB prevalence, between 2.4% and 7.5% of HIV-infected adults may develop active TB each year. In patients with a positive PPD skin test, this rate rises to between 3.4% and 10% per year with a lifetime risk of 50-70%.^{11,80}

Clinical presentation

The presentation of PTB depends on the degree of immunosuppression. At a level of immunity that is still relatively good, it will present as typical cavitary

TB or upper lobe consolidation (post-primary pattern). Pulmonary TB is a WHO stage 3 condition.

At lower CD4 levels atypical presentations are more likely: extra-pulmonary TB (pleuritis, pericarditis and meningitis) and disseminated TB, diffuse pulmonary or miliary infiltrates with usually negative PPD skin tests. Extra-pulmonary TB and disseminated TB is a WHO stage 4 condition.

Diagnosis of extra-pulmonary TB is more difficult.

TB disease in persons with HIV-1 infection can develop immediately after exposure (i.e. primary disease) or as a result of progression after establishment of latent TB infection (i.e. reactivation disease).¹²⁴ In up to 35% of HIV co-infected, patients, signs of primary infection (recent infection) are evident: lower lobe infiltrate, pleural effusion, intra-thoracic adenopathy. Patients with suspected intra-thoracic tuberculosis frequently have palpable extra-thoracic lymph nodes (cervical and axillary).¹²⁹

The most important symptoms in diagnosis of pulmonary tuberculosis are cough more than two weeks, weight loss, haemoptysis, chest pain, breathlessness, fever with night sweats and loss of appetite. Weight loss and fever are more common in HIV-positive pulmonary TB patients, than in HIV-negative patients. Conversely productive cough and haemoptysis are less common in HIV-positive patients. This difference is probably because there are less cavitations, inflammation and endobronchial irritation in HIV-positive patients.

Table 8: Characteristics of PTB in different stages of HIV disease

Features of PTB	Stage of HIV infection	
	Early (CD4>350)	Late
Clinical picture	Often resembles post-primary PTB (cough, sputum, haemoptysis, thoracic pain, dyspnoea)	Often resembles primary PTB Dry cough, no haemoptysis
Sputum smear result	Often positive	Often negative
Chest X-ray appearance	Upper lobe fibronodular infiltrates Often cavities	Lower and middle lobe, miliary infiltrates common with no cavities intrathoracic lymphadenopathy

Diagnosis

Microbiological diagnosis

Sputum examination is the best initial diagnostic test. AFB staining of **expectorated sputum** is positive in around 30%-60% of patients with AIDS-related pulmonary TB. When possible, fluorescence microscopy with auramine staining could be done as its sensitivity is superior to Ziehl-Neelsen, and it is more cost-effective.¹³⁰ Especially in laboratories with a high work load

(more than 30 TB smears/day), the use of a fluorescence microscope is justified.

It is important to take a good sample of sputum. Early morning samples (standard three samples) are best because AFBs concentrate in the respiratory secretions overnight. To reduce delay and lost to follow-up due to sample collection, WHO recommends 3 sputum samples over 24 hours: 1 on the spot, second from next early morning brought by patient and the final sample provided on the spot on that second day. The “on the spot” samples are provided under supervision. This method seems to be almost as sensitive as the 3 morning samples.¹²⁸

Some authors suggest that we can omit a third sample, because more than 99% of smear positives are positive after 2 smears.^{131,131,132} Such a strategy could improve overall diagnostic efficiency (fewer smears per patient) and accuracy (more patients with better quality smear examination because of the reduced workload overall).

Culture is often not available in resource poor settings. It also takes 6-8 weeks to be interpretable which limits the usefulness of culture in clinical decision-making.^{133,134} MGIT (Mycobacteria Growth Incubator Tube) is a more rapid culture technique that allows also for drug sensitivity testing, but has a relatively high contamination rate and high cost.^{135,136}

Countries affected by both HIV and TB have experienced a disproportionate increase in **smear-negative** disease defined as patients with clinical and radiological evidence of pulmonary TB but repeatedly negative sputum investigations.¹³⁷ Smear negative TB has a poorer prognosis in countries with a high prevalence of HIV infection.¹³³

A lot of strategies have been explored to improve the diagnosis of smear-negative TB. There is a consensus that more priority should be given to smear-negative TB especially in high HIV-prevalence settings because delay in diagnosis is resulting in high mortality.

For patients who cannot produce sputum, simple chest physiotherapy may sometimes help. Otherwise **sputum induction** by using ultrasonic nebulizers with hypertonic saline can be used. It enhances diagnostic sensitivity in resource-poor areas, and it is a safe and more simpler alternative to fiberoptic bronchoscopy with bronchoalveolar lavage.^{138,139} The plastic nebuliser tubing needs to be replaced or sterilized in between patients, and this makes it a cumbersome and relatively expensive method. Moreover, it is important to know that the concentration of airborne bacteria (and mycobacteria) increases rapidly during and immediately after sputum induction. Therefore health workers involved in these procedures should wear appropriate respiratory masks.¹⁴⁰

Sputum concentration

Concentration of AFBs in clinical specimens can increase significantly the sensitivity of the smear microscopy.^{135,141} The technique most commonly used is sedimentation and centrifugation of sodium hypochlorite (NaOCl)-treated sputa. Sodium hypochlorite, being a potent disinfectant, is also reducing the

risk of laboratory acquired infections, which is an additional advantage. As with normal smear microscopy the quality of the sample remains an important factor.

Chest X-ray

Atypical presentations are frequent (see Table 8). However, in HIV patients, a chest X-ray should be done early in the diagnostic process in order to reduce the delay in the diagnosis of smear-negative PTB. 44-75% of patients with smear-negative TB have an abnormal chest X-ray.^{142,143} It may also help in making the differential diagnosis with other respiratory conditions.

Antibiotic trial

Most diagnostic algorithms of cough, intending to diagnose or exclude PTB start with an antibiotic trial, followed by a second trial if no response.^{131,131,144} The performance of such algorithms depends on the background prevalence of HIV and other HIV-related conditions that would not respond to antibiotics.¹⁴⁵

Antibiotic trials increase the specificity of the diagnosis of smear-negative PTB, but it also induces an important delay in the start of appropriate anti-tuberculous treatment and loss of patients who do not return for follow-up assessment.¹³³

In patients who have clear symptoms of TB (weight loss, chronic cough, night sweats,...) we should use only 1 trial of broad-spectrum antibiotics while waiting for the result of the sputum.

The choice of antibiotics should be guided by the idea to treat the most likely respiratory pathogens, other than TB.

The first choice is **amoxicillin** which has a slightly broader spectrum than penicillin because it also covers +/- 50% of *H.influenzae* strains.

Cotrimoxazole has a broader spectrum, but in patients on cotrimoxazole prophylaxis, the use of cotrimoxazole to treat bacterial respiratory infections is not indicated.¹⁴⁶ However it remains a useful antibiotic for patients not yet using that prophylaxis.

Erythromycine would also cover against atypical pneumonia (*Mycoplasma* or *Chlamydia*); however, it is not a first choice in treatment of infection by *S.pneumoniae*, *H.influenzae* and *Moraxella cattharalis* because there is a high rate of resistance of all those bacteria to macrolides.

If available **amoxy-clavulanic acid** or **second-generation cephalosporines** (cefuroxime, cefaclor) are a very good alternative because they have very good respiratory coverage and they are active against *S.pneumoniae*, *Moraxella cattharalis* and *H.influenzae*.

Fluoroquinolones, particularly later-generation agents (levofloxacin, gatifloxacin and moxifloxacin) shouldn't be used for an empiric antibiotic trial as they have bactericidal activity against *M.tuberculosis*, cause resistance when used in monotherapy, and delay the diagnose of TB.¹⁴⁷

Lymph node needle aspiration

A study carried out in Harare showed the value of **fine needle aspiration of extra-thoracic lymph nodes** to confirm the diagnosis of smear-negative pulmonary, pleural or pericardial TB. In a group of HIV-positive patients with

suspected smear-negative PTB, who did not respond to penicillin and who had no signs of cutaneous or palatal Kaposi's sarcoma, ZN staining of fine needle aspirate (18G-19G) of supraclavicular, cervical or axillary lymph nodes, gave the diagnosis of TB in up to 87% of cases that were later confirmed to have pulmonary, pericardial or pleural TB!^{129,148}

Tuberculin test, PPD

Reaction to a tuberculin skin test is unreliable in patients with a deficit in cellular immunity. Also BCG vaccination complicates the interpretation of a positive PPD. Therefore the use of PPD skin test will not improve the accuracy of the diagnosis of TB in HIV patients.

Differential diagnosis

Differential diagnosis of smear negative PTB can be difficult and include diseases such as PCP, pulmonary Kaposi's sarcoma and Nocardiosis. In patients with normal chest X-rays who present with cough and fever, Gram negative bacteraemias are a possible diagnosis (see Table 9).

Table 9: Differential diagnosis of smear negative TB

Differential diagnosis	Pointers to correct diagnosis
Congestive heart failure	Symptoms of heart failure (dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea, haemoptysis, oedema, epigastric discomfort from hepatic congestion)
Asthma	Intermittent symptoms, generalised expiratory wheezing
Chronic obstructive airway disease	Risk factor (smoking), chronic symptoms, prominent dyspnoea, generalised wheezing
Bronchiectasis	Large amounts of purulent sputum
Bronchial carcinoma	Risk factor (smoking)
Other infections	
Bacterial pneumonia	Response to antibiotic
Lung abscess	Abscess with fluid level on chest X ray
PCP	Dyspnoea prominent
Nocardia	Cavitary infiltrates, Gram-positive branching bacteria
Cryptococcosis, penicilliosis	Skin lesions
Strongyloidiasis	Larva recurrens, diarrhoea
Paragonimiasis	Endemic region, fresh water shrimps
Kaposi's sarcoma	Skin/oral Kaposi's sarcoma lesions
Lymphoma (exceptional)	

Treatment

HIV-positive patients respond well to treatment with anti-tuberculous drugs. The highest priority is the treatment of smear-positive pulmonary TB.

Short-course therapy with an initial intensive phase of 4 drugs (2 months of INH, RIF, PZA and EMB) followed by a 4-month continuation phase of INH and RIF is superior to the 8-month regimens that use RIF only in the first 2 months.¹⁴⁹ Therefore this is the preferred regimen, although it means prolonged difficulties to combine TB treatment with HAART (see chapter 16, page 306).

Table 10: Recommended first line anti TB drugs

Agent	Daily dose	Adverse reaction	comments
Isoniazid	5 mg/kg PO	Elevated hepatic enzymes, peripheral neuropathy, hepatitis, hypersensitivity	Peripheral neuropathy is common but pyridoxine 50 mg/d is recommended for patients with AIDS. Higher risk when combined with d4T
Rifampicin	10 mg/kg max 600 mg PO	Discoloration urine & nausea vomiting, fever, hepatitis	Accelerated clearance of methadone and other drugs Do not use together with nevirapine
Pyrazinamide	15-30 mg/kg max-2g PO	Hepatitis hyperuricemia, arthralgias, rash, glucose intolerance.	Hyperuricemia, but clinical gout is rare.
Ethambutol	15-25 mg/ kg max-2.5 g PO	Optic neuritis, skin rash	25 mg/kg /day first 1-2 months or if strains resistant to anti TB are suspected.

See also the section on WHO-recommended TB treatment regimens on page 249 of chapter 14, Neurological Disorders).

It can be useful to meet the national authorities and discuss some specific practicalities with them, such as longer duration of treatment in patients with miliary TB or TB meningitis, the acceptance of higher rates of smear-negative TB in HIV patients, or the preference to use the 6 months rifampicin throughout regimen in HIV patients.

Thiacetazone should never be used for people who are known or suspected to be HIV-positive because of the severe hypersensitivity reactions observed (Stevens-Johnson syndrome).

Use of **streptomycine** is discouraged because of the risk of transmission of HIV through needle stick injuries. Moreover, these IM injections are painful in wasted HIV-infected TB patients. Ethambutol has replaced streptomycin in most national TB program regimens.¹²⁸

The **duration** of TB therapy for HIV patients remains controversial. The standard 6-month regimen results in prompt sterilisation of sputum and low rates of treatment failure, similar to those obtained in HIV-negative persons.¹⁵⁰ Despite this some authorities still recommend longer treatment in HIV-positive patients. While awaiting for more studies on this, 6 months of therapy is probably adequate for the majority of cases and 9 months therapy is recommended (as in HIV-negative) for patients with a delayed clinical or bacteriological response to therapy (symptomatic or positive culture results at or after 2 months of therapy, respectively).¹²⁴

Resistance to rifampicin

M.tuberculosis, mono resistant to rifampicin is more often described in HIV patients and in patients with a history of TB.^{151,152} It could be due to poor compliance or decreased absorption of rifampicin in HIV patients, however this is controversial.

For those patients, a minimum of 12-18 months of treatment with INH, EMB and a fluoroquinolone (e.g., levofloxacin) with PZA administered during the first 2 months is recommended.¹²⁴

Multidrug-resistant TB

MDR TB is defined as resistant to INH and rifampicin with or without resistance to other drugs.

Cases of MDR TB are highest in areas with the fastest growing HIV epidemic, particularly the former Soviet republics, China and South Africa. It seems that the spread of MDR TB is being fuelled by a high prevalence of TB in HIV-positive patients, and also by poor adherence to TB medication. HIV care settings are likely to see nosocomial outbreaks of MDR TB. Therefore infection control measures need to receive attention.¹⁵³ WHO has published guidelines for the prevention of TB transmission in care settings, stressing the need to identify and separate coughing patients from others in waiting rooms.

The emergence of MDR TB as a problem in MSF projects highlights the need for development of capacity to do drug susceptibility testing and culture.

The current readily available test for MDR TB is manual culture and sensitivity testing using solid Lowenstein-Jensen medium, at a cost of 1.5 USD but the results take 6-9 weeks.

Use of steroids as adjuvant in TB treatment is indicated for CNS tuberculosis with severe symptoms and for pericarditis (1mg/kg/day during 1 month, slowly tapered over the next 4-6 weeks).¹⁵⁴ A study examining the effect of prednisolone on mortality in HIV-infected patients with pleural TB failed to show any survival benefit, and it even caused an increased risk for KS.¹⁵⁵

Drug interactions with HAART

There are important interactions between rifampicin and NNRTI and PI (see chapter 16, page 306).

Paradoxical reaction

After initial clinical improvement on TB treatment, paradoxical worsening of disease develops in up to 36 percent of patients on HAART, with fever, worsening chest infiltrates on radiography and peripheral and mediastinal lymphadenopathy.

In contrast, only 7% of patients who received antituberculosis therapy but no ARV therapy had paradoxical reaction. In patients with clinical findings that are compatible with the presence of a paradoxical reaction, other diagnosis must be ruled out.

Paradoxical reactions are self-limited and generally last 10 to 40 days. However, some reactions are severe and may require *short* treatment with steroids.¹⁵⁶

For a more in depth discussion on when to start antiretroviral therapy in patients with TB and the possible immune reconstitution syndrome, see chapter 16.

Response to treatment/ Relapses

HIV-positive TB patients have a much higher **case-fatality** rate during and after anti-TB treatment compared with HIV-negative patients. In sub-Saharan Africa, up to 30% of HIV-positive smear-positive PTB patients die before the end of treatment. HIV-positive smear-negative PTB patients have a worse prognosis than those who have HIV-positive smear-positive PTB. Excess death in HIV/TB patients are due to TB and to HIV related problems as septicaemia, diarrhoea, pneumonia, anaemia, KS and cryptococcal meningitis.¹²⁸

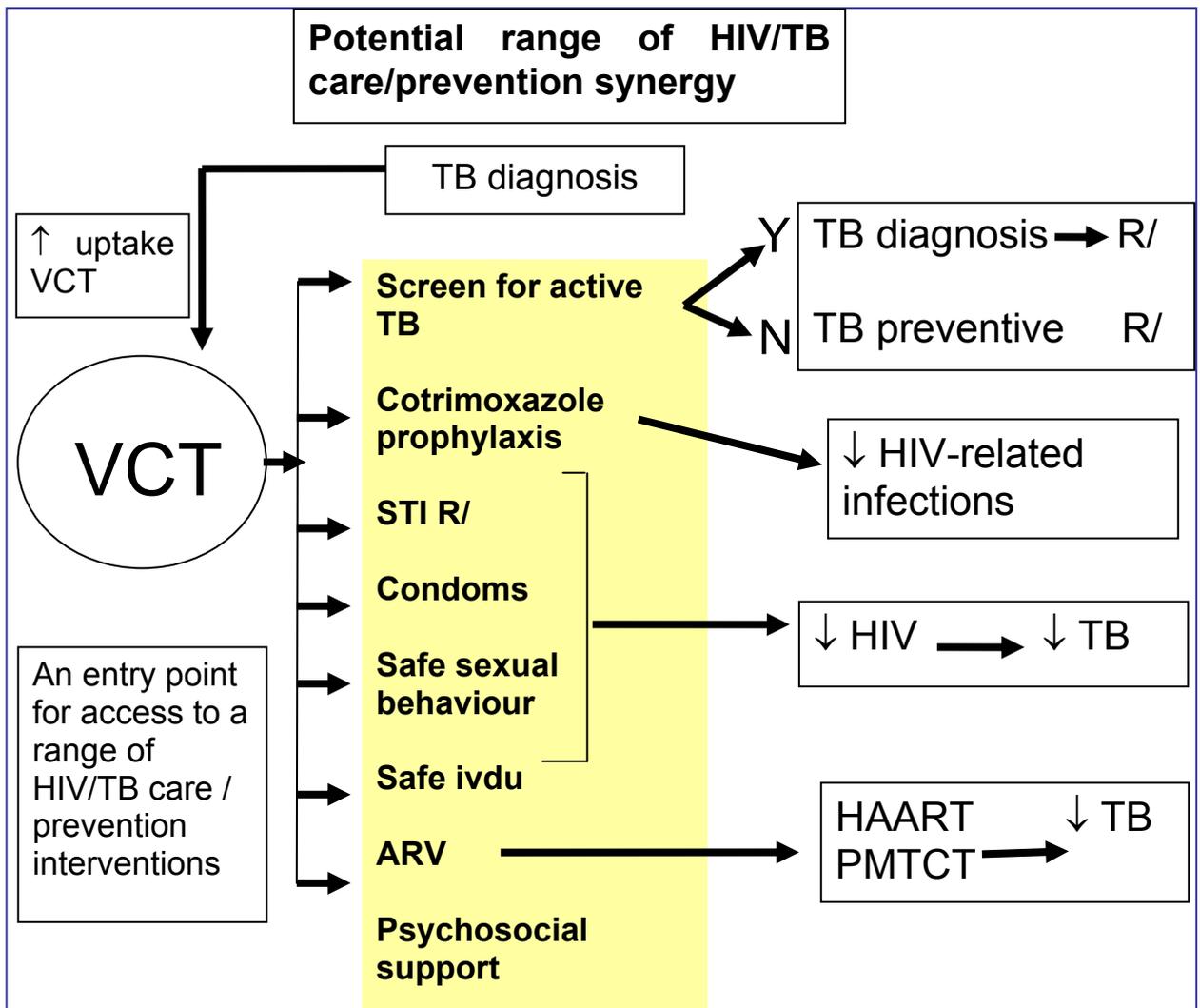
Recurrence rate is higher in HIV-positive than in HIV-negative TB patients. Some studies suggest to extend the duration of treatment to 12 months or to give post treatment prophylaxis (for example INH) but further studies are needed before making recommendations on secondary prophylaxis.¹²⁴

Integration TB/HIV program

50% of the HIV patients will develop active tuberculosis. Up to 10% of HIV-infected patients have active TB at first presentation. Every effort should be done to screen HIV-infected patients in developing countries for TB. It is important that they are seen by a medical doctor and that in case of symptoms a sputum examination, a chest X-ray and/or an abdominal ultrasound is done to diagnose and treat TB. Asymptomatic patients can be started on INH prophylaxis (see chapter 6, Prevention of OI).

TB/HIV co-infected patients who develop active TB benefit from cotrimoxazole prophylaxis and from timely initiation of HAART. Therefore, all TB patients need to be screened for HIV. Once patients start on HAART, paradoxical reactions need to be managed correctly. Again an operational link between TB and HIV services is essential in care for HIV patients (see figure).The best

results are obtained with fully integrated HIV and TB clinics.^{134,157,158}



7.2.2 Bacterial pneumonia

Bacterial respiratory infections are more frequent and severe in HIV patients, and the frequency is related to CD4 count. The most common causes are *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Staphylococcus Aureus*. Other frequent bacterial pathogens include *Moraxella cattharalis*, *Klebsiella pneumoniae*, *P.aeruginosa* and *Mycoplasma pneumoniae*.

Pneumonia in HIV-positive patients is more frequently associated with bloodstream infections and they represent a common cause of early death.

Risk factors for bacterial pneumonia are: intravenous drug use, smoking illicit drugs (cocaine, crack, and marijuana), smoking cigarettes, alcoholism, cirrhosis, asthma, sickle cell disease, low albumin and history of previous pneumonia.¹⁵⁹ In the new interim guidelines for WHO staging, recurrent bacterial pneumonia is a stage 4 event.¹³

Symptomatology

The presentation is similar to that in HIV-negative patients. Most patients have an abrupt onset of fever, chills, cough with sputum production, dyspnoea, and pleuritic chest pain.

An acute respiratory illness in a patient known to be HIV-positive, accompanied by high fever and chills, should be treated as an emergency.

Chest X-ray

Segmental or lobar consolidations are frequent although diffuse reticulonodular infiltrates and patchy lobar infiltrates may also be seen.

Infiltrates that are localised to one lobe, especially when an air-bronchogram is present, are suggestive of bacterial pneumonia, most likely *S.pneumoniae*. More diffuse infiltrates are more likely to be due to *H.influenzae*.

Bilateral patchy consolidations in a critically ill patient suggest staphylococcal pneumonia. Upper lobe consolidation with cavitation has been observed in pulmonary nocardiosis, and can mimic tuberculosis. In nocardiosis there is often evidence of multiple abscesses (brain, lung, skin, etc). A Gram stain will show Gram-positive thin branching (mycelium-like) filaments.

Laboratory findings

The patient usually has a high white blood cell count. Gram stain of sputum and culture yields the diagnosis in 75% of cases. Gram positive diplococci are suggestive of *S.pneumoniae*. Gram negative bacilli are compatible with *H.influenzae*. Nocardia stains weakly acid-fast on Ziehl-Neelsen. They are morphologically different however from tubercle bacilli because of their long branching fine mycelium-like threads. They stain well on Gram stain (see laboratory section at the end of the chapter). Patients with staphylococcal pneumonia often have other signs of staphylococcal infection: pyomyositis, abscess. A Gram stain of aspirated pus (Gram-positive cocci in clusters) can help in the diagnosis.

During an acute pneumonia the CD4 count is often significantly depressed, and the CD4 count should be repeated after the acute event in order to assess the immune status of the patient correctly.¹²³

Treatment

See also the antibiotic trial in TB suspect patients on page 70. **Penicillin** has a narrow spectrum and would only cover *S.pneumoniae* and the anaerobes of the oral cavity involved in aspiration pneumonia. In some countries, more than 30% of streptococci are resistant to penicillin. In that case, do not use penicillin for empirical therapy in lobar pneumonia. The first choice if the condition of the patient is not severe is **amoxicillin or cotrimoxazole**. In patients on cotrimoxazole prophylaxis, the use of cotrimoxazole to treat bacterial respiratory infections is not indicated.¹⁴⁶ However it remains a useful antibiotic for patients not yet using that prophylaxis.

An alternative is **amoxy-clavulanic acid** or **second-generation cephalosporines** (cefuroxime, cefaclor).

Seriously ill patients with a respiratory infection should receive a combination with chloramphenicol or ceftriaxone (if available) to cover for Gram-negative infections. Treatment for severe life-threatening pneumonia could be: **ceftriaxone + amikacin** (Gram-negatives + Gram-positives, also staphylococcus), or **chloramphenicol + cloxacillin** (Gram-negatives + Gram-positives, including staphylococcus, atypical bacteria -chlamydia, mycoplasma).

When a causative agent is identified, treatment is directed against this pathogen.

The antibiotic of choice for **staphylococcal** infections is (flu)cloxacillin 1-2 g 4 x daily IV or 500 mg 4 x daily PO. In addition, chloramphenicol, doxycycline and cotrimoxazole are moderately effective against staphylococci.

The recommended treatment for **Nocardia** is cotrimoxazole 10/50 mg/kg 2 x daily. This usually corresponds with 2-3 DS tablets 2 x daily. The duration of the treatment varies from 6 weeks (for localised disease) to 6 months (for disseminated disease). An alternative treatment for nocardiosis is minocycline 100 mg 2 x daily combined with amikacin 15-25 mg/kg daily IV, once a day, or ceftriaxone 2 g daily combined with amikacin. The use of aminoglycosides should be limited to 14 days to avoid adverse effects.

7.2.3 Pneumonia due to *Pneumocystis jiroveci (PCP)**

Epidemiology

Pneumocystis jiroveci is a ubiquitous organism classified as a fungus but that shares biologic characteristics with protozoa and causes PCP (Pneumocystis Pneumonia). Initial infection with *P.jiroveci* occurs in early childhood. PCP is a result either of reactivation of latent infection or new exposure to the

* previously named *Pneumocystis carinii*(PCP)

organism.¹²⁴ Re-infection may be an important cause of PCP in the immunocompromised. Human-to-human transmission is possible, but only responsible for a minority of cases.

The incidence of PCP varies worldwide, ranging from 64% in the US to <5% in reports from some studies in Africa. PCP occurs frequently in Asia, Central and South-America. PCP is thought to be rare in Africa and Southeast Asia. However, this may be partly due to under-diagnosis due to lack of diagnostic facilities or to early death from tuberculosis and bacterial infections before a sufficient drop in CD4 is reached. Another possibility is that strains of *P. Jiroveci* found in Africa may be less pathogenic.^{160,161} Important regional differences may exist. One study in Zimbabwe found PCP in one-third of patients with acute diffuse pneumonia unresponsive to standard antibiotic therapy.¹⁶² Cases of PCP are now also increasing in Africa but whether this increase results from actual change in PCP incidence or from improved detection techniques is unclear. In contrast to adults, HIV-infected children in Africa have high rates of PCP.¹⁶⁰ The probability of developing PCP rises dramatically as the CD4 count drops below 200. With the occurrence of HAART and use of prophylaxis, the incidence of PCP has dramatically decreased in the Western world. PCP is an AIDS defining event (WHO stage 4 condition).

Symptomatology

PCP is characterised by a sub-acute onset of symptoms gradually getting worse in a period of days to weeks. Patients complain of dyspnoea, fever, and non-productive cough gradually getting worse. The duration of illness until diagnosis is typically 1 to 2 weeks, although considerable variation exists. Dyspnoea on exertion is always present.

Physical examination

Physical findings include tachypnoea, tachycardia, and cyanosis. Auscultation of the chest is generally unremarkable. Some dry crackles can sometimes be found.

Complementary exams

In general the diagnosis is based on the history and physical exam, combined with a suggestive chest X-ray and hypoxia.

It would be good to confirm the diagnosis in the laboratory if possible.

Chest X-ray

The classic findings on chest X-ray consist of bilateral interstitial shadowing, extending from the hilar area (ground glass appearance without air-bronchogram, butterfly pattern). Sometimes there are nodules or cavities, but the X-ray can be (at first presentation) misleadingly normal (25%).

More than 80% of cases of **pneumothorax** in HIV-infected patients are due to PCP.¹⁶³ Therefore all patients with pneumothorax should be given empirical PCP treatment.

Blood Examination

Complete blood count (CBC) and white blood count is variable and usually governed by the patient's underlying disease.

Arterial blood gases demonstrate hypoxaemia, increased alveolar-arterial oxygen gradient and respiratory alkalosis.

If oxygen saturation measurement is possible, it will always show a decrease in O₂ saturation during physical effort in patients with PCP.

Measurement of serum lactate dehydrogenase (LDH) can be helpful. A normal LDH makes PCP unlikely. A strongly elevated LDH (>2 times the normal value) suggests that PCP is likely.¹⁶⁴ Rising LDH levels despite treatment heralds a poor prognosis or may be due to another infection.¹⁶⁵ The mortality rate is also influenced by the CD4 count.

Laboratory diagnosis

Whenever practicable, attempts should be made to identify the organism. *P. Jiroveci* oocysts are rarely present in sputum. They can be demonstrated in specially prepared *induced sputum* smears (sens. 60%) or in bronchoalveolar lavage (BAL: sens. 90%). In patients who are not taking PCP prophylaxis, the sensitivity of induced sputum may be as high as 90%. Spontaneously expectorated sputum has low sensitivity and should not be submitted to the laboratory to diagnose PCP.¹²⁴

Differential diagnosis

The most difficult differential diagnosis is with PTB, and many patients may end up with treatment for both.

In Table 11 we give some guidance how to differentiate between these two frequent pathologies in AIDS patients.

Table 11: Differential diagnosis between PTB and PCP

	Typical of PCP	Typical of TB
Symptoms	Subacute onset (1-2 weeks) Dry cough Sputum mucoid, if any Dyspnoea	Slow onset (>2-3 weeks) Productive cough Purulent sputum Pleuritic chest pain
Signs	Normal Fine inspiratory crackles	Signs of consolidation Signs of pleural effusion
Chest X-ray	Bilateral diffuse interstitial shadowing Normal	Lobar consolidation Cavitation Pleural effusion Intrathoracic lymphadenopathy

Treatment

Supportive: General supportive measures include:

- Maintenance of adequate oxygenation
- Maintenance of fluid and electrolyte balance
- Nutritional support

Drug Treatment:

If possible, it is advised to isolate the patient.¹⁶¹

The two major drugs used in the treatment of PCP have been cotrimoxazole and pentamidine. These drugs are equally effective, with success rates of 50 to 80%. Pentamidine has more side effects (renal failure, hypoglycaemia, hypotension) and therefore the first choice treatment is:

1. Cotrimoxazole IV or PO: cotrimoxazole 20/100 mg/kg daily divided over 4 doses for 21 days. For mild to moderate disease, oral medication can be used throughout the treatment; for severe disease, the first 7-10 days treatment is normally administered intravenously, if possible.

Table 12: Cotrimoxazole dosing for PCP

Weight	Dose in mg	Dose in tablets of 400/80 mg (SS)
30-45 kg	800/160 mg x 4/day	2SS x 4/day
45-60 kg	1600/320 mg x 3/day	4SS x 3/day
> 60 kg	1600/320 mg x 4/day	4 SS x 4/day

Any patient who is hypoxic ($pO_2 < 70$ mmHg) should receive **prednisone**.

The first few days of antimicrobial treatment are critical since the decomposition of many dead parasites exacerbates the pre-existing inflammatory process and aggravates hypoxia. However, the risk of death at this stage can be substantially reduced, especially in patients whose arterial

oxygen tension is less than 70 mmHg, if a corticosteroid is administered. Corticosteroid treatment should be commenced at the same time as anti-PCP treatment. There is no benefit from corticosteroid usage in episodes of mild PCP, when there is no hypoxaemia in rest.

Table 13: Dosing of prednisone in case of hypoxia in PCP

	ADULTS	CHILDREN
D1-5	40 mg x 2/day	1 mg/kg
D6-10	40 mg x 1/day	0.5 mg/kg
D11-D21	20 mg x 1/day	0.25 mg/kg

Evolution under treatment:

Signs of improvement may not be evident for 4-8 days, and treatment with cotrimoxazole should be maintained for 3 weeks.

In case there is no response after 7-10 days always suspect a second infection. Patients may have both TB and PCP; and TB seems to account for the most severe features of disease.¹⁶⁶ CMV, Cryptococcus, Aspergillus, herpes simplex, Candida, M. avium intracellulare, and bacteria have all been identified in or grown from lung tissues from patients with PCP.

In resource-limited settings, with a high prevalence of TB and where bronchoscopic evaluation is not feasible, empiric therapy directed against TB and PCP may be reasonable for patients who are hospitalized with PCP and who are unresponsive to 7-10 days of appropriate anti-PCP treatment.¹⁶⁶

When no improvement is evident after 7-10 days, clinicians often resort to switching to one of the other regimens. The severe toxicity of pentamidine (renal failure, hypotension, hypoglycaemia) compared to the other regimens has limited its use and it is now used only as a last resort. If a switch to pentamidine is being considered, there should be an overlap of 2-3 days to allow pentamidine to accumulate in the body.

2. Pentamidine is given by slow intravenous infusion 4 mg/kg per day for 14-21 days. The infusion should be given over 2 hours while the patient is lying down. In case the patient becomes unconscious during infusion, suspect hypoglycaemia and give glucose 30% IV. Do not give it intramuscular because of the risk of sterile abscesses. Inhaled, rather than intravenous, pentamidine is less effective than cotrimoxazole.

3. Trimethoprim, 15mg/kg/d + **dapsone**, 100 mg/d once daily for 14-21 days

4. Primaquine, 15-30mg daily and **clindamycin** 300-900 mg every 6 hours 14-21 days

5. Atovaquone 750 mg 2 x daily with food, is very expensive, but could be used in patients who do not tolerate sulphonamides and pentamidine, and who have mild to moderate PCP.

Prophylaxis

Every HIV-positive patient who has been successfully treated for pneumonia due to *Pneumocystis jiroveci* should receive continuous prophylaxis. Various estimates place the 3-month relapse rate among patients not receiving prophylaxis following a course of treatment for PCP at 10%-40%; about one in five of such episodes is fatal.

- First choice: cotrimoxazole **1DS daily** (proved to be superior to thrice weekly). Additional benefits: protects against toxoplasmosis and bacterial respiratory tract infections and is inexpensive)
- Second choice: dapsone (less effective than cotrimoxazole, equal to pentamidine or atovaquone)
dapsone and pyrimethamine[†]
- Third choice: pentamidine (nebulised) 300 mg once a month
- Fourth choice: sulfadoxine/pyrimethamine (Fansidar ®) 1-2 tablets weekly.

The secondary prophylaxis can be stopped in patients who show sustained immunological response (CD4>200) on antiretroviral combination therapy (check CD4 at least twice before stopping the prophylaxis).

(For doses and possible side effects: see chapter 6 on *Prevention of OI*)

Resistance to sulphonamides

Sulfamethoxazole and dapsone inhibit the enzyme dihydropteroate synthase (DHPS). This enzyme is doing part of the folate metabolism. Many researchers have reported mutations of pneumocystis in response to the use of sulphonamides in anti-pneumocystis regimens. Whether these mutations increase the likelihood of treatment failure is still unclear.¹⁶⁰

7.2.4 Penicilliosis[‡]

Causal organism & epidemiology

Penicillium marneffe is a fungus commonly causing opportunistic infections in HIV-infected patients in Southeast Asia and Southern China with late-stage disease (CD4<100). There are important regional variations in infection rates.¹⁶⁷ In Northern Thailand, it is one of the most common opportunistic infection (together with extra-pulmonary TB and cryptococcal meningitis). Up to a quarter of AIDS patients are affected, whereas in Southern Thailand the prevalence is ten times less. The exact route of infection in humans is not known. The organism proliferates in macrophages and is disseminated throughout the body, especially in the reticulo-endothelial system.

[†] Pyrimethamine should be added in patients with a CD4 count lower than 100/mm³ and *Toxoplasma gondii* antibody positive, if they do not tolerate Cotrimoxazole.

[‡] Also called 'Penicillinosis'

Clinical presentation

In the majority of patients with AIDS, penicilliosis presents as a disseminated infection, and symptoms are an abrupt onset of fever, anaemia, weight loss, skin lesions but also possible lymphadenopathy and hepatosplenomegaly. Respiratory complaints (cough, shortness of breath) are also common. The skin lesions present as one or multiple papular lesions, often with central umbilication or ulceration, resembling molluscum contagiosum. The lesions are typically on the face, scalp and upper trunk.

The differential diagnosis with TB and disseminated cryptococcal disease must be made.

If there are no skin lesions, the diagnosis is difficult. The characteristic syndrome would be hepatic disease with fever, hepatomegaly and isolated high alkaline phosphatases.

Chest X ray

Diffuse nodular pulmonary infiltrates or cavitory disease

Laboratory findings

The diagnosis is confirmed by culturing the fungus from clinical specimens. The fungus may be seen by microscopic examination of skin scrapings, touch preparations of skin biopsy or lymph node aspirate stained with Wright's stain, or cotton blue stain. Bone marrow aspirate is diagnostic in 100% of cases.

Treatment

Initial treatment should be with amphotericin B 0.7 mg/kg daily IV for 2 weeks, followed by 200 mg 2 x daily for 10 weeks.

Mortality from disseminated *P.marneffei* infection in patients with AIDS is about 20%, despite effective anti-fungal therapy.¹⁰⁴

Long-term suppressive therapy with itraconazole should be given to prevent relapse. Itraconazole in a dose of 200 mg daily is effective in preventing systemic fungal infections although one study in Northern Thailand showed no difference in survival between the treatment and the placebo group.¹⁰⁴ Although ketoconazole is active in vitro, the clinical experience of the research team in Chiang Mai is that it is less active in treating the disease and preventing relapses.

Secondary prophylaxis can be discontinued when CD4 >100 in patients responding to HAART.¹⁶⁸

7.2.5 Cryptococcosis

Infection of the lungs may be the initial manifestation of cryptococcosis, but dissemination to extra-pulmonary sites occurs frequently. Cryptococcosis has a tendency to spread to the CNS. When restricted to the lungs it presents as an atypical pneumonia without meningitis, but there are no controlled trials describing the outcome of therapy for AIDS related cryptococcal pneumonia. Diagnosis is confirmed by sputum culture.

Most patients with cryptococcal meningitis do not have a clinically evident pneumonia. In patients on HAART IRIS secondary to cryptococcosis may present as pulmonary infiltrates and mediastinal lymphadenitis.¹⁶⁹

For the treatment of HIV associated cryptococcal pneumonia, fluconazole 200-400 mg/day appears to be the best choice in patients with mild to moderate symptoms or who are asymptomatic with a positive culture from the lung.¹⁷⁰

7.2.6 Histoplasmosis

Causal organism & epidemiology

Histoplasma capsulatum is a dimorphic fungus that likes soil enriched by dropping of certain birds and bats. It is endemic in certain areas of North and Latin America but cases have also been reported from Europe and Asia. Precise reasons for this endemic distribution pattern are unknown but are thought to include moderate climate, humidity and soil characteristics.

In endemic areas, the incidence of histoplasmosis among patients with AIDS is 5-20%.¹⁷¹

Pathogenesis

Inhaled small spores of *H.Capsulatum* reach the alveoli and with time an intense granulomatous reaction occurs. Caseous necrosis or calcification may mimic tuberculosis. Severity of illness depends on the intensity of exposure and the immunity of the host. Acute and rapidly fatal disseminated infection can occur mainly among young children and immunosuppressed patients, including those with AIDS. In patients with AIDS, histoplasmosis presents as a disseminated infection in 95% of the cases.¹⁷⁰

Symptomatology

Acute pulmonary histoplasmosis presents with cough, fever, malaise, chills, myalgia, anorexia and chest pain (seen in 85-100% of the cases).

Diffuse pulmonary disease in HIV patients must be differentiated from PCP.

Disseminated histoplasmosis has many features in common with hematogenously disseminated TB. Fever, emaciation, hepatosplenomegaly, lymphadenopathy, big oral solitary ulcers and discrete erythematous skin papules may be seen in case of advanced HIV infection. 50% have respiratory symptoms. Disseminated histoplasmosis is a WHO stage 4 or AIDS-defining event.

Chest X-ray

The radiological picture depends on the form. In mild or asymptomatic cases hilar adenopathy with or without one or more area of pneumonitis can be seen.

In chronic pulmonary histoplasmosis retraction and cavitation of upper lobes with spread to lower lobes and other area of the lung, with emphysema and bulla formation is typical.

Disseminated histoplasmosis, which is the most frequent form in AIDS patients presents with a miliary pattern in half of the cases.

Laboratory findings

Sputum culture is the preferred diagnostic method for chronic pulmonary histoplasmosis but often not available. For disseminated forms, culture from bone marrow or blood is advised, however the fungus can sometimes be detected in white blood cells and macrophages in Giemsa stained smears of blood, bone marrow and BAL.^{171,172}

Serum LDH have been proposed as an adjunct laboratory marker as levels of 600 UI/l of greater are suggestive of histoplasmosis rather than PCP in appropriate clinical settings.¹⁶⁵

85% of cases occur in patients with CD4 < 100.¹⁷⁰

Treatment

Treatment starts with an initial 12 week intensive phase to induce a remission of clinical disease, followed by a chronic maintenance phase to prevent relapses.

Intensive phase:

First choice:

- Patient is very ill and hospitalised: use amphotericin B 0.7-1mg/kg/day (see chapter 14 for procedure), replaced by itraconazole 200 mg 2 x daily when the patient doesn't require hospitalisation or IV therapy anymore.
- Less ill, non hospitalised patients: itraconazole 200 mg 3 x daily for 3 days followed by 200 mg 2 x daily for 12 weeks

Alternative: Fluconazole 800 mg daily (those patients need to be followed closely clinically for relapse as it is less effective)

Ketoconazole is not an alternative for AIDS patients as it has been associated with high failure rate (even if successful in non AIDS patients).¹⁷⁰

Maintenance phase:

Relapse occurs in 80% of patients with AIDS that is why secondary prophylaxis is absolutely necessary.¹⁷¹

First choice: Itraconazole 200 mg once or twice daily lifelong

Alternative: amphotericin B 50 mg IV once weekly, not well tolerated or accepted by patients

Other alternative: fluconazole 400 to 800 mg daily, less effective for maintenance therapy of histoplasmosis. Strict clinical follow-up is needed to detect relapse, and some do not recommend it.¹⁷¹

Ketoconazole is ineffective as suppressive therapy.

It appears safe to interrupt the maintenance antifungal therapy in patients who have received >12 months of antifungal treatment and who have experienced sustained immunological improvement (CD4 > 100-150) as a result of antiretroviral therapy.¹⁷³

Primary Prophylaxis

For patients living in hyperendemic area of histoplasmosis (>5-10 cases/100 patients-years) and if CD4 < 100 or 150 you could consider itraconazole 200mg once daily. However, there is no survival benefit demonstrated.¹⁷⁰ The best prophylaxis is to start HAART in a timely manner.

7.2.7 Coccidioidomycosis

Causal organism & epidemiology

Coccidioides immitis is a dimorphic fungus. These fungi are endemic in certain lower deserts of the western hemisphere including southern Arizona, central California, southwestern New Mexico, and west Texas in the United States. They are also found in parts of Mexico, Central, and South America. Late recrudescence of latent infection is possible in AIDS so it is important to be aware of distant past exposure to endemic regions. Risk is increased if CD4<250.

Symptomatology

Primary pulmonary infection is asymptomatic in 40% of cases. Symptoms ranging from mild influenza like illness to severe pneumonia.

Infection in patients with HIV most frequently involves the lungs and diffuse reticulonodular infiltrates are typical. It is sometimes difficult to differentiate from PCP.

Dissemination is frequent in AIDS patients. Possible clinical signs include generalized lymphadenopathy, skin nodules or ulcers, peritonitis, meningitis, liver abnormalities and bone/joint involvement. It can progress rapidly.

Chest X-ray

Primary infection: infiltrate, hilar adenopathy or pleural effusion.

Laboratory findings

CSF (in case of meningitis): glucose > 50mg/dl, protein normal or mildly elevated

Culture from clinical specimens and serology are often not available.

Treatment

Start with fluconazole 400-800 mg/day or amphotericin B 0.5-0.7 mg/kg/day until clinical improvement observed which usually occurs after administration of 500-1000 mg of amphotericin B (10-14 days) followed by lifelong suppressive therapy with fluconazole 400 mg daily or itraconazole 200 mg 2 x daily.^{124,170}

Not enough data exist to recommend discontinuation of secondary prophylaxis. Some say it is reasonable to stop when CD4 >250.

7.2.8 Aspergillosis

Aspergillosis is an infrequent but often fatal fungal infection in HIV-infected people. HIV patients are at increased risk of invasive aspergillosis. Aspergillosis mainly occurs at CD4<50. Two major patterns are observed: invasive pulmonary aspergillosis and obstructing bronchial aspergillosis or necrotising tracheobronchitis. Disseminated forms are also described. Treatment is with amphotericin B but needs to be complemented by antiretroviral therapy to have an impact on survival.¹⁷⁴

7.2.9 Helminthic diseases causing respiratory symptoms

Strongyloides stercoralis and *Paragonimus westermanii*[§] (lung fluke) can cause acute and chronic respiratory symptoms. X-ray appearance can suggest TB or atypical pneumonia. A fresh sputum examination easily identifies the filariform larvae in pulmonary strongyloidiasis and the eggs of *Paragonimus* (see *Laboratory section 7.5.5* page 116).

Paragonimiasis should be excluded in patients with suspected PTB on chest X-ray, who are smear-negative. It is very easy to miss the eggs of *Paragonimus* if the sputum is only examined for *Mycobacterium tuberculosis*. An eosinophilic pleural effusion in endemic regions is suggestive of paragonimiasis. Haemoptoe is also seen with paragonimiasis. The treatment of *paragonimus* consists of praziquantel 75 mg/kg/day divided into 3 doses for 2 days.

Strongyloides infection should be suspected in patients who have serpiginous erythematous skin lesions (larva recurrens), diarrhoea, abdominal pain and cough. The chest radiograph reveals diffuse pulmonary infiltrates. Disseminated strongyloidiasis and heavy worm loads can occur in patients with HIV, but the full blown hyperinfection syndrome is less common.^{175,176,176} In disseminated strongyloidiasis, filariform larvae can be found in stool, sputum, bronchoalveolar lavage fluid, pleural fluid, peritoneal fluid and surgical drainage fluid.

Strongyloidiasis can be successfully treated with ivermectin 12 mg daily for 3 days, and is considered by some as the drug of choice for the treatment of systemic strongyloidiasis.¹⁷⁷ An alternative treatment is albendazole 400 mg 2 x daily for 5 days. A monthly maintenance therapy is necessary to suppress symptomatic infection (albendazole 400 mg or ivermectin 6 mg once a month). (See also the chapter 9)

[§] The *Paragonimus* species is mainly found in Southeast Asia (China, Philippines, Laos and Thailand). Case reports exist from Korea, Japan, Congo, West Africa and Latin American countries bordering the Pacific Ocean.

7.2.10 Toxoplasma pneumonitis

This is rare in HIV patients.¹²⁴ Sometimes it is difficult to distinguish from PCP pneumonia. Toxoplasma pneumonitis should be considered in patients who present with fever, cough, and dyspnoea and where the induced sputum fails to demonstrate PCP.

Diagnosis

Chest X-ray may show diffuse interstitial pattern or reticulonodular infiltrates. The diagnosis of pulmonary toxoplasmosis can be confirmed by Giemsa staining of BAL.

Treatment

A combination of sulfadiazine and pyrimethamine is the regimen of choice. However, studies with high dose cotrimoxazole for the treatment of Toxoplasma encephalitis¹⁷⁸ have shown similar efficacy.^{178,179} Cotrimoxazole is a more readily available drug in developing countries.

7.2.11 Mycobacterium Avium complex (MAC)

MAC rarely gives pulmonary symptoms. It can cause respiratory symptoms in patients on HAART who develop IRIS.

7.2.12 Pulmonary KS

Pulmonary KS is rapidly fatal when left untreated. Patients present with dyspnoea without fever, sometimes with haemoptysis. Visceral involvement is most of the time concomitant with skin lesions.

Generally, lesions are recognised clinically and the diagnosis of KS can be confirmed by biopsy. A chest X-ray may show reticulo-nodular infiltrates, enlargement of the mediastinal shadow and sometimes a pleural effusion.

Typical red purple lesions can be seen on bronchoscopy. A patient with pulmonary KS needs a combination of HAART and chemotherapy (see chapter 15, page 273).

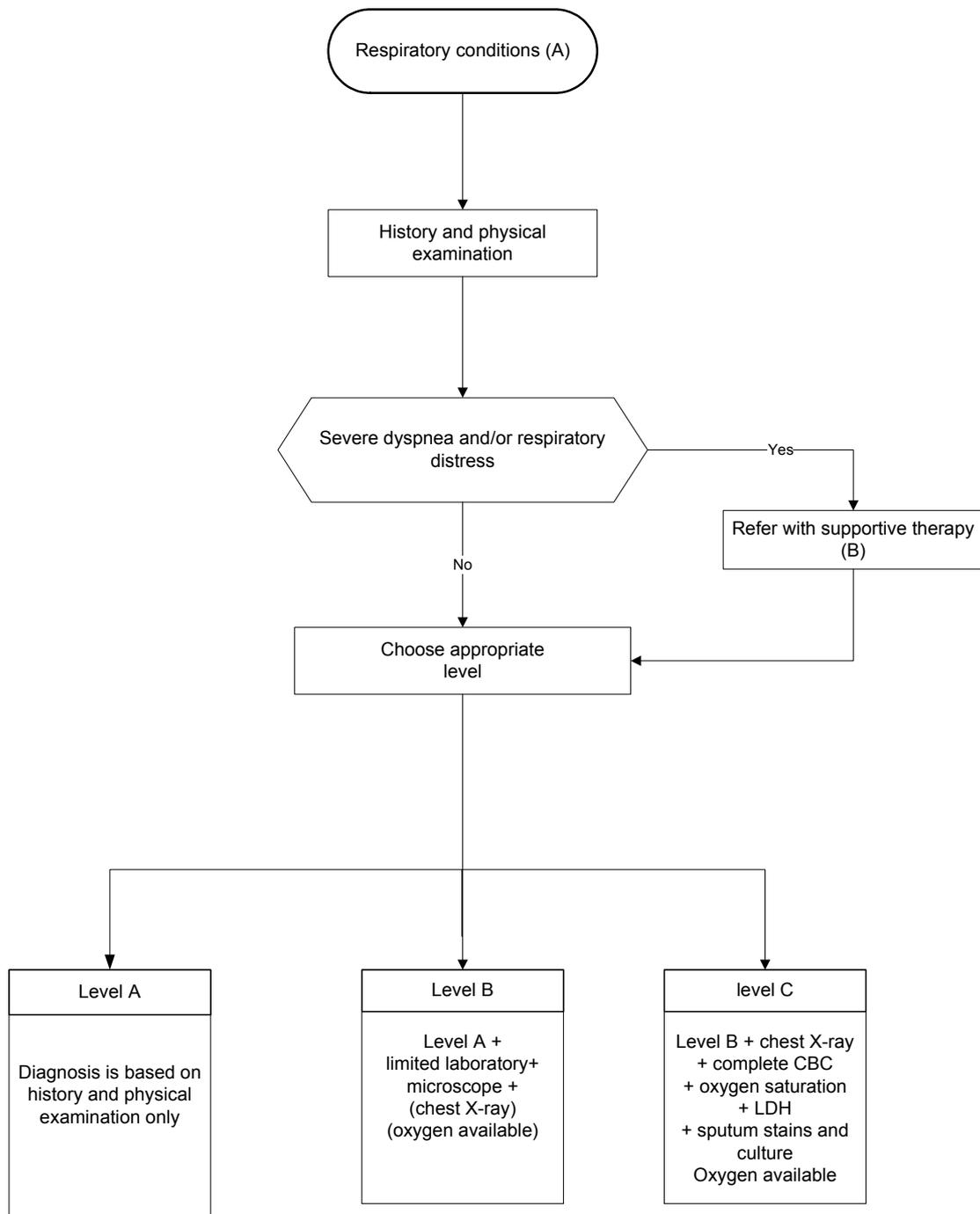
7.3 Clinical management of respiratory problems in HIV patients

Diagnosis of pulmonary disease in HIV-positive patients often requires a multi-step approach, starting with a thorough history and physical examination and leading up to chest X-ray and sputum examination. To use resources rationally, it is important to identify those patients who will benefit from additional tests. E.g. in a smear-positive pulmonary TB patient, the diagnosis of PTB is confirmed by the positive smear and treatment effect can be evaluated by examining the smears at certain intervals. A chest X-ray provides no additional benefit.

It is not rare to find more than one pathogen involved. Therefore, in a patient who does not respond to therapy as expected, do not hesitate to review the history and the physical examination, to repeat the algorithm and to add a second or even a third treatment if necessary.

Many patients, by the time they present with cough to a health worker, have already bought over-the-counter antibiotics or have been treated elsewhere. It is important to take this into account in order not to waste valuable time.

Respiratory conditions



Annotations Respiratory Problems

(A) Definition: cough and/or chest pain and/or dyspnoea in a patient with symptomatic HIV infection.

Possible aetiologies:

1) Infections

- pyogenic bacteria: *Streptococcus pneumoniae*, *Haemophilus influenzae*
- tuberculosis
- PCP
- fungal infections: cryptococcosis, penicilliosis, aspergillosis, histoplasmosis, etc.
- (atypical mycobacteria)
- (CMV, toxoplasmosis).

2) Malignancies

- Kaposi's sarcoma
- lymphoma.

3) Others: lymphoid interstitial pneumonitis.

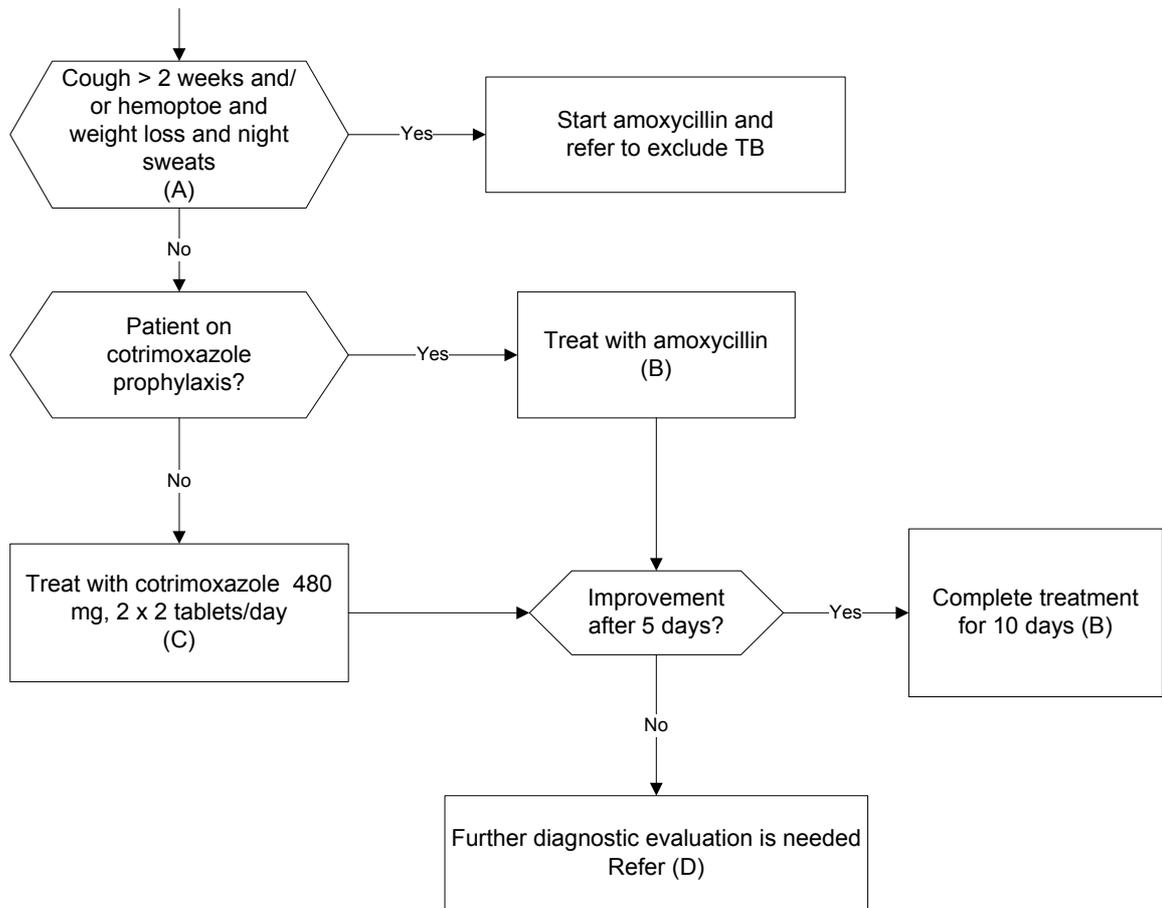
4) Associated problems

- pleural effusion/empyema (often TB)
- pericardial effusion (often TB)
- pneumothorax (associated with TB, PCP, pneumonia or cancer).

5) Heart failure, pulmonary embolism, asthma, severe anaemia.

(B) If hypoxaemia is present, diagnosed on clinical grounds (dyspnoea, cyanosis), oxygen therapy is indicated. A patient with a respiratory rate of more than 30/minute while resting will need hospitalisation and oxygen and must be referred to the appropriate level.

Continued from flowchart 1

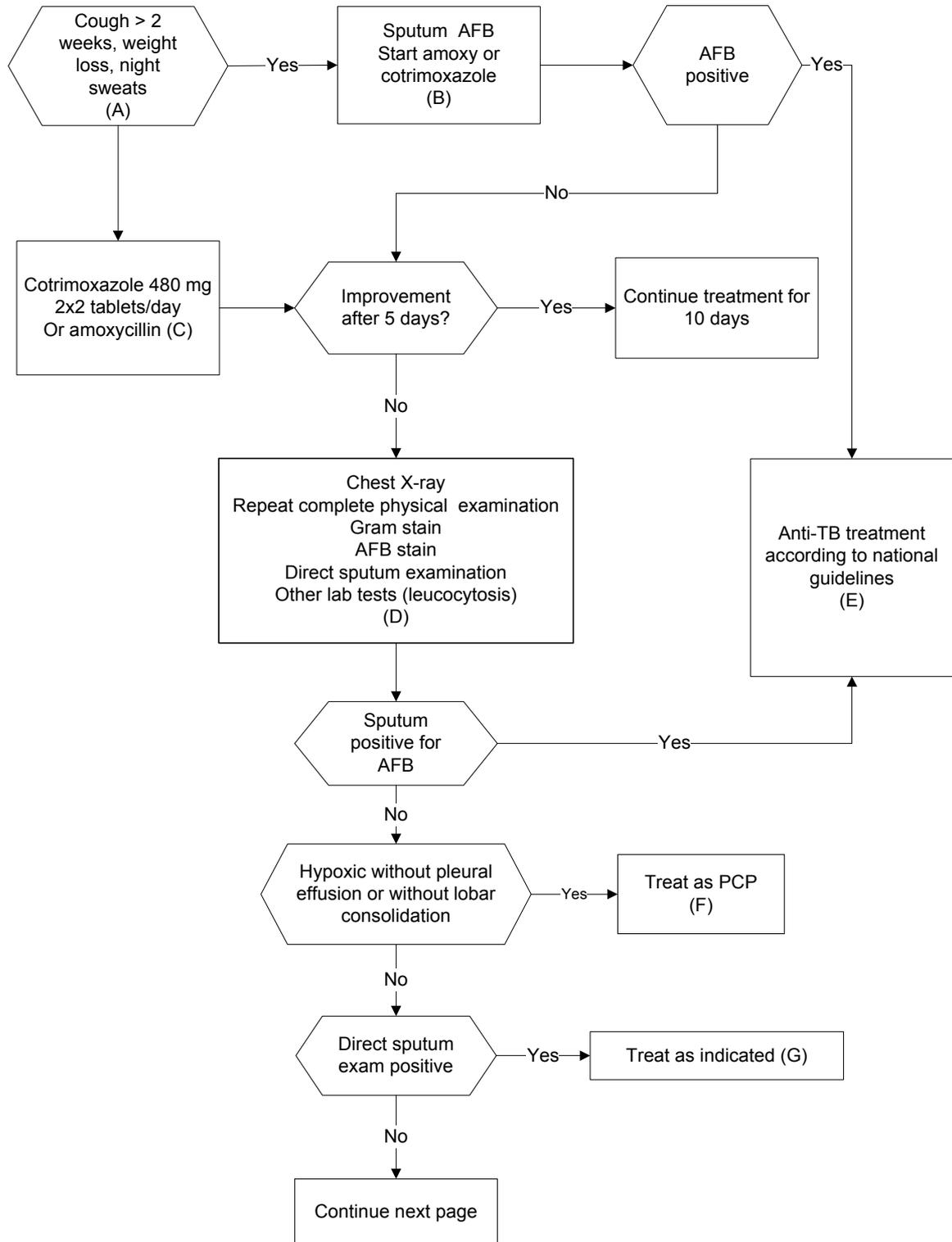


Annotations (level A)

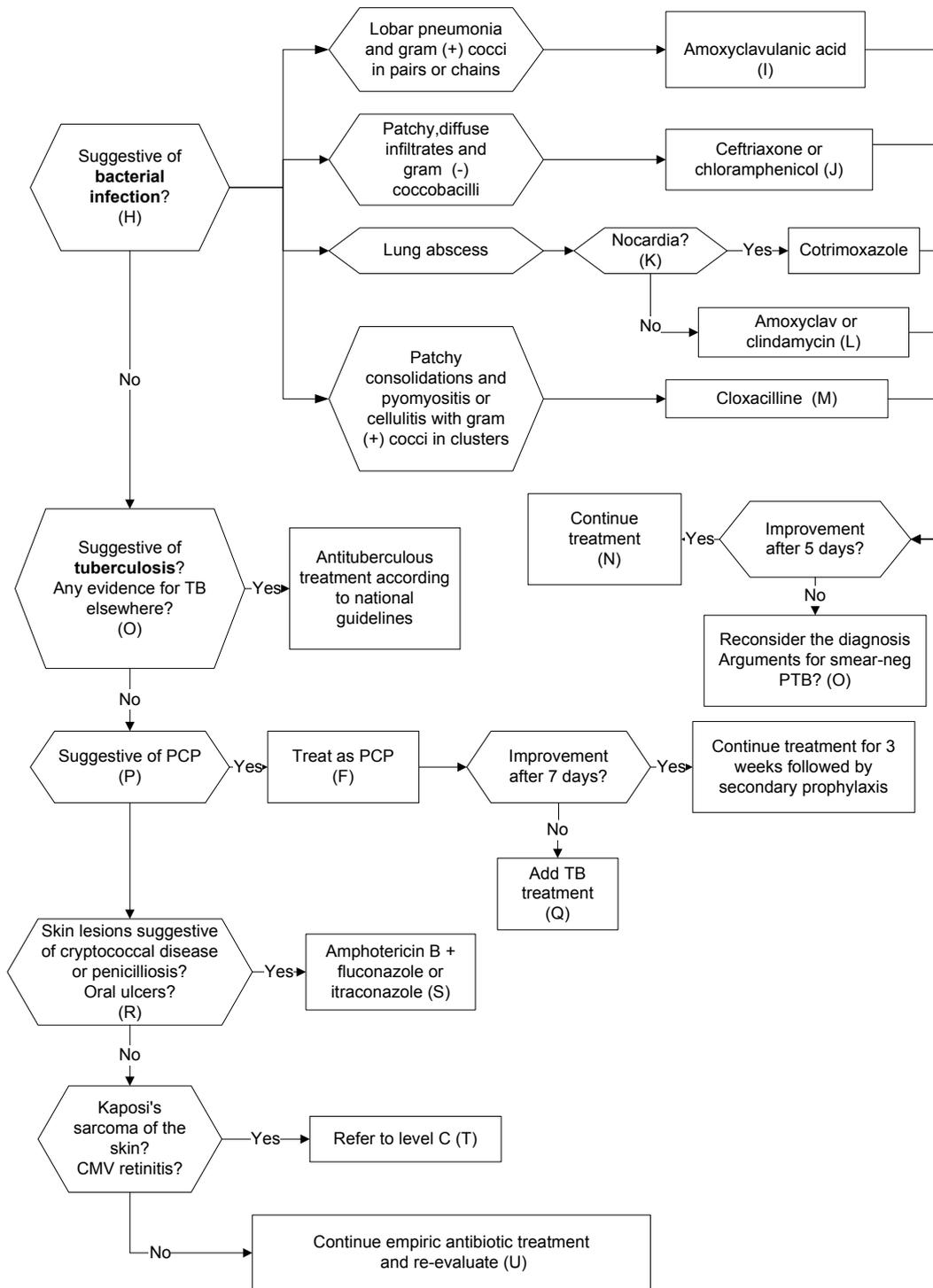
- (A) Tuberculosis is very frequent in HIV-positive patients in developing countries. This condition should be diagnosed or excluded without delay. Therefore, any patient with chronic cough and other symptoms suggestive of TB (night sweats, weight loss) should be referred to a level able of diagnosis PTB.
- (B) In most developing countries, bacterial pathogens are the most probable cause of infection. A trial with antibiotics to treat pneumococcal pneumonia is justified. In patients who were taking cotrimoxazole prophylaxis, it is better to use amoxicillin 500 mg -1 g, 3-4 x daily for 10 days.
- (C) In patients who are not taking cotrimoxazole prophylaxis, the first choice is treatment with cotrimoxazole as it covers the most frequent respiratory pathogens: *S. pneumoniae*, *H. influenzae*, *Moraxella cattharalis* and *Klebsiella pneumoniae*. The dose used is cotrimoxazole 480 mg 2 x 2 tablets daily for 10 days.
- (D) Exclusion of tuberculosis and other OI is now a priority.

Respiratory conditions

Level B (1)



continued from level B (1)



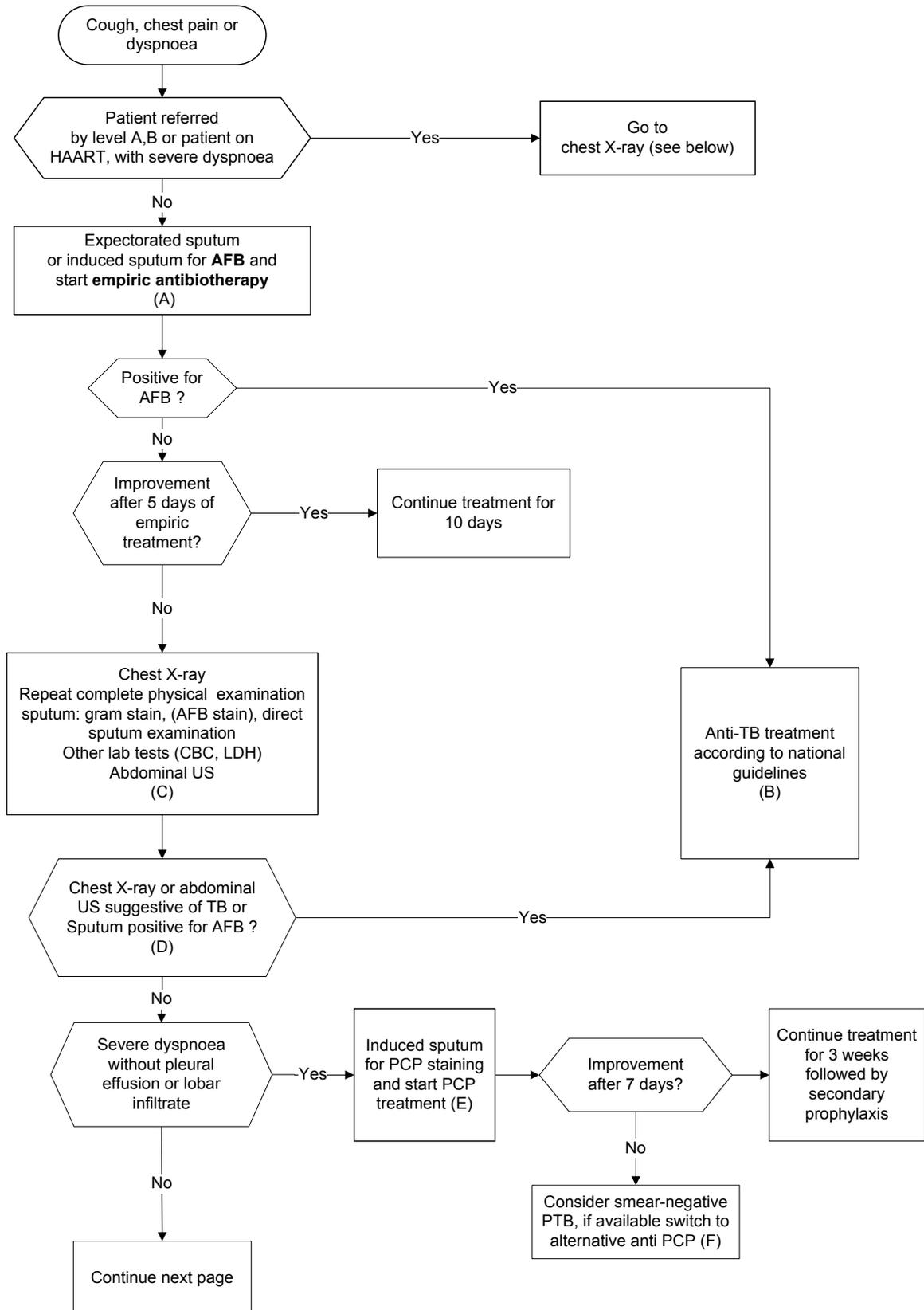
Annotations (Level B)

- (A) To increase the efficiency of the lab and of patient care, it is important to screen those patients who could benefit the most from a sputum examination for TB. The cut-off for chronic cough is generally put at >2 weeks in MSF projects.
- (B) In countries with a high prevalence for TB, sputum examination for AFB is essential. The highest yield of AFB in smear and culture is with expectorated early-morning sputum. Induced sputum should be used only in people who cannot expectorate. The sensitivity of sputum examination is decreased in HIV-positives and is around 50%. While awaiting the result of the sputum, start the patient on a broad-spectrum antibiotic. In case the patient was already on cotrimoxazole we prefer to use amoxicillin.
- (C) In many countries, pyogenic bacteria will be the most probable cause of bacterial pneumonia. If the patient is already using cotrimoxazole prophylaxis, the first choice is amoxycillin. In patients who are not yet on cotrimoxazole prophylaxis, cotrimoxazole is preferred over amoxycillin because of its broader spectrum. If available, amoxy-clavulanic acid or cefuroxime has a broader spectrum and could be the first choice at level B.
- (D) If there is no improvement after a 5-day course of antibiotics, the patient should receive more advanced examinations. Repeat the **history and physical examination** thoroughly. Look for additional signs that may help in the differential diagnosis. Skin lesions are present in Kaposi's sarcoma or disseminated cryptococcosis or penicilliosis. Pyomyositis and cellulitis point toward staphylococcal infection. High fever, pleuritic-type chest pain and productive cough are suggestive of bacterial pneumonia. Lymph nodes are usually seen in TB and lymphoma. A chest X-ray and a sputum AFB and Gram stain should be carried out. Direct sputum examination may reveal *Strongyloides stercoralis* larvae or eggs of *Paragonimus* species. Other lab tests could also be included here: WBC count, Gram stain of pus from other sites, Giemsa stain of bone marrow or blood smear in case of high fever, LDH when available.
- (E) The highest priority is to treat smear-positive pulmonary TB (but MSF is a strong advocate for more rapid diagnosis and treatment of smear-negative and extra-pulmonary TB). Follow national treatment guidelines. Short-course therapy with an initially intensive phase of 4 drugs is usually advised: 2 months of INH, RIF, PZA and EMB, followed by a 4-month continuation phase of INH and RIF.
- (F) A chest X-ray may look normal in PCP, cryptococcus and tuberculosis infections. In case of hypoxia, PCP is the most likely diagnosis in HIV patients. Treatment consists of cotrimoxazole: cotrimoxazole 20/100 mg/kg daily in 4 divided doses. Assessment of benefit will require at least 7 days as PCP may initially worsen. If the patient responds, continue for at least 21 days in the absence of side effects. The risk of recurrence is high

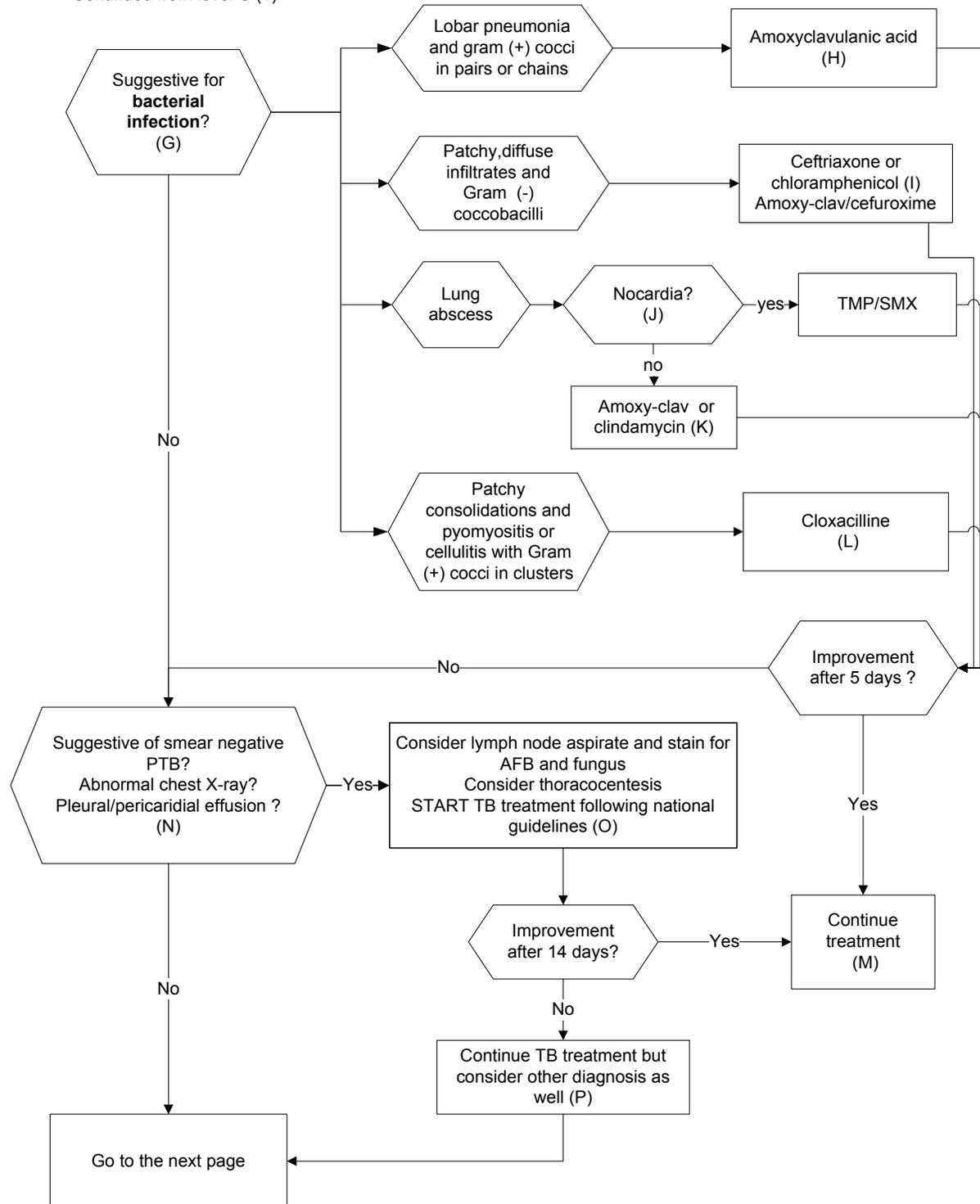
and can be reduced by prophylaxis: cotrimoxazole 480 mg 2 tablets daily. Sometimes 480 mg daily or 960 mg 3xweekly is better tolerated. An alternative is dapsone 100 mg once daily. For the severely ill patient with ongoing dyspnoea despite therapy, or with hypoxaemia since arrival, **prednisolone** is associated in a dose of 40 mg 2 x daily for 5 days, 40 mg once daily for 5 days, then 20 mg daily to completion of treatment.

- (G) Although not a likely cause of respiratory symptoms, *Paragonimus* and *Strongyloides* are easily diagnosed by a direct sputum exam. In endemic regions, such as Southeast Asia, *Paragonimus* (related to eating fresh water shrimps and crabs) should be considered in patients with smear negative PTB. *Paragonimus*: Praziquantel 75 mg/kg/day in 3 divided doses for 2 days. *Strongyloides*: Albendazole 400 mg 2 x daily for 5 days, or ivermectin 12 mg daily for 3 days. Suppressive therapy to prevent recurrence of symptomatic infection: ivermectin 6 mg once monthly, or Albendazole 400 mg once monthly.
- (H) An acutely ill patient, with high fever, high leucocytosis and respiratory symptoms is suggestive of a bacterial cause. Chest X-ray and Gram stain may help to differentiate between different causal agents.
- (I) A lobar pneumonia and a sputum Gram stain with Gram-positive cocci in pairs is very likely a streptococcal pneumonia. The patient did not respond to cotrimoxazole or amoxicillin, try amoxy-clavulanic acid 625 mg 3 x daily or cefuroxime 500 mg 2 x daily. In case the patient is critically ill, use ceftriaxone 2g once a day, IV. Fluoroquinolones should be avoided in respiratory infections because of a possible effect on tuberculosis, and risk for resistant mycobacteria when used in monotherapy.
- (J) More diffuse infiltrates and Gram-negative coccobacilli on sputum Gram stain are suggestive of *H.influenzae*. Treatment of choice is ceftriaxone. Amoxy-clavulanic acid is a good alternative, if available.
- (K) If the X-ray shows an air-fluid level, this indicates a lung abscess. Always carry out a Gram stain on sputum in lung abscess to exclude Nocardiosis. Nocardia can present with multiple abscesses (lung, subcutaneous, etc.). The recommended treatment is cotrimoxazole 10/50 mg/kg 2 x daily (for 6 weeks to 6 months) or minocycline 100 mg 2 x daily for several months, combined with amikacin 15-25 mg/kg for 2 weeks or ceftriaxone 2 g daily (for several months) combined with amikacin for 2 weeks. The surgical drainage of abscesses is sometimes necessary.
- (L) Lung abscess not due to Nocardia: treatment of choice is amoxy-clavulanic acid 625 mg 3 x daily or clindamycin 600 mg 3 x daily.
- (M) The antibiotic of choice for staphylococcal infections is (flu)cloxacillin 1-2 g 4 x daily IV or 500 mg 4 x daily PO. In addition, chloramphenicol, doxycycline and cotrimoxazole are moderately effective against staphylococci.

- (N) Duration of treatment depends on the condition treated; for nocardiosis treatment may be necessary from 6 weeks up to 6 months. A lung abscess generally needs 3-4 weeks of antibiotics. Other bacterial pneumoniae need 10-14 days of treatment.
- (O) A more chronic course, with wasting, night sweats, chest pain and productive cough, high ESR, nodular or cavitary infiltrates, lobar infiltrates that do not disappear with broad spectrum antibiotics, hilar or paratracheal lymph nodes and pleural effusion, are suggestive of pulmonary TB or of pulmonary fungal disease (especially in areas where histoplasmosis is endemic). At this point, the decision must be taken whether or not to start a smear-negative suspected TB patient on TB treatment. Follow the national recommendations regarding smear-negative pulmonary TB. Look for other signs of TB to guide your decision (abdominal ultrasound, peripheral lymph node enlargement). In areas where deep fungal infections are a common cause of respiratory symptoms fungal cultures are helpful at this point.
- (P) PCP can be definitively diagnosed if cysts are found in induced sputum, BAL or biopsy specimens. Often these investigations are not available. The diagnosis therefore depends on the clinical and chest X-ray findings, exclusion of TB and response to high-dose cotrimoxazole (see page 81). For treatment see "annotation F" page 97.
- (Q) Assessment of benefit of PCP treatment will require at least 7 days as PCP may initially worsen. If the patient responds, continue for at least 21 days in the absence of side effects. If the patient does not respond one has to consider alternative diagnosis. Again in developing countries at this point smear-negative PTB is probable.
- (R) Disseminated cryptococcosis and penicilliosis require treatment with amphotericin B. Oral ulcers combined with respiratory symptoms are suggestive for histoplasmosis in endemic areas. If needed refer your patient to level C for appropriate antifungal treatment.
- (S) For histoplasmosis and cryptococcosis see page 85, for penicilliosis see page 83.
- (T) A patient with CMV retinitis or Kaposi's sarcoma is urgently in need of HAART. However, he will need as well ganciclovir (CMV) or chemotherapy (KS). Refer the patient to level C.
- (U) In patients with aspecific respiratory clinical signs, antibiotics other than amoxicillin or cotrimoxazole to cover for atypical bacteria (mycoplasma and chlamydia) can still be tried (doxycycline, erythromycin).



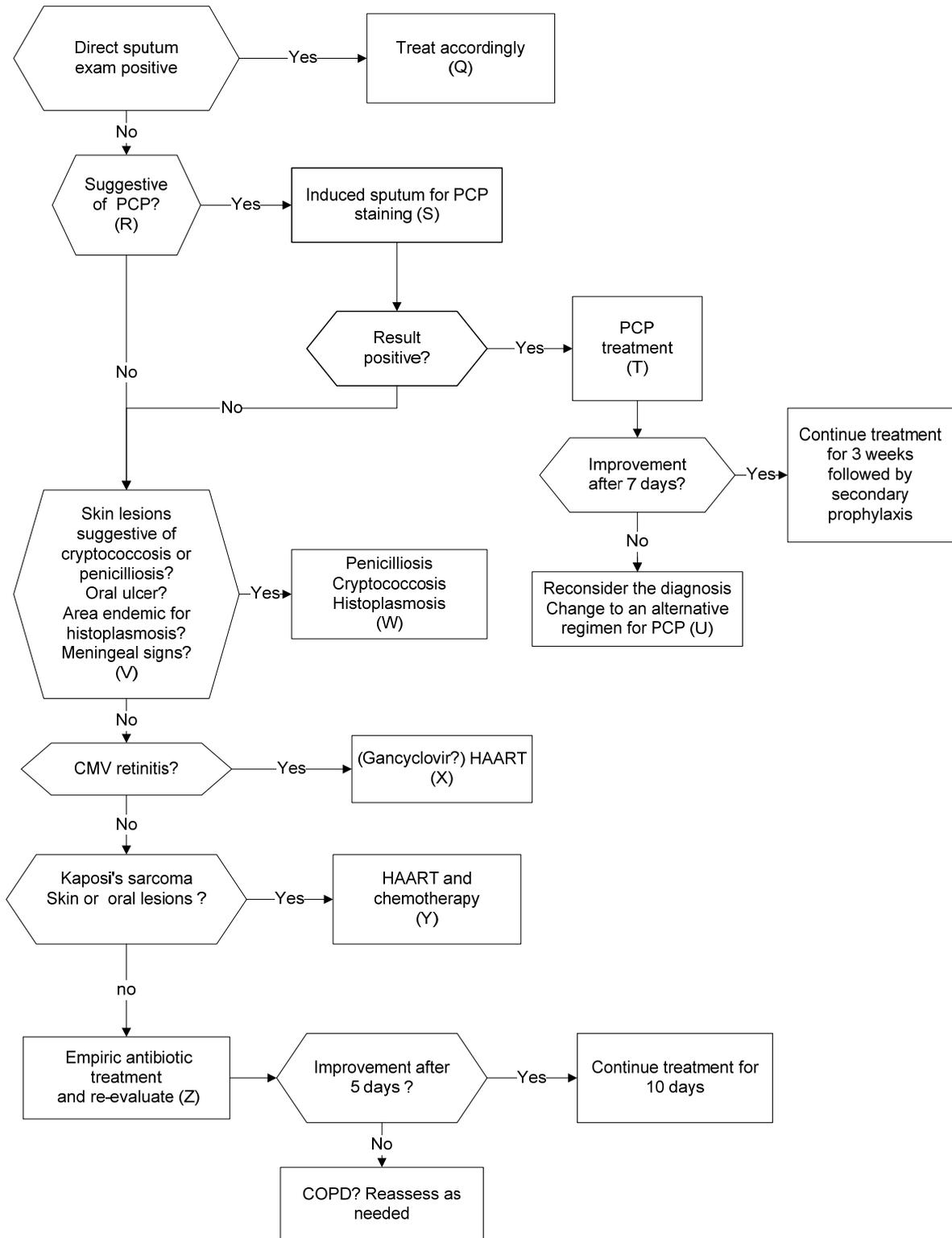
Continued from level C (1)



Respiratory conditions

Level C (3)

Continued from level C (2)



Annotations (level C)

At level C, several examinations will generally take place at the same time, and not sequentially as proposed in level B. Many patients will already be seen by other health workers before ending up at level C. Most of them probably have already been taking antibiotics. Therefore at this level, we consider only the chronic persistent respiratory symptoms.

Cough, chest pain, dyspnoea

(A) When a cough is recent in onset, the most likely diagnosis is a bacterial infection, pneumococcal disease. However, PTB can have an acute and rapid course in HIV patients. It is therefore important to exclude TB in patients with productive cough. The highest yield of **AFB in smear** and culture is with **expectorated sputum**. Induced sputum should be used only in people who cannot expectorate. Sputum sensitivity is decreased in HIV-positives and is around 50%. Start empiric antibiotic treatment while waiting the results of the sputum exam. If the patient is already using cotrimoxazole prophylaxis, the first choice is **amoxicillin**. If the patient is not yet on cotrimoxazole prophylaxis, **cotrimoxazole** is preferred over amoxicillin because of its broader spectrum. However, if available, amoxy-clavulanic acid or cefuroxime is the best choice for empirical therapy in non life-threatening respiratory infections at level C. Follow the national guidelines.

(B) See annotation E page 97.

(C) See annotation D page 97. At level C blood and sputum cultures for fungal infections, as well as mycobacterial cultures of sputum should be considered. Fundoscopy may show CMV retinitis. A chest X-ray and a sputum AFB, Gram stain and direct examination should be carried out. An abdominal ultrasound can highlight hepato-splenomegaly and/or abdominal lymphadenopathy suggestive of systemic mycosis or tuberculosis. Even if former AFB smears were negative, it is useful to repeat this examination in patients who are suspect for pulmonary TB, after a trial with antibiotics, especially if the first samples were done in another centre.

(D) Wasting, night sweats, chest pain and productive cough, high ESR, nodular or cavitory infiltrates, miliary pattern, lobar infiltrates that do not disappear with broad spectrum antibiotics, hilar or paratracheal lymph nodes all suggest TB. When there is no response to one trial of broad spectrum antibiotics, and the chest X-ray is suggestive of TB or the abdominal ultrasound shows big lymph nodes with central necrosis, start with TB treatment.

(E) Staining of induced sputum is a highly sensitive method (60%-90%) to identify *Pneumocystis jiroveci* pneumonia. Staining of BAL has a sensitivity of 95%. It is not useful to stain expectorated sputum for PCP. For the method of sputum induction and staining for PCP, see page 113,

Laboratory section at the end of this chapter. In case of severe dyspnoea, be sure to rule out a pneumothorax, which can be seen in PCP (as well as in TB). If a pneumothorax is present, a chest tube must be inserted. Start PCP treatment with steroids and repeat induced sputum for PCP the following day if the patient is too short of breath to produce induced sputum. PCP treatment: see “annotation F” on page 97.

- (F) If after 7 days there is still no improvement, an alternative diagnosis should be considered. The most likely is again smear-negative PTB. If available you could consider a switch to second line PCP treatment (pentamidine see page 81).
- (G) An acutely ill patient with high fever, high leucocytosis and respiratory symptoms suggests a bacterial cause. Chest X-ray and Gram stain may help to differentiate between different causal agents.
- (H) See “annotation I” page 98.
- (I) See “annotation J” page 98.
- (J) See “annotation K” page 98.
- (K) See “annotation L” page 98.
- (L) See “annotation M” page 98.
- (M) The duration of treatment depends on the underlying pathogen; for nocardiosis treatment may be necessary from 6 weeks up to 6 months. A lung abscess generally needs 3-4 weeks of antibiotics. Other bacterial pneumonias need 10-14 days of treatment. TB takes 6-8 months to treat.
- (N) At this point, the decision must be taken whether or not to start a smear-negative suspected TB patient on TB treatment. In areas where deep fungal infections are a common cause of respiratory symptoms fungal cultures are helpful at this point. A negative sputum culture for fungi (see annotation C) would favour PTB, as would a pleural or a pericardial effusion. Look for other signs like enlarged peripheral lymph nodes.
- (O) Although at level C, all efforts should be directed at excluding other pathogens before deciding to start blind TB treatment, in some patients the clinical picture deteriorates so fast that it is not possible to wait for the results. As a rule of thumb, it is wise to take these difficult clinical management decisions in a small committee whenever possible. If the chest X-ray and the physical examination are compatible with **pleural effusion**, a thoracentesis could be performed. Protein, LDH, cell count and differential count are done on pleural fluid. In situations such as in developing countries where tuberculous effusions are frequent and malignant effusions rare, an exudative unilateral pleural effusion is highly predictive of tuberculosis, especially when protein content >50 g/l. The WBC count is usually elevated (1000-2500/mm³), mostly *lymphocytes*. In

a hospital with limited facilities a patient with unilateral lymphocytic pleural effusion should be treated with anti-tuberculous drugs. ZN staining and culture of the fluid has a low sensitivity. Histologic examination of a closed pleural biopsy has a good sensitivity and a low complication rate in experienced hands.¹⁸⁰

Neutrophilic exudative pleural effusion: the differential diagnosis includes pulmonary embolism, post-pneumonic effusion, malignancy, amoebic liver abscess (right side).

Empyema: if thick pus is aspirated, a chest drain should be placed to evacuate the pus. Send the pus for Gram stain and ZN stain, and culture if available.

An *eosinophilic pleural effusion* is suggestive of Paragonimus in endemic areas. An eosinophilic exsudate is also found in patients with a pneumothorax or a haemothorax. A large globular heart on chest X-ray, orthopnoea, narrow pulse pressure and distended jugular vein should raise suspicion of **pericardial effusion**. The presence of fluid in the pericardial space can be identified by an ultrasound probe on the sub-xyphoid area. In an HIV-positive patient with a pericardial effusion, tuberculosis is the most likely treatable cause. It is justified to start anti-tuberculous treatment without diagnostic pericardiocentesis. The latter is only necessary when cardiac tamponade is evident (severe dyspnoea, circulatory collapse). Unless needed for reasons of dyspnoea or hypotension, this procedure, when used for diagnostic purposes, will often delay the start of appropriate treatment. The same is true for **lymph node biopsies or aspirations**. The diagnostic yield of ZN staining on LN aspirates is quite high. The procedure could be done to have a better idea in the future, in case the patient did not respond to treatment, but in a sick patient, we should not wait for the results of these additional tests.

- (P) When a patient does not respond to his anti-tuberculous treatment after two weeks we should continue the TB treatment but in the same time look for other diagnoses.
- (Q) See “annotation G” page 98.
- (R) Insidious onset, fever on and off, dry cough and dyspnoea on exertion are more suggestive of PCP. Chest X-ray typically shows bilateral alveolar infiltrates but can be normal in 25% of patients. A serum LDH >2 times the upper normal limit is highly suggestive of PCP.
- (S) Staining of induced sputum is a highly sensitive method (60%-90%) to identify *Pneumocystis carinii* pneumonia. Staining of BAL has a sensitivity of 95%. It is not useful to stain expectorated sputum for PCP.
- (T) See “annotation F” page 97.
- (U) If no improvement after 7 days, despite a treatment with cotrimoxazole and prednisolone (in case of hypoxaemia), some physicians prefer to

switch to an alternative PCP regimen: clindamycin IV 600 mg 4 x daily and primaquine PO 15 mg daily or dapsone 100 mg daily and trimethoprim 20 mg/kg once daily or pentamidine (see page 81).

- (V) Fungal respiratory infections are difficult to diagnose in field conditions. Bronchoscopy, cytological examination and special culture techniques are required. However, in some studies in Africa using bronchoscopy and BAL, cryptococcosis was more frequent than PCP. In the presence of skin lesions (or meningitis), the diagnosis of disseminated cryptococcal disease or penicilliosis is facilitated because samples of the skin or CSF are easier to obtain. Cotton-blue stain is an easy method to visualise fungal elements in biopsy material (see *Laboratory* section). In the case of meningeal signs, India ink stain on CSF is a sensitive test for diagnosing disseminated cryptococcosis. If negative, a cryptococcal antigen test on CSF can be done. If no meningeal signs or headache is present, a serum cryptococcal antigen test could be used as an indicator in patients who never received a treatment for cryptococcosis yet. In South-America histoplasmosis is frequent. Very high LDH is more suggestive of histoplasmosis than of PCP in their setting.
- (W) Treatment see page 83, 84, 87.
- (X) CMV pneumonia is part of systemic CMV infection and occurs in patients with advanced immune suppression. Visual disturbance due to CMV retinitis is almost always present. If available, ganciclovir can be used for treatment. However, this drug is beyond the means of most developing countries. HAART will cause immune restoration and will suppress the CMV, but the danger exists for severe IRIS (see chapter 16).
- (Y) Pleural Kaposi's sarcoma often gives a bloody pleural fluid, nodular infiltrates and mediastinal lymphadenopathy. The diagnosis is suggested when associated with typical skin and mouth lesions. Bronchoscopy may reveal bronchial KS lesions. Pulmonary Kaposi's sarcoma is usually aggressive and rapidly fatal. Offer HAART and chemotherapy (see chapter 15).
- (Z) Atypical respiratory symptoms: treat with empirical antibiotic therapy for 10 days. The choice depends on previous antibiotic therapy. Broad-spectrum respiratory coverage is obtained with amoxy-clavulanic acid + doxycycline, or chloramphenicol. If this second trial of antibiotics fails, a re-evaluation is necessary. Arguments for COPD^{**}/asthma? Chronic respiratory symptoms can be due to chronic obstructive lung disease. It is defined as more than 3 episodes of bronchitis/year within the past 3 years. Acute exacerbations are treated with antibiotics and salbutamol inhalations. In case of severe dyspnoea, a short course of steroids is indicated to decrease airway inflammation.

^{**} Chronic obstructive pulmonary disease

7.4 Symptomatic and palliative care

Respiratory symptoms can be very distressful. It is important to know how to relieve them. Information in this chapter is based on a Canadian handbook of palliative care.¹⁸¹

General hygienic rules are:

- Avoid smoking or other irritants in a patient's room.
- Avoid feeding when a patient is in a supine position.
- Assure good ventilation of the room.
- Separate TB patients from non-TB patients as much as possible.

7.4.1 Cough

It is important to distinguish between a productive and non-productive cough. Home-care workers and family members have to be aware of the possibility of TB or another infection whenever a patient is coughing and should send the patient to the appropriate treatment level. If a patient is suspected of TB, also check family members for symptoms and encourage them to seek medical advice. If the patient is under treatment or an infection has been excluded, cough can be combated with symptomatic treatment.

Put the patient in a semi-sitting position. Always ask the patient to cover his/her mouth while coughing. Be sure that expectorations can be collected in a small container or in a tissue, to avoid the airborne transmission of certain pathogens.

Drug: codeine 15-60 mg PO 4-6 x daily (even when taking another opioid).

Besides its antitussive effect, codeine also works as an antidiarrhoeal and analgesic agent. If given for cough, be sure to avoid constipation. Codeine can be given on levels A, B and C.

7.4.2 Increased quantity or difficulty clearing airway secretions

- Maintain adequate hydration.
- Keep mucous membranes moist.
- Increase humidity in the room.
- If available, try nebulised saline to loosen thick secretions (not so often a problem with HIV-related pulmonary diseases).
- Aromatherapy (eucalyptus, pine oil in hot water or to the chest. (Vick, tiger balm).
- Postural drainage.
- Massage/respiratory physiotherapy (gentle clapping on back to move sputum).
- Oropharyngeal or nasopharyngeal suction: try to avoid because it is very irritating.

Drug: atropine: 0.4-0.6 mg SC, IM, IV 6-8 x daily (levels B and C).

7.4.3 Dyspnoea, respiratory distress

- Reduce environmental irritants and smoking.
- Elevate head of bed.
- Use fans to keep air moving.
- Minimise number of people in the room.
- Teach and support family.
- Manage anxiety: (see under respiratory distress and anxiety).

Treat underlying causes of dyspnoea (level B or C)

Bronchospasm in known asthma/COPD patients

Acute phase

- salbutamol nebuliser if available + oxygen
- if no effect, salbutamol 0.5 mg/ml SC or epinephrine 1:1000 0.3 ml SC to be repeated after 20-30 minutes, if necessary.
- If the above therapy has no effect, use aminophylline 6 mg/kg, to be given over a period of 20 minutes, diluted in the same amount of IV fluid; continue with 4 mg/kg 4 x daily.
- Treat acute airway inflammation with a short course of steroids = 1 week 40 mg prednisone daily.

Maintenance

- salbutamol tablets 2-4 mg 3 to 4 x daily, or
- aminophylline tablets 100 mg 3 x daily.

Hypoxia

Use oxygen judiciously (it is a rare resource in most hospitals). It is not essential to reduce the sense of being short of breath. Oxygen is only indicated when the O₂ saturation falls below 90% (pO₂<70 mmHg). Monitor the oxygen saturation percentage to establish ongoing need for oxygen therapy.

Obstruction (stridor)

Often caused by compression of the trachea or the main bronchi by lymph nodes or mass.

Steroids

- prednisone 10-60 mg daily PO
- dexamethasone 1-8 mg 4 x daily (PO, IV or SC)

Pleural effusion:

- thoracocentesis
- for recurrent effusions: insert chest tube to evacuate and perform pleurodesis by injecting powder of tetracycline or talc (retain chest tube with continuous suction for some days to assure good collage).

Pulmonary oedema

- careful salt and fluid management
- appropriate cardiac medication
- diuretics: furosemide 20-240 mg PO, IV as needed
- morphine 2.5 - 5 mg SC.

Pneumothorax

- chest tube.

Severe respiratory distress causing anxiety and restlessness, and no reversible causes of dyspnoea identified.

For opioid naïve

- Morphine 2.5-15 mg PO, SC every hour if necessary.
- For persons already taking opioids, increase the dose of the same opioid by 25-100% every 4 hours.
- For associated anxiety, diazepam 5-10 mg 4 x daily PO.

For extreme distress

- Same doses, but IV.
- Dose of morphine as above combined with 0.4 -0.6 mg of atropine in the same syringe SC. May be repeated after 5-10 minutes.

7.4.4 Last hours of life

- Respiratory failure.
- Oxygen may prolong suffering rather than improve the quality of life and may not be appropriate.
- Provide support for those at the bedside, particularly if the dyspnoea is perceived as being distressing.
- Focus on treating the sense of shortness of breath, clearing or reducing secretions (morphine). Avoid atropine at this stage because of CNS and cardio-respiratory stimulation.
- Cheyne-Stokes breathing is one of the cardinal signs that death is approaching; this respiration is not distressing for the patient.

7.5 Laboratory techniques

7.5.1 Direct smear examination for TB: Ziehl-Neelsen Method

An excellent review about sputum examination for TB has recently been published by the IUATLD¹⁸² (strongly recommended reading).

The method of choice for sputum smear microscopy is the Ziehl-Neelsen (ZN) staining technique. Cold staining procedures such as the Kinyoun are not recommended because they have low sensitivity in paucibacillary samples and the staining fades rapidly. A binocular light microscope with objective x40 and x100 is required. Fluorescence microscopy, which is recommended when the daily workload exceeds 50 specimens, has no place in most of the situations in which MSF is working. The advantage of this method is that it can screen smears quickly under low magnification. It is important to re-check fluorochrome stain positive smears using ZN stain. In this way, +/- 80 smears a day can be examined.

- 100 high power fields (there are about 100 microscopic fields in a 2 cm long smear) must be read before declaring the slide to be negative.
- The reading should be stopped when 10 or more AFB are observed in less than one length). When a drop of immersion oil is put onto the smear slide, this should never be touched with the oil applicator to avoid transfer of AFB from one smear to another.
- A microscopist should take at least 10 minutes to examine 100 fields, and one microscopist should not be expected to process and read more than 25 sputum specimens a day.

Concentration of sputum can increase the sensitivity. The technique most commonly used is the sodium hypochlorite. The most important factor is the quality of the carbol fuchsin. Slide reporting is done in a standardised way.

Standard method of reporting according to IUATLD.

AFB counts	Reporting
No AFB in at least 100 fields	0/negative
1-9 AFB in 100 fields	Actual AFB counts ^{††}
10-99 AFB in 100 fields	+
1-10 AFB per field in at least 50 fields	++
>10 AFB per field in at least 20 fields	+++

Ideally, 2 sputum samples out of 3 should be positive. If only 1 sputum smear is positive, an abnormal chest X-ray is a necessary criterion for the diagnosis of sputum smear-positive pulmonary TB.¹²⁸

Sensitivity: sputum smear microscopy for tubercle bacilli is positive when there are at least 10,000 organisms present per 1 ml of sputum. The likelihood of a positive sputum smear decreases as the degree of immunosuppression deteriorates, because there is less cavitory pulmonary TB, and more extra-pulmonary TB.

Preparation of ZN reagents

(The most important factor in this staining is the quality of the carbol fuchsin.)

Ziehl's carbol fuchsin (Ziehl's solution)

A. **solution A:** 3% fuchsin alcoholic stock solution.

- basic fuchsin.....3 g
- 95% alcohol.....up to 100 ml

B. **solution B:** Aqueous phenol solution

- phenol crystals.....5 g
- distilled water, if possible.....up to 90 ml

- To prepare the 0.3% Ziehl's carbol fuchsin working solution, mix 10 ml of solution A with 90 ml of solution B.
- Add together and mix.
- Let the stain stand for several days to allow all components to go into solution.

^{††} The finding of 1-3 AFB on 100 fields does not correlate with positive TB cultures. It is better to make a new smear from the same sputum sample.

Decolourising agents

Acid-alcohol (decolourise)

- ethanol.....97 ml
- concentrated (35%) HCl..... 3 ml

Add the HCl slowly to the ethanol.

Counterstaining

- methylene blue.....0.3 g
- distilled water.....100 ml

Smearing

- Put the identification number of the sputum on the frosted part of the slide with a pencil, never with a marking pen.
- It is recommended to standardise the size of the smear (20 mm by 10 mm) so that 100 visual fields can be automatically screened to obtain a negative result.
- Before flame-sterilisation, remove the adherent sputum from the used wire loop by moving it up and down in the washing bottle.
- Neither fixed nor unfixed slides should be left on the table without cover because they may serve as a cause of infection to other people and also because they may be damaged by accidental breakage.
 1. Select a small portion of sputum. (Select the most purulent, most bloody, most mucoid, if such is present.)
 2. Spread one loopful of purulent particles **EVENLY** to a size of approximately 20 mm by 10 mm.
 3. Dry it at completely room temperature (+/-30 minutes).
 4. Fix it by passing through the flame (smear side up) 5 times, taking about 4 seconds each time. **DO NOT OVERHEAT. DO NOT** heat-fix moist slides.

Staining

- Observe the quality and the quantity of the reagents before use. If they are not adequate and sufficient to use, prepare new ones.
- Place the fixed smear slides on the staining bridge. Never use the staining jar for staining so that no material can be transferred from one smear to another (this could cause false positive slides).
- Cover the whole surface of the slide (not only the smear) with filtered 0.3% **Ziehl's carbolfuchsin solution.**
- Flame the slide (flooded with Ziehl's solution) to steaming. Never boil it and never allow it to dry out. Heating slides from underneath can be done with the flame of a Bunsen burner, an alcohol lamp or an alcohol soaked cotton swab.
- Keep slides covered with hot, steaming carbolfuchsin for 5 minutes by re-flaming as required.
- Rinse slides gently with water to remove excess carbolfuchsin.
- **Decolourise with acid-alcohol**, until no more stain comes off (3 minutes)
- Gently wash away the acid-alcohol with water.

- **Counterstain with 0.1% methylene blue solution for 1 minute.**
- Rinse slides with water.
- Drain water off the slides; allow them to dry.

Ziehl-Neelsen:

- staining for 5 minutes
- decolourising for 3 minutes
- counterstaining for 1 minute.

7.5.2 Staining methods for *Pneumocystis jiroveci*

From: Bailey W.R. and Scott E.G. *Diagnostic bacteriology*, and Ash L.R. and Orihel T.C. *Parasites: a guide to laboratory procedures and identification*.

- Induced sputum: sputum obtained after the inhalation of hypertonic saline for approximately 10-20 minutes. Up till now there has not been very much experience with this method in developing countries.
- Some use an ultrasonic nebuliser with 3% NaCl solutions for 20 minutes. The equipment needs to be decontaminated (washed and soaked in glutaraldehyde overnight) at the end of each session. It is therefore time-consuming. It is also important to perform sputum induction in a well-ventilated room, or even out of doors, in order to reduce the risk of transmission.
- Alternative method: specimens are collected by allowing the patient to breathe aerosolised droplets of a solution containing 15% NaCl and 10% glycerine for approximately 10 minutes or until a strong cough reflex is initiated. The lower respiratory secretions obtained in this way appear watery, resembling saliva, although they often contain material directly from the alveolar spaces. The sensitivity of this method ranges from 55%-92%.

Method of preparing slides

- A. For tissue (transbronchial biopsy): make touch preparations on clear slides; allow the smears to dry.
- B. For BAL: centrifuge for at least 10 minutes at 3000 rpm, or 15 minutes at 2000 rpm. Pour off supernatant in a recipient. Prepare several slides from the sediment. Allow the smears to dry. If thick consistency, treat the BAL with an equal amount Sputolysine® (Behring diagnostics) (diluted 1/10 in H₂O). Mix and allow to stand for 30 minutes. Centrifuge.
- C. For induced sputum: if thin and watery, simply select smears (choose mucoid-appearing flakes) or centrifuge 10 minutes at 3000 rpm. Prepare slides from the sediment. If thick and mucus-like, combine with equal amount of Sputolysine®, mix and allow standing for 30 minutes. Centrifuge for at least for 10 minutes at 3000 rpm. Pour off supernatant. Prepare slides from sediment.

Staining

Several different stains are available. The best choice is a staining for the cell walls (e.g. Toluidine-blue-O-stain or Gram-Weigert) and a staining for the parasite (e.g. May-Grünwald-Giemsa or methanol Giemsa)

A. Modified Toluidine blue O staining procedure

Reagents

1. Glacial acetic acid.
2. Sulphuric acid, concentrated.
3. Toluidine blue O (52% dye content-Roboz Surgical Instrument Co.).
4. Hydrochloric acid, concentrated.
5. 100% Ethyl alcohol.
6. Xylene or Xyless.

Prepared reagents

1. Sulphating reagent.
 - a) Using a fume hood, pour 45 ml glacial acetic acid into a Coplin jar that has been placed in a plastic tub filled with cool tap water (temperature not below 10°C).
 - b) Using a glass pipette, carefully add, without splashing, 15 ml concentrated sulphuric acid to the acetic acid in the jar and mix gently.
 - c) Apply petroleum jelly to the lid of the Coplin jar and seal. When kept at room temperature, this solution can be kept and used for 1 week.
2. Toluidine blue O stain
 - a) Dissolve 0.3 g toluidine blue O in 60 ml distilled water; add 2 ml concentrated hydrochloric acid and 140 ml 100% ethyl alcohol.
 - b) Store the staining solution at room temperature. It can be used for up to one year.

Procedure

1. Once dry, stain the slides. Note: Always stain a known positive control slide with slides from each patient's specimen.
2. Place the slides in sulphating reagent for 10 minutes. Mix the reagent with a stirring rod when the slides are first placed into the solution and mix again after 5 minutes.
3. Transfer the slides to another Coplin jar and wash gently in cold running tap water for 5 minutes. Drain the water from the slides.
4. Place the slides in toluidine blue O stain for 3 minutes.
5. Drain excess stain from the slides by touching the edges to a paper towel and dip into 95% ethyl alcohol for 10 seconds to remove most of the blue dye.
6. Dip the slides into 100% ethyl alcohol for 10 seconds for further decolourising.
7. Dip the slides into two changes of xylene for 10 seconds per change. A substitute for xylene that may be used is Xyless, a less hazardous clearing agent.

8. Drain excess xylene and, while the slides are moist, mount them with permount or other mounting medium and a cover glass.
9. Examine the slides using 40 x objectives (screening). Afterwards use 100-immersion oil objective to confirm.

Comments

Cysts of *P. jiroveci* will appear rounded, approximately 5 µm in diameter and stain reddish violet; the outlines of the cysts are distinct and the cysts contents stain uniformly. Little background material will be seen. The cysts often appear cup-shaped and may occur singly or in clusters. Non-budding yeast cells may stain similarly, but usual they are more oval in shape. To avoid misdiagnosis when only single organisms are seen in specimens that also contain yeast cells, the slide should be searched until a cluster of characteristic *P. jiroveci* cysts is found.

B. Methanol Giemsa staining of the trophozoites.##

Reagents

- Giemsa solution
- buffer with pH 7.2
- methanol.

Procedure

1. Allow the slides with the thin smears to air-dry.
2. Fix the smears in methanol 100% for 3 minutes. Allow to dry.
3. Stain for 1 hour in Giemsa, 4% diluted in buffered water at pH 7.2. This means 5 drops of Giemsa solution added to 4 ml buffer.
4. Pour off the Giemsa and rinse carefully with water.
5. Allow to dry.
6. Examine with x 100 objective, under oil immersion.

Trophozoites are the free-floating forms of *Pneumocystis*. They are pleomorphic, 2-5 µ in size. They tend to form clusters and resemble platelets. Internal structures of the cysts can be visualised and free Trophozoites (the cyst wall will not stain). They look a bit like *P.falciparum* trophozoites.

7.5.3 Staining method for *Penicillium marneffe*

Cotton blue provides an easy staining method for fungal elements in clinical material and culture.

Especially in inexperienced hands, it is good to combine two types of staining, one for the the cysts and one for the Trophozoites. This will increase the accuracy of the laboratory diagnosis.

Composition

- cotton blue 0.05 g
- phenol 20 g
- lactic acid 20 g
- glycerol 40 g
- distilled water 20 ml

Dissolve in a warm water bath. Cotton blue should be added last.

Procedure

Mix the material to be examined with a drop of the stain and cover with a cover glass.

Penicillium will resemble basophilic elliptical yeast-like organisms with central septation.

7.5.4 Nocardia in pus or sputum

Nocardia asteroides stains weakly acid fast in Ziehl-Neelsen. The best stain to visualise Nocardia species is Gram stain. They appear as beaded, branching and filamentous Gram-positive organisms. Sputum collection should be the same as for tuberculosis (3 samples). Because the samples contain a lot of cellular material, the diagnostic yield is increased if the sample is first treated with a same amount of NaOH (10%-20%). The reading is much clearer still if the mixture is heated during 20 minutes at 45-56°C.

They resemble blue thin mycelium threads.

7.5.5 Paragonimus in sputum

The eggs of the lung flukes are found in stools and sputum. The sputum should be examined by direct microscopy, using the **objective x 10**. Very mucoid specimens are easier to examine if they are first incubated in 2-3 times their volume of a potassium or sodium hydroxide (10%) solution for 1 hour. The deposit produced after centrifugation for 3 minutes at 1500 rpm is then examined in the usual way. Masses of eggs are often contained in the brown specks sometimes visible in the sputum. Take this part for direct examination.



8 ABDOMINAL PAIN

8.1 Introduction

Abdominal pain is frequent in people with HIV/AIDS. Retrospective observations from Western countries have found 12-15% of severe abdominal pain in their patient groups.¹⁸³

One observation from South Africa has shown 45% of HIV-positive outpatients presenting with abdominal pain.¹⁸⁴ Abdominal pain is associated with reduced survival. Very few prospective studies on aetiology of abdominal pain in HIV exist. One retrospective study from Italy showed that CMV, MAC and GI lymphoma were the three most frequent causes of abdominal pain.¹⁸³

On the contrary, a prospective study in South Africa in patients presenting with abdominal pain showed that MAC was rare, and that the most frequent cause of abdominal pain was disseminated TB.¹⁸⁴

Abdominal pain can occur at any stage of HIV infection.

Common bacteria or neoplasm can occur early in the course of HIV infection at CD4 > 200. CMV, fungi, MAC, disseminated TB and unusual protozoa occur at CD4 < 200.¹⁸⁵

It is clear that aetiology will differ according to immune status and geographic location.

8.2 Opportunistic infections as cause of abdominal pain

Mycobacterial infections: *M. tuberculosis*, *M. Avium* complex

Bacterial infection: salmonella, nocardia, staphylococcal, shigella,..

Protozoal infection: microsporidium, cryptosporidium, visceral leishmaniasis

Helminthic infections: strongyloides stercoralis

Fungal infections: cryptococcosis, histoplasmosis

Viral infections: CMV

These conditions need to be differentiated from drug induced abdominal pain and malignancies.

8.2.1 Mycobacterial infections

Mycobacterium tuberculosis

Africa and Asia have a high TB/HIV co-infection rate (40-50%) with the highest burden of TB and HIV co-infections in SSA.^{11,186} Disseminated tuberculosis has been described in 50% to 72% of patient with AIDS and tuberculosis.^{187,188}

Abdominal TB was the commonest cause of abdominal pain in non white persons with advanced HIV infection (CD4<200) in South Africa reflecting the high prevalence of TB in these communities.¹⁸⁴ Abdominal involvement has been found to be universal in HIV-infected persons with disseminated* TB infection.^{184,189}

One autopsy study on 70 HIV patients who died in a department of pulmonary medicine in a hospital in Ivory Coast showed that pulmonary TB was associated with abdominal TB in 93,5% of cases.¹⁹⁰

A retrospective study from Cambodia, based on a chart review of patients treated for tuberculosis, showed that among HIV patients 59% presented with extra-pulmonary TB, and in 60% of them the diagnosis was based on the presence of abdominal lymph nodes.¹⁹¹ 82% of HIV-patients with abdominal pain in that setting had abdominal lymph nodes due to tuberculosis.¹⁹²

Symptoms & Physical exam

The clinical presentation of TB depends on the degree of immune-suppression. Patients with moderate immune-suppression (CD4 350-500) demonstrate features similar to non HIV patients. A big psoas abscess or tuberculous peritonitis can present with abdominal pain in early stages of HIV disease. However, advanced stage AIDS patients show a high incidence (60-70%) of disseminated TB.^{187,189,193}

Symptoms and signs of abdominal TB are non specific.

The most common presenting symptoms in abdominal TB in HIV are prolonged high fever and chills (usually >39 °C), night sweats, anorexia, progressive weight loss, abdominal pain, diarrhoea (less common).

The most common physical findings are abdominal tenderness, abdominal swelling and/or mass, and peripheral lymphadenopathy (>1.5cm in diameter). Unlike in non HIV patients ascites and jaundice are rarely seen.¹⁹⁴

Diagnosis

The diagnosis of abdominal TB is often missed during life, as shown in an autopsy study in Ivory Coast.¹⁹⁰

Non-invasive tests often fail to yield a diagnosis and undiagnosed disease results in significant morbidity and mortality.

Common, but non specific, laboratory findings are anaemia, elevated serum alkaline phosphatase concentration and elevated percentage of mononuclear cells in peritoneal fluid. Hyponatremia (< 135 mmol/l) was found in 60% of patients with a diagnosis of generalized TB.¹⁸⁷

* 3 or more non-contiguous sites affected by TB, or blood culture positive, or miliary pattern on chest X-ray.

Ultrasound of the **abdomen** often shows multiple intra-abdominal LNs >1.5cm or one mass of adherent lymph nodes with central necrosis or multiple hypoechogenic nodules or abscesses in the spleen^{195,196} and in the liver.¹⁹⁵⁻¹⁹⁸ The diagnostic yield of an abdominal ultrasound is so high in abdominal pain in HIV, that all physicians taking care of HIV patients should develop or have access to skills in ultrasound.

Ascites and omental thickening are rarely found in HIV patients with abdominal TB. Results from a Ugandese study suggest that in a population with high HIV and TB prevalence, HIV-infected patients with abdominal pain and systemic symptoms suggestive of TB, who have enlarged peri-aortic or mesenteric lymph nodes should be started on TB medication.¹⁹⁹

Chest X-rays show evidence of pleuro-pulmonary disease in the majority of patients (pleural effusion, parenchymal infiltrates, miliary pattern, peri-hilar lymphadenopathies).¹⁹⁴

A normal chest X-ray does not exclude the diagnosis of abdominal TB, however.

Mycobacteriological diagnosis

Delayed diagnosis of TB may result in early mortality in AIDS patients. As many patients with abdominal TB have disseminated TB (93%), an effort should be made to isolate AFB from one or other site.¹⁹⁴

In a study in the US AFB smear from any site (peripheral LN, abdominal LN, stool, blood culture, sputum, urine and peritoneal fluid) were positive in 84% of cases with abdominal TB.¹⁹⁴ The value of AFB smears on stool in the diagnosis of abdominal TB is unclear. A study from Congo and one from Zambia showed that mycobacteria did not play a role in chronic diarrhoea in AIDS patients, but did not look into the problem of abdominal lymph nodes, and the value of AFB smears on stools to diagnose abdominal TB.^{200,201}

Faecal smears have a low sensitivity for atypical mycobacteria, but again their usefulness was never assessed for *Mycobacterium tuberculosis*.²⁰² If AFB on stool culture are identified as *Mycobacterium tuberculosis*, they are always considered pathogenic.

Blood culture and urine culture are positive in 50-70% of patients with disseminated disease and a CD4<100.²⁰³

Differential diagnosis

Abdominal tuberculosis has to be differentiated from *Mycobacterium avium* complex, but this is a rare pathology in developing countries (see below). The presenting symptoms are similar to TB infection.^{193,200} One distinguishing feature of TB is that peripheral lymphadenopathy is more frequently present in TB than in MAC.^{42,193}

Lymphoma and Kaposi's sarcoma can present with abdominal pain and enlarged lymph nodes.¹⁸⁴ Some of the deep mycoses (cryptococcosis, histoplasmosis) can present with bulky abdominal lymph nodes causing pain. In patients presenting with splenic abscesses, visceral leishmaniasis has to be excluded.¹⁹⁷ This disease is a frequent cause of fever in HIV patients living in Mediterranean countries, the horn of Africa and India.²⁰⁴

Nocardiosis can present with multiple abscesses.

Treatment

Based on National TB guidelines; see chapter 7 on page 72.

Prophylaxis

See chapter 6.

Mycobacterium avium complex

The most common non-MTB organisms responsible for pulmonary and disseminated disease are part of MAC, which includes both *M. avium* and *M. intracellulare*. More than 90% of MAC isolated from AIDS patients is *M. avium*. It occurs mainly in PLHA with CD4 < 100.²⁰⁵

MAC has been isolated from a variety of sources around the world, including soil, natural water, municipal water system, food, house dust, wild & domestic animal.

Disseminated infection results from recent infection (ingestion or inhalation) rather than reactivation of a previous infection.

MAC infection has not clearly emerged as a problem in the developing world where *Mycobacterium tuberculosis* appears to be the predominant pathogen.²⁰¹ It is speculated that acquired immunity against mycobacteria through previous infection with tuberculosis or through vaccination with BCG provides protection against MAC. Another possible explanation is the difficulty to diagnose MAC in resource-poor settings, and the short life expectancy of patients with HIV infection. In the MSF home care project in Bangkok, out of 601 patients between 1995 and 2000, 3.3% had MAC confirmed by blood culture. In several recent studies from Africa and Thailand disseminated MAC was diagnosed in 5-10% of febrile hospitalised HIV-patients with low CD4 counts, indicating that under-diagnosis plays a factor in the low incidence of MAC in an African setting.^{42,206,207}

One study from Spain showed MAC is the third aetiology of splenic abscesses (15%) after tuberculosis (43%) and visceral leishmaniasis (21%).¹⁹⁷

Symptoms and signs

Typically MAC presents with prolonged fever, gradual wasting, severe anaemia and neutropenia. The CD4 count is usually less than 30. MAC infection frequently involves gastrointestinal tract, liver, abdominal lymph nodes and spleen. More than 70% of patients have gastrointestinal or hepatobiliary symptoms: diarrhoea, abdominal pain, hepatomegaly, and raised alkaline phosphatase (more than 2 x ULN) and gamma GT levels (more than 3 x ULN). When compared with disseminated TB, MAC patients have absence of peripheral lymphadenopathy, and more severe anaemia and neutropenia.

IRIS

In patients on HAART, a MAC lymphadenitis can develop and is considered an immune reconstitution inflammatory syndrome (IRIS). The onset is a few weeks to months after the start of HAART.^{208,209} MAC IRIS is a localized lymphadenitis; organisms are confined to the infected LN and surrounding soft tissues. Lymph node inflammation can occur in the neck, in the axillary region, but also mediastinal²¹⁰ and abdominal (mesenteric and retroperitoneal) lymph nodes. In case of abdominal lymphadenitis the patient presents with a picture of severe abdominal pain, high fever and leucocytosis.²¹¹

Diagnosis

The diagnosis of disease caused by MAC requires isolation of the organism and compatible clinical and pathologic features. Identification of MAC in a single sputum culture does not mean MAC disease, as colonization can occur in healthy and immunocompromised patients.

Blood cultures are highly sensitive for detection of disseminated MAC in AIDS patients (a single blood culture has a 90 to 95% sensitivity).²⁰⁵ However, in rare cases, bone marrow and liver biopsy may be useful.

Stool cultures are often positive, but not helpful to diagnose MAC disease, as they are also present in 50% of healthy patients.²¹²

In a resource-poor setting without possibility to do mycobacterial cultures the diagnosis is often made by exclusion, in a patient with symptoms compatible with disseminated TB or MAC, who fails to respond to TB medicines. Absence of peripheral lymphadenopathy and severe anaemia and neutropenia favour the diagnosis of MAC.^{42,193}

In AIDS patients with a focal lymphadenitis syndrome (IRIS), blood cultures are often negative and a LN biopsy is required for diagnosis.

Differential diagnosis

Tuberculosis and other atypical mycobacteria can only be distinguished through culture and identification.

Other pathologies that present with prolonged fever and lymphadenopathies are fungal infections, lymphomas and visceral leishmaniasis.

Prolonged fever and abdominal pain are found in enteric bacteremias, CMV infection and AIDS wasting syndrome.

Prognosis and treatment

In a resource-poor setting the diagnosis and treatment of MAC is difficult to realize.

MAC infection occurs in patients with advanced disease, and the median survival without treatment after the initial diagnosis is around 3 months.²¹³

However, with HAART the life expectancy has improved, and in case of sustained immune restoration (more than 6 months CD4 > 100) the secondary prophylaxis for MAC can be interrupted.

For details on treatment, primary and secondary prophylaxis, see chapter 9, chronic diarrhoea.

Clear guidelines about **when to start HAART after starting the treatment of MAC** are not yet available. It is generally recommended to delay HAART for 1 month after the start of MAC treatment.¹²⁴ In case of MAC IRIS causing abdominal pain, the difficulty is to exclude TB or side effects due to HAART. In case of MAC IRIS, there is no need to interrupt HAART. The patient should be treated with anti-MAC treatment and there is usually a good response. HAART should be continued if possible, unless symptoms are too severe and require temporary discontinuation of HAART. Steroids (20-40 mg prednisone QD during 4-8 weeks) may be needed in case of severe inflammatory reactions, where NSAID are insufficient to control symptoms. There have been reports about repeated MAC IRIS.²¹¹ In cases of late MAC (up to 25 months after start of HAART) treatment should be the classical treatment, during 12 to 18 months, followed by life long suppressive therapy.¹⁰⁶

8.2.2 Bacterial infections

In HIV patients the bacterial causes of GI disease are the same as in the general population: *S. Typhi* and non *S. Typhi*, *Shigella*, *Campylobacter*, and *Clostridium difficile*.

However, the incidence of severe disease is higher than in the general population.

Bacterial infections have often a chronic relapsing course and are accompanied with bacteraemia. In the same way, common bacterial infections that cause abdominal pain (PID, appendicitis, liver abscess, renal abscess, cholecystitis) can also be found in HIV patients.

Salmonella can lead to peritonitis due to perforation. Secondary bacterial peritonitis may happen in patients with bowel perforation due to CMV, Kaposi's sarcoma, tuberculosis and lymphoma.²¹⁴

Liver and spleen abscesses have multiple infectious causes: staphylococcal, salmonella, nocardia, mycobacterial, bacillary angiomatosis and visceral leishmaniasis. Bacillary angiomatosis (*Bartonella henselae*) causes hemangioproliferative lesions that have to be distinguished from KS because they respond to erythromycin or doxycycline (see chapter 13, page 209: Skin lesions).

Disseminated nocardiosis is mostly localized in skin, brain, lungs and musculoskeletal system. Less-common sites include spleen and liver.²¹⁵

Symptoms

Most of them present with acute diarrhoea, high fever, and diffuse abdominal pain. Patients look toxic.

In the case of acute bloody diarrhoea and tenesmus, *Campylobacter* and *Shigella* are suspected. When there is a history of previous antibiotic intake and hospitalization *Clostridium difficile* is possible.

In the case of nocardiosis there is often evidence of multiple abscesses. With bartonellosis, skin lesions that have to be differentiated from KS, are often present.

Diagnosis is based on blood and stool culture.

C.difficile requires Clostridium toxin assay on stool.

Gram stain and AFB stain of pus of abscesses may help to differentiate between staphylococcal (gram positive cocci in clusters), nocardiosis (thin branching gram + filaments that stain also weak acid fast) and mycobacterial disease.

Treatment depends on the underlying cause.

Campylobacter, Salmonella, Shigella, Clostridium difficile: see treatment of bacterial gastroenteritis page 150, in the chapter: Chronic Diarrhoea.

Nocardia: cotrimoxazole 10/50 mg/kg 2 x daily for 6 weeks to 6 months (in case of multiple abscesses). Sometimes surgical drainage of the abscesses is necessary.

Any peritonitis due to bowel perforation (free air under diaphragm) should receive surgical attention.

8.2.3 Gastrointestinal Parasites and Protozoan infections[†]

Gastrointestinal parasitic infection is a major source of disease in people living with HIV/AIDS, especially in tropical countries.²¹⁶ Most of morbidity and mortality of advanced AIDS is associated with GI disease, especially ***Microsporidia*** and ***Cryptosporidia*** because they are difficult to treat.²¹⁷

Parasites commonly involved with abdominal pain are *Cryptosporidium parvum*, *Isospora belli* and ***Strongyloides stercoralis*** in hyperinfection syndrome.

Both microsporidium and cryptosporidium cause chronic watery diarrhoea and sclerosing cholangitis.

Visceral leishmaniasis is a frequent cause of fever in PLHA in countries where co-infection can occur (Mediterranean countries, Horn of Africa, Sudan and Indian subcontinent, North Eastern Brazil). It is estimated that between 7-17% of HIV patients are co-infected with leishmania in Southern Europe.²¹⁸ It is identified as a cause of splenic abscesses and fever in Spain, but does not present as abdominal pain, unless there is splenomegaly.¹⁹⁷ HIV patients can have atypical localisations of the parasite, e.g. in the gastrointestinal tract.

Strongyloides stercoralis is the only *Nematode* that has been implicated as a cause of GI symptoms in HIV patients. Auto infection through rhabditiform larvae leads to massive infection in immune-compromised persons. But the typical hyperinfection syndrome is rare.^{176,219} Also one study in Kinshasa among HIV-patients showed a high infection rate with *S. stercoralis* (20-50%), but no increase in the incidence of hyperinfection syndrome.¹⁶⁷

Enteric protozoan infections in PLHA cause cramping abdominal pain and often present with diarrhoea, malabsorption and wasting. Sclerosing cholangitis and acalculous cholecystitis present with RUQ pain and increased alkaline phosphatase. Causative agents are cryptosporidium, microsporidium,

[†] For more detailed description we refer to the chapter diarrhoea.

rarely isospora and CMV.

Diagnosis of gastrointestinal parasites is done by stool microscopy (see chapter 9, page 168).

The diagnosis of visceral leishmaniasis (VL) is made by demonstration of leishmania amastigotes in blood or bone marrow smears. In HIV patients the classic serologic methods to diagnose VL have a lower sensitivity (50% instead of 90%), but the parasites are more easily found in the peripheral blood monocytes (50% sensitivity for a Giemsa stained blood smear, 70% culture of buffy coat).²²⁰ In case of lymphadenopathy, microscopic examination of lymph nodes aspirate has a similar sensitivity as bone marrow aspirate.²²¹ The diagnosis of AIDS cholangiopathy and acalculous cholecystitis is suggested by the presence of RUQ pain, abnormal ultrasound and increased alkaline phosphatase.

Treatment

Some pathogens like microsporidium and *Cryptosporidium parvum* are difficult to treat (see chapter diarrhoea). They respond to HAART.

Visceral leishmaniasis is treated with pentavalent antimony 20 mg/kg/day during 30 days or amphotericin B 0.7 mg/kg/day during 28 days. The response to treatment is similar for both regimens. Pentavalent antimony therapy has a higher degree of cardiotoxicity and pancreatitis but amphotericin B has a higher degree of nephrotoxicity. Drug toxicity is more frequent than in immunocompetent persons. Relapses are frequent despite HAART. A study from Ethiopia showed that HIV patients had a significant lower cure rate (43% at 6 months) than non-HIV patients, higher relapse rates and a higher mortality.^{204,222} Secondary prophylaxis with antimonial compounds or amphotericin B is necessary in HIV patients.^{167,223} However, no standard approach for prophylaxis has been established (see also chapter 10).

8.2.4 Fungal infections

Candidiasis

Although the incidence of oro-esophageal **candidiasis** in HIV-infection is high, disseminated candidiasis, involving the liver, spleen and kidney is rare in HIV-infected persons. If it is diagnosed, severe neutropenia due to medications (chemotherapy) or an indwelling IV catheter is usually present.¹⁹⁸ *Candida* oesophagitis represents 50-70% of dysphagia in AIDS patients, and may cause in severe cases epigastric pain. In case of odynophagia, the cause is more likely CMV, aphthous ulcerations or herpes simplex (see chapter dysphagia/odynophagia). The presence (or absence) of oral thrush has a high positive and negative predictive value for the diagnosis of candida esophagitis (resp. 90% and 82%), but the absence of oral thrush does not completely exclude the diagnosis.²²⁴ Especially patients who first have been treated with local lozenges for oral thrush may present with oesophagitis without oral lesions.²²⁵

Treatment of candida oesophagitis is with fluconazole 200 mg daily (see chapter 12). When disseminated candidiasis is suspected, prolonged treatment with fluconazole 400 mg daily is preferred. In patients who are acutely ill, an initial regimen with amphotericin 0.7 mg/kg/day during 1-2 weeks can be given, followed by a course of fluconazole.²²⁶ Therapy should be continued at least 3 weeks after resolution of lesions in the spleen or the liver, or after negative blood culture. Secondary prophylaxis with oral fluconazole 200 mg daily is recommended as long as immune suppression persists, but there is a risk of azole resistance with this long term use.⁴⁵

Cryptococcosis

Cryptococcus neoformans is the most common life-threatening fungal infection in patients with AIDS. It is the first cause of meningitis in patients with AIDS in Africa and Asia. When CD4 < 50, 90% of AIDS patients infected with *Cryptococcus neoformans* will present with meningitis.

Extraneural cryptococcal disease, including cryptococemia, pneumonia, and ulcerative skin lesions or umbilicated papules mimicking molluscum contagiosum, is present in 25-50% of cases.²²⁷ Rarely, cryptococcal infection can give rise to bulky abdominal lymphadenopathy, which may cause abdominal pain.²²⁸

Diagnosis of disseminated cryptococcosis is based on serum cryptococcal antigen tests, or isolation of the pathogen from biological material such as CSF, lymph nodes, sputum or ulcerative skin lesion.

Treatment of disseminated cryptococcosis is with amphotericin B and fluconazole (for details, see *Neurologic Disorders*, chapter 14).

Secondary prevention with fluconazole 200 mg/day is necessary to reduce relapse rates.

In countries with a high incidence of cryptococcal disease it is worthwhile to consider primary prophylaxis with fluconazole (see chapter 6).

Penicilliosis

Penicillium marneffe is a common cause of opportunistic infection in HIV-infected patients in Southeast Asia and Southern China with late-stage disease (CD4 < 100), but rarely causes abdominal pain.

Histoplasmosis

Histoplasma capsulatum is rarely seen in developing countries, but may be underdiagnosed. The most endemic areas are at Ohio and Mississippi River valleys. The overall incidence of disseminated histoplasmosis (DH) in HIV-infected persons in these areas varies from 5% to 27%.²²⁷ Gastrointestinal histoplasmosis differs from other forms of DH in that pulmonary symptoms and fever may be absent. An oral ulcer is the most common manifestation, besides splenomegaly, lymphadenopathy (30%) and hepatomegaly (26%).

Diagnosis of DH depends on tests usually not available in resource-poor

settings: Antigen testing in urine and serum (sensitivity of 90% and 70% respectively), blood culture (sens 50-70%), bone marrow aspiration or biopsy for fungal stain or culture (positive in 75% of cases).

In developing countries the diagnosis will be clinically and suggested by response to treatment.

Treatment: Amphotericin B 0.5-1 mg/kg daily IV for at least 6 weeks.²²⁹ The recommended cumulative dose of amphotericin B in histoplasmosis is 10-15 mg/kg. Patients should be maintained on oral antifungals, itraconazole 200 mg twice daily life-long or as long as immune suppression is present.

Coccidioidomycosis and Aspergillosis are rare in HIV-patients in developing countries.

8.2.5 Cytomegalovirus infection

CMV GI disease is an uncommon but serious complication of AIDS which can cause severe pain or diarrhoea which are difficult to treat.

Epidemiology

CMV gastrointestinal disease occurs in up to 5% of patients with AIDS, primarily in those with a CD4 < 50.²³⁰

In the industrialized world the incidence of CMV GI disease has decreased substantially since HAART became available.

Pathology

CMV GI disease is characterized histologically by mucosal inflammation and tissue necrosis with vascular endothelial involvement.

Cytomegalovirus enterocolitis may result in deep ulcers, fistulas, and bowel perforation.

Symptoms depend on the localization. Nearly all patients with gastrointestinal CMV have fever. CMV oesophagitis presents with odynophagia (see chapter 12). CMV gastritis presents with substernal and/or epigastric burning pain. CMV pancreatitis presents with epigastric pain irradiating to the back. CMV small bowel disease is manifested clinically by generalized abdominal pain and sometimes diarrhoea. CMV colitis causes abdominal pain and bloody diarrhoea and rebound tenderness. CMV of small bowel and colon can cause perforation, leading to peritonitis. CMV can rarely cause large, painful ulcers of the mouth, pharynx, or anus. CMV proctitis presents with tenesmus.

The other origin of abdominal pain unique to HIV-positive patients is an AIDS related sclerosing cholangitis caused by CMV.²¹⁹

Disseminated CMV infection can show multifocal hepatic lesions with increased echogenicity.

Diagnosis and differential diagnosis

In practice in a developing country the diagnosis is suspected in patients with AIDS and abdominal pain, bloody diarrhoea and/or mucosal ulcers, which do not respond to common antibacterial and antifungal therapy.

A hint towards the diagnosis of CMV gastrointestinal disease is the presence of CMV retinitis.

Treatment

HAART with immune restoration is one of the most effective methods to control CMV disease.

Two antiviral drugs that are recognized for the treatment of CMV are ganciclovir and foscarnet. Both drugs are very expensive and have serious side effects.

They are not available in developing countries because of their exorbitant cost.

8.3 Drug induced abdominal pain/problems

Many drugs can cause GI upset, a few of them may cause life threatening pancreatitis or hepatitis.

8.3.1 Drug induced pancreatitis

In general acute pancreatitis is much more common in HIV-infected patients than in the general population.²³¹ In one series pancreatitis was diagnosed in 4.7 percent of 939 hospitalized PLHA.²³² It mostly occurs as a complication of medications taken to combat the virus or treat opportunistic infections (**sulphonamides, didanosine, stavudine, pentamidine**). Drug induced pancreatitis may not develop until after many months of use. Especially the combination of didanosine and stavudine carries a high risk for pancreatitis. High triglyceride levels (>1000 mg/dl) can be seen in patients on protease inhibitors, and can cause pancreatitis.

Other causes of pancreatitis in HIV patients include CMV and MAC.

Patients with HIV have less biliary stone induced pancreatitis.

Pancreatitis presents similar as in non HIV patients with acute upper abdominal pain. The onset is rapid, but not as abrupt as that with a perforated viscus, reaching maximum intensity in many cases within 10 to 20 minutes. One characteristic of the pain that is present in about one-half of patients and suggests a pancreatic origin is band-like radiation to the back.

The pain of pancreatitis is classically relieved by sitting up and leaning forward. In contrast to peritonitis that often causes patients to lie motionless on their backs because any motion causes pain.

Unlike biliary colic, which lasts a maximum of six to eight hours, the pain of pancreatitis lasts days.

Hyperamylasemia (more than 3 times the normal value) is frequently seen in pancreatitis. 25 % have an abnormal pancreas on abdominal ultrasound. In the absence of abdominal pain, routine check of amylase levels is not needed, as it is difficult to interpret the results. In conditions affecting the salivary glands, amylase (non-pancreatic origin) can be high as well. This may happen in patients that take drugs which causes dry mouth (didanosine, amitriptyline). HIV patients tend to have more fever, hepatomegaly, diarrhoea, anaemia and leukopenia. The prognosis of drug-induced pancreatitis is generally excellent. Treatment is similar to non HIV patients: cessation of potential pancreatotoxic medications, cessation of enteral feedings, IV hydration, gastric decompression with nasogastric suction, analgesia). Didanosine should never be restarted again after a drug-induced pancreatitis. Stavudine must be withdrawn but can be re-introduced carefully after symptoms and serum amylase have returned to normal. A reduction of the dose of stavudine from 40 to 30 mg should be considered. Prophylactic antibiotics (amoxycyclavulanic acid, quinolones) are only necessary in case > 30% of the pancreas seems to be affected on US.

8.3.2 Drug induced hepatitis

Drug related hepatotoxicity can occur in earlier stage HIV infection (CD4 > 200). Patients may experience malaise, jaundice, anorexia, nausea, vomiting, abdominal pain, and weight loss. Drug-induced hepatitis is the most frequent cause of jaundice in HIV patients, most often related to antituberculous medication and carries a high mortality rate.²³³

INH induced hepatitis

Elevated liver enzymes are observed in 10% of adults taking INH. About 1% of patients develop INH-induced hepatitis. The onset of INH - induced hepatotoxicity is observed within the first two months of therapy in approximately 50 percent of patients. Some factors are related with increased risk: patients >35 years old, those receiving concurrent hepatotoxins (rifampicin, ketoconazole, pyrazinamide), chronic alcohol use, concurrent liver disease, African-American and Hispanic women, postpartum women, injection drug users.

Patients who are asymptomatic with AST/ALT elevations less than five times the upper limit of normal can usually be continued on INH therapy. In many such cases, AST/ALT elevations decline spontaneously.

If transaminases are increased more than 5 times the upper limit, or the patient has developed jaundiced, INH (and also rifampicin and pyrazinamide) should be interrupted until the jaundice has disappeared.¹¹

In most patients treatment can be restarted with the same regimen without problem. In case of severe disease, alternative anti-tuberculous treatment is recommended in the meanwhile (streptomycin, ciprofloxacin and ethambutol).

ARV and hepatitis

All antiretroviral drugs are potentially hepatotoxic. Approximately 6-30% of patients develop an increase in serum liver enzymes when on HAART. Patients with hepatitis B or hepatitis C co-infection and patients taking nevirapine and ritonavir have a higher risk (up to 20%) to develop severe hepatotoxicity. In Thailand in the HIV-NAT Trials cohort the incidence of severe hepatotoxicity was 14% per year in the group of patients taking nevirapine.²³⁴ Usually hepatitis occurs within the first months after the start of the treatment. The median duration of treatment before the detection of severe hepatotoxicity was 137 days for nevirapine (IQR 49 – 305 days) and 100 days (IQR 35 – 196 days) for efavirenz. However, occurrence of severe hepatotoxicity is described in > 50% of patients treated with NNRTI after 12 weeks.²³⁵ Therefore monitoring is needed in all patients on HAART, also after the 3rd month.

The decision to stop ARV in case of raised liver enzymes has to be taken with caution, because alternative treatment may even be more toxic. Patients with an underlying active hepatitis may have abnormal baseline liver function. Sulkowsky therefore handles a modified toxicity grading to define grade 3 and 4 toxicity (severe) depending on the baseline enzyme levels.²³⁵ (See chapter 16) In case the liver enzymes are more than 5 times the ULN the drug should be stopped. In case a patient had already abnormal liver enzymes before the start of HAART, the cut-off to stop the offending drug is an increase of enzymes 3.6 x the baseline value.

Even when a patient has experienced severe hepatotoxicity on either EFV or NVP, the switch to the other compound after normalisation of liver function tests is not accompanied with an increased risk.

Less frequent is a hypersensitivity syndrome (DRESS = drug rash, eosinophilia, systemic symptoms: lymph adenopathy, hepatitis, nephritis, myocarditis). This is seen with efavirenz, nevirapine and abacavir and occurs usually within the first 6 weeks. This is always a reason to interrupt the treatment, whatever the level of transaminases. Stop the offending drug and treat with prednisone 1 mg/kg.²³⁶ Do not reintroduce the offending drug.

It seems to be a drug effect and not a class effect, so patients developing hypersensitivity on NVP can be restarted on EFV and vice versa.

8.3.3 Renal colics, nephrolithiasis

Indinavir and sulfadiazine are eliminated as crystals in the urine. If the patients fail to drink enough water or do not get sufficient fluid during treatment, they may develop renal stones and as a consequence present with colicky abdominal pain.

This is more frequent in patients who are on the higher dose of indinavir 800 mg thrice daily or the boosted indinavir 800 mg twice daily. Other signs of indinavir toxicity are dry skin, hair loss and paronychia of the toe nail.

Also high dose sulfadiazine may cause renal colics.

8.3.4 Lactic acidosis

The NRTI (especially didanosine, stavudine) have a high capacity to inhibit the activity of DNA γ -polymerase, resulting in mitochondrial dysfunction and subsequently in an overproduction of lactic acid. All NRTI, except abacavir, have been associated with the syndrome. The onset is acute or subacute. Asymptomatic hyperlactatemia (not predictive of the development of lactic acidosis) occurs in 5-25% of the patient treated with HAART. Symptomatic hyperlactatemia is rare (1 per 1000 patient-years) but life threatening with a mortality rates from 40-77%.²³⁷ Besides the use of NRTI, especially ddl and d4T, possible risk factors associated with lactic acidosis include female sex (conflicting data), obesity, hepatic steatosis, impaired renal function, severe malnutrition and low nadir CD4 count.

The highest risk is in pregnant women who are treated with ddl and d4T.

Symptoms are non specific and have an insidious onset: fatigue, shortness of breath, nausea, vomiting, lack of appetite, **abdominal pain**, weight loss, muscle pain and numbness or tingling sensations. More severe symptoms are cardiomyopathy, peripheral neuropathy, ascending neuromuscular weakness, (lower extremity motor weakness that developed over a period of days or weeks), pancreatitis, bone marrow suppression and lipo-atrophy.

The laboratory tests that confirm the diagnosis of lactic acidosis are an elevated venous lactate ($> 5\text{mmol/L}$) and an arterial pH less than 7.3. Both tests are usually not available in resource-poor settings. There is also a low bicarbonate level, a widened anion gap (sodium – (chloride + bicarbonate) > 13), an elevated LDH, ALT/AST and CPK.

The routine screening of lactate levels is not recommended as asymptomatic hyperlactatemia is poorly predictive for lactic acidosis.

Differential diagnosis has to be made with other causes of acidosis (sepsis, hypotension, renal failure).

Treatment consists of supportive treatment with correction of the acidosis: IV fluids to diminish the risk of hypovolemia, oxygen, sodium-bicarbonate (only if arterial pH < 7.1), and stop of all ARV drugs. Studies have looked at the possible role of thiamine and riboflavin in the management of severely ill patients. It is advised to give vitamin B complex as well as coenzyme Q50 and L-carnitine (variable success).

In patients who survive, the venous lactate level returns to normal level 4 to 12 weeks after the stopping of the NRTI. NRTI should be stopped for at least a month.

When restarting HAART, avoid the use of NRTI, except abacavir and tenofovir. Also 3TC seems to be associated with a lower risk for lactic acidosis.

8.4 Malignancies

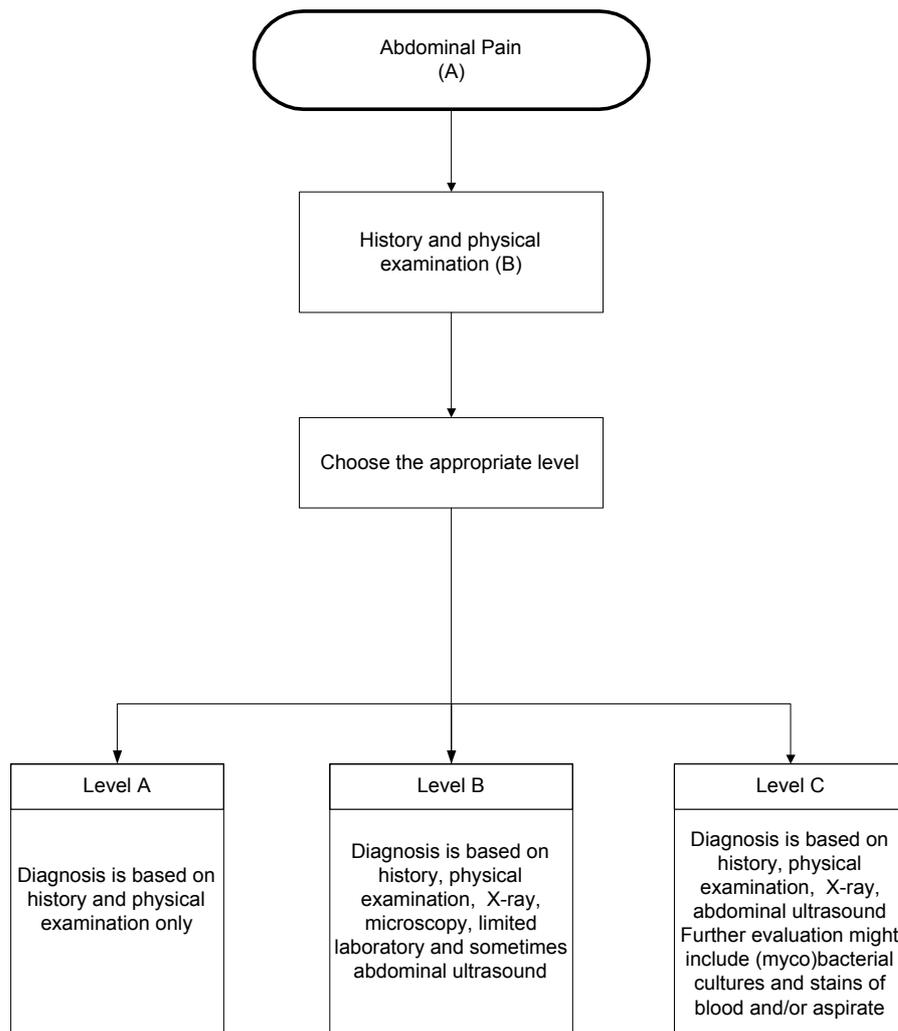
Infection with HIV has been associated with an increased risk for cancers, like Kaposi's sarcoma, non-Hodgkin lymphoma, cervical cancer.²³⁸ In Africa, the AIDS epidemic has led to Kaposi's sarcoma becoming the most frequent cancer in men, and is related to sexually transmitted HHV8 infection.²³⁹ NHL is rarely diagnosed in Africa, but this may be due to early mortality in HIV patients from other causes. In a developing country setting the treatment of malignancies is often limited to palliative care. Kaposi's sarcoma lesions can subside with HAART; however, in visceral KS chemotherapy is needed as adjuvant of HAART (see chapter 15, Kaposi's sarcoma).

Hepatitis B and C have a higher risk for a chronic course in HIV patients. They also tend to evolve more rapidly to cirrhosis, and therefore hepatocellular carcinoma (HCC)(although conflicting data).^{240,241} End stage liver disease and HCC are the most frequent causes of death in hospitalised patients treated with HAART in European cohorts. HCC in the US is mainly associated with hepatitis C. But in developing countries hepatitis B is more frequent, and acquired in young age, which leads to more chronic disease. The importance of HCC and hepatitis B and C patients is not well documented in HIV patients in developing countries.

8.5 Clinical management of abdominal pain

The differential diagnosis of disorders that cause abdominal pain in PLHA is very broad. A good history and physical examination may orient the further investigations. Any common causes of abdominal discomfort that occur in non-HIV-infected patients also occur in PLHA. The management of dyspepsia, peptic ulcer disease, PID, biliary and renal colics, appendicitis, etc. does not differ from the non-immunocompromised host.

Abdominal pain

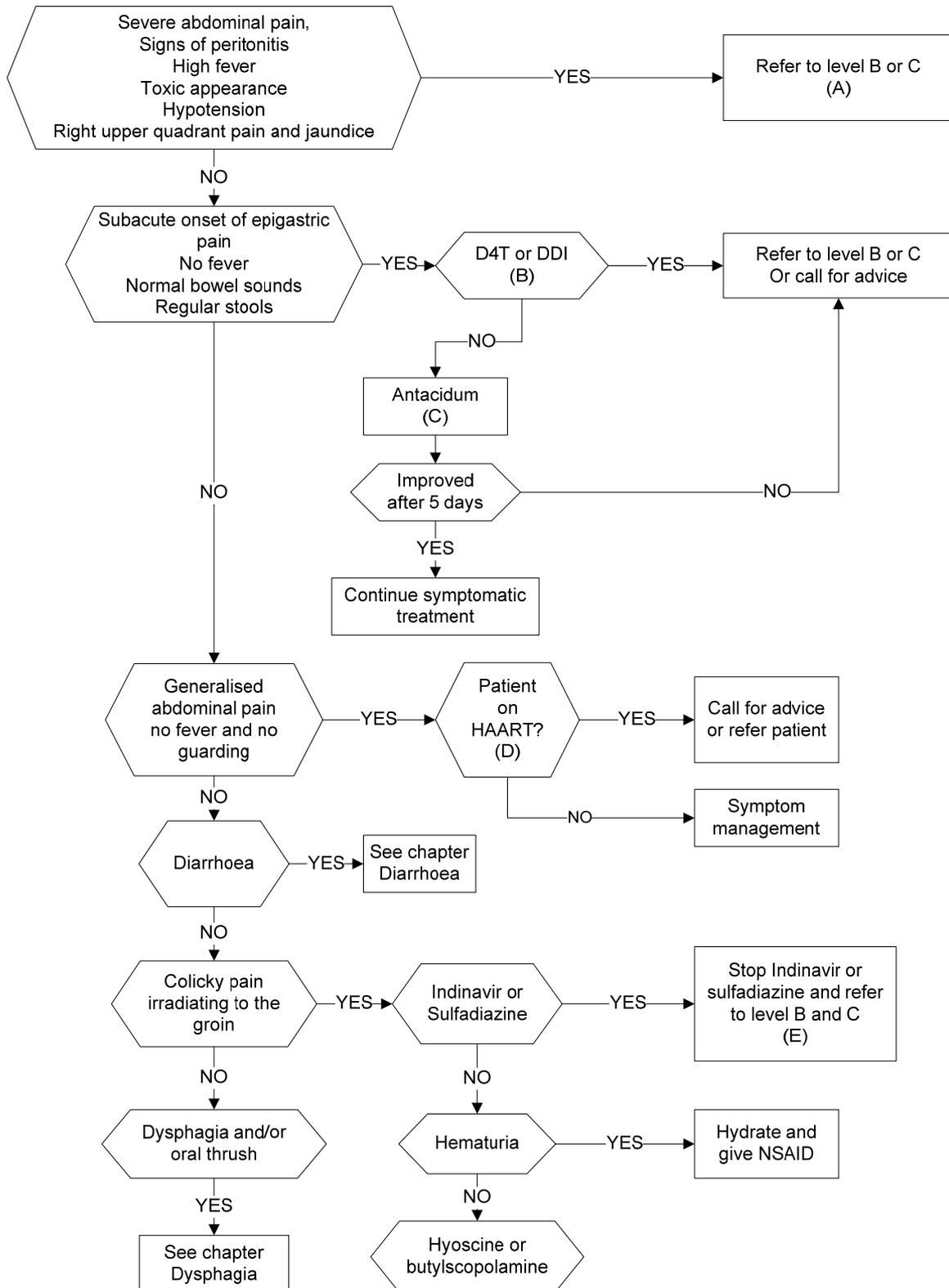


Annotations Abdominal Pain

- (A) Abdominal pain may be constant, intermittent (colic, cramps), diffuse or localized, chronic or acute, burning, associated with food or not, radiate to the back, chest or groin. Clinical signs and symptoms are rarely diagnostic. The aetiology is very broad, and evaluation should go from least invasive to more invasive. Evaluation should focus on emergency causes of abdominal pain and on the detection of treatable causes.
- (B) The differential diagnosis of abdominal pain in AIDS can be narrowed by a good history and physical examination. Dull pain, diarrhoea and vomiting are suggestive for infectious enteritis. Right upper quadrant pain suggests a hepatobiliary origin like cholecystitis, cholangiopathy, liver abscess, hepatocellular carcinoma. Severe acute pain, absence of bowel sounds, and peritoneal irritation suggest perforation or an infectious peritonitis. Epigastric pain in HIV can be due to severe oesophagitis or pancreatitis. History of drug intake may point to drug induced hepatitis or pancreatitis. Colicky flank pain and hematuria indicates renal stones. Vaginal discharge and lower abdominal pain may suggest PID. In case a patient recently started on HAART always think about an IRIS on an underlying mycobacterial or fungal infection.

Abdominal pain

Level A



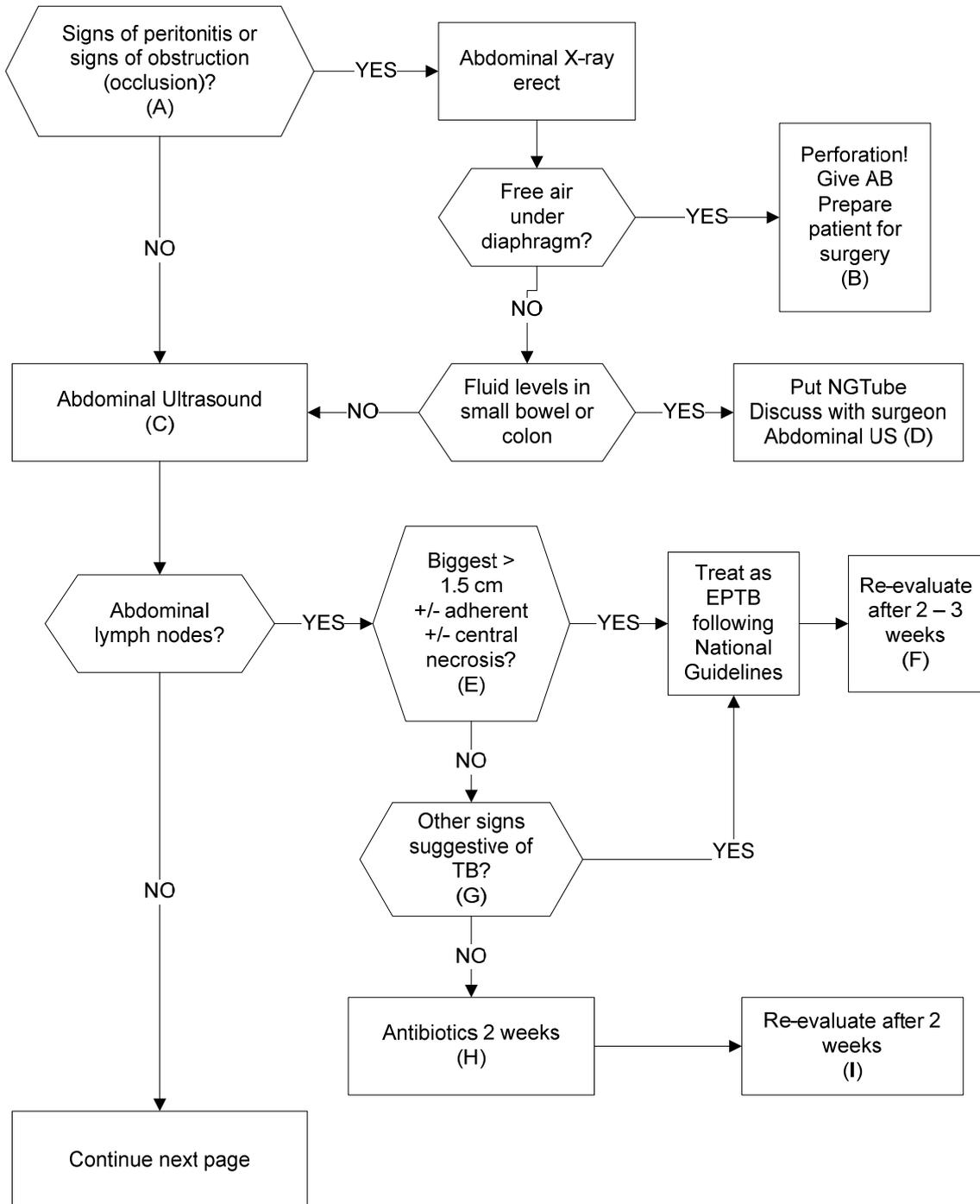
Annotations (level A)

- (A) Signs of peritonitis may include acute, generalized abdominal pain, exacerbated by movement, fever, vomiting, no gas, no stool, abdominal distension, diffuse rebound tenderness, decreased or absent bowel sounds, hypotension, tachycardia, dyspnoea. A rectal exam is generally very painful. Right upper quadrant pain and fever may be severe hepatitis, cholecystitis or cholangitis. The patient needs referral for appropriate diagnostic procedures and treatment. A frequent cause of abdominal pain with fever is abdominal tuberculosis, which is treatable, and therefore it is important to refer these patients for diagnostic reasons. In case a patient started on HAART recently an IRIS due to MAC or TB is also possible.
- (B) Subacute onset of epigastric pain without alarm signs can be treated at level A. However, if the patient is on HAART, especially stavudine and didanosine containing regimens, he may develop a pancreatitis. Call for advice or refer the patient to level B or C, where ultrasound and measurement of serum lipase or amylase is possible.
- (C) Ranitidine can be safely used with all antivirals, except atazanavir. Cimetidine should not be used with efavirenz and atazanavir and omeprazole should not be used in patients taking lopinavir, indinavir or atazanavir.
- (D) Generalised abdominal pain without fever can be a first non specific sign of lactic acidosis. Other signs are weakness, dyspnoea, nausea, vomiting, etc. Call an HIV expert to see if the patient needs to stop his antivirals. In case of doubt refer the patient to level B or C. If the patient is not on HAART, provide symptomatic pain relief (see page 147).
- (E) Indinavir and sulfadiazine can cause renal colics due to renal stones. This may cause renal impairment. Stop the drug that is responsible. In case of indinavir stop, it is important to stop all the antiviral drugs. A new antiviral treatment will have to be described. Indinavir is already a second line treatment, so advice from level B or C is needed for this treatment switch.

Abdominal pain

Level B and C

Continued from flowchart 1

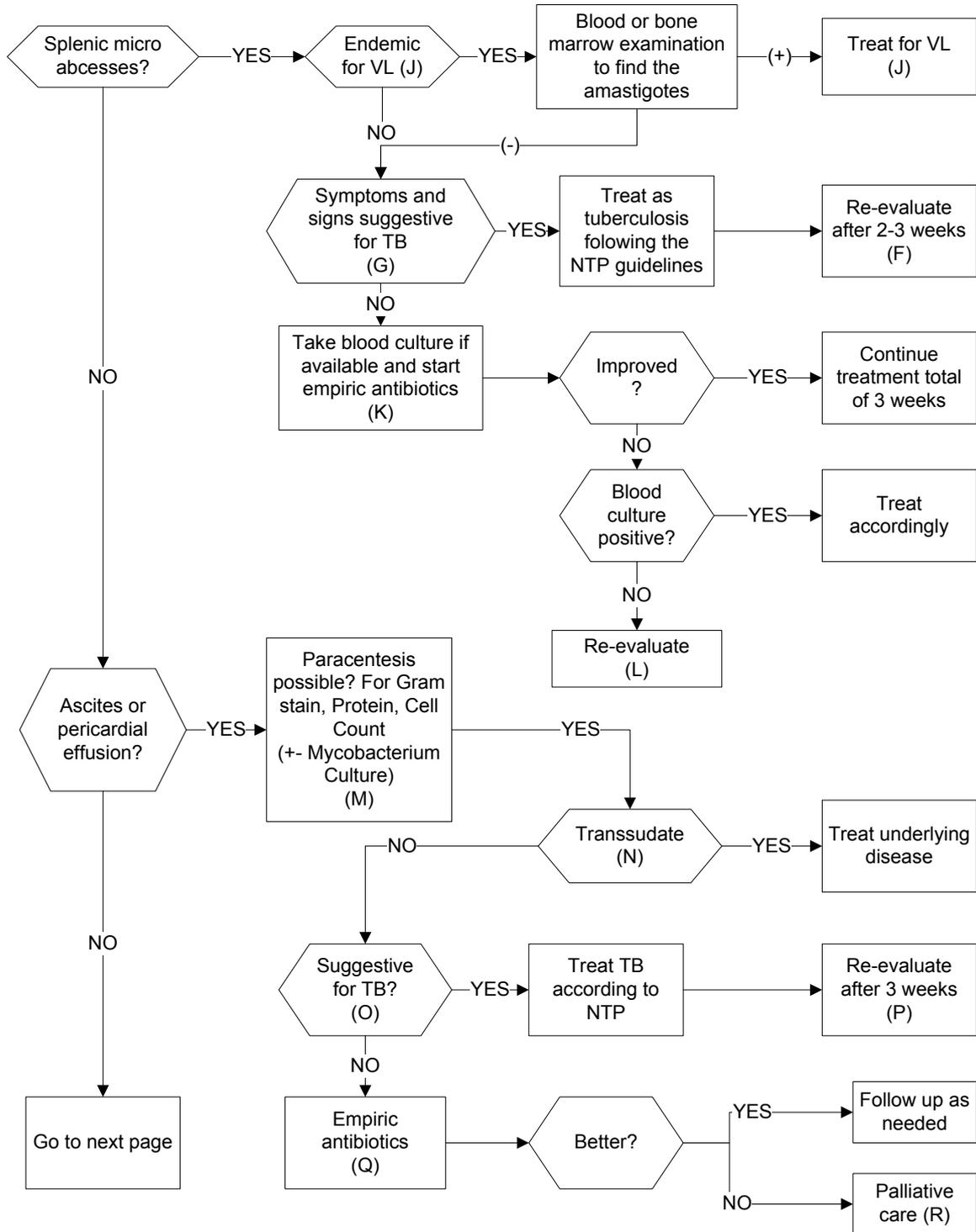


Annotations (levels B and C)

- (A) Signs of peritonitis may include acute, generalized abdominal pain, exacerbated by movement, fever, vomiting, no gas, no stool, abdominal distension, diffuse rebound tenderness, decreased or absent bowel sounds, hypotension, tachycardia, dyspnoea. A rectal exam is generally very painful.
- (B) An erect abdominal X-ray can show free air under the diaphragm. Perforation in HIV patient frequently results from CMV infection, but also typhoid fever can cause perforations. Surgery should not be deferred, as it is the patient's only chance. Survival depends on the underlying cause and the degree of immune suppression. While waiting for surgery start broad spectrum antibiotics IV: ceftriaxone 2 g IV and metronidazole 500 mg IV 3x daily. Insert a nasogastric tube (NGT), keep patient NPO (nothing per os) and give IV fluids.
- (C) Abdominal X-ray may reveal nothing, or show fluid levels. In both cases the next step is an abdominal ultrasound. Intestinal obstruction may result from huge adherent lymph nodes or intestinal malignancies. If there are no signs of peritonitis, an abdominal ultrasound is a useful exam to start with and frequently will reveal the diagnosis.
- (D) In case the obstruction is due to TB lymph nodes, surgery may be avoided if we relieve the symptoms by decompression through a NGT, by keeping the patient NPO and by treatment of underlying cause. In case the patient has a malignancy, surgery may still be considered for palliative reasons.
- (E) Big abdominal lymph nodes, especially if they are adherent and show central necrosis are according to clinicians (and studies) in developing countries sufficient evidence for tuberculosis.
- (F) After two or three weeks of treatment the patient should be re-examined. If the diagnosis of TB was correct, usually the symptoms will have much improved by now. Continue according to the NTP. In case the patient did not improve or got worse, we'll have to look for other causes: Nocardia, MAC, visceral leishmaniasis, fungal, NHL. Repeat the physical examination and look for enlarged lymph nodes, abscesses, or fluid that can be aspirated by FNA to do AFB smear and Gram's stain. If lymph node biopsy is possible it can be considered at this point. Cryptococcal antigen on serum is sensitive in identifying cryptococcal disease. Blood cultures are helpful to diagnose invasive mycosis. If the patient is on HAART, focal lymphadenitis not responding to TB medication may be due to MAC IRIS. Add azithromycin and ciprofloxacin and continue HAART if possible. Provide pain relief (NSAID). In case of severe inflammation, prednisone (0.5 mg/kg/day) during 4 – 8 weeks is indicated.

- (G) In case of smaller lymph nodes, without central necrosis, look for other signs that may suggest tuberculosis. In HIV patients with abdominal tuberculosis 93% have disseminated TB. Therefore it is worthwhile to look for pleural or pericardial effusion, for **peripheral lymph nodes** that can be aspirated with fine needle aspiration for Ziehl Neelsen staining, a chest X-ray may reveal **miliary TB**, or typical upper lobe infiltrates, **intrathoracic** (perihilar or paratracheal) **lymphadenopathy**, multiple zones of pulmonary infiltrates, etc. HIV patients with disseminated TB often present with hyponatremia. **Splenic micro abscesses** are highly suggestive of tuberculosis in countries with a high HIV/TB co-infection rate. In case there is no response to antituberculous drugs suspect MAC infection and add azithromycin 500 mg daily, keep the TB meds including ethambutol and add ciprofloxacin 500 mg twice daily.
- (H) Antibiotic of choice is directed against a possible bacterial cause of abdominal lymph nodes. Salmonella, Campylobacter, etc... Ciprofloxacin 500 mg 2 times daily or Ofloxacin 400 mg 2 times daily for **2 weeks**.
- (I) Re-evaluate your patient after 2 weeks. If better, follow-up as needed. If no improvement we have to reconsider the possibility of tuberculosis as it is such a frequent cause of abdominal pain. Therefore, it is useful to **repeat the abdominal US and the chest X ray**. In HIV patients the clinical picture sometimes changes quickly. Repeat the physical examination and look for lymph nodes or abscesses that can be aspirated by FNA to do AFB smear and Gram's stain. If lymph node biopsy is possible it can be considered at this point.
- (J) Visceral leishmaniasis is treated with pentavalent antimony 20 mg/kg/day during 30 days or amphotericin B 0.7 mg/kg/day during 28 days. The response to treatment is similar for both regimens, but overall patients with HIV have high relapse rates.^{167,223} There are no studies that compare different regimens for secondary prophylaxis.
- (K) A bacteria commonly involved in splenic abscesses is Salmonella. Ciprofloxacin 500 mg 2 x daily or Ofloxacin 400 mg 2 x daily for 2 weeks

Continued from flow chart 2

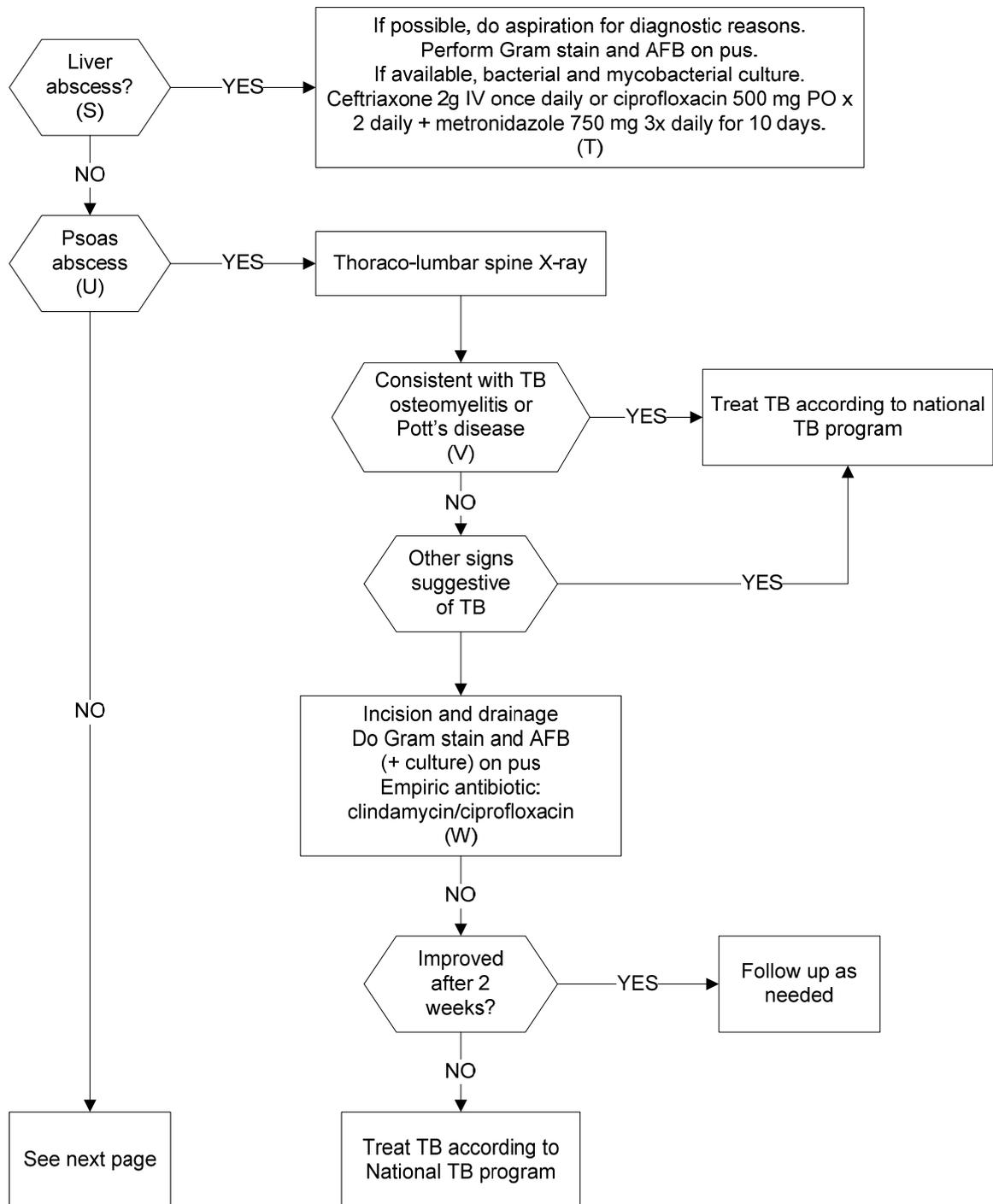


- (L) If the patient does not improve on antibiotics and the blood cultures remain negative, other causes of splenic abscesses need to be considered. We have to reconsider the diagnosis of tuberculosis as it is such a frequent cause of abdominal pain. Therefore, it is useful to **repeat the abdominal US** and the **chest X ray**. In HIV patients the clinical picture sometimes changes quickly. Repeat the physical examination and look for lymph nodes or fluid that can be aspirated by FNA to do AFB smear and Gram's stain. If lymph node biopsy is possible it can be considered at this point. Disseminated candidiasis is rare, but can happen in patients who are neutropenic and/or have an indwelling IV catheter. Treatment consists of amphotericin B or fluconazole (see introduction).
- (M) Ascites is seen less commonly in PLHA because of immune suppression that does not allow them to mount a significant amount of ascites. Abdominal paracentesis is a safe procedure in HIV patients and may guide to diagnosis. AFB stain is very insensitive on ascitic fluid. Culture is preferred for the definite diagnosis. In resource-limited setting the diagnosis is mainly based on cell count and whether the fluid is an exsudate or a transsudate. Pericarditis can also present with abdominal pain, and is most likely caused by tuberculosis in PLHA.
- (N) Protein less than 2.5 g/dl and cell count less than 200 is usually considered a transsudate. Causes are similar as in non-HIV patients: nephrotic syndrome, heart failure, cirrhosis, chronic renal failure and severe malnutrition. Treat the underlying cause.
- (O) Protein above 2.5 g/dl and cell count above 200 usually indicates an exsudate. If cells are predominantly lymphocytic we suspect TB peritonitis. Although bloody ascites is likely malignant it is occasional seen in TB peritonitis. Look for other signs of TB as PLHA with abdominal TB often have disseminated TB and try to confirm the diagnosis. In case the diagnosis of TB is likely, start TB treatment. When paracentesis is not possible, look for signs suggestive of TB (see annotation G, page 138).
- (P) Re-evaluate your patient in 2-3 weeks. Usually response to treatment is very good, if the diagnosis was correct. If not improved, re-examine your patient, and repeat the algorithm.
- (Q) If the exsudate is neutrophilic, a secondary bacterial peritonitis is likely. Consult with surgery, and start broad spectrum IV antibiotics during 10 days: ciprofloxacin 400 mg 2 x daily or ceftriaxone 2g 1xdaily, combined with metronidazole 500 mg 3 x daily IV. If the patient has bowel sounds and is not vomiting PO medication is appropriate.
- (R) Repeat the algorithm to exclude any treatable cause of abdominal pain and ascites. Untreatable causes of ascites are malignancies: cervical carcinoma, NHL, metastatic adenocarcinoma, etc. Several chemotherapeutic agents have been used with some success, but this

is not feasible in developing countries. Give palliative care. If Kaposi's sarcoma is suspected, refer to chapter KS.

- (S) In HIV patients, amebic liver abscesses can be solitary or multiple. This is also true for bacterial liver abscesses. If accessible fine needle aspiration of the pus should be done to assess the nature of the pus, do gram stain, bacterial culture and AFB smear and culture. Hypoechoic lesions can also be found in TB. In case of TB lesions in the liver, usually there will be other abdominal involvement as well: lymph nodes, spleen.
- (T) Invasive amoebiasis should be treated with metronidazole 750 mg 3 x daily over 10 days followed by a contact amebicide: diloxanide furoate (Furamide®) 500 mg 3 x daily over 10 days or paromomycin 500 mg 3 x daily over 7 days. A big abscess in a patient with high persistent fever after aspiration and 48 hours antibiotics is suggestive for a bacterial cause. Empiric therapy consists of quinolones or ceftriaxone combined with metronidazole.
- (U) A big psoas abscess may present with abdominal pain as the main complaint. It can be caused by bacteria and mycobacteria.
- (V) Spinal TB occurs usually at one level. Mostly the anterior part of the vertebral body is affected. Paravertebral abscesses may become apparent on plain films. If no clear Pott's disease, look for other signs of TB: abnormal chest X-ray, lymph nodes, etc.
- (W) Bacterial psoas abscesses usually present with severe lower back pain or upper leg pain, with fever. The patient cannot walk, and cannot fully extend his leg. Bacterial psoas abscess may arise from hematogenous spread, or by contiguous spread from an intra-abdominal process. The usual bacterial isolates are *S.Aureus* and a mixture of gram negative enteric bacteria. Empiric therapy therefore consists of ciprofloxacin 500 mg PO twice daily and lincomycin 600 mg 3-4 x daily for two weeks.

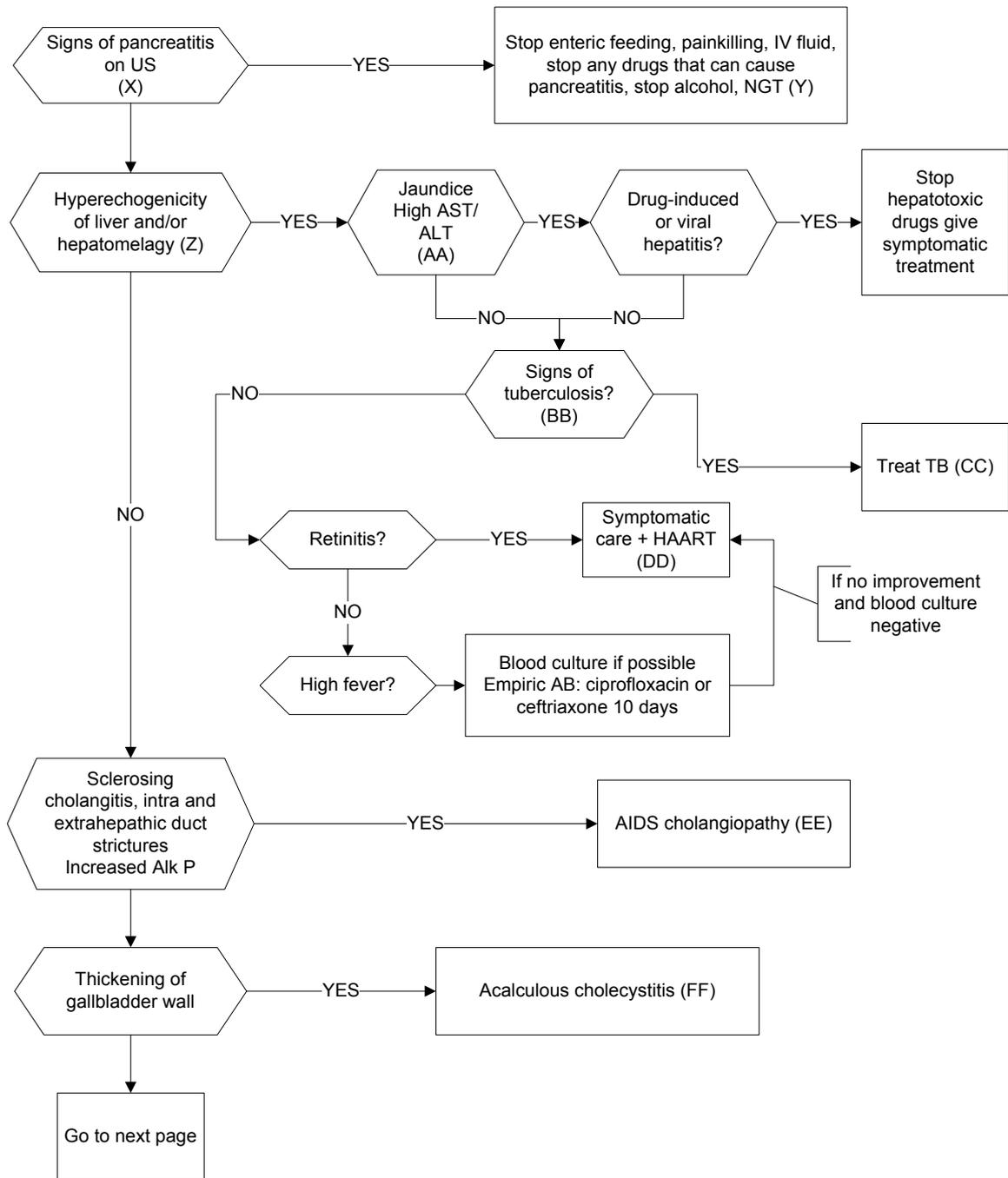
Continued from flowchart 3



Abdominal pain

Level B and C

Continued from flowchart 4

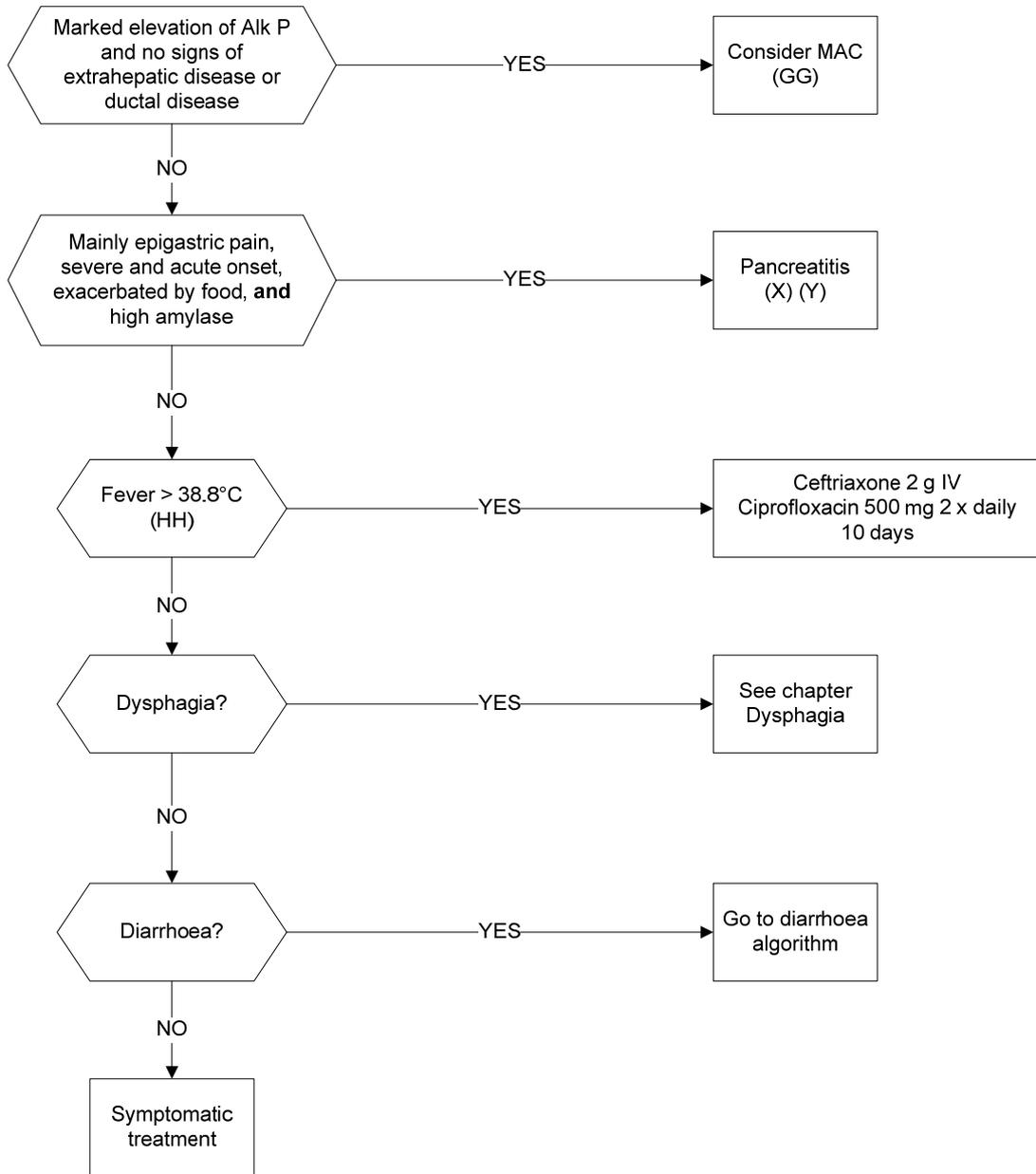


- (X) In case of acute pancreatitis, 25% will have an abnormal pancreas on ultrasound. If more than 30% of the pancreas is affected, prophylactic antibiotic should be given as part of the treatment. High amylase is frequent. A plain abdominal X-ray may show a dilated small bowel loop (sentinel loop) in the region of the pancreas.
- (Y) In case of drug induced pancreatitis the offending drug should be withdrawn. Didanosine should never be started again. Stavudine can be carefully reintroduced once the symptoms and the amylase have normalised. Consider dose reduction of d4T.
- (Z) Hyperechogenicity of the liver has multiple causes: cirrhosis, steatosis, hepatitis, CMV. In case of neoplasm or infection, usually the liver is not the only site of involvement. Look for other signs and symptoms. High fever, retinitis and bloody diarrhoea suggest CMV infection. Recent onset jaundice suggests hepatitis. Spider naevi and palmar erythema with ascites point to liver cirrhosis.
- (AA) Mildly elevated (< 2 x upper limit of normal) transaminases are frequent and do not require extensive work up. In case of markedly elevated transaminases (> 5 x ULN), hepatitis serology to rule out acute viral hepatitis, and a careful drug intake history should be done. Grade 3 and 4 toxicity requires discontinuation of the offending drug. In case a patient is on HAART and has an underlying hepatitis C or B, IRIS should be considered. Unless severe hepatotoxicity (>3.6 x the *baseline* transaminases level, grade 3-4), continue the drugs but organise a close follow-up (every 2 weeks).
- (BB) Liver infiltration with tuberculosis will seldom be an isolated phenomenon. Check lymph nodes, abdominal ultrasound and chest X-ray for other signs of TB.
- (CC) In case the jaundice is due to infiltrative mycobacterial disease, the transaminases will usually decrease after the start of the TB treatment.
- (DD) Patients with CMV disease need HAART, because ganciclovir IV is not available. Intra-ocular ganciclovir, before and after the start of HAART may decrease the problem of immune-mediated uveitis.
- (EE) AIDS cholangiopathy is a syndrome of biliary obstruction due to strictures of the biliary tract associated with infections.²⁴² It occurs in patients with CD4 < 100. Most frequent underlying cause is cryptosporidium. In case of severe abdominal pain, there is usually papillary stenosis. In case of diarrhoea, the cryptosporidium oocysts can be found by stool exam. Other pathogens are microsporidium and CMV. Patients present with RUQ pain and increased alkaline phosphates (AlkP) levels (mean 700-800 IU/L). However, elevated AlkP are frequently seen in AIDS patients. In the absence of ductal pathology, markedly elevated AlkP may indicate MAC or other disseminated infection. In case blood cultures for mycobacteria and for

fungi are available, this should be considered. If not, consider presumptive treatment for MAC if patient has chronic fever, pancytopenia and wasting. In AIDS cholangiopathy jaundice is rare. Although the underlying cause is infectious, medical treatment does not influence the symptoms. Symptomatic relief is obtained by sphincterotomy. This is not feasible in most developing countries. Therefore, symptomatic care is the only available treatment.

- (FF) Acalculous cholecystitis is also a late stage complication. Thickening of the gallbladder is evident on US. Opportunistic pathogens involved are CMV, cryptosporidium, microsporidium and *Isospora belli*.²¹⁴ Cholecystectomy is curative. HAART is probably better than surgery.
- (GG) In patients with markedly elevated Alk P (more than 2 times the upper limit of normal) without evidence of extrahepatic disease the diagnosis of MAC should be considered, especially when they present with prolonged fever, hepato-splenomegaly and severe anaemia and neutropenia.
- (HH) In case of high fever and abdominal pain, treat as typhoid fever with ceftriaxone 2g IV daily or ciprofloxacin 500 mg 2 x daily PO. If you work in an area endemic for malaria you have to rule out malaria as well.

Continued from flowchart 5



8.6 Symptomatic and palliative care

Pain¹⁸¹

Abdominal pain is a common pain syndrome in AIDS patients and often underestimated, under-diagnosed and under-treated.²⁴³ It is important to accurately diagnose the cause of the pain, but symptomatic relief should not wait for a definite diagnosis.

In general the 3-step analgesic ladder for the control of pain is also suitable for abdominal pain.²⁴⁴ See chapter 14: neurological disorders.

Colics and cramps

- Avoid foods that may cause gas or cramps, like beans, cabbage, broccoli, highly spiced foods or too many sweet or carbonated drinks.

-

- *In case of reversible obstruction* codeine 30-60 mg po (as needed) but max 240 mg/day.

For opioid naïve morphine 5-10 mg po, or sc 6 x daily, for those on opioids increase the dose by 25-50% or add codeine.

If necessary add loperamide 2-4 mg PRN, max 16 mg a day

Hyoscine butylbromide 10-20 mg po, sc, im or iv 1-5 times daily.

In case of irreversible obstruction always add loperamide routinely, if necessary complete with opioids.

Peritoneal pain (rebound tenderness)

Provide stepwise analgesia, NSAID may be very helpful

Visceral pain, organomegaly

Provide stepwise analgesia.

Steroids may be very helpful

Prednisone 10-80 mg po od

Dexamethasone 1-8 mg po, iv, sc, im 4 times daily

NSAID may also be helpful

Alternative therapy

Abdominal massage to reduce tension in abdominal wall

Aromatherapy



9 CHRONIC DIARRHOEA

9.1 Introduction

Chronic diarrhoea is defined as 3 or more loose stools a day, intermittently or continuously, for at least one month. It is a very frequent and frustrating problem in PLHA, and is experienced by at least 50% of them at some time during the evolution of the disease. Chronic diarrhoea has a significant impact on quality of life. It is often accompanied by nausea, weight loss, abdominal cramps, fever and dehydration. There is often intermittent watery diarrhoea, without blood or mucus and in one-third to two-thirds of cases, no cause is identified.

In areas with a high prevalence of HIV infection, chronic diarrhoea is almost invariably due to symptomatic HIV infection. Whenever possible, the cause of the diarrhoea should be established and specific treatment provided. Failing this, management is symptomatic. A high energy and protein intake reduces the degree of muscle wasting. The use of anti-diarrhoeal agents such as codeine phosphate is justified when symptom relief is a major consideration. Antiretroviral treatment able to cause immune restoration is very effective in decreasing the prevalence of diarrhoea (an increase of 50 in CD4 count decreases prevalence by 87%).²⁴⁵ Therefore, if appropriate investigation does not lead to the diagnosis of a specific cause and antiretroviral therapy is available, it may be more efficient to start HAART than to continue searching for a cause and specific treatment.

Prevention consists of: attention to personal hygiene (hand-washing), drinking boiled water, and eating only thoroughly cooked meat and cooked or thoroughly washed fruit and vegetables.

9.2 Causes of diarrhoea in AIDS patients

An infectious agent can be identified in about 50% of patients with AIDS-associated diarrhoea.^{216,229,246,247}

Protozoal infection: *Cryptosporidium parvum*, *Giardia lamblia*, *Isospora belli*, *Entamoeba histolytica*, *Microsporidium* species (sources vary widely but all indicate that up to 50% or more are caused by protozoa)

Toxin induced: *E. Coli* and *Clostridium difficile* (10-25% USA)

Mycobacterial infection: *M. avium* complex (25-40%USA), *M. tuberculosis*

Viral infection: *Cytomegalovirus* (13-19% USA), *Herpes simplex virus*
Bacterial infection: *Campylobacter*, *Shigella*, and *Salmonella* species
Helminthic infection: *Strongyloides stercoralis*
Fungal infection: *Candida* species (seldom a cause of diarrhoea)

Non-infectious disorders: Kaposi's sarcoma, lymphoma
AIDS enteropathy: direct cytopathic effect of HIV disease
Drugs: antibiotics, antiretrovirals

9.2.1 Bacterial gastroenteritis

Invasive bacterial pathogens such as *Campylobacter*, *Shigella* and *Salmonella* species can cause severe and prolonged illness in PLHA. They are, however, not a frequent cause of chronic diarrhoea.

Salmonellosis is much more frequent in PLHA and is a frequent cause of bacteraemia. The only symptoms may be fever and general malaise, sometimes without GI symptoms. Treatment consists of: cotrimoxazole 960 mg 2 x daily or chloramphenicol 250 mg 4 x daily for 3 weeks. In case of signs of sepsis, IV therapy is necessary. Shorter regimens or suitable alternatives in case of high resistance rates are: ciprofloxacin 500 mg 2 x daily or ofloxacin 400 mg 2 x daily or ceftriaxone 2 g IV for 7-10 days. However, a lot of patients relapse after treatment and chronic maintenance therapy (cotrimoxazole 1DD daily) is sometimes necessary.

Shigella infection usually presents with high fever, abdominal pain and bloody diarrhoea. Treatment consists of cotrimoxazole 960 mg 2 x daily for 5 days or amoxicillin 500 mg 3 x daily for 5 days. In many developing countries, however, resistance of *Shigella* (and *Salmonella*) to cotrimoxazole and amoxicillin has increased. The antibiotic of choice has become ciprofloxacin 500 mg 2 x daily, ofloxacin 400 mg 2 x daily, norfloxacin 400 mg 2 x daily for 5 days, or nalidixic acid 1 g 4 x daily for 10 days.

Campylobacter enteritis is more frequent in PLHA and is characterised by fever, bloody diarrhoea, abdominal pain and weight loss. After the diagnosis has been confirmed by stool culture, erythromycin (500 mg 2 x daily for 5 days) is the first choice treatment. Fluoroquinolones are also effective but resistance rates of 30%-50% have been reported in Spain, Greece and some developing countries.

It is clinically impossible to distinguish the different agents without stool culture. Moreover, an organism may be found on microscopy or culture, but not be the cause of the diarrhoea.

Cotrimoxazole is the recommended first line treatment in many guidelines but in countries with high resistance rates for *Salmonella* and *Shigella*, initial treatment with fluoroquinolones* should be considered. An adapted WHO guideline using norfloxacin and/or metronidazole was shown to induce remission of chronic diarrhoea in 85% of patients in Kenya, but cure was less

* Fluoroquinolones should be avoided as empirical therapy in patients with a suspicion of TB

likely when metronidazole had not been used.²⁴⁸ Therefore, for chronic diarrhoea we recommend empiric therapy with: cotrimoxazole 1DS twice daily or fluoroquinolones + metronidazole 500 mg three times daily for 7 days.

9.2.2 Cryptosporidiosis

Cryptosporidium parvum is a small, obligate, intracellular protozoan that occurs widely in nature and causes disease in cattle and humans. Cryptosporidia are highly infectious and can be transmitted through water, food, animal-to-human and human-to-human contact. Because of cryptosporidia's ubiquity and ease of transmission, people with compromised immune systems should take special precautions to avoid exposure. It is recommended that people with HIV and a CD4<200 should boil tap water for at least one minute to reduce the risk of ingestion of the oocysts in potentially contaminated public drinking water.

Cryptosporidium is an important cause of debilitating watery diarrhoea and weight loss in HIV-infected patients. It is more frequent when the CD4 count is less than 100. The small bowel is extensively colonised and invasion of the biliary tree occasionally results in stenosis and cholecystitis. In PLHA with CD4>200, cryptosporidiosis presents as an acute self-limiting disease that does not require treatment. In patients with lower CD4 counts, it may present as chronic diarrhoea or as fulminant disease with 20 or more stools a day. The organism can be easily detected in the stool by using a modified acid-fast stain.

Before the introduction of HAART, the diagnosis of cryptosporidiosis was associated with increased mortality. Median survival in the US was 200 days for HIV patients who had diarrhoea due to cryptosporidiosis.

Treatment

The use of ARV is protective against cryptosporidiosis and ARV may therefore be the most effective therapy for this protozoan infection.^{249,250} Paromomycin (500 mg 4 x daily for 2 weeks; maintenance 500 mg 2 x daily), an orally poorly absorbed aminoglycoside, has been evaluated in small and uncontrolled studies. One clinical controlled trial, involving only 10 patients, showed a decrease in daily stool excretion and total oocysts excretion.²⁵¹ However subsequent studies did not support the use of paromomycin.²⁵² We do not recommend its use as it is expensive and has no demonstrated efficacy. Azithromycin 500mg daily for 7 days was shown to be beneficial in symptomatic disease, but not in eradication.²⁵³ Nitazoxanide 500mg 2 x daily for 3-14 days has been shown to be effective, but the supportive data for its use in PLHA is limited.^{254,255}

9.2.3 *Isospora belli* infection

Isospora belli infection presents in a way that is clinically indistinguishable from disease caused by *Cryptosporidium parvum*. It can be detected in stools by the same techniques as those developed for *Cryptosporidium* species. *Isospora belli* oocysts are relatively big (20-30 µm) and can be easily identified in unstained wet preparations.

Treatment

Most cases are readily treatable with a high dose of cotrimoxazole 1DS (= double strength = 800 mg sulfamethoxazole and 160 mg trimethoprim) 4 x daily for 10 days, followed by 1DS 2 x daily for 3 weeks, then chronic suppression with the same dose of cotrimoxazole as used for PCP prophylaxis (1DS daily or 1DS 3 x weekly as tolerated). In case of intolerance to cotrimoxazole, ciprofloxacin (500mg 2 x daily for 7 days) is an acceptable, but slightly less effective alternative.²⁵⁶ As with all HIV patients at clinical stages 3 and 4, cotrimoxazole prophylaxis is recommended. This will also provide protection against *Isospora belli*. In settings where primary prophylaxis with cotrimoxazole is implemented, this is a rare parasite (the same is true for *Cyclospora*).

9.2.4 *Cyclospora*

Cyclospora infection also occurs in HIV-infected patients. It is rarely found in patients on cotrimoxazole prophylaxis. *Cyclospora* also stains with modified acid-fast stain. It is important to distinguish the larger *Cyclospora* oocysts (8-9 µm) from the smaller *cryptosporidium* oocysts (5 µm) because the treatment is different (cotrimoxazole 1DS 4 x daily for 10 days). In case of intolerance to cotrimoxazole, ciprofloxacin (500mg 2 x daily for 7 days) is an acceptable, but slightly less effective alternative.²⁵⁷ Both have to be followed by secondary prophylaxis with cotrimoxazole.

9.2.5 Microsporidiosis

The most common manifestation of intestinal microsporidiosis in PLHA is profuse, watery, non-bloody diarrhoea, sometimes accompanied by abdominal pain and cramping, nausea, vomiting and weight loss. Species of microsporidia have been linked with disseminated disease: cholangitis, keratoconjunctivitis, hepatitis, peritonitis and infections of the lungs, muscles and brain. However, the presence of microsporidia does not always correlate with symptomatic disease. Diagnosis is made by modified trichrome stain to identify the spores in stool specimens.

Treatment

The use of ARV is protective against microsporidiosis and ARV may therefore be the most effective therapy for this protozoan infection.²⁵⁰ A well-validated specific treatment is not available for most of the microsporidial infections. *Encephalitozoon* species responds clinically (reduction in diarrhoea and weight gain) to albendazole 400 mg 2 x daily for 2-4 weeks.²⁵⁷ However, parasites are not cleared and long-term therapy is often needed. In a small but randomized, double-blind, placebo-controlled trial *Enterocytozoon bieneusi* responded both microbiologically and clinically to treatment with fumagillin 20mg 3 x daily for 14 days.²⁵⁸ However, this is expensive and HAART is probably more cost-effective.

9.2.6 AIDS enteropathy

Patients can be identified with symptoms of diarrhoea and weight loss, but without any known parasite and several hypotheses about the pathogenesis have been put forward. It may be due to unknown or undetected enteric pathogens or it might be a result of a direct mucosal HIV infection by the virus. A third suggestion is that bacterial overgrowth, possibly related to gastric hypo-acidity, may play a role. AIDS enteropathy also seems to respond to antiretroviral treatment.

9.2.7 Mycobacterium Avium Complex (MAC)

Organisms of the MAC comprise two closely related species: *M. avium* and *M. intracellulare*. The organism is ubiquitous in the environment and disseminated infection results from recent infection rather than reactivation of a previous infection. Infection is rare in patients with CD4>100. The most common findings at diagnosis are fever and severe anaemia (denoted by a haematocrit of <26 percent). More than 70% of patients have gastrointestinal or hepatobiliary symptoms: diarrhoea, abdominal pain, hepatomegaly, and greatly increased alkaline phosphatase levels.

MAC infection occurs in patients with advanced disease, and the median survival after the initial diagnosis is around 3 months.²¹³

In a resource-poor setting the diagnosis and treatment of MAC is difficult. Disseminated MAC infection is most readily diagnosed by mycobacterial culture of blood or bone marrow. In developing countries, very few data are available about MAC incidence in HIV-infected people. The identification of MAC in the stool is not an argument for MAC infection as MAC may colonise the epithelial linings of the GI tract without causing invasive disease.²⁰⁰ Stool microscopy does not differentiate between MAC and TB.

Treatment including azithromycin or clarithromycin is effective and well tolerated. At least two drugs should be used to avoid emergence of resistance. Clarithromycin 500 mg 2 x daily or Azithromycin 500 mg daily and ethambutol 15 mg/kg daily with or without rifabutin 300 mg daily.

Rifabutin is not readily available in resource-poor settings. Standard treatment

in Thailand with clarithromycin 500 mg 2 x daily and ethambutol 800 mg daily, costs USD 42 per month. This is more expensive than the cheapest ART regimens.

Moreover, in the absence of ARV therapy the benefit of treatment for MAC is questionable as despite potent regimens it is associated with shortened survival.¹⁹³

Some experts add ciprofloxacin for a higher efficacy.²⁵⁹ Treatment should be given for 24 weeks, followed by secondary prevention with azithromycin (1200 mg per week) or clarithromycin 500 mg twice daily lifelong or until immune restoration (CD4 > 100 for 12 months) in patients treated with HAART.

Some experts say that in case of doubt between tuberculosis and MAC, one could add clarithromycin to the tuberculosis treatment while awaiting the results of the culture.²²⁸ In general, the combination of clarithromycin and rifampicin is not recommended because of drug interactions (rifampicin induces cytochrome P450 leading to reduced blood levels of clarithromycin). A better choice would be azithromycin because of the absence of drug interactions with rifampicin and ART.

In settings where TB culture is not available, the choice should be to treat tuberculosis as it is more frequent. In case there is no improvement and the patient has fever, diarrhoea and very high alkaline phosphatase levels, empiric therapy for MAC should be considered, especially in patients who are ready to start with HAART. In these patients the likelihood of immune reconstitution inflammatory syndrome (IRIS) is significant. Therefore, if MAC is strongly suspected or confirmed, it is easier to first treat MAC and start ARV after 1-2 months to reduce the risk of IRIS. In patients taking ART it is recommended to use azithromycin instead of clarithromycin because there is less interaction with antiretrovirals.

Primary prophylaxis

In Europe and the USA MAC prophylaxis is recommended when CD4<50. In patients on ART, azithromycin (1200 mg/week) has fewer interactions with HAART than clarithromycin, and is therefore preferred. Both drugs have also an additional protective effect against bacterial infections and PCP.

In developing countries the disease is rare, and it has therefore not been widespread practice to use primary prophylaxis for MAC. The Thai opportunistic infections guidelines 2002 recommend primary prophylaxis against MAC. However, azithromycin prevention costs USD 5.9 per week, and in the absence of mycobacterial cultures it is difficult to exclude active disease. On the other hand, MAC is frequently associated with IRIS and can cause significant morbidity and complication soon after the start of HAART. This could be an additional reason to consider MAC prophylaxis.

Secondary prophylaxis

In the absence of HAART, lifelong treatment is necessary.

Lifelong MAC prophylaxis may not be necessary for HIV-infected patients who respond to HAART with increases in CD4 to >100 for more than 12 months.⁴⁵

9.2.8 *Clostridium difficile*

Clostridium difficile may be underestimated as a cause of diarrhoea in AIDS patients in the tropics because of difficulty in making the diagnosis. The presence of faecal leucocytes and blood supports the diagnosis. In a study of causes of diarrhoea in Peruvian AIDS patients, *Clostridium difficile* was the most prevalent pathogen and it was associated with a significant increase in mortality. Frequent hospitalisation and exposure to antibiotics puts AIDS patients at high risk of infection with the toxin-producing strain of *C.difficile*.²⁶⁰

Treatment is with metronidazole 500 mg x 3 daily for 7 days.

As in HIV-negative patients, 5%-30% of patients with *C.difficile*-associated diarrhoea experience relapse.

9.2.9 *Strongyloides stercoralis*

S. stercoralis can complete its life cycle entirely within the human host.¹⁷⁷ As a result, the burden of adult worms in infected humans can increase substantially through a cycle of auto-infection. In immuno-compromised patients, it can cause overwhelming infection, especially when cell-mediated immunity is impaired. This serious complication is called strongyloides hyperinfection syndrome and has a high case-fatality rate.

Strongyloides infection should be suspected in patients who have serpiginous erythematous skin lesions (larva currens), diarrhoea, abdominal pain and cough. Full-blown hyperinfection syndrome has the characteristics of a Gram-negative sepsis, with ARDS (acute respiratory distress syndrome), DIC (disseminated intravascular coagulation) and secondary peritonitis. The chest X-ray reveals diffuse pulmonary infiltrates. Hyperinfection strongyloidiasis is generally associated with other conditions of depressed host cellular immunity. Disseminated strongyloidiasis and heavy worm loads can occur in patients with HIV, but the full-blown hyperinfection syndrome is less common.^{175,176} The likelihood of developing the hyperinfection syndrome is also increased in patients taking high-dose steroids.

Therefore, any patient started on immunosuppressive doses of steroids for a prolonged period of time (more than 1 month), should receive treatment with albendazole, before the start of steroids.

In uncomplicated strongyloidiasis, the sensitivity of a single stool examination to detect filariform larvae is low. In HIV patients, this is probably higher because of higher worm burdens. In disseminated strongyloidiasis, filariform larvae can be found in stool, sputum, broncho-alveolar lavage fluid, pleural fluid, peritoneal fluid and surgical drainage fluid.

Strongyloidiasis can be successfully treated with ivermectin 12 mg daily for 3 days, and this drug is also considered by some as the drug of choice for the treatment of systemic strongyloidiasis.¹⁷⁷ An alternative treatment is albendazole 400 mg 2 x daily for 5 days. A maintenance therapy once a month is necessary to suppress symptomatic infection (albendazole 400 mg or ivermectin 6 mg once monthly).

For other helminths, the regular dose of mebendazole 100 mg twice daily for 3 days, or the 500 mg STAT dose are sufficient.

Some authors say that helminthic infections cause immune activation which favours HIV progression.¹²⁰ For that reason treatment of helminthic infections is important, even in asymptomatic carriers. Some projects have incorporated a STAT dose of mebendazole 500 mg or albendazole 400 mg at the inclusion of a patient in a treatment program.

9.2.10 Drugs

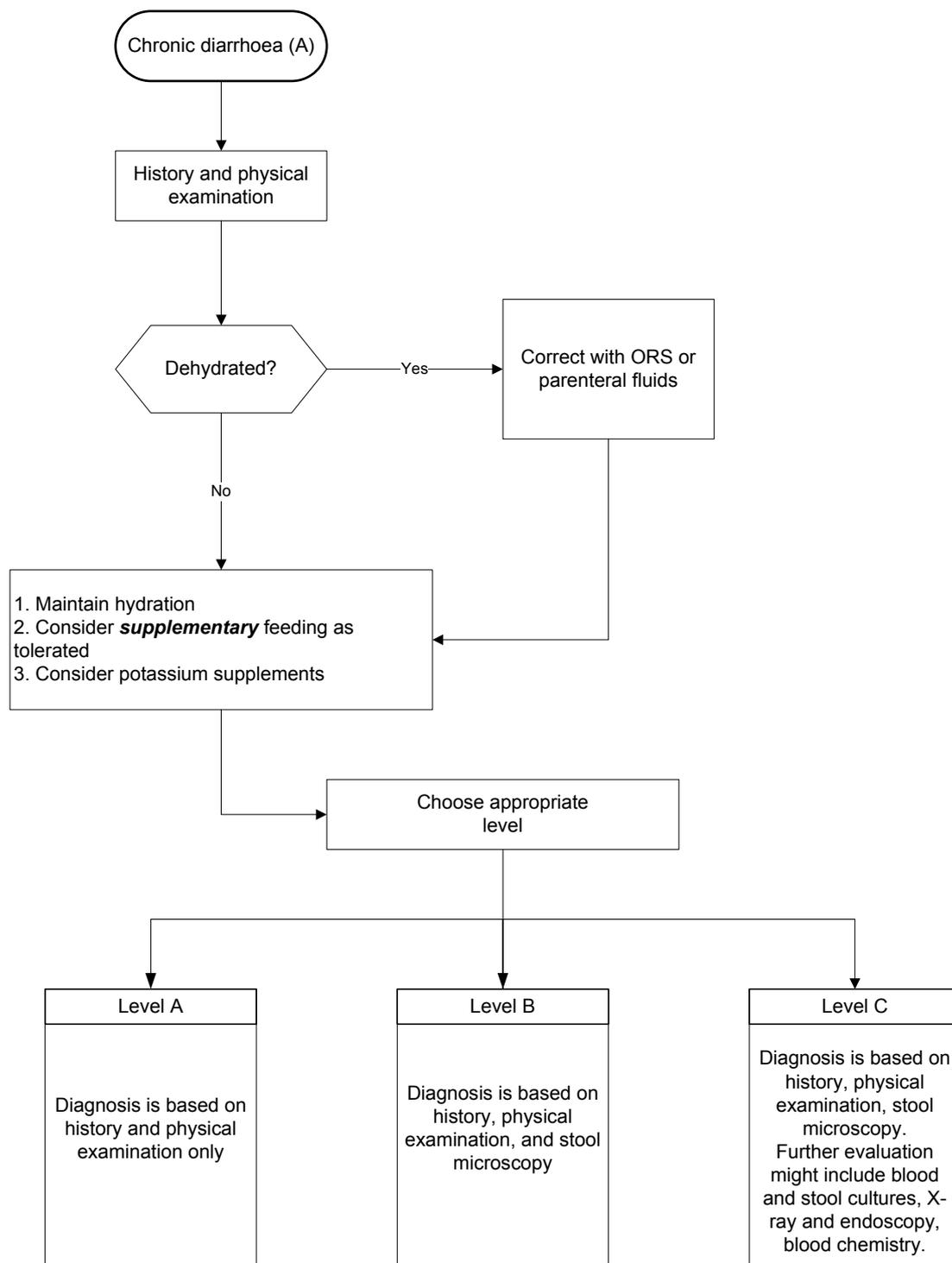
Most antibiotics can cause diarrhoea due to either bacterial overgrowth or selection of *Clostridium difficile*. Cotrimoxazole, however, is not a frequent cause of diarrhoea. For simple antibiotic-related diarrhoea the treatment is to stop the antibiotic if possible. For *Clostridium difficile* stopping the antibiotic helps, but specific therapy with metronidazole is required.

Patients under antiretroviral therapy have an increased likelihood of drug-induced diarrhoea, while the risk of opportunistic infections has been greatly diminished. Protease inhibitors (PI) such as nelfinavir, ritonavir and lopinavir/ritonavir have been associated with diarrhoea in between 10 and 30% of patients. Also zidovudine and didanosine (with a formulation that includes a sodium citrate or sodium phosphate buffer) have been associated with diarrhoea. Further investigation is rarely needed and treatment in these patients is symptomatic. In case of severe antiretroviral-induced diarrhoea, switch of treatment regimen should be considered. Studies have shown benefit with Oat Bran 1500 mg twice daily, an increase in dietary fibre intake and CaCO₃ 500 mg three times daily in PI-induced diarrhoea.^{261,262}

9.2.11 Other

Bedridden patients, especially when they are on opiate analgesics, are prone to constipation and faecal impaction. This may result in overflow diarrhoea. It is useful to teach home care teams how to check with gloves for the presence of impacted faeces. Patients who are taking opiates should also be prescribed medication to prevent constipation unless they are suffering from diarrhoea.

9.3 Clinical management of diarrhoea in HIV patients



Annotations Chronic Diarrhoea

(A) Definition: liquid stools 3 or more times daily, continuously or episodically for more than one month in a patient with HIV infection.

Aetiology is listed in the introduction.

It is important to ask about history of the following in a patient with diarrhoea:

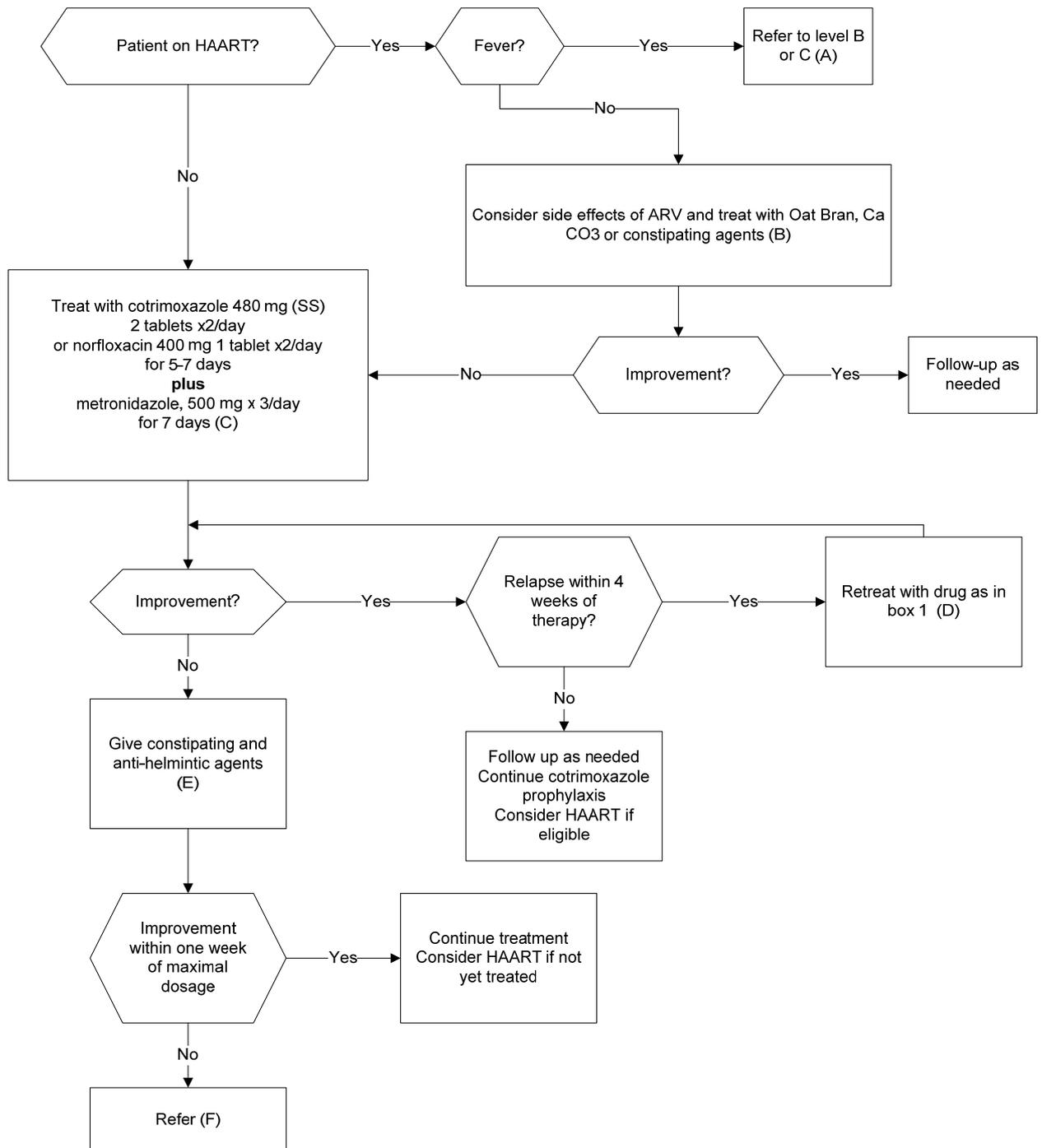
- fever
- blood or mucus in the stools
- drugs, including ARV
- previous antibiotic use and hospitalisation.
- abdominal pain. In case this is the predominant symptom please go first to the abdominal pain guideline.

A physical examination should assess the degree of hydration and the nutritional status.

Nutritional support is very important to avoid wasting. Try giving regular small meals as tolerated by the patient. At least 2500 kcal daily are needed.

At all levels of care, time must be taken to instruct the patient's family about how to handle soiled bed linen and the disposal of faeces. It may be necessary to give them appropriate materials (gloves, buckets, etc.).

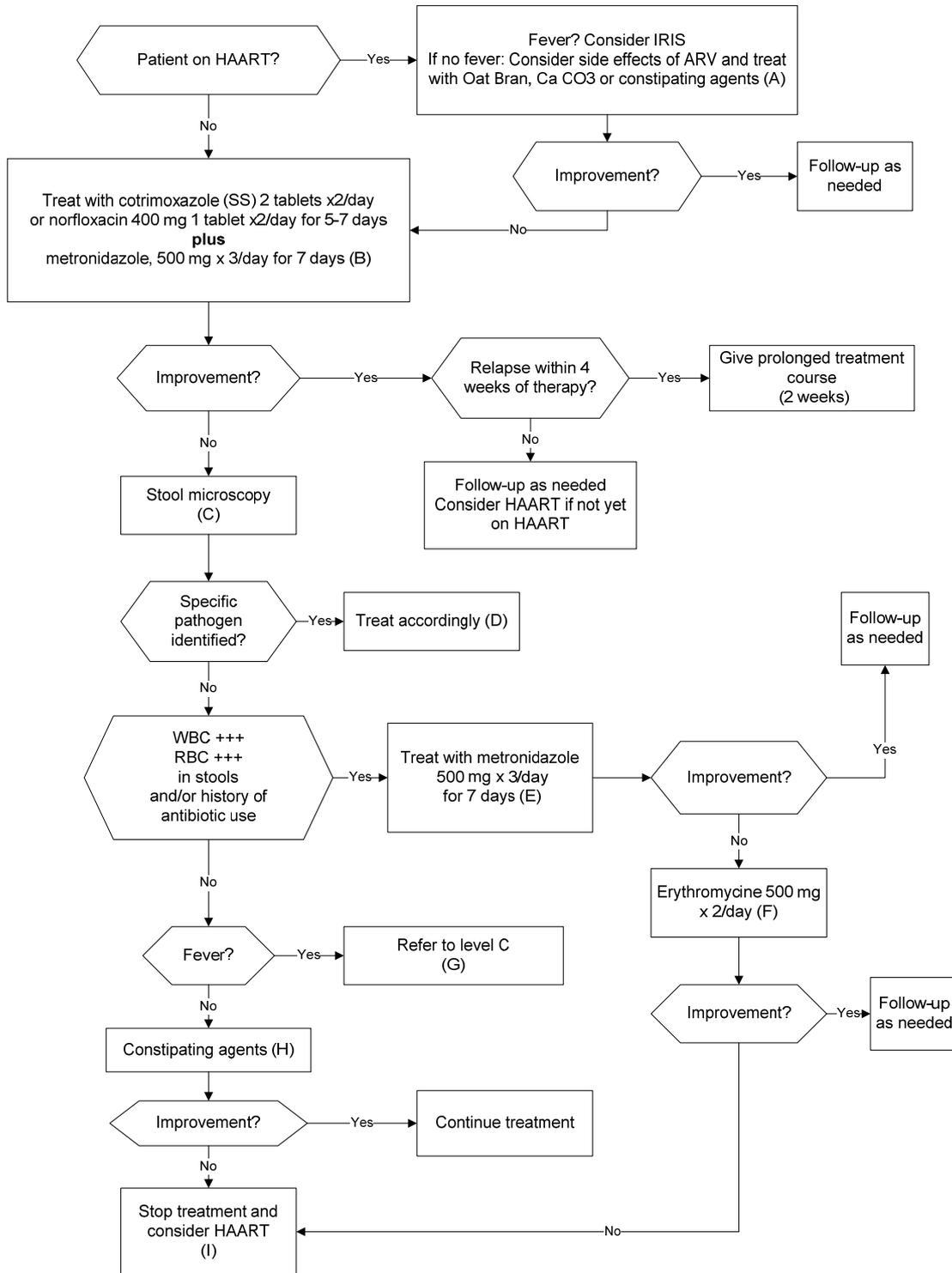
Continued from flowchart 1



Annotations (level A)

- (A) In patients who recently started on HAART, diarrhoea with fever can be part of an immune reconstitution syndrome- especially with TB or MAC. Patients usually have fever and are sick. Also Graves' disease has been described as IRIS and can give diarrhoea.²⁰⁹
- (B) Many antiviral drugs can cause diarrhoea but it occurs predominantly with protease inhibitors such as nelfinavir and lopinavir/rtv and with formulations of didanosine that include a sodium citrate or sodium phosphate buffer. PI-induced diarrhoea may decrease with CaCO₃ or with oat bran. If debilitating, consider constipating agents or switching to another HAART regimen.
- (C) Any episode of diarrhoea in an AIDS patient lasting longer than 5 days is worth an empirical treatment with antibiotics, in association with ORS. Cotrimoxazole is the recommended first line treatment in many guidelines but in countries with high resistance rates for Salmonella and Shigella, initial treatment with fluoroquinolones should be considered. For chronic diarrhoea we recommend empiric therapy with: (cotrimoxazole 1DS twice daily **or** fluoroquinolones) + metronidazole 500 mg three times daily for 7 days.
- (D) It is possible to repeat the initial treatment and sometimes a prolonged course is recommended (2-3 weeks). However, it is useless to repeat courses of antibiotics that have not been effective in the past.
- (E) For example, loperamide, 4 mg initially, followed by a further 2 mg after each liquid stool. The maximum daily dose should not exceed 16 mg. An alternative is codeine phosphate from 30 to 60 mg 3 to 6 x daily. Constipating agents should not be given to patients with bloody diarrhoea. An anti-helminthic drug should be given first. Mebendazole 100 mg 3 x daily for 7 days is partially effective against strongyloidiasis, the only helminthic infection causing diarrhoea. Albendazole 400 mg daily for 3 days is a broader spectrum anti-helminthic, but not often available at home-care level. For other helminths the regular dose of mebendazole 100 mg twice daily for 3 days, or the 500 mg STAT dose is sufficient.
- (F) When diarrhoea is disabling, refer to a centre with better care facilities. If no cause is found, they may decide at the referral level to start HAART, which is an effective treatment for AIDS enteropathy, and most of the protozoan diarrhoeas.

Continued from flowchart 1



Annotations (level B)

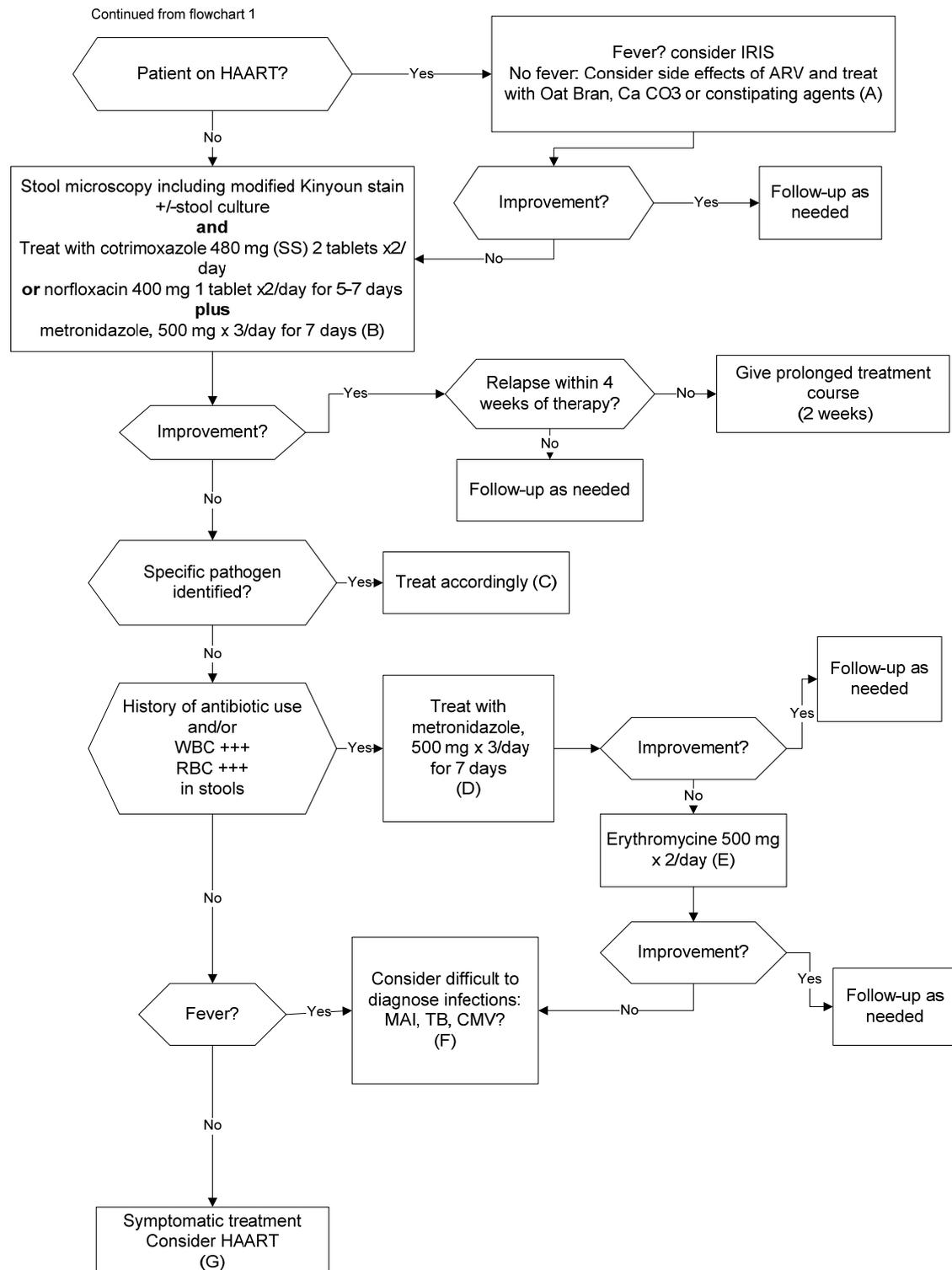
- (A) In patients who recently started on HAART, diarrhoea with fever can be part of an immune reconstitution syndrome- especially with TB or MAC. Patients usually have fever and are sick. Also Graves' disease has been described as IRIS and can give diarrhoea due to IRIS.²⁰⁹ Many antiviral drugs can cause diarrhoea but it occurs predominantly with protease inhibitors such as nelfinavir and lopinavir/r. PI-induced diarrhoea may decrease with CaCO₃ or with oat bran. If debilitating, consider constipating agents or switching to another HAART regimen.
- (B) If the patient was not yet treated, a trial with antibiotics is justified, always associated with ORS and feeding instructions. In countries with high resistance rates for Salmonella and Shigella, initial treatment with fluoroquinolones should be considered. Because of the frequency of clostridium difficile and antibiotic-associated diarrhoea, we recommend the simultaneous use of metronidazole in the empiric treatment of diarrhoea in HIV patients. Avoid repeating a treatment that brought no improvement. If the patient has already received a treatment for this episode of diarrhoea without success at level A, a stool examination should be performed for the detection of specific pathogens. Three stool samples may increase the diagnostic yield of parasites.
- (C) A fresh stool examination (direct and after concentration) and a lugol stained wet mount is necessary at this level.
- (D) Strongyloidiasis can be successfully treated with ivermectin 12 mg daily for 3 days. An alternative treatment is albendazole 400 mg 2 x daily for 5 days. A once-monthly maintenance therapy is necessary (albendazole 400 mg or ivermectin 6 mg once monthly). Trophozoites of Entamoeba histolytica should be treated with metronidazole 750 mg 3 x daily for 10 days followed by a contact-amoebicide: diloxanide furoate (Furamide®) 500 mg 3 x daily for 10 days or paromomycin 500 mg 3 x daily for 7 days. (In some countries Intetrix® is still available: 1 caps. 4 x daily for 10 days). Giardia lamblia is treated with metronidazole 250 mg 3 x daily for 5 days. Isospora belli is treated with higher than usual cotrimoxazole: 1DS 4 x daily for 10 days followed by 1 DS 2 x daily for 3 weeks. Single doses are not recommended in HIV patients because of unreliable gastric absorption.
- (E) As in HIV-negative patients, 5%-30% of patients with Clostridium-associated diarrhoea relapse. The treatment with metronidazole should be repeated.²⁶⁰
- (F) At this point, a course of erythromycin might be tried in a dose of 500 mg 2 x daily for 5 days for Campylobacter dysentery.
- (G) In case of long-lasting or severe diarrhoea with fever, that has not responded to antibiotics and metronidazole, severe infections such as MAI, TB or CMV may be the underlying cause. In case of abdominal pain it is a good idea to do an abdominal ultrasound before referral. If there are

enlarged intra-abdominal lymph nodes with central necrosis, the diagnosis of extra-pulmonary tuberculosis is likely, and anti TB treatment may quickly resolve the symptoms. If there is no pain or the abdominal ultrasound is normal we have to refer the patient to level C for diagnostic work-up. If no cause for the diarrhoea is found, it may be decided at the referral level to start HAART, which is an effective treatment for AIDS enteropathy, and most of the protozoan diarrhoeas.

(H) For example, loperamide 4 mg initially, followed by a further 2 mg after each liquid stool. The maximum daily dose should not exceed 16 mg. An alternative is codeine phosphate 30-60 mg 3-6 x daily. Constipating agents should not be given to patients with bloody diarrhoea.

(I) If the patient has had diarrhoea for a long time without alteration of the general condition or fever, observation combined with symptomatic treatment is justified. If available, HAART should be started in these patients, as most of the remaining causes will only improve with HAART. At level C, special stains or stool cultures could be performed to identify remaining treatable conditions. In small field laboratories where modified acid fast stain or trichrome stain are not available, Cryptosporidiosis, *Isospora belli* and Cyclospora are not easily identified. If referral is not possible (low geographical or financial accessibility), a treatment trial for remaining treatable causes should be started.

Isospora belli: will respond to higher than usual doses of cotrimoxazole (1DS 4 x daily for 10 days followed by 1 DS 2 x daily for 3 weeks) This infection is less likely to occur, however, in patients who are on cotrimoxazole prophylaxis. Cotrimoxazole is also treating cyclospora. In case of giardiasis, not responding to metronidazole, Nitazoxanide 1.5 g x 2 daily during 30 days may be effective.²⁶³



Annotations (level C)

(A) In patients who recently started on HAART, diarrhoea with fever can be part of an immune reconstitution syndrome- especially with TB or MAC. Patients usually have fever and are sick. Also Graves' disease has been described as IRIS and can give diarrhoea.²⁰⁹ Many antiviral drugs can cause diarrhoea but it occurs predominantly with protease inhibitors such as nelfinavir and lopinavir/rtv. PI-induced diarrhoea may decrease with CaCO₃ or with oat bran. If debilitating, consider constipating agents or switching to another HAART regimen.

(B) *Stool microscopy*: fresh examination and after concentration. Multiple stool samples may be necessary.²⁴⁹ At this level do a modified Kinyoun stain. It can indicate that protozoa are the cause of the chronic diarrhoea and this condition is best treated with HAART.

Stool culture: if available, will be useful to detect resistant enteropathogens. Systematic stool culture at this level may also help in orienting empiric therapy at the lower levels of care.

While waiting for the results of the stool exam a trial of antibiotics (cotrimoxazole or fluoroquinolones[†], in combination with metronidazole[‡]) is justified, but only if this is a new case of diarrhoea. Always consider previous treatment in order to avoid re-running the same algorithms every time without success. If your patient is referred from level B, and has reached the point where referral was necessary, wait for the results of the stool exam.

(C) Strongyloidiasis can be successfully treated with ivermectin 12 mg daily for 3 days. An alternative treatment is albendazole 400 mg 2 x daily for 5 days. A once-monthly maintenance therapy is necessary (albendazole 400 mg or ivermectin 6 mg once monthly). Trophozoites of *Entamoeba histolytica* should be treated with metronidazole 750 mg 3 x daily for 10 days followed by a contact-amoebicide: diloxanide furoate (Furamide®) 500 mg 3 x daily for 10 days or paromomycin 500 mg 3 x daily for 7 days. (In some countries Intetrix® is still available: 1 caps. 4 x daily for 10 days). *Giardia lamblia* is treated with metronidazole 250 mg 3 x daily for 5 days. *Isospora belli* is treated with higher than usual cotrimoxazole: 1DS 4 x daily for 10 days followed by 1 DS 2 x daily for 3 weeks. On rare occasions, Cyclospora, another protozoon, can be detected on the stains for Cryptosporidium. The Cyclospora oocysts are a little bit bigger (8-9 µm) than cryptosporidium oocysts (5 µm). Cyclospora can be treated with cotrimoxazole 1DS 4 x daily for 10 days, followed by secondary prophylaxis with cotrimoxazole. There is no good treatment for cryptosporidiosis. Often symptomatic control with anti-diarrhoeal agents is the only recourse. None of the treatments proposed in the introduction have really proven to be beneficial in large series, and they are expensive.

[†] In countries with high resistance rates for Salmonella and Shigella, initial treatment with fluoroquinolones should be considered.

[‡] Knowing that *Clostridium difficile* is probably more frequent than simple bacterial infections and can be worsened by antibiotic treatment, we recommend the concomitant use of metronidazole in empiric treatment for diarrhoea.

Therefore the only valid alternative for these patients is to start with HAART.

- (D) Frequent hospitalisation of AIDS patients and exposure to antibiotics puts them at high risk of infection with the toxin-producing strain of *Clostridium difficile*.²⁶⁰ 5%-30% of patients with Clostridium-associated diarrhoea relapse. The same treatment with metronidazole should be repeated.
- (E) At this point, a course of erythromycin might be tried in a dose of 500 mg 2 x daily for 5 days for Campylobacter dysentery.
- (F) In patients with chronic diarrhoea and fever without response to antibiotics and metronidazole, and where the stool exam did not reveal any significant abnormalities, the differential diagnoses comprises CMV enteritis, AIDS enteropathy, intestinal TB and atypical mycobacteriosis. If possible, a blood culture for mycobacteria can be helpful. Most people with GI CMV will also present with ocular lesions. In the absence of ganciclovir, the only available treatment is HAART. An abdominal ultrasound may reveal large intra-abdominal lymph nodes which makes the diagnosis of TB more likely. MAC should be suspected in patients with high fever, increased alkaline phosphatase and diarrhoea without other evident causes. In that case it is wise to start with anti-MAC treatment (clarithromycin and ethambutol) and delay the start of HAART a few weeks.
- (G) Loperamide or codeine phosphate. For symptomatic treatment see *Palliative Care* section. Treatment is often not successful, especially for cryptosporidiosis and microsporidiosis. Do not continue an ineffective treatment. Switch to symptomatic treatment and consider antiretroviral treatment carefully. This patient may have an underlying OI, not diagnosed so far. Soon after the start of HAART immune reconstitution may cause symptoms. Especially TB and MAC are known for this complication, called IRIS.

9.4 Symptomatic and palliative care

Diarrhoea

At all levels of care, time must be taken to instruct the patient's family in how to handle soiled bed linen and the disposal of faeces. It may be necessary to give them appropriate materials (gloves, buckets, etc.).¹⁸¹

- Maintain adequate hydration.
- Assure ready access to a bathroom or toilet.
- Use devices for incontinence (protective bed coverings, clothes, sheets, nappies, etc.) to prevent soiling.
- Keep the perianal region dry. If fissures or ulcers develop, use sit baths to improve hygiene and cover the lesions with zinc oxide ointment.
- Deodorise.
- Maintain dignity and privacy while toileting.
- Maintain good perianal care.

Cramping

If cramping is a problem, foods that may cause gas or cramps should be avoided: beans, cabbage, cauliflower, highly spiced foods, sweet or carbonated drinks. Increase bulk by providing fibre.

Transient diarrhoea

This can be managed by:

- Actapulgate: 2 tablespoons PRN (when needed), (in combination with furazolidone in home-care project in Nairobi).
- Aluminium antacids: 15-30 ml PO 6 x daily PRN.
- Bismuth salts: 15-30 ml 2-4 x daily.
- CaCO₃ 500 mg 3 x daily.

Peristalsis

This can be reduced by:

- Diphenoxylate (Lomotil®): 2,5-5 mg 4-6 x daily, max 20 mg/24hr.
- Loperamide (Imodium®) 4 mg PO first dose followed by 2 mg-4 mg after each unformed stool (max 16 mg daily).
- Codeine 30-60 mg 3-6 x daily. Maximum dose = 200-300 mg in a day.
- Strong opioids: morphine
 - for opioid-naïve: morphine 5-10 mg PO, SC every 4 hours
 - for those already receiving opioids: increase the dose by 25%-50%, or add codeine.

9.5 Laboratory techniques[§]

Level B

- *Stool microscopy*: multiple stool samples may be necessary.²⁴⁹ Examine the stools fresh and after concentration (the formol ether concentration technique is most frequently used).

Level C

- *Modified acid-fast stain*: Formaline specimens are concentrated by the formaline-ethyl acetate procedure. Formaline-treated concentrated stool sediment is coloured with modified Kinyoun (carbol fuchsin) staining. *Cryptosporidium* cysts stain pink and are small (5 µm). *Cyclospora* are a little bigger (8-9 µm) and *Isospora belli* oocysts are very big (20-30 µm).
- *Weber's modified trichrome method*: for the detection of microsporidia. Thin smears of unconcentrated stool-formaline suspension or of duodenal aspirates are stained (100 oil immersion fields should be examined). Against a blue or green counter stain, the microsporidia spores stain pink with a clear posterior vacuole and a pink diagonal stripe within the spore. Spores are small, 1-3 µm x 1,5 - 4 µm.
- *Stool culture*.

[§] Techniques are described in detail in 'District Laboratory Practice in Tropical Countries' Part 1. Monica Cheesbrough. Tropical Health Technology. Cambridge University Press 1998.



10 LYMPHADENOPATHY

10.1 Introduction

Swelling of lymph nodes is a frequently encountered symptom in HIV-positive patients. It is important to carry out a careful history and physical examination after which the cause of lymphadenopathy often becomes obvious. In more complicated cases, laboratory tests and a lymph node aspiration or biopsy may be necessary to establish a definite diagnosis.

The differential diagnosis includes:

HIV-related

- Persistent generalised lymphadenopathy (PGL)

Opportunistic infections

- Tuberculous lymphadenitis
- CMV
- Toxoplasmosis
- Syphilis
- Fungal infections: histoplasmosis, penicilliosis, cryptococcosis, etc.
- Infections with *Nocardia* species
- Visceral leishmaniasis (kala azar)

HAART-related

- Immune reconstitution inflammatory syndrome (IRIS)

Malignancies

- Lymphoma, Kaposi's sarcoma

Reactive lymphadenopathy

- Pyomyositis
- Pyogenic skin infections
- Ear, nose and throat (ENT) infections.

STI

- Inguinal lymphadenopathy can be due to donovanosis, chancroid or lymphogranuloma venereum.
- (See STI guidelines produced by WHO or MSF).

Other causes of lymphadenopathy

- Carcinomatous metastases
- Brucellosis
- Sarcoidosis
- Trypanosomiasis
- Rickettsial disease
- Infectious mononucleosis
- Drug reactions: e.g. phenytoin hypersensitivity.

10.2 Causes of lymphadenopathy

10.2.1 Persistent Generalised Lymphadenopathy (PGL)

PGL is a feature of HIV infection that develops in up to 50% of HIV-infected individuals. A patient who has PGL is in WHO stage 1. There is no specific treatment. The diagnostic criteria for PGL are as follows:

Lymph nodes larger than 1.5 cm in diameter, in 2 or more extra-inguinal sites, usually symmetrical, of duration of 3 or more months, more frequent in the beginning of HIV infection.

The nodes are non-tender, symmetrical, and often involve the posterior cervical, axillary, occipital and epitrochlear nodes. PGL may slowly regress during the course of HIV infection and may disappear before the onset of AIDS.

In populations with a high HIV prevalence, PGL is the commonest cause of lymphadenopathy. In HIV-positive patients, PGL is a clinical diagnosis. No further examinations are necessary, unless there are features of another disease.

Features of lymph nodes that warrant further investigation¹¹

- large (>4 cm diameter) or rapidly growing lymph nodes
- asymmetrical lymphadenopathy
- tender/ painful lymph nodes not associated with a local infection
- matted/fluctuant lymph nodes
- obvious constitutional symptoms (fever, night sweats, weight loss)
- hilar or mediastinal lymphadenopathy on chest X-ray
- suspicion of pulmonary TB
- evidence of abscesses (cutaneous, pulmonary, etc).

10.2.2 Tuberculous lymphadenopathy

This is one of the commonest forms of extra-pulmonary TB in HIV patients. The lymph nodes most commonly involved are the cervical nodes. The usual course of lymph node disease is as follows:

Firm, discrete nodes → fluctuant nodes matted together → skin breakdown, abscesses, chronic sinuses → healing with scarring.

Fluctuant cervical nodes that develop over weeks to months without significant inflammation or tenderness suggest infection with *M.tuberculosis*, atypical mycobacteria or cat scratch disease (*Bartonella henselae*).

In severe immunocompromised patients, tuberculous lymphadenopathy may be acute and resemble acute pyogenic lymphadenitis. In HIV patients there is a high rate of positive smears for acid-fast bacilli on wide-needle aspirates* of the involved lymph nodes. In smear-negative pulmonary TB it is worthwhile aspirating extra-thoracic lymph nodes to confirm the diagnosis of TB (80% positive, see chapter 7).

Miliary TB is an important consideration in patients with generalised lymphadenopathy. Many of these patients also have abdominal lymph nodes and present with abdominal pain (see chapter 8). Treatment should be started following the national TB guidelines.

* 18-Gauge wide needle aspiration of the largest node should be performed. Disinfect the skin; the plunger of a 10 ml syringe is pulled back as far as possible and three to five passes of the needle are made through the node. Material aspirated from the node is spread on glass slides, air-dried and examined for AFB using Ziehl-Neelsen or Auramine staining. Observe universal precaution during the procedure.

10.2.3 Secondary syphilis

Generalised painless lymphadenopathy occurs in 90% of patients with secondary syphilis. Other classic manifestations are maculo-papular, papular or pustular rash on the entire body, especially on palms and soles, locations that strongly suggest the diagnosis. Highly infectious lesions may also develop on mucous membranes (lips, mouth, pharynx, vulva, glans penis). These lesions, mucous patches, are silvery grey superficial erosions with a red halo, which are not painful unless there is a secondary infection. About 40% of patients will have CNS involvement during this stage, with headache and meningismus. The CSF shows increased protein and lymphocytic pleocytosis. Acute aseptic meningitis develops in 1%-2% of patients.

Although the CDC recommends the same treatment for primary and secondary syphilis in PLHA as in people who are HIV-negative (1 injection of benzathine benzyl penicillin 2.4 MIU IM), some clinicians prefer to give this injection once a week during 3 weeks in HIV patients.

In case of penicillin allergy:

- doxycycline 100 mg PO 2 x daily for 21 days, or
- ceftriaxone 1 g IM/IV daily for 14 days

PLHA often have high VDRL/RPR levels, and delayed regression to non-reactive levels, after apparently adequate treatment.^{264,265} It is important to follow-up VDRL after treatment, at 6, 12 and 24 months. If the VDRL fails to decline fourfold over 6-12 months, the patient must be retreated and a CSF examination done to rule out neurosyphilis.^{266,267} In case of neuro-syphilis, treat with penicillin G 18-24 MIU/day IV 14 days.

10.2.4 Visceral leishmaniasis (kala-azar)

Epidemiology

According to data from the World Health Organization the areas where HIV/*Leishmania* co-infection is distributed are extensive.²⁶⁸ It is a particular frequent co-infection in HIV-positive IV drug users (IVDU) in the Mediterranean countries and in HIV patients in Somalia, Sudan, Eritrea, Ethiopia and certain zones in Kenya. In Asia, co-infections are increasingly being reported from India, Bangladesh and Nepal, countries that are also facing antimonial resistance.²⁶⁹

HIV infection is leading to an increase in incidence of visceral leishmaniasis (VL), often with a more severe and prolonged course, and a poorer response to treatment with a high rate of relapse.

Due to impaired cellular immunity in HIV, VL in HIV patients is also characterised by the presence of numerous leishmanial amastigotes in the skin and peripheral blood. HIV-infected patients become infected either after a bite by an infected sandfly or by use of contaminated syringes. Therefore, HIV-infected individuals enlarge the number of human reservoirs in areas where transmission of leishmaniasis is already anthroponotic and add an

anthroponotic focus of transmission in areas where the spread of leishmaniasis has traditionally been zoonotic. 50% of HIV+ VL cases in Spain are IVDU, and they constitute a reservoir of the parasite.²⁷⁰ Needle sharing by intravenous drug users (IVDUs) has been proposed as providing an alternative, artificial, and anthroponotic cycle for Leishmania transmission.²⁷¹ In Spain VL is the fourth most common opportunistic parasitic disease in HIV-positive individuals in Spain after pneumocystosis, toxoplasmosis, and cryptosporidiosis.²⁷²

Clinical presentation

VL cases in HIV-positive individuals present with the clinical features of classic kala-azar. Splenomegaly is less frequent, but cytopenia is more frequent in HIV-infected patients than in immunocompetent individuals.

Constitutional symptoms (asthenia, anorexia and loss of weight) are seen in approximately 50-70% of co-infected patients, and **lymphadenopathy** is seen in 15-60% of patients.

Frequently, VL is diagnosed during the assessment of a fever of uncertain origin.

In countries where there is a combined problem of IVDU, HIV infection and visceral leishmaniasis, this diagnosis should be considered in every HIV patient with fever. In Spain, Italy and Portugal, 17% of HIV-positive patients who present with fever have visceral leishmaniasis.

Most cases of leishmaniasis in HIV-positive patients appear in the advanced stages of disease (in 77-90% of patients, the CD4 is <200), and as such visceral leishmaniasis behaves as an opportunistic infection.²⁷³ It is considered that 33-78% of co-infected patients with a first episode of VL have had a previous AIDS defining event.²⁷⁴

However, VL can be the first HIV-related serious infection in 13 to 47% of patients.^{223,272,275}

Cutaneous involvement of VL is a rare finding but it is characteristic of HIV-related VL. Specimens from skin lesions should be obtained whenever there is a suspicion of leishmaniasis in HIV-infected patients. Any Leishmania amastigotes found in a skin biopsy of an HIV-infected patient should raise in the first place the suspicion of VL rather than a primary cutaneous leishmaniasis.

Diagnosis

Because of deficits in humoral and cellular immunity, skin test (Montenegro) and antibodies are less useful in HIV/Leishmania co-infection.²²¹ Only about 40-50% of HIV/Leishmania co-infected patients have a positive Leishmania serology.^{272,276} There is a problem of cross-reactions with other OI.

The gold standard for the diagnosis of leishmaniasis in HIV-infected patients remains the isolation or identification of the parasite. Samples of tissue or body fluid can be smeared, stained (Giemsa stain) and examined for amastigotes under the microscope. Bone marrow aspirates are sensitive and safe.

Because of dissemination of the parasite in HIV patients there are high

numbers of amastigotes in the peripheral blood. The direct examination of amastigotes in peripheral blood provides the diagnosis in up to 50% of patients, and when using the buffy coat the sensitivity increases to 70%.^{277,278}

Treatment

Treatment is similar as in HIV-negative patients. Meglumine antimoniate (20 mg/kg/day) has demonstrated similar efficacy and toxicity rates than amphotericin B (0.7 mg/kg/day) both given for 28 days.

The problem in HIV patients is the low rate of clinical and parasitological response, and frequent relapses. Only about 60% of patients respond clinically or parasitologically to therapy regardless of the regimen used. Part is explained because of early interruption of treatment due to side effects, especially with amphotericin B. For patients completing the 28 days of amphotericin B the response is 85%-93%, however, 25-60% of patients experience relapses during the first year after treatment completion.^{271,272,279}

HIV-infected patients are more likely to suffer treatment-related adverse events than the HIV-negative population.^{279,280}

Pentavalent antimonials remain the treatment of choice for HIV-associated VL because the efficacy and the rate of adverse events are comparable to amphotericin B, with less cost. Due to the emergence of parasite resistance in India, amphotericin B is the treatment of choice in this region.²⁶⁹

A new drug, miltefosine, an oral drug, will hopefully improve the future treatment of HIV-positive patients.²⁸¹

Assessment of efficacy of treatment is difficult because patients die due to advanced AIDS < 200. Death occurs in 11-27% patients in the month following the diagnosis of VL.

Prevention and Treatment of Relapses

No specific studies are available comparing the different alternatives to prevent or to treat relapses of VL in HIV co-infected patients. In case of relapse liposomal amphotericin B is effective, but does not prevent future relapses.

Antimonials are considerably less effective in relapse.

Secondary Prophylaxis

The monthly administration of 20 mg/kg meglumine antimoniate or sodium stibogluconate, intravenously or intramuscularly seems to prevent relapses. Amphotericin B monthly or every 3 weeks (0.3 mg/kg) is another regimen used.

HAART and VL

Although HAART seems to be effective in preventing or decreasing annual disease incidence, the effect of HAART on leishmaniasis is not as clear cut as for other OI.

70% of patients still experience relapse < 24 months even when VL is undetectable.²⁷⁴ *Leishmania* secondary prophylaxis can be withdrawn when

CD4 > 200.²⁸²

VL has a negative effect on immune recovery with HAART.

10.2.5 Deep fungal infections

Disseminated fungal infections can present with fever and lymphadenopathy. There are often concomitant skin lesions (*Penicillium marneffe*, *Cryptococcus neoformans*) or lung lesions (*Histoplasma capsulatum*). Biopsy for histology and culture of skin lesions or lymph nodes usually reveals the diagnosis. Diagnosis can sometimes be made based on needle aspiration. Initial treatment for histoplasmosis and penicilliosis is amphotericin B for moderate-to-severe cases: 0.7 mg/kg IV during 10 days followed by itraconazole 200 mg 3 x daily for 3 days, then 200 mg 2 x daily for 12 weeks. For mild cases the induction with amphotericin B can be omitted.²⁸³ Careful: itraconazole needs an acid pH and should be taken with an acidic drink. Itraconazole has a lot of interactions with NNRTI and PI. As long as a patient is on itraconazole, triple nukes should be considered. Itraconazole 200 mg daily is the preferred lifelong maintenance therapy. If itraconazole is not available, use ketoconazole 400 mg daily. For cryptococcosis, 2 weeks amphotericin B (IV) 0.7 mg/kg daily followed by fluconazole 400 mg once a day for 8-10 weeks. After that, maintenance therapy consists of fluconazole 200 mg once a day. Lymph node involvement was extremely rare before the HAART era, but now several case reports exist of patients who present with IRIS due to cryptococcosis a few weeks up to 8 months after the start of HAART.

10.2.6 Lymphoma and Kaposi's sarcoma

The diagnosis is confirmed by histopathology. Kaposi's sarcoma often presents with characteristic skin lesions. Lesions can be found in the oral cavity, the gastro-intestinal tract and the respiratory tract as well. If there is lymph node involvement with a limited number of skin lesions and no oedema, HAART alone is probably enough to cause a regression of the lesions (see chapter 15). When skin lesions are extensive and massive lymph oedema is present chemotherapy will be needed in addition to HAART. Radiotherapy is also effective in reducing lymph oedema due to KS. The prognosis of HIV-related lymphoma has improved with HAART; however, the chemotherapeutic drugs to treat lymphoma are usually not available in developing countries.

10.2.7 Nocardiosis

While nocardiosis is a rare cause of lymphadenitis in immune-competent patients, the diagnosis should be considered in HIV-infected patients with chronic lymphadenopathy and abscesses (skin, pulmonary, etc.). The organism may stain weakly acid-fast. However, they are morphologically different from the Koch bacilli because of their long branching thread-like filaments. Nocardia organisms are easily recognised on Gram stain (see chapter 7). The recommended treatment for Nocardia is cotrimoxazole 10/50

mg/kg 2 x daily or minocycline 100 mg 2 x daily combined with amikacin 15-25 mg/kg daily or ceftriaxone 2 g daily combined with amikacin. The use of aminoglycosides should be limited to 2 weeks.

10.2.8 Lymphadenopathy in the framework of immune reconstitution inflammatory syndrome (IRIS)

The topic of IRIS is extensively discussed in chapter 16. IRIS is defined as a clinical deterioration due to clinically silent diseases becoming evident after the introduction of HAART. IRIS may also occur in those who are receiving appropriate treatment for a previous recognized OI, together with HAART. Despite the clinical deterioration, IRIS indicates a successful (but undesirable) effect of HAART: IRIS is in most cases associated with a marked fall in VL and a rapid increase in CD4 (often to a level well above the threshold for certain OIs). The risk for IRIS is higher when the CD4 count at initiation is low (<50 cells/mm³) and when HAART is initiated shortly after the treatment of OI.²⁰⁸ IRIS often occurs in the first weeks or months after starting HAART, but a second wave of IRIS up to more than 3 years later has been observed. It is a manifestation of the increased reactivity of the immune system after the instauration of HAART against a latent infection or against residual antigen in the tissues.

Focal lymphadenitis is a typical manifestation of *Mycobacterium avium complex* (MAC) and *Mycobacterium tuberculosis* (TB) associated IRIS, clearly differing from the classic disseminated multi-organ disease in advanced immune-deficiency. The lymphadenitis is often painful and associated with fever. Worsening radiographic appearances or inflammatory masses (e.g. skin) can be present as well. The peripheral lymphadenopathy may be associated with lymphadenitis in other locations (e.g. intra-thoracic, abdominal).

The histological examination of the lymph nodes reveals granulomatous inflammation, sometimes containing acid-fast organisms. MAC or TB can be cultured from the lymph nodes and blood, but a negative culture certainly does not exclude MAC or TB IRIS.

Cryptococcus species can also cause lymphadenitis in the framework of IRIS. Systemic and neurological signs can be absent. Culture of aspirated pus is usually negative, organisms can be found on pathology specimens. A combination of antifungal and anti-inflammatory treatment usually leads to cure.²⁸⁴

Other diseases associated with IRIS causing lymphadenopathy are Kaposi's sarcoma²⁸⁵, presenting with non-tender LN and increase of pre-existing lesions, lymphoma²⁸⁶, Histoplasma species, *Bartonella henselae*²⁸⁷ and sarcoidosis.²⁸⁸

The majority of cases of lymphadenopathy in the framework of IRIS can be managed by continuing the HAART, and adding the specific antimicrobial or antitumoral treatment. In case the patient was already taking the antimicrobial treatment when developing the IRIS, an intensification/modification of therapy

is not required. In case of serious and/or persisting symptoms (EXCEPT in KS IRIS), prednisolone should be added (e.g. prednisolone 1 mg/kg, 2 weeks -1 month) and tapered off according to the clinical evolution.^{208,289-291} Surgical drainage of the lymph nodes might be required.

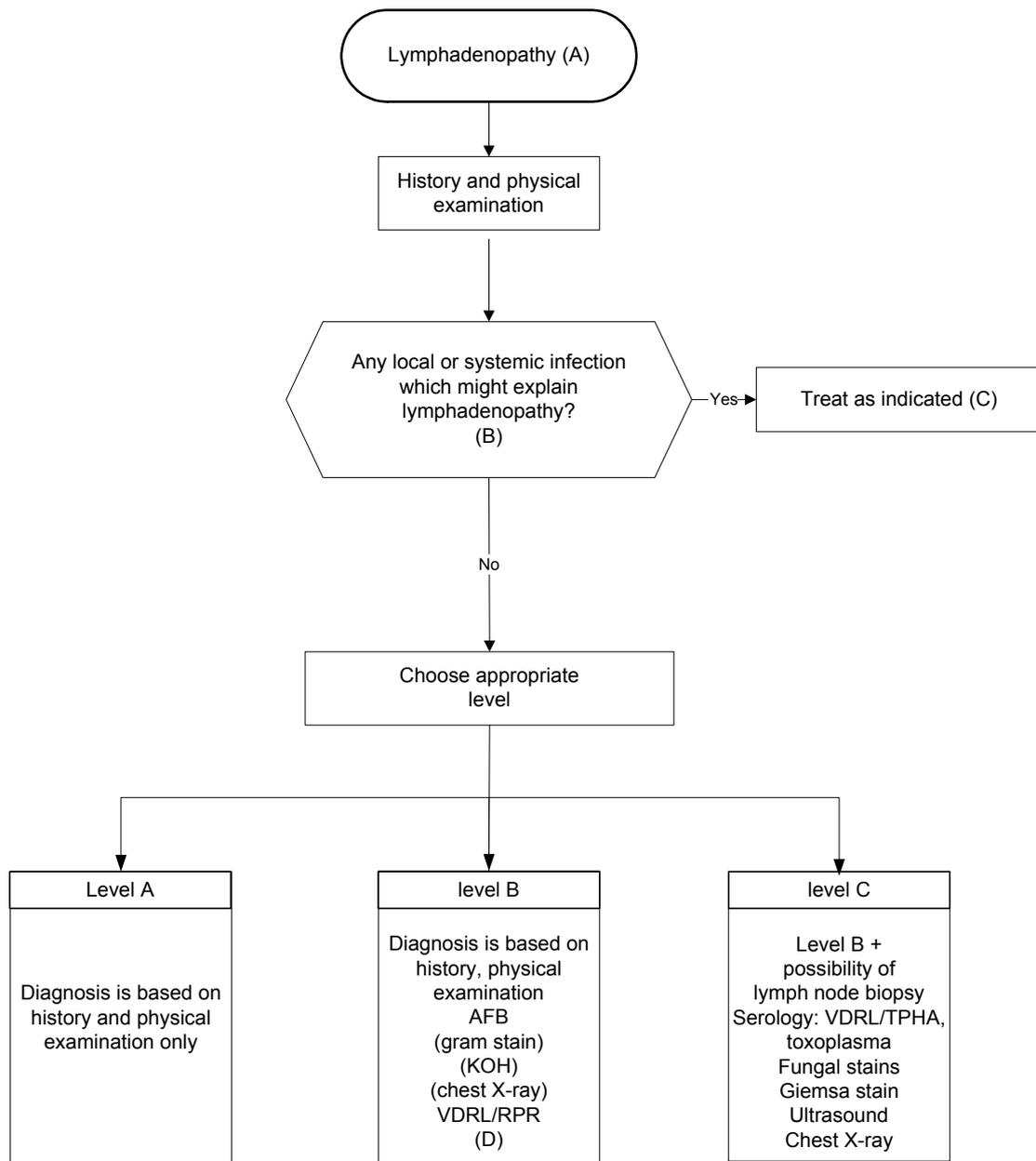
For cryptococcal or MAC lymphadenitis occurring more than a year after the instauration of HAART, in the framework of IRIS, one could consider to observe the patient closely. In some of these cases, the lymphadenitis may not require specific MAC or cryptococcus treatment.²⁰⁸

10.3 Clinical management of lymphadenopathy in HIV patients

PGL is very frequent in HIV patients, but other treatable conditions need to be excluded. Therefore the algorithms try to identify those lymph nodes that need further investigation.

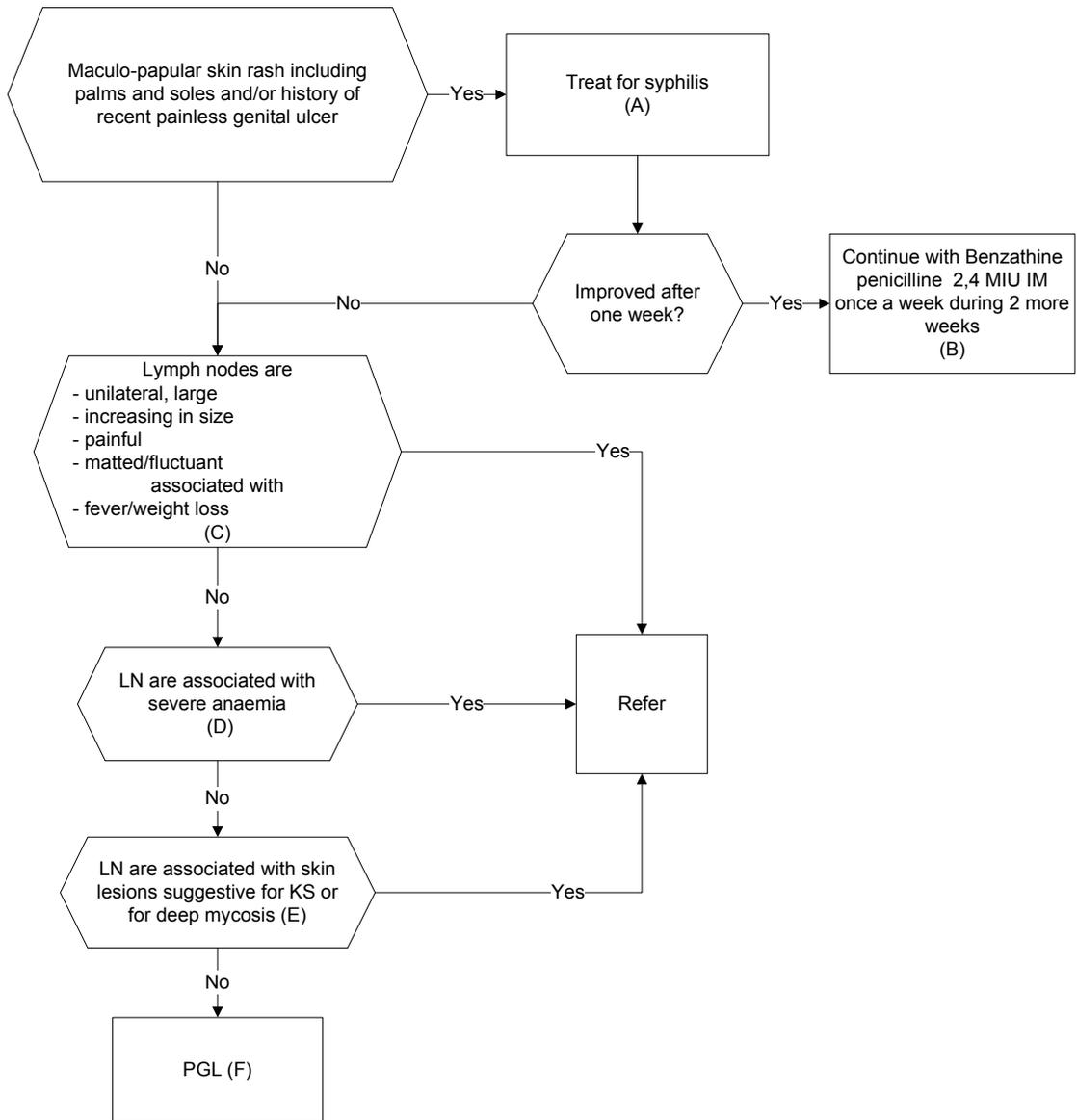
Syphilis, although not very frequent, is considered in most algorithms as the first condition to treat. Penicillin is a widely available antibiotic and it is therefore good to consider this diagnosis before undertaking more invasive tests like biopsies.

Lymphadenopathy



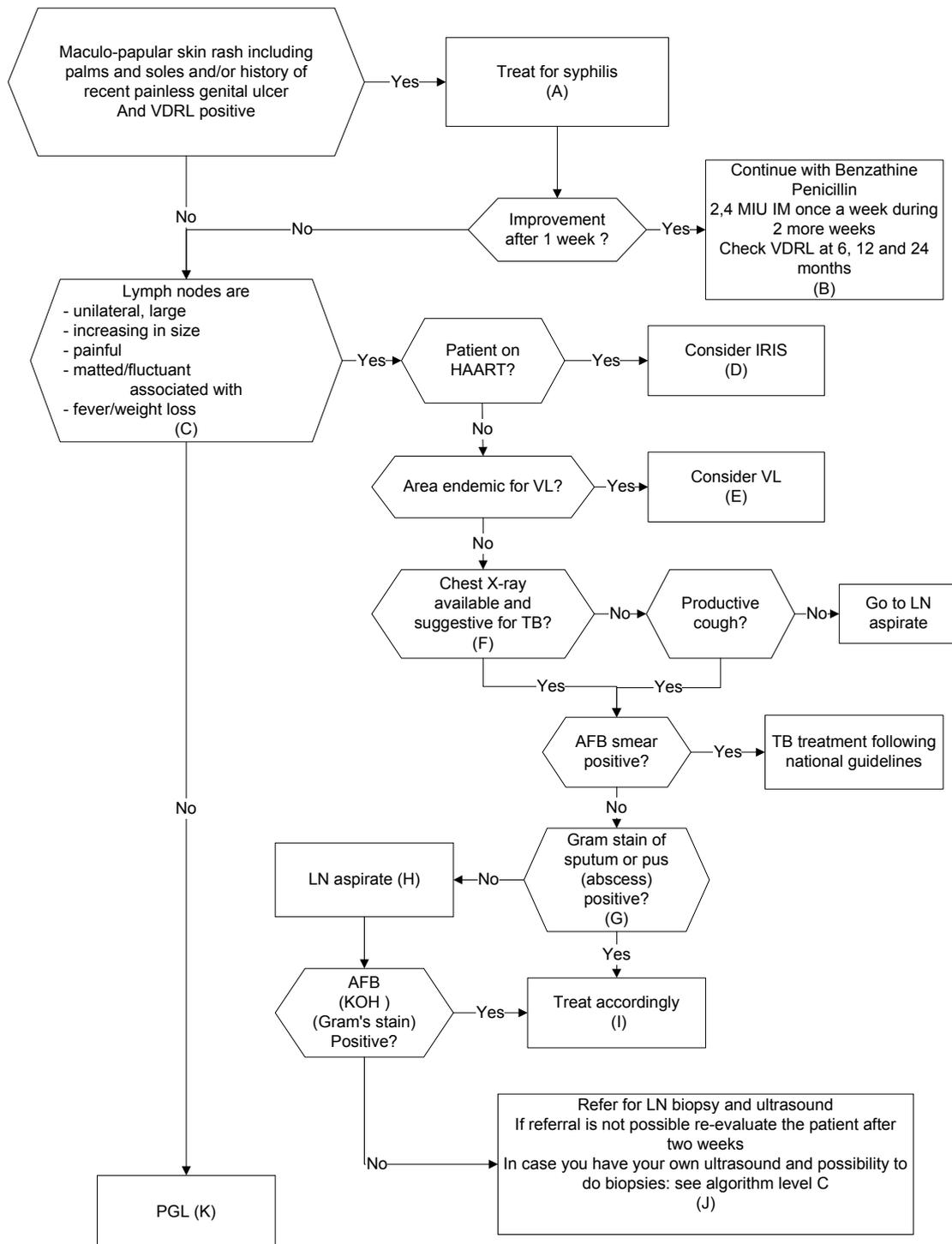
Annotations Lymphadenopathy

- (A) Any lymph node swelling in a PLHA. For possible causes, see page 170.
- (B) In early HIV, upper respiratory tract infections are common, and painful cervical lymph nodes are often reactive lymph nodes in the drainage area of ENT infections. Any pyogenic infection can cause regional lymphadenopathy. Many infectious diseases that are prevalent in tropical countries also need to be considered: sleeping sickness in Africa, rickettsial diseases after tick bite or epidemic louse-borne-typhus, bubonic plague, brucellosis.
- (C) From the history and the physical examination, try to narrow down the different diagnostic possibilities. Cervical lymphadenitis that has developed from a pharyngeal or periodontal focus responds well to penicillin treatment, e.g. penicillin V 500 mg 4 x daily, or amoxicillin 500 mg -1 g 3 x daily. Pyogenic lymphadenitis and complicated skin infections usually originate from staphylococcal or streptococcal infections. In these cases, the preferred treatment is a penicillinase-resistant penicillin such as flucloxacillin. In the more acutely-ill patient, IV antibiotics are preferred (penicillinase-resistant penicillin such as cloxacillin, flucloxacillin or a first generation cephalosporine like cefazoline). If there is no improvement, surgical drainage or aspiration to detect other pathogens is necessary (tuberculosis, nocardiosis, etc.).
- (D) Health centres with medical doctors, or district hospitals that see a lot of HIV patients, should include simple staining techniques such as KOH and Gram stain of needle aspirate of lymph nodes to broaden their diagnostic capacities. Stains for AFB are a priority when a microscope is available, and when quality control is feasible. In areas where leishmania/HIV co-infection is a problem a Giemsa stain of blood smears can provide the diagnosis in 50% of cases. If no chest X-ray is available, referral to the next level or request for an X-ray in another facility should be considered, depending on what is financially or geographically acceptable for the patient.



Annotations (level A)

- (A) This symptom set suggests secondary syphilis. See page 172.
- (B) In HIV-infected patients with syphilis the response to treatment needs to be closely monitored by following up the VDRL/RPR. At 6 months at least a 4-fold decrease in titer should be noted.
- (C) At level A, the health care worker has to look for features of lymph nodes that indicate further investigation: see page 171.
In case the patient was recently started on HAART, IRIS due to underlying mycobacterial or fungal infections could cause big abscesses and lymphadenitis.
Refer the patient for further investigation.
- (D) In areas endemic for visceral leishmaniasis, this diagnosis has to be considered in patients presenting with fever and cytopenia.
- (E) KS skin lesions could be treated with HAART alone, but a careful physical exam and more investigations are needed to determine the stage of KS. The diagnosis and treatment of systemic mycoses are usually not possible at level A.
- (F) Persistent generalised lymphadenopathy. In an asymptomatic patient no further investigation or treatment is necessary. This is a WHO stage 1 condition. The patient should be reassured. However, the patient should be asked to come back whenever constitutional symptoms develop, or the lymph nodes tend to increase in size. In that case, referral to level B for further evaluation will be necessary.

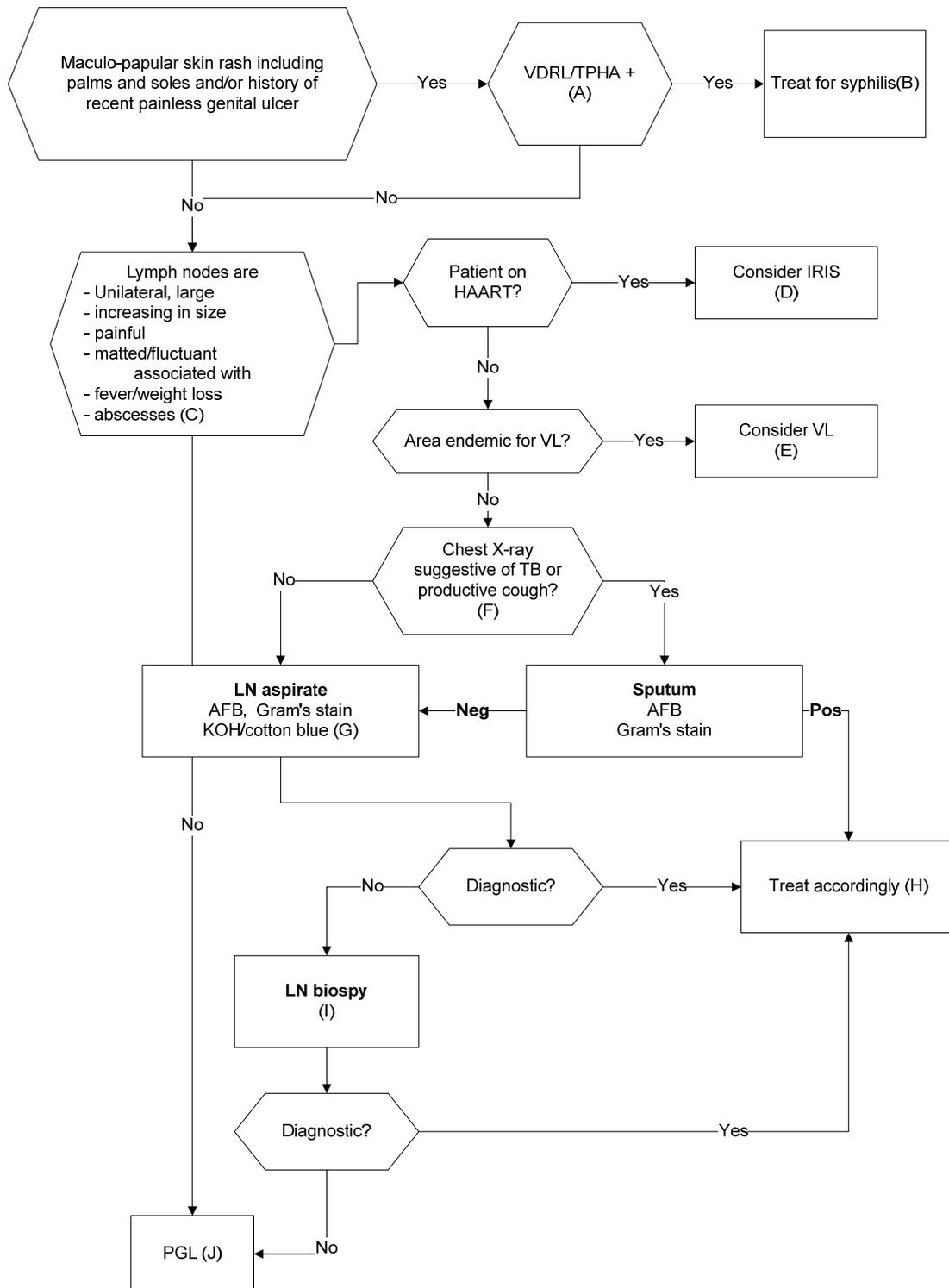


Annotations (level B)

- (A) Although the CDC recommends the same treatment for primary and secondary syphilis in PLHA as in people who are HIV-negative, some clinicians prefer the once weekly benzathine benzyl penicillin 2.4 MIU IM, during three weeks. In case of penicillin allergy doxycycline or ceftriaxone can be used (see page 172).
- (B) Although there is a clinical improvement, VDRL decline is often delayed. Repeat VDRL test after 6, 12 and 24 months. Earlier relapses of mucocutaneous disease can occur, and are usually accompanied by a sharp rise in VDRL. In that case, the patient needs to be re-treated.
- (C) Certain lymph nodes need investigation: see page 171.
- (D) Patients on HAART can develop lymph nodes in the framework of an immune reconstitution inflammatory syndrome (IRIS), especially with TB and MAC, but also with *Cryptococcus* and malignancies. See page 176.
- (E) Especially in patients who have severe anaemia, and live in an area endemic of visceral leishmaniasis, it is worthwhile to exclude this diagnosis (Giemsa Stain, DAT serology). If this is not possible in your centre, go through the rest of the algorithm, before referral, because also TB and MAC can cause anaemia.
- (F) When you don't have a chest X-ray, or the chest X-ray is not suggestive of TB, but the patient has productive cough, it is useful to do a sputum acid-fast (AFB) stain. If there is no sputum production, go to lymph node aspirate (see H). If the sputum is positive for AFB, start TB treatment according to national guidelines.
- (G) *Nocardia* may present with upper lobe cavitary lung disease and lymphadenopathy. A Gram stain of sputum and/or of pus obtained from a subcutaneous abscess will show Gram-positive, long, branching, thread-like filaments. Treatment consists of cotrimoxazole 10/50 mg/kg 2 x daily for 6 weeks to 6 months.
- (H) Do a wide needle aspirate (18G needle) of lymph nodes, without anaesthesia, and stain the material for AFB and Gram stain (and KOH).
- (I) In patients with fluctuant nodes or with fistula, pus may be stained for AFB at an earlier stage. If you can do a Gram stain, you will be able to detect pyogenic lymphadenitis and *Nocardia* infections. KOH preparation may allow you to find hyphae and yeast cells in systemic mycosis. Most of the deep mycosis require tissue diagnosis and special stains. For the treatment of the different pathologies, see Introduction section.
- (J) If the chest X-ray is suggestive of TB and the needle aspiration did not yield a diagnosis, you could also follow here the algorithm of suspect smear-negative TB. In case of lymphadenopathy without associated

respiratory signs or symptoms, in some situations an abdominal ultrasound may show intra-abdominal enlarged lymph nodes, suggesting tuberculosis.

(K) Likely PGL. However ask the patient to return whenever he develops systemic symptoms or the lymph nodes increase in size.



Annotations (level C)

- (A) VDRL/RPR can be false positive. TPHA is a confirmatory test. If the patient has symptoms of secondary syphilis, but the VDRL/RPR is negative, repeat the VDRL after dilution of the serum (prozone effect: see also chapter 14). Repeat the VDRL test after 6, 12 and 24 months. If the VDRL fails to decline, re-treat the patient and do an LP to exclude neuro-syphilis.
- (B) Although the CDC recommends the same treatment for primary and secondary syphilis in PLHA as in people who are HIV-negative (single dose Benzathine Penicillin), some clinicians prefer the once weekly benzathine benzyl penicillin 2.4 MIU IM, during three weeks. In case of penicillin allergy doxycycline or ceftriaxone can be used (see page 172).
- (C) Lymph nodes that require further investigation: see page 171.
- (D) Patients on HAART can develop lymph nodes in the framework of an immune reconstitution inflammatory syndrome (IRIS), especially with TB and MAC, but also with cryptococcosis and malignancies. Investigations for the causative OI should be done including LN aspirate and biopsy. Blood cultures can be considered but will often be negative. HAART should be continued, except in the case of life-threatening situations (e.g. associated intra-thoracic lymph nodes causing dyspnoea). Treatment for OI should be started if the patient is not yet taking it. Steroids (prednisolone 1 mg/kg/day) should be added in case of a serious/persisting problem. Surgical drainage is sometimes necessary. If possible, exclude a drug-resistant OI (e.g. MDR TB). In case of late IRIS, perform a viral load to differentiate late IRIS from failure of the HAART regimen.
- (E) In countries where visceral leishmaniasis and leishmania/HIV co-infection is a common problem, this diagnosis should be suspected in patients with lymph node swelling and pancytopenia. A blood or bone marrow smear stained with Giemsa has a sensitivity of 50%, and when using the buffy coat the sensitivity goes up to 70%. Treatment and secondary prophylaxis: see page 174-174.
- (F) In case of an abnormal X-ray, the next logical step is a sputum exam for AFB and a Gram stain. But even in a patient with a normal chest X-ray who presents with productive cough, a sputum exam for AFB and a Gram stain is worthwhile.
- (G) If the patient has a chest X-ray compatible with TB, but remains smear-negative, and does not respond to antibiotics, a wide needle aspirate of extra thoracic lymph nodes is a sensitive method to confirm the diagnosis. In patients with normal chest X-rays but with fluctuant nodes or with fistula and sinuses, it is probably more effective to stain pus immediately for AFB and do a Gram stain and cotton blue stain (or KOH). An abdominal ultra-sound may reveal big peri-aortic LN with central necrosis suggestive of tuberculosis.

- (H)- Nocardia: high dose cotrimoxazole.
- TB: TB treatment.
 - Fungal infection: amphotericin B + fluconazole or itraconazole / ketoconazole (see *Introduction* section).
- (I) If after a LN aspirate, an X-ray and a sputum exam, the diagnosis is still not clear, a lymph node biopsy is justified. In case of skin lesions, it is useful to do a skin biopsy as well. Always make touch preparations of the cut surface and stain them for bacteria, fungi, leishmania (in case of endemic area) and mycobacteria. When the cut surface of the lymph node shows caseous material, treat for TB. Histology will also yield the diagnosis of malignancies (lymphoma, Kaposi's sarcoma), fungal infections and granulomatous infections like tuberculosis. When only hyperplasia of lymph nodes is seen PGL is more likely.
- (J) In the asymptomatic patient no treatment is required.



11 ORAL LESIONS

An excellent review with good photographic illustrations of the most common oral manifestations in PLHA was published in 1998 on the website of HIV Insite and can be accessed free of charge.²⁹²

11.1 Introduction

Many different conditions involving the oral cavity are encountered in patients with AIDS. The most frequent are oral candidiasis, oral hairy leukoplakia, necrotising ulcerative gingivitis and recurrent aphthous stomatitis. An examination of the mouth needs to be part of the physical examination of every patient suspected of HIV infection, even in the absence of complaints. In practice, people often present with another complaint and it is the presence of oral thrush that raises the suspicion of HIV infection. Sometimes oral lesions are debilitating because they interfere with correct nutrition and increase the risk of weight loss. Oral disease significantly affects quality of life in HIV patients.²⁹³ Some mouth lesions have a prognostic value, and are helpful to determine the stage of HIV disease, in the absence of viral load and CD4 count.²⁹⁴ Since the use of HAART the prevalence of oral lesions has significantly decreased, except for oral warts.²⁹⁵ No studies have evaluated the usefulness of oral lesions to predict treatment success or treatment failure in patients who are treated with HAART in the absence of viral load and CD4 count.²⁹³

11.2 Aetiology of oral lesions

11.2.1 Acute primary HIV infection

90% of patients develop symptoms 3-6 weeks after the primary infection. However, it is often not recognized as acute HIV. Oral lesions that may be found during this acute phase are HIV mouth ulcers and oral candidiasis. Primary care providers should suspect HIV infections in patients who present with these types of mouth lesions. Accompanying symptoms are fever, myalgia and headache.

11.2.2 Oral hairy leukoplakia

OHL is present in up to 30% of patients with HIV in developing countries.²⁹⁶ It is less frequent in children. This condition is neither dangerous nor painful. It presents as non-removable whitish plaques with vertical folds, mostly on the lateral surface of the tongue, and is caused by the Epstein-Barr Virus (EBV). If the lesions are very extensive taste may be affected. It does not require any treatment. However, OHL is a sign of immune suppression, implies a high viral load and heralds a poor prognosis without HAART.

11.2.3 Oral thrush

Candida albicans is an endogenous yeast. In healthy individuals it dwells predominantly in the gastrointestinal tract, and sometimes in the respiratory tract. It can be pathogenic in immunocompromised patients.

Oral candidiasis is frequently the first indication of immune impairment in HIV-infected patients. It is often used as an indicator disease for starting cotrimoxazole prophylaxis. One study showed that 59% of patients with an episode of oral thrush acquired a major OI or KS at a median of 3 months, if $CD4 < 200$.²⁹⁴ Over 60% of patients with $CD4 < 100$ will develop oropharyngeal candidiasis each year. Oesophageal candidiasis will develop in 10%-20% of AIDS patients.²⁹⁷

Pseudomembranous candidiasis (thrush) is characterised by white sloughs covering areas of superficial ulceration on the gums, palate and tongue, which contain many yeast organisms and are readily detached. In severe cases, these lesions extend into the lower pharynx and oesophagus to cause dysphagia, nausea and epigastric pain. Recurrent episodes of oral candidiasis usually occur in patients with $CD4 < 300$.²⁹⁸

Oropharyngeal candidiasis may present atypically with erythematous lesions, with atrophic ulcers or as angular cheilitis with localised disease at the corners of the mouth. Before starting a trial with antifungal drugs, it is useful in these atypical presentations to demonstrate the presence of budding yeasts and pseudohyphae in mouth scrapings (Gram stain or potassium hydroxide (KOH)), in order to avoid sequential drug trials and resistant candida infections. Indeed, if only yeast cells are found without pseudohyphae, this is an indication of colonisation of the oral cavity rather than infection.

Topical antifungal therapy

Topical therapy requires contact for a sufficient time (20-30 minutes) between the drug and the oral mucosa and sufficient saliva to dissolve the medication. Treatment with only topical agents becomes less effective once the disease progresses.

Nystatin: one tablet 500,000 IU 4 x daily; tablets should be sucked and retained in the mouth for as long as possible. Therapy should be continued for

at least 48 hours after symptoms have resolved. The suspension is less effective because of shorter contact time with the oral mucosa.

Gentian violet: local application of Gentian Violet 1% aqueous solution 2 x daily for 1 week is effective. However, the acceptability of this treatment may be low in adults.

Miconazole gum patch once daily for 7 days. Case reports also mention its efficacy in treating oesophageal thrush.*

Miconazole oral gel: 60 mg 4 x daily

Ketoconazole: less effective and less well tolerated

Continuous use of antifungals should be avoided, except in patients who have been treated for systemic fungal infections and patients with severe and recurrent oropharyngeal candidiasis (OPC).

Systemic therapy

Where no improvement is seen after 7 days of a topical treatment, a switch should be made to a systemic antifungal therapy.

First choice:

Fluconazole: 200 mg daily until symptoms have resolved. Doses of up to 400 mg daily have been used in resistant cases. Fluconazole is preferred to ketoconazole and itraconazole, because they are hepato-toxic and interacting with some ARVs. Both are also contra-indicated in patients on TB treatment (INH, rifampicin).

Second choice:

Itraconazole: Doses start at 100 mg 2 x daily and can be increased to a maximum of 400 mg daily, for 10-14 days. The capsules should be taken with food or an acid drink (e.g. coca-cola,) to increase their bioavailability. Drugs that increase the pH of the stomach (i.e. antacids, H2 blockers) can lead to decreased itraconazole absorption. Concurrent rifampicin therapy should be avoided: rifampicin induces the metabolism of itraconazole, and itraconazole is thought to inhibit the absorption of rifampicin.

Third choice:

Ketoconazole*: 200 mg - 400 mg daily until remission is obtained. Concurrent rifampicin therapy should be avoided: rifampicin induces the metabolism of ketoconazole and itraconazole resulting in decreased plasma levels of theazole drug. Ketoconazole is thought to inhibit the absorption of rifampicin.

* Its low price (US\$1 per week) makes it an interesting alternative. Moreover, the compliance with this formulation is very good and it is an ideal drug to use in the home care setting. Unfortunately, this drug is not yet widely registered

* In the 1999 WHO MEDL (Model Essential Drug List), ketoconazole was replaced by fluconazole, which has a better therapeutic profile and less hepatotoxicity.

Treatment should be withdrawn in case of evidence of severe hepatocellular damage.

11.2.4 Oral manifestations of deep systemic mycosis

Cryptococcosis, penicilliosis, histoplasmosis and aspergillosis can all present with palatal, lingual, gingival, and labial papules or ulcers. A definitive diagnosis is made by culture or biopsy. However, accompanying systemic signs may suggest the diagnosis of a deep mycosis (pulmonary lesions, CNS infections, fever and lymphadenopathy).²⁹⁹

The treatment of cryptococcosis is amphotericin B and fluconazole (see chapter 14). Penicilliosis, aspergillosis and histoplasmosis are treated with amphotericin B 0.7 to 1mg/kg for 2 to 3 weeks. As soon as the patient improves clinically and fever has disappeared, the therapy can be switched to itraconazole 200 mg twice daily. For mild cases, use itraconazole 200 mg three times daily for three days to achieve steady state serum concentrations more rapidly and then 200 mg once or twice daily, depending upon the severity of the infection.³⁰⁰

11.2.5 Aphthous ulcers

The aetiology of recurrent aphthous stomatitis is unknown.²⁹³ This condition, involving any part of oral mucosa, can lead to painful large lesions. To distinguish aphthous ulcers from herpetic lesions it is important to check the localisation. Herpetic ulcers are located exclusively on the keratinised mucosa (hard palate and gingiva) and rarely on the dorsum of the tongue; while aphthous ulcers typically appear on the non-keratinised mucosa.²⁹² Steroids are very effective for deep ulcers of unknown origin (1 week prednisolone 20-40 mg daily). However, avoid long-term use of steroids in HIV patients because of the additional immune suppression they cause. Treatment with painkillers and topical use of antiseptics can be helpful.

As an alternative for large ulcers, a suspension of 1 tablet tetracycline 250 mg dissolved in 15 cc of water can be tried. This suspension should be kept in the mouth for a few minutes while gargling and preferably not swallowed. Bartlett gives a composition of a Mile's solution for mouthwashes 1 to three times a day.²⁸³

- 60 mg hydrocortisone
- 20 cc nystatin suspension
- 2 g tetracyclines
- 120 cc of viscous lidocaine .

A small randomised controlled trial showed significant benefit of thalidomide in recurrent oral aphthosis. But 80% of patients experienced side-effects, although these were mild (skin rash).³⁰¹ Because of its teratogenicity, the side effects (skin rashes and neuropathy with prolonged use) and because of its low availability (only through special access programmes e.g. leprosy programmes) it is unlikely that this drug will be available in resource poor

settings for the treatment of oral ulcers in HIV patients.

Some prescribers use colchicine 0.6 mg 2 x daily. However, a systematic review showed insufficient evidence of efficacy against aphthous ulcers.

11.2.6 Necrotising ulcerative gingivitis

This condition is seen in 17 to 27% of HIV patients in developing countries.^{299,302} This is an inflammation of the gums that can become very extensive and necrotic and may lead to tooth loss. It also causes an increase in salivary viral load.²⁹⁹ It is caused by oral anaerobic flora and thus responds frequently to oral hygiene, antiseptic mouthwashes and antibiotics effective against anaerobic infections.²⁹³

- metronidazole 500 mg, 3 x daily for 7 days, or
- penicillin V 500 mg, 4 x daily for 7 days. or
- Clindamycin 300 mg x 3/day for 7 days

11.2.7 Herpes simplex stomatitis

Herpes simplex virus 1 and 2 (HSV) are common in HIV-positive patients, often occurring as one of the earlier infections associated with HIV infection. For some, HSV remains asymptomatic or causes only occasional outbreaks. For others, in the presence of severe immuno-deficiency, HSV mucocutaneous lesions may persist or continue to enlarge, exposing the patient to extreme pain and the risk of secondary infection. They are located on the keratinised mucosa (hard palate and gingival) unlike aphthous lesions.²⁹² Treatment consists of topical antiseptics to avoid secondary infection and oral acyclovir: start with 200 mg 5 x daily. If no response, increase the dose to 400 mg 5 x daily for 1 week.

11.2.8 Kaposi's sarcoma

Kaposi's sarcoma (KS) can involve the oral cavity, and is then considered to be an aggressive form. KS is a stage 4 disease. HAART should be considered in all patients with KS. Whether to add chemotherapy depends on the stage of KS.

For a more detailed discussion on KS and HAART, we refer to chapter 15.

11.2.9 Salivary gland disease and xerostomia

Protein-energy malnutrition and lymphocytic infiltration contribute to salivary gland dysfunction with xerostomia (dry mouth) as a consequence. Other causes of dry mouth in HIV patients are caused by drugs (ddl, anti-anxiety drugs, antidepressants). Sugarless candies and gum and frequent sips of diluted fruit juices may relieve the dry mouth symptoms.

11.2.10 Oral warts

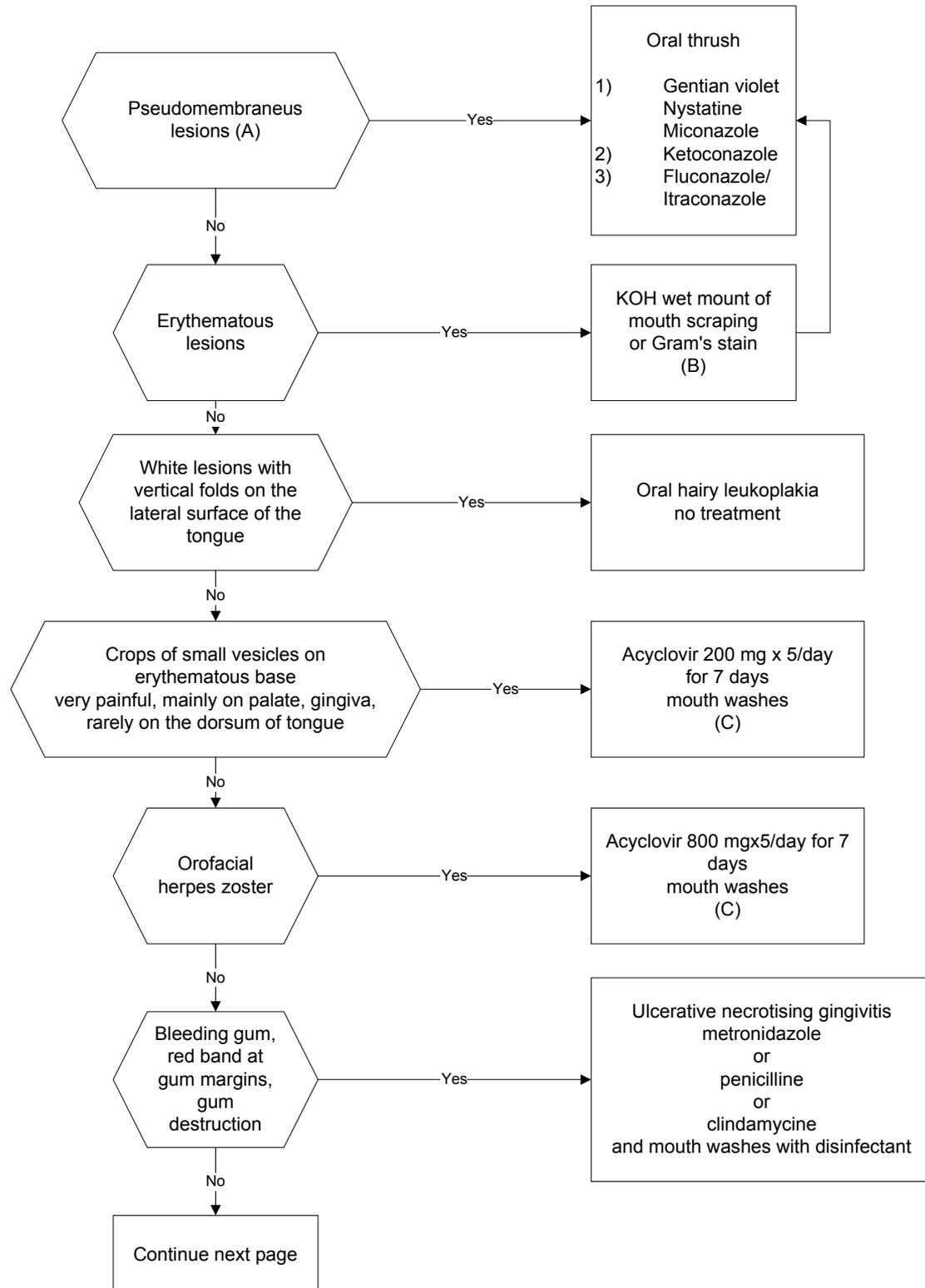
Oral warts are also caused by HPV (Human Papilloma Virus). Lesions can be solitary or multiple, sessile or pedunculated or cauliflower like.

They are more frequent in HIV patients than in the general population and unlike other mouth lesions the prevalence of oral warts is not decreasing with the advent of HAART. Treatment consists of surgical excision under local anaesthesia.²⁹²

11.3 Clinical management of oral lesions

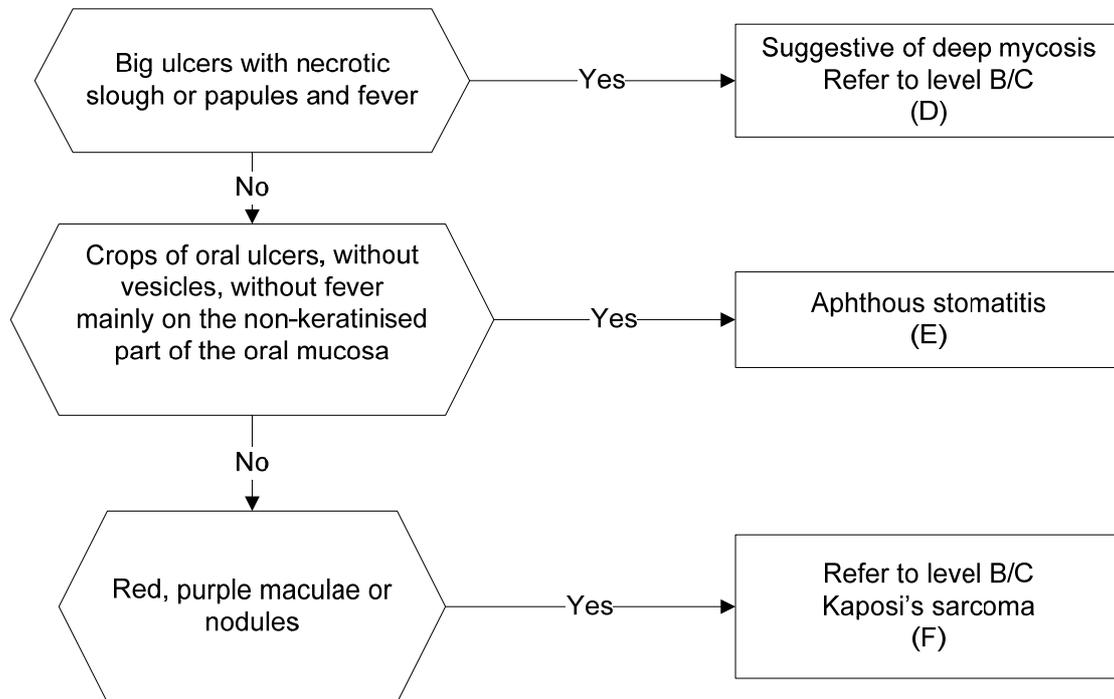
The management of oral lesions will be different at different levels of care, and is determined by the availability of chemotherapy for KS and antifungal therapy for deep systemic mycosis. Timely initiation of HAART will decrease the prevalence of mouth lesions by 50%. Although not immediately life-threatening, mouth problems can significantly hamper quality of life. Efforts should be directed at decreasing pain as mouth lesions can be extremely painful. Particular attention should also be paid to appropriate fluid and food intake, as malnutrition risks worsening the mouth lesions.

Oral Lesions (1)



Oral Lesions (2)

Continued from oral lesions (1)



Annotations Oral Lesions (level A, B and C)

- (A) The clinical diagnosis of oral candidiasis is often obvious. Treatment with topical antifungals can be started without further investigation. Recurrences are frequent. When the patient has pain or difficulty when swallowing, **oesophageal** candidiasis is likely. In that case, start with systemic treatment.
- (B) In case of doubtful lesions (erythematous without white sloughs), take a sample of mouth scrapings and make a KOH wet mount or stain it with Gram stain. A lot of yeast cells and pseudohyphae can be found in mouth scrapings of patients with oral thrush. If only yeast cells are found without pseudohyphae, this is an indication of colonisation of the oral cavity rather than infection.
- (C) When acyclovir is not available, provide sufficient pain control and use antiseptic mouthwashes to prevent secondary bacterial infection.
- (D) Deep fungal infections sometimes present with mouth lesions. Usually the patients are very sick and have other symptoms: fever, pulmonary lesions (histoplasmosis and aspergillosis) or skin lesions or meningitis. Refer the patient to level C. Definite diagnosis can be made through fungal blood cultures, or biopsies of lesions. Sometimes the organisms can be found on blood smears stained for malaria. Treatment consists of amphotericin B 0.7-1 mg/kg/day for 2-3 weeks, until the patient is clinically better, followed by fluconazole (cryptococcosis) 400 mg daily for a total of 10 weeks, followed by secondary prophylaxis with fluconazole 200 mg daily. For all other deep fungal infections amphotericin B and itraconazole are the preferred drugs. The maintenance dose of itraconazole is 200 mg twice daily followed by secondary prophylaxis of 200 mg itraconazole daily. The secondary prophylaxis can be interrupted when somebody has been treated with HAART for 6 months and the CD4 count is above 100 at least twice with a three month interval between tests.
- (E) Mouthwashes, topical steroids, oral steroids when severe, suspension with tetracycline and steroids, etc. (See page 192).
- (F) KS is an indication for HAART. In limited lesions (T_0) HAART alone will be enough to induce a regression of the lesions. In some instances chemotherapy is necessary. See chapter 15.

11.4 Symptomatic and palliative care

11.4.1 Mouth care in general

Avoid dry mucous membranes

- Use baking soda mouth wash every hour: 1 teaspoon baking soda, 1 teaspoon salt, 250 cc lukewarm water.
- Apply mouthwash with sponge swabs.
- Avoid commercial mouthwashes.
- Chew on sugarless gum or candies.
- Take frequent sips of diluted fruit juices.

11.4.2 Pain

Analgesics

- Provide stepwise analgesia (paracetamol/NSAID-codeine-morphine). See chapter 14.
- NSAID may be particularly helpful.

Anaesthesia

- Lidocaine mouth gel.



12 ODYNOPHAGIA AND DYSPHAGIA

(Pain (odynophagia) or difficulty (dysphagia) when swallowing)

12.1 Introduction

Oesophageal complaints are common in HIV-infected patients, occurring in at least one-third of patients at some point during the course of their disease. The incidence is higher in patients with CD4 < 200. It is an important problem in AIDS patients because it interferes with adequate nutrition and considerably decreases quality of life. Most oesophageal conditions are an indication of severe immune suppression (WHO stage 4) and are therefore an indication for HAART.

12.2 Causes of odynophagia and dysphagia

The causes of dysphagia or odynophagia are multiple. Infections most commonly involved in oesophageal disease are *Candida albicans* (50-70%), followed by CMV (10-20%) and aphthous ulcers (10-20%). Very few infections are due to herpes simplex (2-5%). Other possible causes of dysphagia/odynophagia are: reflux-oesophagitis, neurological deficits due to PML, HIV encephalopathy or Toxoplasma brain abscess, cachexia or malignancies (KS, lymphoma). It is important to identify the treatable causes.

12.2.1 Candida oesophagitis

Candida oesophagitis is the most common cause of dysphagia in AIDS patients. In two prospective studies, candida oesophagitis was detected by endoscopy in up to 64% of symptomatic patients. The presence of oral thrush has a high positive predictive value for the diagnosis of candida oesophagitis (90% in the presence of oesophageal symptoms), but the absence of oral thrush does not completely exclude the diagnosis.²²⁴ Patients complain of dysphagia and retrosternal pain. Odynophagia is less severe than in CMV oesophagitis. Barium-meal studies are not sufficient to distinguish candida oesophagitis from malignancy or viral infection, and should be avoided. Definitive diagnosis of oesophageal candidiasis requires the demonstration of tissue-invasive mycelia on endoscopic biopsy. However, presumptive diagnosis and empiric therapy are acceptable, especially when oral thrush is present, and in sites where there is no access to complex investigations. Treatment consists of **systemic** antifungal drugs.

Fluconazole is the preferred systemic therapy for oesophageal candidiasis and

for oropharyngeal candidiasis that does not respond to topical antifungal therapy.

Fluconazole: 200 mg daily during 2 weeks. Doses of up to 400 mg daily have been used in resistant cases (*Candida albicans* semi-resistant to fluconazole, *Candida* species other than *albicans*). Fluconazole is preferred to ketoconazole and itraconazole, because less hepatotoxic and less interactions with ARVs. Both itraconazole and ketoconazole are also contra-indicated in patients on TB treatment (INH, rifampicin).

Secondary prophylaxis for esophageal candidiasis is only indicated in case of severe and frequent recurrences.

If fluconazole is not available:

Ketoconazole*: 200 to 400 mg daily until remission is obtained. Concurrent rifampicin therapy should be avoided. Rifampicin induces the metabolism of ketoconazole, and ketoconazole is thought to inhibit the absorption of rifampicin. Treatment should be withdrawn in case of evidence of severe hepatocellular damage.

Itraconazole: Doses start at 100 mg 2 x daily and can be increased to a maximum of 400 mg daily, for 10-14 days. The capsules should be taken with food or an acid drink (e.g. Coca-cola) to increase their bioavailability. Drugs that increase the pH of the stomach (i.e. antacids, H₂ blockers) can lead to decreased itraconazole absorption. Concurrent rifampicin therapy should be avoided: rifampicin induces the metabolism of itraconazole, and itraconazole is thought to inhibit the absorption of rifampicin.

12.2.2 CMV oesophagitis

The most frequent clinical manifestation of CMV disease is retinitis, but it can cause gastrointestinal symptoms. CMV oesophagitis presents with odynophagia and clinically it cannot be distinguished from candida oesophagitis. Usually patients have more systemic symptoms, fever, nausea and vomiting (although the temperature can be normal). CMV infection should be considered in patients with oesophageal symptoms that do not respond to empiric antifungal therapy.

On endoscopic examination CMV oesophageal ulcers are usually single or few in number, large and deep, and are often located in the lower third of the oesophagus.³⁰³ Most oesophageal ulcers are due to CMV infection (45%), the other main cause being aphthous ulcers (40%). In the presence of fever, CMV infection is more likely than aphthous lesions. The two antiviral drugs that are currently approved for treatment of CMV infection are (val)ganciclovir and foscarnet. If not available, palliative care is often the only option (see section on *Palliative Care* page 206). When antiviral therapy is started, these patients should be watched carefully for IRIS: an indolent CMV retinitis may become

* In the 1999 WHO MEDL (Model Essential Drug List), ketoconazole was replaced by fluconazole, which has a better therapeutic profile and less hepatotoxicity.

apparent and can lead rapidly to blindness. It is not clear whether intra-ocular injections of ganciclovir are able to prevent these worsening eye symptoms after the start of HAART. Patients should be warned about this phenomenon.

12.2.3 Aphthous oesophagitis

After CMV infection, most oesophageal ulcers are due to aphthous ulcers (40%). If very debilitating, a trial with steroids is justified: prednisolone 20-40 mg once daily for 7-14 days and tapered over 1 month has been shown to be effective. In the presence of fever, CMV is more likely than aphthous ulcers and treatment with steroids is contra-indicated.

12.2.4 Herpes simplex oesophagitis

This is a rarer cause of viral oesophagitis in AIDS patients (2-5%). Patients present with retrosternal pain and odynophagia. Without biopsy and tissue cultures it is difficult to make the differential diagnosis between HSV and CMV ulcerative oesophagitis. Often there are bacterial and fungal secondary infections and an empiric antifungal treatment may slightly improve symptoms. The presence of small painful crops of vesicles in the mouth that evolve into destructive gingivostomatitis is suggestive of HSV infection. Treatment consists of acyclovir 800 mg 3 x daily for 1 week. In case of frequent relapses maintenance therapy with 400 mg 2 x daily can be considered. Epstein-Barr virus infection (EBV) ulcers are usually located in the mid-oesophagus and the patient often also has oral hairy leukoplakia. Both conditions may respond to acyclovir treatment.

12.2.5 Neurological disorders leading to dysphagia

- a) - HIV encephalopathy.
 - PML: progressive multifocal leuko-encephalopathy. If available, a treatment with AZT-containing HAART regimen may improve the symptoms.
- b) Neurological sequelae of toxoplasma brain abscess, cryptococcal meningitis (see section on *Palliative Care*, page 206).

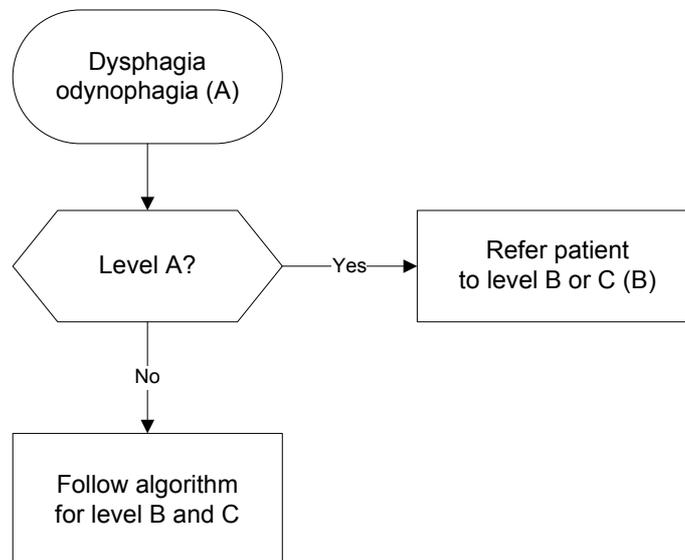
12.2.6 Kaposi's sarcoma

GI lesions of KS are usually symptomless, but they can ulcerate and cause bleeding. Usually there are associated skin and mouth lesions. The presence of oesophageal KS denotes a more advanced stage (T_1) of KS than only skin lesions (T_0). However, in the absence of pulmonary KS lesions, the prognosis is good after the start of HAART, with a three year survival of 77%.³⁰⁴ Patients with a diagnosis of oesophageal KS should therefore be started on HAART as soon as other active OI are stabilised (see chapter 15).

12.2.7 Other

Gastro-oesophageal reflux (heartburn, hyperacidity)
Hiatus hernia
Irritants: alcohol, spicy foods
Stress
Cachexia.

12.3 Clinical management of dysphagia/odynophagia



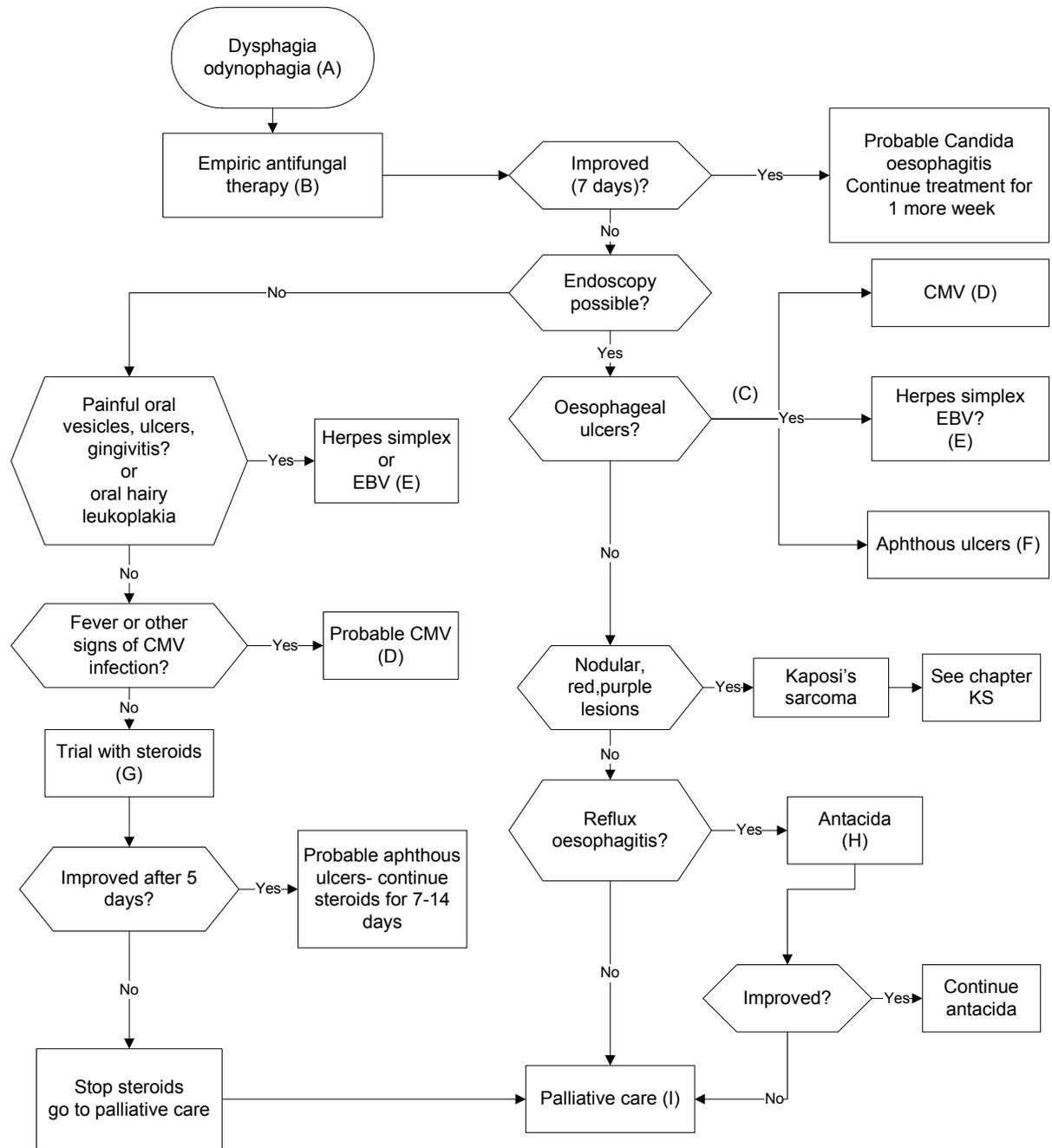
Annotations Dysphagia/Odynophagia

- (A) Difficulty or pain when swallowing. Possible causes: see page 199.
- (B) *At level A*, no systemic antifungal or antiviral drugs are available. There are two possible situations:

- 1. The patient is in a generally good condition:** this problem needs to be treated as soon as possible to avoid weight loss and deterioration in the general condition. Refer the patient to levels B or C where treatable causes of odynophagia/dysphagia can be excluded or treated.

Before starting palliative care, all treatable causes should be excluded at level B or C.

- 2. The patient is terminally ill and severely cachectic:** it may be mutually agreed between the patient, caregiver and health professional to withhold further treatment except for palliation (see section on *Palliative Care*).



Annotations (Levels B and C)

- (A) Odynophagia: pain when swallowing. Dysphagia: difficulty when swallowing. Important questions to ask and areas to examine are whether the symptoms are worse with food than with fluids, whether there are symptoms of reflux, or whether the patient has other OI, or skin lesions that may suggest a diagnosis.
- (B) Candida oesophagitis is the most common cause of oesophagitis in patients complaining of dysphagia. Empirical treatment with systemic antifungal drugs is justified, especially when oral thrush is present (see page 199).
- (C) Two possibilities
- Biopsy and histopathology possible: treat according to the result.
 - Biopsy and histopathology not possible: it is difficult to make a differential diagnosis only on the basis of clinical symptoms and endoscopic appearance of ulcers. *Solitary or a few large, deep ulcers* in the *lower third* of the oesophagus are mostly due to CMV. Herpes simplex ulcers occur also in the *lower third of the* oesophagus, but are usually *shallow and multiple*. They are frequently associated with mouth ulcers. *Mid-oesophageal multiple* ulcers may be associated with EBV. Look for oral hairy leukoplakia. Herpes simplex and possibly EBV respond to acyclovir.
- (D) In the presence of fever, CMV is more likely than aphthous ulcers and treatment with steroids is contra-indicated. Ganciclovir or foscarnet if available, if not, pain relief and HAART.
- (E) Definitive diagnosis of Herpes and EBV oesophageal ulcers requires endoscopic biopsy and histopathology. These conditions may respond to acyclovir 800 mg 3 x daily for 7 days.
- (F) Aphthous lesions of the oesophagus. If very debilitating, a trial with steroids is justified: prednisolone 20- 40 once mg daily for 7-14 days.
- (G) In the absence of fever, a trial of steroids for aphthous ulcers could be justified. In a palliative care setting there should be no hesitation about using steroids.
- (H) The use of antacida can interfere with the absorption of some drugs that need a low pH for optimal absorption (itraconazole, indinavir, lopinavir/ritonavir, fluoroquinolones and tetracyclines). The antiviral drug atazanavir cannot be used together with omeprazole.
- (I) Palliative care consists of adapted feeding practices, painkillers and antacida (see following section on Palliative Care).

12.4 Symptomatic and palliative care

Several good reference works on palliative care exist. This section is based on a palliative care handbook used in Canada.¹⁸¹

12.4.1 Gastro-oesophageal reflux

- Raise head of bed so that patient lies in an upright position.
- To neutralise excess acid: aluminium or magnesium hydroxide: 2-4 tabs 4 x daily, after meals and at bedtime.
- To reduce acid production: cimetidine 200 mg 2 x daily, or 800 mg at bedtime.

12.4.2 Difficulty when swallowing

- Test the patient's ability to swallow with a small quantity of water before each feeding to avoid aspiration of food.
- Minimise oral medication. Or crush the tablets, open the capsules when possible
- Establish whether fluids or soft foods are easier to swallow.
- Cool, soft foods may be easiest to swallow.
- Let the family prepare small, but frequent meals.
- Feed slowly in the upright position.
- Nasogastric feeding tubes may be needed if long-term support is required, e.g. a patient who has a neurological deficit after cryptococcal meningitis or Toxoplasma encephalitis, but who is otherwise in good physical condition.
- For odynophagia, the use of a nasogastric feeding tube should be discouraged as it often increases the likelihood of infection (Candida) and adds considerably to the discomfort.
- Give enough painkillers to allow food intake.

12.4.3 Pain

Analgesics

Provide stepwise analgesia (see chapter 14, page 267).

Avoid NSAID when there is a history of reflux pathology or symptoms that improve with antacids or H₂ blockers.

12.4.4 Last hours of life

- Loss of gag reflex and inability to swallow is one of the cardinal signs that death is occurring.
- No further administration of fluids and food.

- Fluids (saliva) may build up in the back of the throat and present as gurgling (death rattle). This is often perceived as choking and is distressing for the family and caregiver. Provide information and support.
- Keep mucous membranes moist, not wet.
- Scopolamine may reduce saliva production. An alternative is atropine (0.5 mg SC as often as needed), but this leads to cardiac, respiratory and CNS stimulation, which is not desired in this stage.
- In extreme situations oropharyngeal or nasopharyngeal suction may be needed (often very irritating).



13 SKIN LESIONS

13.1 Introduction

Many patients with HIV infection (80%-100%) develop dermatological conditions at some point in the course of the disease.^{305,306} Skin conditions may be very disabling, disfiguring and even life-threatening.

13.2 Aetiology of skin lesions

13.2.1 Acute HIV infection

The acute retroviral syndrome occurs approximately 1 month after primary infection. It may present as fever and rash. The rash is usually erythematous and maculo-papular. Other symptoms may be: arthralgia, lymphadenopathy, weight loss, meningo-encephalitis and pharyngitis. HIV antibody tests may still be negative. Some physicians in the west prefer to start HAART in this early phase in an attempt to preserve the immunity. This remains a controversial topic, and for developing countries a non-issue as the majority of patients will be diagnosed with chronic HIV infection in a later stage. If the diagnosis of acute retroviral syndrome is made no specific treatment for the skin rash is needed.

13.2.2 Opportunistic infections and other disorders

The differential diagnosis includes the following pathogens:

Bacterial infection: Staphylococcus aureus, Streptococcus species, Treponema pallidum, Bartonella species

Mycobacterial disease: M. tuberculosis, M. Avium complex, M. leprae

Viral infection: Herpes simplex and zoster virus, molluscum contagiosum, condyloma acuminata

Infestations: Scabies

Fungal infection: seborrheic dermatitis, tinea corporis, pityriasis versicolor, *Penicillium marneffeii*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, Candida species.

These conditions should be differentiated with:

Non-infectious disorders: drug eruptions, severe psoriasis, papular pruritic eruption (PPE), xerosis.

Cancer: Kaposi's sarcoma, squamous cell carcinoma, lymphoma

13.2.3 Bacterial infections

Staphylococcal and streptococcal infections

Staphylococcal infections of the skin and staphylococcal bacteraemia are common problems among AIDS patients.

Folliculitis and furunculosis, which are usually caused by staphylococci, need careful management in HIV patients because life-threatening disseminated infections occur. Carbuncles (clusters of furuncles) with multiple openings appear as a result of invasion and necrosis of the subcutis. Indwelling vascular catheters, neutropenia and lymphoedema due to Kaposi's sarcoma are risk factors for the development of staphylococcal bacteraemia.

Multiple anorectal abscesses are frequently seen and need surgical intervention.

Pyomyositis, caused most commonly by *Staphylococcus aureus*, has emerged as an unusual complication of HIV in Africa. In Tanzania, 62% of a series of patients with pyomyositis were HIV-infected. In the Northern hemisphere individual cases have been reported, but the condition is rare.

The presentation is in two phases, starting with vague complaints, muscle pain and low grade fever, followed by worsening of pain, swelling, fever and abscess formation in the muscle. It can lead to septicaemia and possible septic shock.

Pyomyositis is often associated with a CD4 count of less than 150 cells/mm³.^{307,308}

Cellulitis and erysipelas are streptococcal infections of the subcutaneous tissue resulting from contamination of minor wounds. In patients who remain untreated, life-threatening systemic infections may occur.

In general, HIV patients should have a local antiseptic at home to apply to minor wounds after washing. Mild localised infections are effectively treated with a topical antiseptic such as: gentian violet, polyvidone iodine, potassium permanganate or chlorhexidine.

However, when there is a deep-seated infection or high fever, systemic antibiotics should be prescribed.³⁰⁹

Treatment cellulitis/erysipelas

- (flu)cloxacillin 0.5 to 1 gram PO 4 x daily for 10 days, or

- (flu)cloxacillin 1-2 g IV 4 x daily for 10 days.

Avoid manipulations of furuncles in the face: this can cause thrombosis of the cavernous sinus.

Treatment pyomyositis

In the case of pyomyositis, surgical drainage is necessary together with antibiotics ((flu)cloxacillin).¹¹ Gram stain of pus can confirm the presence of Gram-positive cocci in clusters.

Syphilis

Caused by *Treponema pallidum*.

Primary syphilis: a painless, indurated genital ulcer (chancre) at the site of inoculation, usually accompanied by inguinal lymphadenopathy. Even without treatment, chancres usually heal within a few weeks. VDRL or RPR is not positive until 7-10 days after appearance of the chancre.

Secondary syphilis: Weeks to months later, about 25% of untreated patients will develop a systemic illness with fever, rash, condyloma lata, lymphadenopathy and oral lesions (mucous patch). The rash typically involves the palms and the soles, and is maculo-papular.

Treatment of primary and secondary syphilis is benzathine benzyl penicillin 2.4 MIU IM once or erythromycin 4 x 500 mg daily for 4 weeks in case of penicillin allergy. Based on an accelerated course of infection and higher relapse rates after treatment many clinicians prefer the once weekly benzathine benzyl penicillin 2.4 MIU IM, during three weeks, in HIV patients. It is important to follow-up VDRL after treatment, at 6, 12 and 24 months. If the VDRL fails to decline fourfold over 6-12 months, the patient must be retreated and a CSF examination done to rule out neurosyphilis.^{266,267} In case of neurosyphilis, benzathine benzyl penicillin is not recommended because of poor CSF penetration.

Bacillary angiomatosis

Bacillary angiomatosis (BA) and bacillary peliosis are newly-recognised opportunistic infections in PLHA.³¹⁰ They are caused by tiny Gram-negative bacilli that are difficult to cultivate in the laboratory: *Bartonella henselae* and *Bartonella quintana*. These diseases are characterised in immunocompromised persons by angio-proliferative lesions (that look like Kaposi's sarcoma) in the skin and bone (bacillary angiomatosis) or in the liver and the spleen (peliosis hepatis)*.

BA is epidemiologically linked to exposure to cats, especially to young cats infested with fleas. Symptoms include fever, malaise, headache, hepatomegaly and skin lesions. Cutaneous lesions start with small red papules that gradually expand into large papular, nodular, pedunculated forms. They have a vascular appearance and the surface is friable and easy to bleed. Bacillary angiomatosis may be a life-threatening disease if it is not recognised early and treated promptly with antibiotics.

Differential diagnosis with Kaposi's sarcoma is not always easy. Treatment consists of erythromycin 500 mg 4 x daily for 2 months. An alternative is doxycycline 100 mg 2 x daily.

* In immuno-competent persons, *B.henselae* infection may cause granulomatous lymphadenitis, or cat scratch disease. The latter has been associated with cat scratches, rarely bites.

13.2.4 Mycobacterial disease

Even in HIV patients, disseminated miliary tuberculosis of the skin is a rare form of tuberculosis.³¹¹ The diagnosis should be suspected in a patient who has a papulo-pustular eruption on the trunk and the extremities and who is severely ill. It is caused by the haematogenous spread of tubercle bacilli to multiple organs including the skin. Microscopic examination of the skin biopsy reveals numerous acid-fast bacilli. However, the diagnosis of disseminated tuberculosis is often evident on clinical grounds, and aspiration and/or biopsy of lymph nodes has a higher diagnostic yield than a skin biopsy in extra pulmonary TB.³¹²

Although skin involvement with *M. avium intracellulare* is not uncommon in cases of disseminated disease, localized cutaneous infection without bacteremia is rare.³¹³

Exacerbation of skin mycobacterial disease has been reported after starting HAART.³¹⁴

A case of IRIS pyomyositis due to MAC has been described.³¹⁵ Leprosy is not more frequent in patients with HIV. However, after the start of HAART, immune reconstitution may cause an exacerbation of leprosy skin lesions with inflammatory symptoms similar to a type 2 leprosy reaction.³¹⁶⁻³¹⁸

13.2.5 Viral infections

Chronic muco-cutaneous herpes simplex

This is one of the most annoying skin conditions in AIDS patients and tends to give rise to very painful and extensive lesions.

The usual localisation is ano-genital, although oro-labial lesions can be seen. Chronic (>3 weeks) ulcers are only seen with advanced immune suppression. If untreated, they can last for months and finally involve most of the genital and peri-anal skin and mucous membranes. Genital herpes has also been identified as an important risk factor for HIV transmission.³¹⁹

Diagnosis

Most often diagnosis is clinical.

Laboratory tests include Tzanck test and viral culture. The Tzanck preparation is done by smearing cells taken from a fresh blister or ulcer onto a microscope slide. The cells are stained with a special stain, such as Wright's stain, and then examined under a microscope for characteristic changes caused by a herpes virus. Herpes causes giant cells with multiple nuclei. The shape of each nucleus appears moulded to fit together with those adjacent. The background of the cell looks like ground glass and contains small dark spots called inclusion bodies.

Viral culture is usually not possible in resource-poor settings.

Treatment

Mild mucocutaneous disease - acyclovir 200-400 mg PO 5 times/day 7-10 days (alternative when available: valaciclovir, famciclovir). In disseminated mucocutaneous herpes simplex infection treatment for 2 weeks or longer is often necessary.

If acyclovir is not available, the alternative is topical antiseptics (gentian violet, potassium permanganate), paracetamol and amoxycillin in case of secondary infections.

Supportive care: Analgesic for associated pain and fever. Antibiotic therapy if secondary bacterial infection occurs.

Prevention

Recurrences occur frequently (more than 6 episodes in a year) in some patients. In that case, they may require lifelong suppressive therapy: acyclovir 200 mg 2 x daily or if not successful increase to 400 mg 2 x daily (or valaciclovir 500 mg once daily). This will decrease symptomatic episodes and viral shedding. Even if supporting evidence from clinical trials is not yet available, it is probable that preventing genital herpes recurrences will reduce transmission of HIV to a partner, as HIV virus has been consistently detected in herpes ulcerations.³²⁰

Differential diagnosis

Besides the treatable sexually transmitted genital ulcerative diseases (syphilis, chancroid, donovanosis, lymphogranuloma venereum), the differential diagnosis of anogenital ulcers should include: tuberculosis, malignancies, mucocutaneous candidiasis, cytomegalovirus, deep mycosis, Behçet disease, amoebiasis, fixed drug reactions, varicella zoster virus and acyclovir resistant HSV. Resistance to acyclovir is very low but treatment failures are more frequent in patients with low immunity.³²⁰

Options for treating acyclovir resistant HSV like IV foscarnet or cidofovir, are costly and not available in most settings.

HAART

A worsening of HSV lesions has been described in association with an immune reconstitution inflammatory syndrome, between 1 and 6 months after starting HAART.^{321,322} The lesions are irresponsive to acyclovir although there is no resistance. Steroids are not useful in this case. Continue HAART, disinfect.

Shingles (Herpes zoster)

Herpes zoster in a young person is highly predictive for HIV infection and an indicator of at least WHO stage 2. Almost 25% of PLHA experience recurrences of herpes zoster.³²³ HIV patients have more frequent multidermatomal involvement, involvement of the trigeminal nerve and the presence of systemic symptoms. Mean time to cessation of new vesicle formation, crusting and resolution of zoster associated pain were also

significantly longer in HIV patients.³²⁴ Lesions can become necrotic and extensive (involve several dermatomes), taking a long time to heal. They show frequent secondary bacterial infection and deep scarring. If they involve the ophthalmic branch of the trigeminal nerve (V), they can involve the cornea and cause corneal scarring with loss of vision in that eye.

Diagnosis

Most often a clinical diagnosis is made based on symptoms and signs. A Tzanck test smear of material scraped from the basis of a lesion will show multinucleated giant cells with inclusion bodies, which are pathognomonic.

Treatment

Severe (extensive necrotic lesions) and disseminated herpes zoster or involvement of the trigeminal nerve: acyclovir 10 - 12 mg/kg IV every 8 hours; for 7-14 days, or if IV acyclovir is not available: acyclovir, 800 mg 5 x daily for 7 days (or valaciclovir, famciclovir).

Dermatome Zoster: acyclovir 800 mg PO 5 times daily, 7-14 days

Supportive care

Additional treatment consists of topical antiseptics to accelerate drying of the lesions and to prevent secondary bacterial infection. If necessary, add systemic antibiotics. Analgesics for pain and fever: NSAID and/or carbamazepine 200-600 mg daily or amitriptyline 25-75 mg. Amitriptyline and carbamazepine are also effective in controlling post-zoster neuralgias.

Uncontrolled studies suggest that a milky extract from the frangipani tree would accelerate healing and decrease pain (communication from MSF-Nairobi).

Prevention

Primary varicella and herpes zoster are potentially infectious. Risk of nosocomial infection, especially in the immunocompromised patient, is high. Strict isolation is recommended if the patient is hospitalized. Universal precautions are implemented for wound care.

HAART

From 1 up to 4 months after initiating HAART, herpes zoster is commonly seen as a manifestation of immune reconstitution. HAART must be continued, and the treatment of the lesions and neuralgia is the same as described above. There is no place for corticosteroids in this case.^{325,326}

Molluscum contagiosum

A viral skin infection, characterised by centrally umbilicated, non-pruritic papules on the face, neck, and ano-genital areas, which is more commonly

seen in PLHA. Lesions in the face tend to proliferate, especially if injured during shaving. Differential diagnosis has to be made with disseminated cryptococcosis, histoplasmosis and penicilliosis. Those systemic mycoses are usually associated with fever, pulmonary or meningeal involvement.

Treatment

Molluscum contagiosum usually does not require treatment. It is possible to prick the centre of the lesion with a needle dipped in 80% phenol or iodine, or with 60% to 88% saturated tri-chloroacetic acid, followed by expression of the central core. Alternatively cryotherapy (liquid nitrogen), electrocoagulation or curettage can be proposed.

HAART

An exacerbation of existing lesions can occur in patients taking HAART, shortly after initiation, due to immune reconstitution. HAART should not be interrupted, and even giant lesions can reduce spontaneously with HAART alone after some time.^{327,328}

Genital warts (Condyloma accuminata) and verruca vulgaris

Genital warts can be seen as STI in any patient (caused by Human Papilloma Virus, HPV), but they are much more frequent in HIV-infected patients. The lesions can be very extensive and cauliflower-like, involving both the genital and the peri-anal region. Certain strains of HPV are associated with cancer of the cervix and anal cancer. Patients with small numbers of warts are often asymptomatic.

Other patients may have pruritus, bleeding, or pain.

Treatment

If the number of lesions is small, treatment is best done by the patient with daily podophyllotoxin 0.5% solution[†] strictly on the lesions. Let it dry. Protect the unaffected skin with vaseline or zinc ointment. Wash with water and soap after 1-4 hours. Apply twice a day and repeat every day for 3 consecutive days per week for 4 weeks maximum.

For vaginal and anal lesions it is often difficult to correctly self administer the treatment, and this should preferably be done by the health care worker.

Allow drying before removing speculum in vaginal warts.

Improper treatment can cause painful ulcerations. Total volume of podophyllotoxin should not exceed 0.5 ml per day. Podophyllotoxin should not be used during pregnancy. It is also contra-indicated for cervical, urethral, anorectal and buccal condylomata.

Remission is often only temporary and relapses extremely frequent.

More extensive lesions (condyloma >3 cm) should be treated by cryotherapy

[†] Podophyllotoxin is preferred above Podophyllum resin 10 or 25%, which is much more caustic and has to be applied by the health staff.

or cauterisation. Large to giant genital warts are malodorous and they isolate patients socially. Even if no other treatment is available bathing in antiseptics and antibiotics for secondary infection will help alleviate symptoms.

Other commonly occurring HPV infections are common warts (**verruca vulgaris**) appearing as extensive plantar warts and confluent periungual warts, extensive flat warts (verruca plana) with a Koebner phenomenon, and filiform warts often located in the beard area,. It may occur in unusual sites, such as the lips, tongue and oral mucosa.

Common warts can have a temporary exacerbation after initiation of HAART, but will reduce spontaneously later in most cases.

13.2.6 Scabies

Scabies can lead to extensive disease in AIDS patients, with hypertrophic, hyperkeratotic lesions that become secondarily infected with bacteria. This condition is called Norwegian scabies. It can be life-threatening when secondary infection is severe.

Diagnosis

The mites can be seen by microscope on a KOH preparation of skin scales. Histologic examination of scraping or biopsy of the papules reveals the mite and its ova within the cornified layer of the epidermis. Often the diagnosis is made clinically.

Any long-lasting itchy dermatitis in HIV-infected patients which does not respond to topical antifungal drugs justifies a trial with benzyl benzoate.

Treatment

Benzyl benzoate 20% (3 consecutive nights on whole body except the face, washed out after 24h) or gamma benzene hexachloride (GBH) 1% lotion or cream (not in pregnant/breastfeeding women or in children below 12 years of age) Itching can be relieved by chlorpheniramine 4 mg, 3-4 tabs daily. After treatment, all clothes and bed linen should be thoroughly washed, dried and ironed to kill the mites (or dried in the sun). Do not forget to treat family members who have scabies as well.

Persistent itching after treatment is frequent and can be treated with a steroid cream (hydrocortisone 1%).

Ivermectin is an effective alternative when available (dose: 12 mg (2 tablets) in a single dose). In case of Norwegian scabies, it is best to combine ivermectin with the topical treatment of benzyl benzoate lotion. Before applying benzyl benzoate thick crusts can be removed using keratolytics eg salicylic acid 5-10% ointment.

In case of scabies with secondary infection, treat first the infection with local antiseptics and antibiotics (cotrimoxazole, or cloxacillin or doxycycline).

After 3 days, start benzyl benzoate lotion.

Children: Application of 12.5% benzyl benzoate emulsion to the affected skin to be washed off after 24 hours. Repeat 3 times.

13.2.7 Fungal skin disease

Fungal skin disease is extremely common in HIV-infected patients.²⁹⁸ It sometimes responds to topical antifungal drugs (Whitfield's, gentian violet, imidazole cream, ketoconazole cream), but many times you need systemic antifungal treatment.

Seborrheic dermatitis

Seborrheic dermatitis is a very common complaint and is one of the earliest clinical markers of HIV infection. It is classified as a WHO 2 condition. The most common locations are in the hairline, eyebrows, nasolabial folds and chest. Involvement of the armpit and groin is also frequently noted. The role of *Pityrosporon ovale* in causing seborrheic dermatitis is controversial. This condition may respond well to topical antifungals but often anti-inflammatory treatment needs to be added, preferably topical steroids: imidazole cream (miconazole, clotrimazole) 2 x daily with or without hydrocortisone.

In general, treatment needs to be continued for 14 days after symptoms have disappeared.

For refractory cases, oral ketoconazole can be added: 200 mg daily for 7-14 days.

For severe acute cases use a combination of imidazole cream, hydrocortisone cream and ketoconazole 200 mg daily for 7-14 days.

Pityriasis versicolor and Malassezia folliculitis

These conditions rarely require treatment except for aesthetic reasons. Pityriasis versicolor (caused by overgrowth of *Malassezia furfur*) is neither more common nor does it present clinically differently in HIV-positive patients compared to HIV-negatives.

Treatment consists of a single oral dose of ketoconazole 400 mg, or 200 mg daily for 3 days, or topical application of selenium sulphide or ketoconazole cream 2% or ketoconazole shampoo. Scrubbing the skin with a (tooth)brush will take away a lot of the infected scales.

M. furfur can cause folliculitis in HIV-positive patients. *Malassezia folliculitis* responds well to treatment with ketoconazole (200 mg daily for 10-14 days) or itraconazole (100 mg twice daily 10-14 days).

Dermatophytosis

Tinea corporis, tinea pedis, tinea cruris all occur more frequently in patients with HIV infection. This is usually severe and often widespread characterized

by scaly, red, pruritic, papules and plaques. Dermatophytosis in HIV-infected individuals is usually extensive and resistant to topical antifungal agents. They are classified as WHO 2 condition.

Diagnosis

Skin scraping and KOH preparation
(Fungal culture)

Treatment

In uncomplicated cases, treatment with local imidazole cream (1% clotrimazole, 2% miconazole) or Whitfield's ointment is sufficient. Treatment is necessary for 4 weeks. In severe cases, oral griseofulvin (10 to 20 mg/kg daily for 4 weeks) may be necessary. When there is severe pruritis a mild steroid cream can be added.

Onychomycosis is also frequent in HIV-positive patients. Direct microscopy of KOH preparations of nail scrapings is enough to make the differential diagnosis with dystrophic nails. Griseofulvin 10 to 20 mg/kg daily should be given for 12-18 months. Griseofulvin is effective for dermatophytoses but not for yeast infections such as *Candida*. Up to 50% of onychomycosis, especially of fingernails, are mixed infections. In these cases treatment with ketoconazole or itraconazole is preferred eg pulsed therapy with itraconazole[‡] (200 mg 2 x daily for the first 7 days of each month for 4 months).

In the case of *scalp ringworm*, treat with griseofulvin 10 to 20 mg/kg daily for at least 6 weeks. Topical application of Whitfield's ointment or an imidazole cream may accelerate clearing of scaly lesions on the scalp.

Muco-cutaneous candidiasis

The most frequent presentation is oral thrush (see Oral Lesions, chapter 11, page 190).

Vulvovaginal candidiasis

Nystatin 100,000 intravaginal at night during 7 days

OR

Miconazole ovules intravaginal at night during 3 days

Severely immunocompromised patients may have **balanitis, distal urethritis, or paronychia** (nail wall infection).

KOH preparation of affected areas may show pseudohyphae and budding yeasts.

Topical anti-fungal cream twice a day is usually effective (clotrimazole cream 1%, miconazole cream 2%). This treatment can be combined with topical application of gentian violet to keep the lesions and the surrounding skin dry.

In generalised skin infections, oral fluconazole 50 mg 2 x daily for 2 weeks is effective.

[‡] Fluconazole is not effective against dermatophytosis

Children: For severe skin involvement not responding to topical treatment, systemic ketoconazole, 3 mg/kg/day or fluconazole, 3 mg/kg/day for 7 days should be considered.

Deep mycosis

70% of patients with disseminated *Penicillium marneffe* infection (Southeast Asia and China) will have skin lesions. Histoplasmosis and cryptococcosis can also present with pustules, nodules, ulcers and papules. Patients with cryptococcosis and penicilliosis may have molluscum contagiosum-like, centrally umbilicated lesions. These are typically located on the trunk and face.

Any disseminated endemic mycosis is classified in WHO stage 4, and therefore is an AIDS defining event.

Diagnosis is suggested by the clinical picture. Patients usually have high fever and other symptoms such as severe anaemia, cough, lymphadenopathy, hepatomegaly and meningeal signs, which suggest the diagnosis.

The organism may be seen by microscopic examination of skin scrapings, touch preparations of skin biopsy or lymph node aspirate stained with Wright's stain, or Cotton-blue stain. Bone marrow aspirate is diagnostic in 100% of cases of disseminated infections. The diagnosis is confirmed by culturing the fungus from clinical specimens.

Those techniques are not readily available in developing countries.

Initial **treatment** of penicilliosis should be with amphotericin B 0.7 mg/kg daily IV for 2 weeks, followed by itraconazole 200 mg 2 x daily for 10 weeks. Mortality from disseminated *P. marneffe* infection in patients with AIDS is about 20%, despite effective antifungal therapy.¹⁰⁴ Long-term suppressive therapy with itraconazole 200 mg daily should be given to prevent relapse.

The treatment of choice for cryptococcosis is amphotericin B 0.7 mg/kg daily followed by fluconazole 400 mg daily for 8 weeks. Secondary prophylaxis with fluconazole 200 mg daily is necessary to prevent relapse. In non-severely ill patients, oral itraconazole (400 mg daily for histoplasmosis or penicilliosis) or oral fluconazole (400 mg daily for cryptococcosis) may be sufficient.

13.2.8 Itchy skin eruptions

This affects up to 30% of HIV patients.

Papular pruritic eruption

PPE is a chronic symmetric papular eruption, predominant at the extensor surface of upper and lower extremities. It may be an allergic reaction to arthropod bites³²⁴ and is very itchy and frequently secondarily infected. PPE is a stage 2 defining condition, however most patients with PPE have CD4 < 100 indicating stage 4 disease.^{329,330}

Treatment success has been achieved with UV light, antihistamines, and potent topical steroids. Also HAART is effective, and skin lesions rapidly disappear after the start of HAART and this can be used as a marker of treatment response.³³¹

Eosinophilic folliculitis

Eosinophilic folliculitis (EF) is characterised by urticarial follicular papules above the nipple line. There is mainly truncal involvement, but a significant proportion of patients also have neck and face involved. Involvement of limbs is rare (contrary to PPE). It is seldom possible to differentiate clinically from other types of folliculitis. Although the exact aetiology of EF remains obscure, studies have favoured an autoimmune process directed against some components of sebum.

Potent topical steroids and antihistamines are the first choice of treatment. Good results have been obtained with metronidazole or itraconazole, but the series reports were of small size.³³² 5% permethrin cream application has been described as beneficial.

An increase in CD4 due to HAART has been associated with a temporary increase in eosinophilic folliculitis.³³³

Xerosis

This skin condition is frequently encountered in PLHA.³⁰⁶ The aetiology is not known. Lesions consist of a diffuse, pruritic, scaly rash, involving mainly the limbs and the back. Treatment is topical with hydrating ointments such as urea 10% ointment, emulsifying ointment, or vegetable oils such as coconut oil. For pruritus: chlorpheniramine 4 mg 3 x daily for 1 month. Do not use Calamine lotion in case of xerosis, because this further dries out the skin.

Comment:

Every pruritic rash justifies a trial with benzyl benzoate. After this, symptomatic treatment with calamine lotion, bath oil, antihistamines (chlorpheniramine 4 mg 3 x daily), topical steroid cream can be tried. In Thailand, antidepressants have been recommended in case of refractory, invalidating prurigo.

13.2.9 Kaposi's sarcoma (KS)

For a detailed description of KS see chapter 15 page 273.

This cancer of the skin and the blood vessels is an indicator disease of symptomatic HIV infection. It is associated with a sexually transmitted Human Herpes Virus (HHV8). Lesions are usually multiple and can involve the skin as well as mucous membranes. Cutaneous lesions occur most commonly on the trunk, the extremities and the face.

Initially lesions are papular. Later the papules become nodules and plaques, and the colour changes from dark brown to violet. Since the use of HAART in the US, the incidence of Kaposi's sarcoma has dramatically decreased. In Asian patients, Kaposi's sarcoma is very rare.³⁰⁶

Treatment of localised disease

In the group T₀S₀ (limited lesions (T₀) and no systemic signs (S₀)) it is likely that HAART alone is sufficient in the majority of patients. In case it is needed intralesional bleomycin, cryotherapy and radiotherapy are also effective in localised disease.

Treatment of systemic KS

Local therapy is not recommended for treatment of systemic AIDS-related Kaposi's sarcoma, characterized by at least 10 new lesions in the prior month, symptomatic lymphoedema, symptomatic pulmonary Kaposi's sarcoma, or symptomatic visceral disease.

HAART is also effective against systemic KS, but usually not alone without chemotherapy.

13.2.10 Psoriasis

Psoriasis is not more frequent in HIV-positive than in HIV-negative persons. However, extensive severe psoriasis is often observed in AIDS patients.³³⁴ All patients should expose their skin lesions to UVB (walk in the sun in the early morning and late afternoon in the tropics).

For limited disease

- For thick plaques use keratolytics (eg salicylic acid 5%) in combination with topical steroids
- Betamethasone 0.1% cream applied on the lesions 1 x daily for 2 weeks.
- 5% LCD (liquor carbonis detergens) in triamcinolone 0.1% (2 x daily) or bethamethasone (1 x daily) applied on skin lesions until recovery. Mild topical steroids are not effective in psoriasis, you need class III or IV. Exceptions are the skin folds where certainly class I or II is strong enough (1% hydrocortisone cream on the lesions 2 x daily)
- Coal tar 5 – 10% ointment or coal tar in salicylate ointment 2 x daily.
Scalp: Polytar shampoo once a day.

Generalised disease

Topical treatment as in limited disease combined with (if available) etretinate 0.75 to 1 mg/kg daily in 2-3 divided doses (max 75 mg daily) for 2-4 weeks, followed by 0.5 mg/kg daily for another 6-8 weeks. Etretinate is contraindicated in pregnancy. Methotrexate, a frequently used alternative treatment for severe psoriasis, is also used in severe psoriasis in HIV patients. Caution should be exerted because of additional immune suppression.

Good results have been described with HAART.

13.2.11 Bedsores

This is a frequent problem in bedridden patients. Clean the wound every day with normal saline and keep it as dry as possible. Apply zinc oxide ointment around the wound and iodine in the wound. In case of secondary infection, use antibiotics. Prevention: frequent massages on pressure points by family members (instructed by physiotherapist). Turn the patient over in bed every 3-4 hours. Avoid moist or wet bed sheets.

Pain treatment is provided with stepwise analgesia.

In case of malodorous wounds, crushed metronidazole tablets can be put on the lesions.

13.2.12 Drug reactions

Drug reactions are common in PLHA and are directly related to the degree of immunosuppression. The drugs most frequently involved are cotrimoxazole, dapsone, INH, and amoxicillin. A morbilliform rash is most frequently observed.

Treat with chlorpheniramine 4 mg 3-4 x daily.

In case of severe reactions, stop the drug.

Several antiretroviral drugs can cause skin eruptions as well.

Rash is a well-known side effect of **nevirapine** occurring in 16% of patients, mostly within the first 6 weeks. If the rash is dry and without fever or systemic symptoms, the drug usually can be continued, in association with chlorpheniramine and close follow-up. In case systemic symptoms (fever, arthralgia, myalgia, eosinophilia, hepatitis) or a wet rash occur, nevirapine should be switched to efavirenz. There is no cross reactivity between NVP and EFV and one drug can be substituted for the other in case of uncomplicated rash. This is not the case for a patient who developed Steven Johnson, where it is probably better to switch to a PI containing regimen. DRESS syndrome has been associated with nevirapine.³³⁵ DRESS stands for drug rash with eosinophilia and systemic symptoms. The clinical manifestations include diffuse maculopapular rash, fever, eosinophilia, multiple organ involvement, atypical lymphocytosis and abnormal liver function tests. Cutaneous manifestations respond well to topical steroids, but when there is systemic involvement treatment with systemic steroids is proposed. Mortality of DRESS is 10%, therefore patients should be closely monitored and all drugs discontinued.

Cases of Steven-Johnson due to nevirapine occur rarely.

Efavirenz can cause a rash as well, and the same recommendations as for NVP could be used.

In case of a rash in patients taking **abacavir** (ABC), ABC should be interrupted and never restarted again.

Nelfinavir and atazanavir have also been associated with rash. Alopecia and paronychia, as well as dry skin have been described as a side effect of **indinavir**.

Zidovudine can cause blue discoloration of the nails.

If Stevens-Johnson syndrome occurs, the patient needs to be admitted to a hospital for aggressive treatment (rehydration, nasogastric tube feeding, antiseptic treatment of areas of epidermolysis. Early in the course, before extensive skin breakdown, it is useful to give steroids: prednisolone 1 mg/kg daily for 1 week.

In case of extensive epidermolysis, do not use steroids because of the risk of infection and bacteraemia. In case of high fever, treat with broad-spectrum antibiotics that cover both Gram-positives and Gram-negatives (ceftriaxone + amikacin or ciprofloxacin). However, do not use the culprit drug!!

13.2.13 Leishmaniasis

Leishmaniasis is a protozoal disease with clinical manifestations which can vary according to the infecting species (over 20 pathogenic species are known) and the immune response of the host.

The disease is transmitted by the bite of an infected sandfly. Leishmania-HIV co-infection mostly causes visceral leishmaniasis.

Among South European AIDS cases, it is the fourth cause of opportunistic parasitic disease after toxoplasmosis, pneumocystosis and cryptosporidiosis.

Cutaneous leishmaniasis

Cutaneous leishmaniasis (CL) is common in South Europe, South-western, central and eastern Asia (India and Pakistan), Africa and Latin America. It can present with ulcers, papules or nodules of the skin. In HIV patients, CL often presents as a disseminated form with multiple papules and nodules which can ulcerate.

PLHA with CL should be checked carefully to exclude VL (bone marrow aspirate, buffy coat). In HIV-infected patients cutaneous lesions may be the first presentation of visceral leishmaniasis.²⁷⁰

Many parasites can be found throughout the skin that looks normal or has diffuse papules.

Amastigotes can be found in healthy skin of HIV patient with visceral leishmaniasis, because the cellular immune mechanisms fail to eradicate the parasite.

The differential diagnosis has to be made with Kaposi's sarcoma, bacillary angiomatosis, herpes zoster, disseminated cryptococcosis. Incidental finding of leishmania has been described in Kaposi's sarcoma^{336,337}, herpes zoster lesions³³⁸, herpes simplex, cryptococcosis and bacillary angiomatosis.³³⁹

Treatment

CL can heal spontaneously after 1 month up to 3 years. Deciding on whether to treat or not depends on the risk for developing mucocutaneous leishmaniasis and the place of the lesions (face and joints involvement favours treatment).

Pure CL in initial HIV stage responds to intralesional antimonial treatment: once or twice weekly an infiltration with sodium stibogluconate (100mg/ml 0.3-3 ml/lesion) or meglumine antimonite (0.2-0.8 ml/lesion) from all sites, until the lesion has blanched. Per infiltration max 5 ml should be used and a maximum of 20 mg Sb/kg. Two to fifteen infiltrations are needed to achieve cure.³⁴⁰

Mucocutaneous leishmaniasis

Mucocutaneous leishmaniasis (MCL) appears in 2 to 3% of all cases of HIV-Leishmania co-infection. This form occurs rarely outside Latin America, but the mucosal form can occur in East-Africa. Practically all of the Leishmania species can be responsible for MCL lesions. Although the nasal septum and the soft palate are usually affected by MCL due to metastasis from a primary lesion, it can also appear as a primary lesion. Nasal biopsy specimens are commonly needed to elucidate a definitive diagnosis of MCL.

Treatment

Sodium stibogluconate or meglumine antimonite 20 mg/kg/day IV during 20-30 days

Amphotericin B 1mg/kg/day on alternate days for 2 months³³¹

Visceral leishmaniasis

The visceral form (Kala Azar) is spread over Africa, Asia (India, Pakistan, Bangladesh, China, and Nepal), Southern Europe and Latin America (see chapter 10, page 172).

Usually, cutaneous manifestations are rare in visceral leishmaniasis, but AIDS is resulting in the development of new forms of cutaneous involvement.

2 types of skin lesions have been described in visceral leishmaniasis and HIV co-infected patients: lesions caused by leishmania and lesions in which the finding of leishmania is incidental.³³⁹ Lesions caused by VL can present in subcutaneous nodules³⁴¹, dermatofibroma-like lesions³⁴², Kaposi-like lesions³⁴³, linear brown lines³⁴⁴, or a dermatomyositis-like picture.³⁴⁵

Amastigotes have also been reported in healthy skin of HIV-leishmania co-infected patients. The presence of skin lesions in an HIV-positive patient in an area where visceral leishmaniasis is endemic may disclose a diagnosis of visceral leishmaniasis, since the lesions may provide an accessible tissue site for diagnosis and treatment response, in contrast with a spleen or bone marrow aspiration.

Diagnosis

See chapter 10.

Treatment

Various treatments have been proposed.

Amphotericin B dosed as 1 mg/kg/day every other day for 30 days seems a feasible option in HIV programs, since this drug may be readily available for treating cryptococcosis and staff is already experienced in its use. The relapse rate in HIV co-infected patients is high. No treatment can provide a complete sterilization, and HIV-positive patients generally can not develop cellular immunity to Leishmania.

Post Kala-azar dermal leishmaniasis (PKDL)

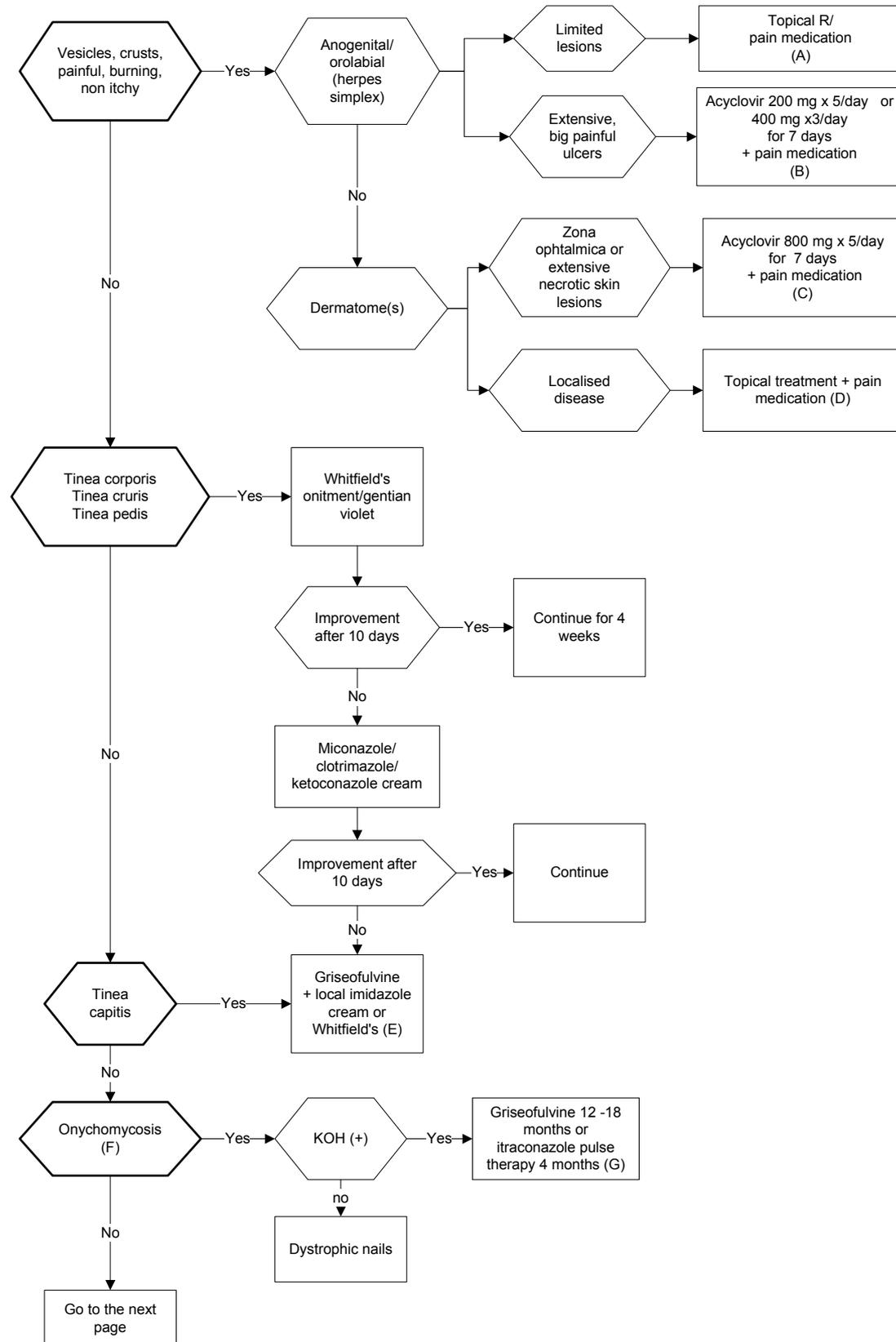
PKDL is a cutaneous manifestation caused by the same parasite which causes kala-azar and usually occurs weeks after recovery of kala-azar. The rash is usually macular, papular or nodular. The lesions can be limited to the face only, but can also cover most of the body, including mucosa of lips and mouth, with ulcers and crusting.

PKDL is not very common in HIV/AIDS.

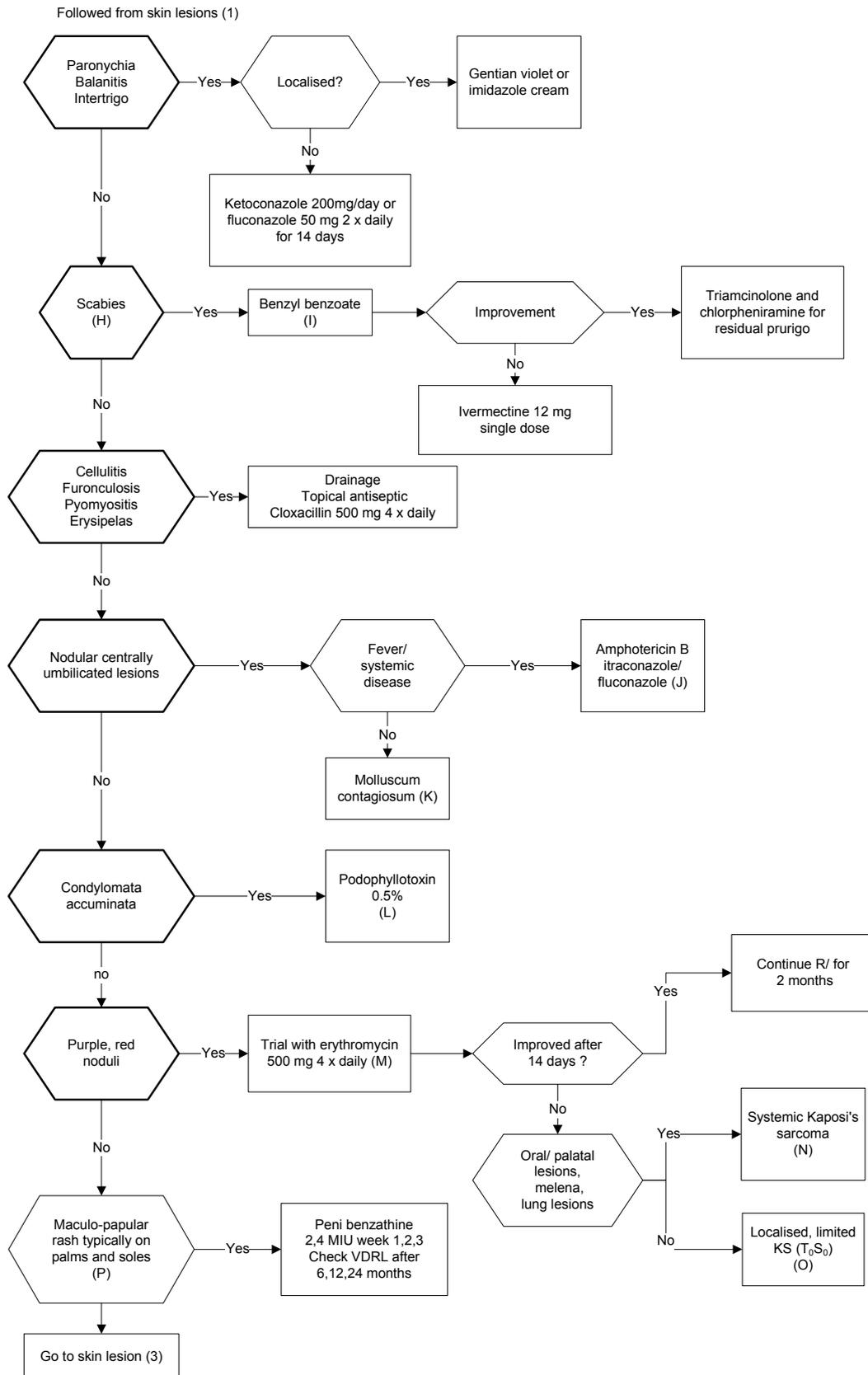
13.3 Clinical management of skin lesions

The differential diagnosis of skin lesions is not so easy in HIV patients. Some of the lesions can be treated at the level of the health centre, others are an expression of an underlying systemic infections, in which case the patient needs a referral to a higher level of care. For this symptom we did not construct different algorithms according to the level of care. The approach of a patient with skin lesions in each setting will depend on the availability of drugs and expert opinion.

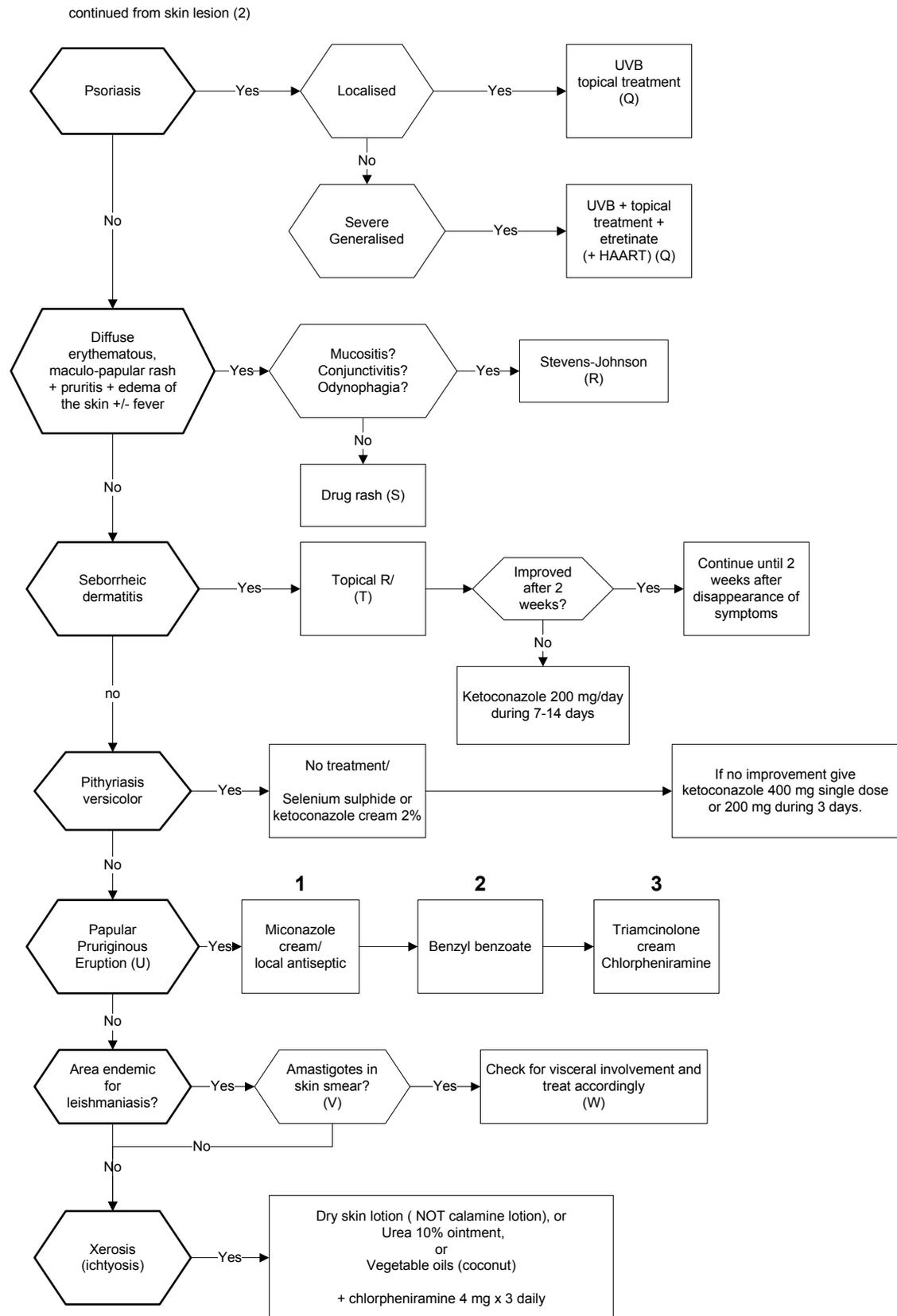
Skin Lesions (1)



Skin Lesions (2)



Skin Lesions (3)



Annotations Skin Lesions

There is no distinction between levels of care here.

- (A) NSAID, paracetamol and gentian violet, or polyvidone iodine.
In case of anogenital lesions, consider other causes (see page 212) if vesicles are absent in current or previous history and/or of no improvement is seen.
- (B) Pain medication: stepwise analgesia (see chapter 14). If recurrences are frequent, give suppressive therapy: acyclovir 200 mg 2 x daily or 400 mg 2 x daily.
In case of anogenital lesions and if vesicles are absent in current or previous history and/or of no improvement is seen, consider other causes (see page 212)
- (C) In addition to acyclovir, topical antiseptics, NSAID and carbamazepine 200-600 mg daily or amitriptylin 25-75 mg daily in the evening (see chapter 14)
- (D) Gentian violet + NSAID + carbamazepine or clomipramine.
- (E) Tinea capitis requires treatment with griseofulvin 10-20 mg/kg daily for at least 6 weeks. Addition of imidazole ointment or Whitfield's will clear scalp scales more rapidly. Severe dermatophytosis or ringworm infection resistant to local therapy may also be treated with griseofulvin 10 -20 mg/kg daily for 4 weeks.
- (F) Dermatophytosis of the nail (onychomycosis) has to be distinguished from infection of the nail wall or nail bed, which is usually due to candida (paronychia) (see page 217)
- (G) Not all patients with dystrophic nails have a fungal infection. Because the treatment is long, it is good to confirm the diagnosis. Direct microscopic examination of a KOH preparation of subungual scrapings will show the presence of hyphae in the case of onychomycosis. In that case, treat with griseofulvin 10-20 mg/kg daily for 12-18 months. If available, pulsed therapy with itraconazole (200 mg 2 x daily for the first 7 days of each month for 4 months) is better because 50% of the onychomycosis, especially the fingernails, are mixed infections. Candida does not respond to griseofulvine.
- (H) In case of scabies with secondary infection, it is better to treat this secondary infection first. Start some days later with benzyl benzoate.
- (I) Apply benzyl benzoate 20% on the whole body, except the face (see page 216).
In case of Norwegian scabies, use ivermectin 12 mg PO combined with benzyl benzoate topical. Thick crusts can be removed before the application of benzyl benzoate by using a few days Whitfield's ointment.

- (J) In a patient with nodular skin lesions, ulcers, papules and lymphadenopathy and who is severely ill, the differential diagnosis between disseminated deep fungal infections and disseminated mycobacterial disease has to be made. In the absence of a skin biopsy and appropriate staining, this may be challenging. Try to find other arguments for mycobacterial disease (miliary TB, AFB on lymph node aspirate, etc). In the case of meningeal involvement, perform an Indian ink stain on CSF. In case of productive cough, do AFB, Gram stain and Cotton-blue stain.
- (K) Molluscum contagiosum usually is asymptomatic. It might be decided to treat it for aesthetic reasons (see page 214)
- (L) Apply podophyllotoxin 0.5% twice daily strictly on the wart (see page 215).
Do not use in pregnant women.
- (M) Because it is sometimes difficult to distinguish clinically between bacillary angiomatosis and Kaposi's sarcoma, a trial with erythromycin or doxycycline is justified. If no response after 14 days, start treatment for Kaposi's sarcoma (see chapter 15).
- (N) In case of systemic Kaposi's sarcoma HAART is needed in combination with chemotherapy (see page 220).
- (O) In case of limited KS, localised on the skin only, or a small oral lesion, HAART may be enough to make the lesions disappear.
- (P) Very suggestive for secondary syphilis. Check VDRL (rarely negative in secondary syphilis). Patients sometimes do not remember that they had a primary chancre. Treat with 3 injections of 2.4 MIU Penicillin Benzathine. Follow-up VDRL at 6, 12, 24 months (see page 211).
- (Q) See: psoriasis page 222.
- (R) Diffuse erythematous or maculo-papular rash, fever and mucositis (oral and vaginal lesions, conjunctivitis, and inability to swallow), are suggestive of Stevens-Johnson syndrome. This is a life-threatening disease and requires hospitalisation in an ICU if available. It is most often associated with the intake of sulphonamides (cotrimoxazole and dapsone) or thiacetazone. It can also occur with nevirapine. Stop the offending drug, in case of HAART: stop all drugs until the patient has recovered. If epidermolysis is not yet present, corticosteroids may reverse the inflammatory process (prednisolone 40-60 mg daily for one week). In case of extensive skin breakdown, steroids enhance the risk of secondary infections. The patient should be treated as a burn patient. Use aseptic techniques to clean and cover the wounds, give aggressive IV rehydration, provide feeding via NG tube. In case of high fever and/or

chills, start broad-spectrum antibiotics (ceftriaxone/amikacin). Stevens-Johnson syndrome has a mortality rate of 50%.

(S) Drug rash: In case of a drug rash when taking ABC, stop ABC and substitute by another drug. Do not rechallenge with ABC again, this can cause fatal reactions.

Nevirapine rash usually occurs in the first 6 weeks of treatment. In case of a nevirapine dry rash without fever or systemic symptoms, continue the drug with close monitoring and give chlorpheniramine 4 mg 3-4 x daily and triamcinolone cream.

In case of fever and/or systemic symptoms (arthralgia, myalgia, hepatitis and eosinophilia): stop all drugs until symptoms resolved. Restart HAART, but do not rechallenge with nevirapine.

In case of a non-life-threatening rash due to cotrimoxazole, consideration might be given to re-trying the therapy after two weeks.⁶⁹ The reason for doing this is that cotrimoxazole is such a valuable drug for prophylaxis of PCP, toxoplasmosis and bacterial infections in PLHA.

Example of a regimen of gradual dose escalation: see page 53.

After desensitisation, under surveillance, up to 70% of patients may again tolerate cotrimoxazole.³⁴⁶

(T) Topical treatment that may have an effect on seborrheic dermatitis:

- gentian violet
- Whitfield's ointment
- miconazole or clotrimazole cream
- ketoconazole cream.

Apply treatment 2 x daily and, if effective, continue treatment for 2 weeks after all symptoms have disappeared. Usually it is necessary to add a steroid cream (hydrocortisone 1%).

(U) Chronic symmetric papular eruption, often with secondary infection.

Underlying causes can be scabies, fungal and bacterial disease. These need to be treated first (see page 219) Do a trial with miconazole, local antiseptics. All pruriginous lesions that do not respond to antifungal therapy justify a trial with benzyl benzoate. When there is no response to antifungals and anti-scabies treatment, give symptomatic treatment.

When the lesions are localised on the trunk and not on the arms and legs, eosinophilic folliculitis is more likely. Potent steroid creams and antihistamines are needed (see page 220).

(V) In HIV patients, due to lack of cellular immunity, it is sometimes easier to detect amastigotes in the skin. It may be primary CL, but it can also be an accidental finding in a skin smear leading to a diagnosis of VL (buffy coat, bone marrow +)

(W) In case of CL, treatment is conservative or with intralesional glucantime (see page 223). In case of VL treatment is with antimonials or amphotericin B (see chapter 10)

Recommended reading

An excellent illustrated booklet on skin diseases in Africa is available online through the ITM telemedicine website.

Van Hees C, Naafs B. Common skin diseases in Africa. An illustrated guide, 2001. (<http://telemedicine.itg.be/> → *Education* → *Lectures/reading suggestions* → *Booklets*).

- A colour atlas of AIDS in the tropics. *Ansary M, Hira S, Bayley A, Chintu C, Nyaywa S; 1994. ISBN:0.7234.1629.X.*
- *Atlas of HIV infection (Asian Patients). Vithayasai P, Vithayasai V, Chiang Mai University, 2nd edition October 1994.*
- Diagnostic picture tests in dermatology. Wolfe Medical Publication Ltd 1986. GM Levene and SK Goolamali. ISBN 0 72340910 2.
- Differential diagnosis in AIDS: a colour guide. Roche Scientific Service. Wolfe Publications Ltd. 1991. JM Parkin and BS Peters. ISBN 3-905283-103-4.
- Dermatology. Churchill Livingstone 1998. JD Wilkinson and S Shaw. ISBN 0 443 058520.
- HIV-related skin diseases. Tschachler E, Bergstresser PR, Stingl G, Lancet 1996: 659-663.



14 NEUROLOGICAL DISORDERS

14.1 Introduction

The reported incidence of neurological abnormalities on clinical examination varies greatly, from 16% to 72% among hospitalised AIDS patients.³⁴⁷ A wide range of neurological manifestations is reported: cognitive defects, focal deficits such as hemiplegia and acute peripheral facial palsy, painful feet syndrome, encephalopathy, etc. Some of these manifestations are directly caused by HIV itself; others are the result of OI caused by different pathogens.

Focal signs include seizures, any sort of paralysis, cranial nerve lesions, and visual disturbance.

Visual impairment in PLHA is mostly due to CMV retinitis. This condition can affect both eyes and lead to progressive loss of vision. Catastrophic vision loss may occur in patients with cryptococcal and tuberculous meningitis due to severe intracranial hypertension.

Meningitis in PLHA can have different causes: early in the course of the infection, it is due to HIV itself; later on to cryptococcal meningitis, TB meningitis, bacterial meningitis (meningococcal and pneumococcal).

The most accurate data on the aetiology of neurological disease in Africa come from autopsy studies in Ivory Coast. Cerebral toxoplasmosis was the third most common cause of death in HIV-infected people, accounting for 10% of deaths.³⁴⁷

Neurological HIV-related pathologies in autopsy studies in Ivory Coast show:

- cerebral toxoplasmosis: 15%
- tuberculous meningitis: 8%
- purulent meningitis: 5%
- cryptococcal meningitis: 2%.

In Central Africa, cryptococcal meningitis is the leading cause of meningitis in HIV patients.³⁴⁸ In South African gold miners cryptococcal meningitis is a frequent cause for admission and accounts for 44% of deaths in hospitalised HIV-patients.⁴¹

In Southeast Asia, fungal infections (cryptococcal meningitis and penicilliosis) are more frequent than in other regions, affecting up to 38% of patients hospitalised at Bamranaradura hospital, Bangkok, between 1993 and 1996.³⁴⁹ In 2002, Preah Baht Norodom Sihanouk hospital in Phnom Penh reported that

25% of admissions were attributable to cryptococcal meningitis and the risk to develop cryptococcal meningitis in their patients in follow-up was 6.4/100 PY, only second to pulmonary tuberculosis.^{350,351}

Also in Latin and Central America cryptococcal meningitis is the first cause of meningitis in AIDS patients.^{352,353}

14.1.1 Conditions caused by HIV itself

Acute retroviral syndrome

Early-stage symptomatic meningitis occurs in a minority of patients, but when present indicates an increased risk for more rapid disease progression.³⁵⁴ *Acute aseptic meningitis* is associated with a high viral load in the CSF. The result of the CSF exam is usually normal. This condition resolves spontaneously and does not require treatment. *Acute inflammatory demyelinating polyneuropathy* (AIDP) can be seen during acute seroconversion and resembles Guillain Barré Syndrome (GBS). In this case there is lymphocytic pleocytosis in CSF in contrast to the non-HIV associated GBS. Steroids may help.³⁵⁵

Mononeuropathy and polyneuropathy

Neuropathy is one of the most common neurological manifestations in AIDS patients, occurring in as many as 30 % of the patients. Nearly every patient has one of four readily distinguishable syndromes (see Table 14).

Mononeuropathy multiplex (MM)

This neuropathy may occur during latent or early symptomatic stages. Facial palsy (Bell's palsy) is a common presentation. Clinically they present with patchy, asymmetric sensory and motor deficits. It can be due to immune dysfunction or to vasculitis. In the latter, pain is usually the first symptom, and in that case steroids may help.³⁵⁶

Distal, symmetrical polyneuropathy (DSPN)

This is the most common type of neuropathy seen. It is associated with lower CD4 counts and high viral load and causes painful paresthesias and numbness of fingertips and toes, which progresses proximally. Symptoms are usually worse at night and are aggravated by contact with bed sheets or wearing shoes. In severe forms, the painful paresthesias and burning can prevent patients from walking despite intact motor function. On physical examination there is a decreased sensation to pinprick, light touch and vibration, and the ankle reflexes are diminished.

It can be caused by HIV itself or by other viral infections such as Herpes zoster and CMV. CMV is an unlikely cause of neuropathy if vision and fundoscopy are normal. MAC infection has been associated with DSPN.³⁵⁷ Nutritional deficiencies (vitB6, vitB12) and syphilis can also cause DSPN. Drug-associated neurotoxicity as it is the case with isoniazid (INH) is a well-know phenomenon, and is more frequent in HIV-infected patients. INH should always be associated with pyridoxine to prevent neuropathy (10-50 mg daily).

In case the National TB program (NTP) does not provide it, the HIV clinic should do so for each HIV patient under TB treatment. Once INH induced neuropathy is established the dose of pyridoxine should be increased to 100-200 mg daily.

In case of positive VDRL the patients need treatment for neurosyphilis (see page 250).

Also antiretroviral drugs, especially nucleoside analogues are frequently responsible for peripheral neuropathy (d4T 23%, ddI 13%). The onset can be as early as one week after the start of the treatment. Ritonavir can give perioral paresthesias, and in rare cases distal sensory neuropathy. The patients should be carefully monitored and when the neuropathy is extending above the level of ankles and/or hands, or if the neuropathy prevents the patient from sleeping, one should consider switching to another non-neurotoxic drug. Waiting too long before switching can cause irreversible damage. Symptoms continue to worsen after interruption of the offending drug, but usually improve over a period of months.

Chronic inflammatory demyelinating polyneuropathy (CIDP)

CIDP is another type of polyneuropathy, which can be the presenting illness in HIV. It occurs at a CD4 count between 200 and 500. It is considered a chronic GBS, with absent or reduced ankle reflexes, progressive symmetrical loss of sensation or pain in fingers and hands and/or feet and legs. Treatment with steroids may help, but is potentially problematic in the setting of immune suppression due to HIV.³⁵⁶ When these patients are started on HAART it is better to avoid potential neurotoxic drugs.

Progressive Polyradiculopathy (PP)

Usually develops in patients with low CD4 count (<50). Patients present with subacute low back pain and radicular pain over a period of a few days, evolving in flaccid paralysis, sphincter dysfunction and areflexia. Usually only the lower extremities are involved. The most common cause is CMV. In the absence of anti-CMV therapy, treatment is supportive.

Table 14: the major peripheral neuropathy syndromes in HIV-infected patients

Syndrome	Clinical features	Cause / differential diagnosis	Treatment
Mononeuropathy multiplex (MM)	Occurs in early HIV infection Self-limited sensory and motor-deficits in the distribution of individual peripheral nerves (Bell's palsy is a typical example) Multiple MM may occur in advanced disease CSF: WBC: mononuclears, protein: high and glucose: normal	HIV	Steroids can help in case of pain
Distal Symmetrical Polyneuropathy (DSPN)	Most common In advanced immune suppression Painful parasthesias and numbness Mainly sensory CSF: protein high, WBC, glucose: normal	HIV, herpes zoster, CMV, nutritional deficiency (vitB6), syphilis, INH ARV	Symptomatic (amitriptyline or carbamazepine + ibuprofen) Discontinuation of neurotoxic agents Trial with VitB6
Chronic demyelinating polyneuropathy	CD4 200-500 Progressive symmetrical loss of sensation or pain in fingers and hands and/or feet and legs. Often become unable to walk. May be rapidly progressive and resemble Guillain-Barré. CSF: WBC: mononuclears, protein: high and glucose: normal	HIV EMG shows demyelination	Steroids HAART, avoid d4T and ddl
Progressive Polyradiculopathy (PP)	In patients with low CD4 count flaccid paraparesis Radiating pain and paresthesias sphincter dysfunction Areflexia CSF: polymorphonuclears, high protein and normal glucose	CMV (and HIV)	Anti-CMV treatment if available NO steroids HAART

Treatment of neuropathies in HIV

Treatment of sensory neuropathy is largely symptomatic (see page 270). Offending drugs should be discontinued. Vitamin B complex should be given to replace possible nutritional deficiencies. Amitriptyline or clomipramine at bed time, starting from a low dose and then gradually increasing till 75 µg, can be tried. In case of lancinating pain, carbamazepine seems to be more effective (100 mg twice daily, can be increased to a maximum dose of 400 mg twice daily).

The only therapies shown to be effective in placebo controlled trials so far is

lamotrigine (anti-epileptic) and recombinant human nerve growth factor. The latter is not commercially available. Lamotrigine is most effective in neuropathy caused by antivirals and has no drug interactions with antivirals.

Acute neuromyopathia and lactic acidosis syndrome

This syndrome is characterized by ascending paresis, areflexia and cranial nerve lesions, compatible with Guillain-barré syndrome, sometimes with severe neuropathic pain and muscle weakness.³⁵⁸ The differential diagnosis has to be made with myelitis and botulism. It often occurs in association with lactic acidosis in patients with prolonged use of stavudine.

Case definition for Acute Neuromyopathy and Lactic Acidosis Syndrome (ACTG Neuropathy working group)

1. New onset of limb weakness, with or without sensory involvement.
 - Either acute (1-2 weeks) or sub-acute (> 2 weeks)
 - Affecting either lower or both lower and upper extremities.
2. Absence of potentially confounding illnesses excluded by comprehensive neuromedical evaluation (e.g. myasthenia gravis, myelopathy, hypokalemia, stroke)

HAART needs to be stopped immediately. Case studies and uncontrolled trials have supported the use of anti-oxidants or co-factors in the oxidative phosphorylation: thiamine (100-300 mg/day), riboflavine (vitamine B2 50-400 mg/day), vitamine C (25 mg/kg/day), co-enzyme Q (3.5-4 mg/kg/day), carnitine (50-200 mg/kg/day).³⁵⁹

After a few weeks patients can start again on an alternative regimen, but containing drugs that have less mitochondrial toxicity (abacavir, tenofovir, lamivudine).³⁶⁰

Generalised motor weakness

Extreme muscle weakness with inability to walk can be due to severe hypokalemia. Low potassium is frequently encountered in AIDS patients with chronic diarrhoea and during treatment with amphotericin B.

HIV myelopathy

HIV-related spinal cord involvement is rare. It presents as spastic paresis with bowel and bladder dysfunction, gait ataxia, incontinence and variable sensory loss.

This condition can respond to HAART. DD has to be made with cord-compression (epidural abscess, tumor), vitamin B12 deficiency or other viral infections (varicella, CMV, HTLV-1)

HIV encephalopathy / AIDS dementia

Approximately 7-9% of patients with AIDS develop dementia.

The initial manifestations are loss of memory and strange behaviour. These will later be associated with various degrees of incontinence and gait disturbances with ataxia. In very advanced stages, patients may become completely demented with associated mutism and even paraplegia. It is a diagnosis of exclusion, because depression and infectious causes of

encephalitis may mimic dementia. The CSF is usually normal, although 20% of cases may have a mild mononuclear pleocytosis (<50 WBC/mm³) with slightly increased protein content (<200 mg/dl).

When available, an AZT or d4T-containing HAART regimen is an effective treatment for HIV-associated dementia. There is not enough evidence to promote adding a PI rather than a NNRTI to the 2 NRTIs.³⁶¹

14.1.2 Opportunistic infections involving the brain

The differential diagnosis includes the following pathogens:

- Protozoal infection: *Toxoplasma gondii*, *Trypanosoma Cruzi*
- Mycobacterial infection: *M. tuberculosis*, *M. Avium* (in immune reconstitution syndrome)
- Fungal infection: *Cryptococcus neoformans*, Histoplasmosis, Coccidioidomycosis, *Candida* species (rare)
- Viral infection: Cytomegalovirus, Herpes simplex virus, Varicella zoster virus, JC virus (slow virus causing progressive multifocal leukoencephalopathy - PML).

Since neurological involvement in AIDS patients can present in many different ways and since some of the conditions can be treated, early diagnosis is important. This is true for TB meningitis, toxoplasma brain abscess and fungal meningitis. The threshold for performing an LP should therefore be kept very low in AIDS patients who have headache. Even in the presence of papilloedema, an LP seems to carry no excessive risk in TB meningitis or toxoplasmosis, and is even indicated for treating intracranial hypertension in the case of cryptococcal meningitis.

Cryptococcus neoformans

Cryptococcus neoformans is the most common life-threatening fungal infection in patients with AIDS. It is the first cause of meningitis in patients with AIDS in Africa, Latin America and Asia. It occurs most often in HIV-positive patients with CD4 <50. In this group of AIDS patients, 90% of those infected with *Cryptococcus neoformans* will present with meningeal involvement. However, less than 50% have meningeal signs. The onset is insidious, fever and headache being often the only symptoms. Neck stiffness can be absent, and thus prolonged headache and fever, behavioural changes and confusion justify a lumbar puncture.

Other fungal infections, like coccidioidomycosis and histoplasmosis can also cause chronic meningitis and should be considered in meningeal syndromes in HIV patients in South and Central America.

Diagnosis

By lumbar puncture: increased opening pressure, sometimes only slightly

elevated WBC count (predominantly lymphocytes). Up to 25% of patients can have a normal cell count.³⁶²

Staining is easy: India ink and direct microscopic examination: positive in most cases (82%-85%).^{363,364}

Note: A positive India ink staining in a patient, who completed treatment and has no symptoms anymore, does not prove active infection or failure of therapy.

A positive culture always proves active infection.

Because timely diagnosis is very important for treatment outcome several projects have started to use the cryptococcal Ag test on CSF (CRAG latex agglutination). This test has a sensitivity of 92%, and is highly specific.

Active cryptococcal infection can be present in some patients with a positive serum CRAG (sCRAG) but negative fungal cultures, which encourages clinicians to treat HIV patients with a positive sCRAG even in the absence of symptoms. The serial monitoring of CRAG in serum or CSF has no clinical utility to monitor the response to therapy. Cryptococcal antigen can remain positive for up to 7 months after cure of the infection.³⁶⁵

Serum CRAG can be used to diagnose cryptococcosis in a patient with cachexia and fever before the start of HAART, but without focal signs and no previous treatment for cryptococcosis (see chapter 16).

Treatment

Regimen most frequently used

Several combinations of treatment have been studied in clinical trials. The best survival at 2 months is reached with the combination amphotericin B and fluconazole, together with regular spinal taps to decrease intracranial hypertension.^{364,366-368}

We recommend for all MSF missions the combination of amphotericin B and fluconazole.

Amphotericin B (IV) (0.7 mg/kg daily by slow IV injection for 2 weeks) followed by fluconazole 400 mg daily for 8 weeks, followed by fluconazole 200 mg daily as secondary prophylaxis.

In children: Amphotericin B, 0.7-1mg/kg/d IV diluted in 5% glucose infused by slow drip over 4 hrs, during 2 weeks, followed by maintenance therapy of fluconazole 10-12 mg/kg during 8 weeks.

Secondary prophylaxis: fluconazole 5mg/kg/day lifelong, or until immune restoration after HAART (CD4 > 100 during 3-6 months)

2nd choice

In patients with less severe disease, oral fluconazole treatment alone (400 mg once daily during 10 weeks, after an initial loading dose of 800 mg during 3 days) may be sufficient. This should be used in patients with less severe headache who have a negative CSF exam, but CRAG is positive on CSF.

Children: fluconazole 10-12/mg/kg once daily during 10 weeks always followed by secondary prophylaxis.

All regimens that do not contain fluconazole in the maintenance phase

(itraconazole 200 mg daily or Amphotericin B weekly) are less effective.

How to safely administer amphotericin B?

Reconstitute amphotericin with non-bacteriostatic water (no preservatives) and dilute in dextrose or glucose 5% in water (amphotericin precipitates in salt solutions). Infuse amphotericin B over 4-6 hours. Rapid infusion is associated with hypotension, hypokalemia, shock and arrhythmias and should be avoided.

Infusion-related reactions such as nausea and vomiting are common with amphotericin B. They usually occur between 15 minutes and 3 hours following the start of the infusion. Drug-induced fever, chills and headache are also seen. These symptoms can be prevented by premedication with 1 g of paracetamol and 25 mg of promethazine. For severe chills and rigors, pethidine 25 mg IM or IV is frequently prescribed. The severity of the reactions tends to decrease with subsequent doses of amphotericin B. Some clinicians prefer to start with a lower dose (0.3 mg/kg) the first day. Severe hypokalemia can occur during treatment with amphotericin B due to a potassium wasting nephropathy. In some patients, this leads to severe muscle weakness, muscle cramps, chest pain, palpitations, drowsiness and mental status changes.

Replacement with oral potassium and magnesium supplements is indicated. Prehydration with 1 litre normal saline can help reduce the incidence of nephrotoxicity.³⁶⁹

Close medical supervision is required throughout treatment. Check the renal function once a week if possible or monitor the urine output. When renal failure develops, interrupt the treatment or increase the dosing interval of amphotericin B. Thrombocytopenia and hypoglycaemia are other possible side effects. Patients may become hypotensive or hypertensive, in which case the rate of the infusion needs to be slowed down, after a temporary interruption of 30 minutes.

Safe use in pregnancy has not been established. However, one has to weigh the risks and the benefits for the mother and the foetus. Fluconazole in higher doses is teratogenic as well.³⁷⁰ Amphotericin B remains the therapy of choice in life threatening fungal infections in pregnant women.

Risk factors for poor prognosis in cryptococcal meningitis are lethargy and obtundation (GCS <13) at admission, hyponatremia, high titre of cryptococcal Ag in CSF (>1: 1024), low WBC count in CSF (<20 cells/mm³) and high opening pressures.

Example of treatment protocol for the safe administration of amphotericin B

Daily procedure

1) Take history:

- Nausea, vomiting, diarrhoea, anorexia, severe muscle cramping, weakness, chest pain, palpitations, CNS disturbance (lethargy, sleepiness), decreased urination, black stool or easy bruising/bleeding, pain at previous IV site.

2) Laboratory if indicated:

- Routine monitoring: potassium, creatinine, blood urea nitrogen, complete blood count, glucose (day 1,7, 14) If you do not have this, the most important is to observe well your patient. Give him enough food, and supplements of potassium and magnesium.
- More frequently as indicated (in case of bleeding, decreased urination, mental changes to evaluate symptoms elicited in the history).

3) Pre-medication 30-60 minutes before infusion:

- Paracetamol 1 gm PO, Promethazine 25 mg PO.
- (hydrocortisone 50 mg IV if severe rigor/chills occurred on previous infusion).

2) Record vital signs:

- Temperature, heart rate, respiratory rate and blood pressure, initially and every 30 minutes during infusion.

5) Hydrate NS 500 -1000 ml IV (over 2 hours) to avoid nephrotoxicity

6) Infuse amphotericin B over 4-6 hours

- Starting dose: Day 1 :0.3 mg/kg in 250 ml dextrose 5%.
- Full dose: Day 2-14 :0.7 mg/kg in 250 ml dextrose 5%.
- Adjusted dose: if decline in renal function during therapy, or significant adverse reactions may cut full dose in half.
- The total cumulative dose should remain the same when dose is adjusted.
- If chills/rigor develop give Pethidine 25 mg IV, hydrocortisone 50 mg IV.

7) Lumbar Puncture (LP) if patient has known or suspected increased intracranial pressure – (>25 cm of H₂O)

- Measure and record openings pressure (OP) at each LP.
- If > 25cm H₂O drain 30cc of CSF.
- Repeat daily until OP < 25 cm.
- Repeat later on if patient's headache increases again

8) Review instructions to patient:

- Drink 2-3 liters of fluids per day.
- Small frequent meals
- Replace with oral Magnesium, one tablet daily and KCL 600 mg twice daily (caution with K replacement if significant pre-existing renal failure).

9) For seizures:

- Benzodiazepines IV or IR, then load with phenytoin. If seizures do not recur, the phenytoin may be interrupted during the maintenance phase.

10) Begin fluconazole 400 mg per day for 8 weeks upon completion of the 14 day amphotericin B regimen.

Treatment of increased CSF pressure

The management of high intracranial pressure (ICP) is considered one of the most important factors influencing early mortality.³⁷¹ High ICP is present in more than 50% of patients with cryptococcal meningitis (CM). It is associated with massive fungal burden and low host immune response. CM is a chronic granulomatous meningitis without evidence of obstructive hydrocephalus but

with increased intracranial pressure because of impaired resorption of CSF in the arachnoid granulations. It is thought that it are the yeasts themselves which block the outflow, more than the inflammation.³⁷²

Even in the US with the current treatment regimens, there is a high rate of acute mortality during initial therapy (10%-25%).³⁷³ Often there is a sudden deterioration and catastrophic visual loss in patients with elevated intracranial pressure.^{364,366} The only effective therapy to reduce the severe headache is to lower intracranial pressure by repeated spinal taps. Most patients declare dramatic relief of headache within minutes of the procedure. There is no place for corticosteroids as adjuvant therapy in cryptococcal meningitis, except in IRIS (see further).

If the initial opening pressure was normal, perform a follow-up LP at 1 and 2 weeks or if any worsening of headache, visual or hearing problems.

If the initial opening pressure was >250 mmH₂O, perform a spinal tap sufficient to achieve pressure < 200 mmH₂O or 50% of initial opening pressure. You can tap up to 30 ml each time.

Daily taps should be performed until opening pressure is less than 250 mm H₂O.

For the first diagnostic LP, use a 20-22 G needle. For therapeutic tapping, an 18G needle can be used.

Primary prevention

Fluconazole is effective to prevent a first episode of cryptococcal meningitis. Different dosing schedules have been studied and seem to have similar efficacy; fluconazole 200 mg thrice weekly, 200 mg once daily, 400 mg once weekly and fluconazole 100 mg once daily.^{102,374-376} The target group for primary prophylaxis are patients with CD4 <100. In case CD4 count is not available patients with WHO stage 4 conditions are eligible. Exposure to fluconazole reduces the risk of CM with 82%.³⁷⁷ Also itraconazole in a dose of 200 mg daily is effective for the primary prevention of cryptococcosis and penicilliosis.³⁷⁸ There are concerns, however, that primary prevention of cryptococcosis could promote azole-resistant *Candida* species. For patients on HAART, primary prevention can be stopped when the CD4 has been >100 for at least 3 months.³⁷⁹

In the case of pregnant women, high dose fluconazole as used in treatment, is teratogenic.³⁷⁰ Fluconazole used in doses < 150 mg daily seems to be safe. In practice we would not recommend fluconazole primary prophylaxis for pregnant women, but still recommend it in secondary prophylaxis, because of the high risk of relapse.

Secondary prevention

Without secondary prevention the recurrence of cryptococcal meningitis in the pre HAART era 50-60% in 1 year.³⁸⁰ The preferred regimen is fluconazole 200 mg daily. It is safe to discontinue secondary prophylaxis when the patient is on HAART and his CD4 count is > 100 for 3-6 months.^{106,107} The patient should be monitored closely for recurrence and it may be prudent to empirically treat patients whose sCRAg becomes positive again.³⁸⁰

Less effective alternatives for secondary prophylaxis are itraconazole, 200 mg po 2 x daily or amphotericin B, 1 mg/kg IV 1 to 3 times per week.

IRIS

In patients with advanced immune deficiency, partial immune restoration after the initiation of HAART can cause an immune reconstitution inflammatory syndrome (IRIS). Patients with a latent cryptococcal meningitis or in patients who have had a cryptococcal meningitis in the recent past and who have residual antigen in the CSF can present with inflammatory meningitis, headache or focal neurological signs after the start of HAART.¹⁶⁹ The immune restoration only prevents disseminated disease but still causes symptoms due to local inflammatory reactions against residual antigen or against a latent infection.²⁸⁴ It is seen most frequently between 1 week and 8 months (typically 1-6 weeks) after starting HAART and is usually associated with high ICP.³⁸¹

Diagnosis

A lumbar tap may show yeasts, but it is difficult to know whether this is IRIS (with dead yeasts) or relapse of infection. Patients are often on secondary prophylaxis with antifungals. Most of the cases described have negative culture results, a low antigen titre, but cryptococcal compatible forms are detected in biopsy material.³⁸¹

Evidence of immune restoration is suggested by a sharp decrease in viral load, a significant increase in CD4 count and inflammatory changes in the CSF (WBC count > 10 x 10⁶/L).

Prevention

One case study suggested that the presence of residual cryptococcal antigen in the CSF predicts the onset of clinically apparent meningitis after the start of HAART.¹⁶⁹ Inadequate treatment of the initial infection does not explain the occurrence of IRIS. However, in order to reduce the risk of IRIS related cryptococcal infection, it is probably wise to delay the start of HAART until completing the first 2 months of treatment (before secondary prophylaxis) for cryptococcal meningitis. There is not enough evidence to support the use of corticosteroids to prevent IRIS.

Treatment

The treatment of IRIS related cryptococcal infection is identical to the one mentioned above. In case of high ICP it is important to do frequent LPs with evacuation of 30 cc of CSF.

Some restart antifungal therapy (fluconazole 400 mg daily or amphotericin B for 14 days) and lumbar taps in case of meningitis, others just add steroids and continue the secondary prophylaxis. There are no comparative data. Treatment with HAART should be continued if the patient tolerates it.

In case of life threatening symptoms (severe ICP) with focal neurological lesions it is useful to give steroids.

Toxoplasma encephalitis or brain abscess

Toxoplasmosis was a common CNS infection in patients with advanced HIV disease in Europe and the USA in the early years of the epidemic. Between 5% and 47% of HIV-infected patients with serologic evidence of *Toxoplasma gondii* infection will develop symptomatic disease. In Southeast Asia,

toxoplasmosis appears to be infrequently reported (1% to 2%). This can be due either to the limited diagnostic capacity or to a real low incidence of *Toxoplasma encephalitis*. A serologic study on pregnant women and blood donors in Cambodia showed a low percentage of seropositivity for *Toxoplasma gondii* (13,1%).^{382,382} This makes cerebral toxoplasmosis an unlikely diagnosis in an HIV-positive patient in Cambodia.

Toxoplasma gondii, a protozoan parasite of mammals, is transmitted when oocysts are ingested, either via excretion by household pets or their presence in undercooked meat. Invasive forms enter the bloodstream to reach the brain, heart and lungs where they form cystic aggregates that remain latent, but subject to reactivation throughout the life of the host. In many communities, the majority of people will have been infected by early childhood, but otherwise healthy persons do not develop clinically evident disease.

The pathogenesis

Primary infection may result in focal necrotizing encephalitis and occasionally chorioretinitis and pneumonitis as a result of the unrestrained multiplication of tachyzoites. Reactivation of latent bradyzoites produces focal neurological signs mainly in patients with CD4<100. Hemiparesis, cognitive disorders, seizures and other signs suggestive of an intracerebral space-occupying lesion tend to develop subacutely over several weeks, and they are sometimes accompanied by symptoms of a diffuse encephalopathy.

Symptoms

Symptoms are variable, but typically subacute over several weeks. Fever is present in about 50% of patients and headache, which may be very prominent, is present in 50%-70% of patients. 50% of patients have hemiplegia or hemiparesis. 30% have seizures.¹⁷⁹ Meningeal irritation is infrequent.

Diagnosis

CSF findings are non-specific or normal. If a CT scan is available, the presence of an intracranial mass lesion in a patient who has a positive serology and no prophylaxis is very suggestive for toxoplasmosis. A CT scan is not absolutely necessary to make the diagnosis of *Toxoplasma* brain abscess. In many countries, *Toxoplasma gondii* is the most common cause of focal brain disease in HIV patients. It is therefore worth treating any HIV-positive patient presenting with headache, fever and focal neurological signs, and who has normal CSF findings, for toxoplasmosis. If the diagnosis of toxoplasmosis is correct, 74% of patients will have responded to treatment by day 7 and 91% by day 14. The median time to response is 5 days.³⁸³ Response to empirical therapy is currently being considered as a diagnostic criterion. If possible, *Toxoplasma* antibody (IgG) can be useful, because the negative predictive value is high (94-97%).³⁸⁴ In other words, *Toxoplasma* brain abscess is less likely if the *Toxoplasma* serology is negative. If there is no response to empirical therapy after 2 weeks an alternative diagnosis needs to be considered.

Treatment

First choice: sulfadiazine and pyrimethamine and folinic acid for 6-8 wks.

- pyrimethamine 100 mg loading dose, followed by 50 mg daily
- sulfadiazine 1-2g 4 x daily (100 mg/kg daily)
- folinic acid 10 mg daily.*

Sulfadiazine and pyrimethamine is the treatment of choice for HIV-positive patients suspected of having acute toxoplasmosis (including children and seriously ill pregnant women). Both drugs are cheap and penetrate into the cerebrospinal fluid in therapeutically active concentrations. The relatively high doses used can, however, lead to toxicities, so careful monitoring is important. Overall 45-70% of patients will develop side effects and 33% require a change in therapy. Leukopenia, thrombocytopenia and rash are common. Folinic acid, which counteracts the blockade of folate metabolism in mammalian cells without affecting antiprotozoal activity, should be administered regularly to reduce the risk of myelosuppression. Patients should be advised to maintain a high fluid intake and urine output to prevent the development of sulfadiazine induced crystalluria, and to watch for signs of 'gravel' (sulfadiazine crystals) in their urine.

Second choice: high dose cotrimoxazole (10/50 mg/kg daily) for 4 weeks.

Several Italian studies have shown that, high dose cotrimoxazole 10/50 mg/kg daily PO or IV, divided over 2 doses for 4 weeks, followed by a lifelong maintenance of 1 DS (960 mg) cotrimoxazole daily is effective in the treatment of *Toxoplasma* encephalitis, and has fewer side effects than the combination sulfadiazine/ pyrimethamine.^{178,179,385 178,178,385,385}

Third choice: clindamycin and pyrimethamine and folinic acid for 6-8 wks.

- clindamycin 600 mg 3 x daily
- pyrimethamine 100 mg daily loading dose followed by 50 mg daily[†]
- folinic acid 10 mg daily.

Other measures

In case of intracranial hypertension: papilloedema, vomiting: corticosteroids: prednisolone 40 mg 4 x daily or dexamethasone 4 mg 4 x daily.

If there is no sign of mass effect avoid using steroids because it may be difficult to assess the response to empirical treatment.

Anti-epileptic treatment in case of seizures: phenytoine 100 mg 2-3 x daily (after a loading dose of 15 mg/kg daily the first day).

* It is important to remember that folic acid counteracts the anti-protozoal activity of pyrimethamine and is not a good alternative for the expensive folinic acid.

† Note that of the commercial antimalarial drugs, Maloprim® contains dapsone 100 mg/pyrimethamine 12.5 mg and Daraprim® contains pyrimethamine 25 mg.

Primary treatment should be continued for 4 (cotrimoxazole) to 6 (sulfadiazine, clindamycin) weeks. After this, the doses are reduced and patients should remain on this maintenance therapy for life.

Maintenance therapy

- **cotrimoxazole: 1DS daily** or
- Or dapsone 200 mg weekly or 50 mg daily + pyrimethamine 75 mg weekly + (folinic acid 25 mg weekly)
- Or sulfadiazine 500 mg 2 tablets 2 x daily + pyrimethamine 25 mg daily + (folinic acid 25 mg weekly)

Primary prophylaxis

The risk of transmission can be reduced if meat is adequately cooked and if vegetables and fruit are washed carefully before they are eaten. In HIV-positive patients with CD4<100 and *T. gondii* antibody positive, prophylaxis with either **cotrimoxazole** or dapsone and pyrimethamine at doses used for the prevention of PCP, have been shown to reduce the incidence of toxoplasmosis.

- cotrimoxazole: 1DS daily or
- Dapsone 200 mg weekly or 50 mg daily + pyrimethamine 75 mg weekly + folinic acid 25 mg weekly

Primary and secondary prophylaxis can be stopped if the CD4 count is above 100-200 cells/mm³ for at least 6 months, in patients taking HAART.^{63,379}

Tuberculous meningitis

Up to 10% of AIDS patients who present with TB will show involvement of the meninges. This results from rupture of a cerebral tuberculoma or is blood-borne.

Be aware of IRIS related TB meningitis, especially in the first 6 weeks after starting HAART.

Symptoms

- Gradual onset of headache and decreased consciousness, low-grade fever.
- Neck stiffness and positive Kernig's sign.
- Cranial nerve palsies result from exsudate around the base of the brain.

Diagnosis

The diagnosis of tuberculous meningitis relies on isolation of *Mycobacterium tuberculosis* from the CSF. Unfortunately this is a slow process, and therefore not helpful in clinical decision making.

Direct Ziehl-Neelsen staining on the deposit of CSF is a rapid method but very insensitive. CSF microscopy only seldom shows AFB. You can increase the diagnostic pick-up rate by the following:

- examine the deposit after centrifugation of a 10 ml CSF sample
- examine the deposit for at least half an hour before reporting it as negative

- examine several CSF samples obtained over a few days.
- Lumbar puncture is mostly safe in tuberculous meningitis.
- CSF may look cloudy. WBC: 500/mm³; lymphocytes (early in the course: granulocytes).
 - High protein level (40 -100 mg/dl).
 - Low glucose level (<20 mg/dl).

Diagnostic rules developed for the diagnosis of TB meningitis are hampered by lack of sensitivity and specificity. Nevertheless, therapy is usually started in an empirical way and therefore simple diagnostic algorithms are useful to standardise clinical practice in a given setting with a high TB prevalence. A group in Vietnam has studied a diagnostic index (DI) system based on age (< 36 years old), CSF cell count (> 900/ μ l), duration of illness (<6 days) and % of neutrophils (>75%) to distinguish between bacterial or tuberculous meningitis in patients who have a CSF:blood glucose ratio of less than 50%. In their setting (high TB prevalence, low HIV prevalence) they used a score of 4 or less as a diagnostic threshold for TB meningitis see Table 15. This diagnostic index had a sensitivity of 97% and a specificity of 91%.³⁸⁶

Table 15: Diagnostic index of clinical parameters to differentiate between tuberculous and bacterial meningitis in patients with CSF/serum glucose < 0.5 (adapted from Thwaites et al)³⁸⁶

	<u>Diagnostic index</u>
Age \geq 36 years	2
Age < 36 years	0
Blood WBC \geq 15,000/mm ³	4
Blood WBC < 15,000/mm ³	0
Sick \geq 6 days	-5
Sick < 6 days	0
CSF WBC count \geq 900	3
CSF WBC count < 900	0
CSF % neutrophils \geq 75%	4
CSF % neutrophils < 75%	0
TOTAL SCORE	X

Always exclude cryptococcal meningitis by CSF microscopy (Indian ink stain).

Differential diagnosis of TB meningitis on CSF findings

See Table 16.

Several studies have demonstrated the usefulness of urine sticks for determining proteins and WBC in CSF. The use of this method in HIV/AIDS patients with meningitis is not yet evaluated.

Table 16: Differential diagnosis of tuberculous meningitis ¹²⁸

	CSF abnormalities					
Disease	Appearance	Opening pressure	WBC/mm ³	Protein	Glucose	Microscopy/ other tests
Tuberculous meningitis	Opalescent	I	25-1000* mainly L	45-500	10-45	AFB (25% sensitivity)
Cryptococcal meningitis	C	I	I but <800 L> PMN	I but <500	Slightly decreased	Positive India ink staining Ag: Cryptococcal sensitivity 92%
Bacterial meningitis	O or P	I	25-10.000 mainly PMN	50-1500	0-45	Bacteria on Gram stain: 60-90% sensitivity
Viral meningitis	N or O	N	20-300 L>PMN	Increased	Normal	
Neuro-syphilis	N	N	10-150 mononuclear	50-300	Normal	Usually high VDRL
African Late stage trypanosomiasis			Elevated (L>PMN)	Increased	Decreased	Motile trypanosomes
Toxoplasmosis	N	I	N	N	N	
PML	N	N	N	N	N	
HIV encephalopathy	N	N	<50	I but < 200	N	Abnormalities in the CSF are present in 20% of patients

Key: I: increased, O: opalescent, P: pus, C: clear, N: normal, PMN: granulocytes, L: lymphocytes

* In HIV patients the number of WBC in CSF can be lower than 25, also in TB meningitis

Treatment

Whenever available, the national TB programme protocols should be used. Prolonged treatment: a **7-month continuation** phase with **daily isoniazid and rifampicin** (7HR) is recommended for category 1 patients with the following forms of TB: TB meningitis, miliary TB, spinal TB with neurological signs.³⁸⁷ In case of severe neurological signs (cranial nerve lesions, drowsiness, coma) the use of **steroids** (prednisone 1 mg/kg for 2-4 weeks, then tapered off over 4-6 weeks) is good clinical practice. Patients treated with steroids have more rapid symptomatic relief and less neurological sequelae.¹⁵⁴

Thioacetazone should not be used in persons known to be or suspected of being infected with HIV because of the occurrence of severe hypersensitivity reactions.

Note:

There is a higher incidence of paradoxical reactions if patients are started on HAART and TB treatment at the same time.^{128,388} Therefore always start first TB treatment and add HAART when the treatment is tolerated between 2 weeks and 2 months (WHO) or when the intensive phase of 2 months with rifampicin is finished.

TB meningitis during immune reconstitution inflammatory syndrome (IRIS) can sometimes have a very fulminant course if not recognized. Steroids should always be added to the TB *treatment* in case of IRIS related TB meningitis. HAART can be continued, but in severe cases, a temporary interruption may be justified. Switch to efavirenz (EFV) if the patient was taking a Nevirapine-containing regimen, but keep in mind that giving EFV to a patient with neurological problems can worsen the clinical picture due to EFV side effects. If efavirenz is not available you can continue nevirapine. However, watch out for hepatotoxicity.

Cytomegalovirus (CMV)

CMV disease in PLHA is due to reactivation, occurring in patients with CD4<50 and presenting with gastrointestinal disease and retinitis. 50% of PLHA with active CMV disease, will have CMV retinitis. Neurological manifestations include myelopathy and encephalitis. Clinically encephalitis presents as a rapidly progressive delirium, cranial nerve deficits, nystagmus and ataxia. The diagnosis is difficult. CSF exam may reveal lymphocytic pleocytosis, low glucose and increased protein, therefore indistinguishable from tuberculous meningitis. In case of radiculomyelitis the CSF show predominant neutrophils. PCR for CMV on the CSF has a good sensitivity and specificity but is rarely available. Serology has no place in the diagnosis of CMV.³⁸⁴

Prognosis is poor for patients with CNS CMV disease. Induction therapy with IV ganciclovir effectively treats retinitis in 70%-90% of patients, but the effect is much less in CNS disease. Lifelong maintenance therapy is necessary. Severe bone marrow suppression can occur. The drug is expensive and

beyond the reach of most developing countries. All patients should be treated with HAART, as immune reconstitution will improve survival. However, patients should be informed about the possibility of IRIS after the start of HAART, which in the case of CMV may cause blindness (usually after 1-2 months), due to immune recovery uveitis (IRU) or vitritis.

In the first months of HAART CMV neuropathy can worsen and present with painful radiculopathy, sometimes associated with spastic paresis. This is another manifestation of IRIS. Continue HAART, add steroids* to reduce the inflammation and give symptomatic relief.

Syphilis

Tertiary syphilis involving the brain and spinal cord used to be common before the availability of antibiotics. In PLHA, syphilis can occur even in people who had previously a complete course of antibiotics, and it can occur without a rise in VDRL or RPR. VDRL/RPR can be false positive. When available it should be confirmed by a specific treponemal antibody test. TPHA is such a confirmatory test. If clinical suspicion is high and serology is negative, the VDRL should be rechecked after dilution of the sample (to rule out the prozone effect = false negative tests due to excessive presence of antigen). Although serum VDRL has a high sensitivity (90%) and low specificity, this trend is reversed on the CSF sample. CSF VDRL has high specificity but low sensitivity. A positive VDRL on CSF confirms the diagnosis of neuro-syphilis. All the classical presentations of neuro-syphilis are seen again: tabes dorsalis, gumma (meningo-vascular disease), etc.

Treatment of neuro-syphilis:

- Peni G 12-24 MIU daily for 14 days, followed by benzathine penicillin 2.4 MIU once weekly for 3 weeks. Check VDRL again at 6, 12 and 24 months. If VDRL fails to decline, repeat treatment.

- Alternative: Benzylpenicillin procaine IM 1-1.5 MIU (one vial of 1MIU or half a vial of 3 MIU) once daily plus probenecid PO 500 mg 4 x daily for 10-14 days, followed by benzathine penicillin 2.4 MIU once weekly for 3 weeks.

* Prednisolone 40 mg/day for 2 weeks, followed by prednisolone 20 mg/day for 1 week, followed by 10 mg/day for another week

Progressive multifocal leukoencephalopathy

This is a viral opportunistic brain infection caused by the JC virus. It occurs in up to 4% of patients with advanced AIDS. CSF is typically normal. A positive PCR for JC virus on CSF has a high positive predictive value, but is rarely available in resource-limited settings. Patients have hemiparesis, cortical blindness, dysarthria, hemianopsia, cerebellar ataxia, speech deficits, but they remain alert and rarely have seizures. CT scan shows single or multiple hypodense lesions in the white matter without mass effect. Rapid clinical progression is common and death usually occurs within 6 months of diagnosis. Specific antiviral therapy (cytarabine, cidofovir, acyclovir, alpha-interferon) does not alter the prognosis.³⁸⁴ HAART is the standard of care for PML. However some patients develop PML while on HAART and also cases of IRIS have been described with PML, in patients responding well to HAART.

Chagasic meningoencephalitis

Significant flare-up of Chagas' disease can happen in HIV patients. The most common manifestation in AIDS patients, is a CNS tumour like lesion, that has to be differentiated from toxoplasma brain abscess.^{389,390} At times *T. cruzi* may even be detected in the cerebrospinal fluid. With suggestive symptoms and a positive *T.cruzi* serology (IgG) treatment with benznidazole is recommended; 5-10 mg/kg/day orally for 1 to 2 months. Administration (generally 100 mg tablets) is twice daily. There are insufficient data concerning chemoprophylaxis.

14.1.3 Stroke

The incidence of strokes in HIV patients exceeds the one in non-HIV patients. Multiple causes of stroke need to be taken into consideration.³⁹¹⁻³⁹⁴ MSF-Thailand identified cerebral vascular disease as an important cause of hemiplegia (26%) in AIDS patients, second only in frequency to toxoplasmosis (33%).³⁹⁵

Possible reasons for stroke are endocarditis, cocaine use, herpes zoster with arteritis of the middle cerebral artery (frequently but not always accompanied by zona ophthalmica on the contralateral side) and hypercoaguability.

In AIDS patients presenting with stroke or transient ischemic attack, potentially treatable causes, such as cerebral co-infection or tumor, should be sought.³⁹⁶

14.1.4 Malignancies

If a mass lesion/focal lesion of the brain in an AIDS patient does not respond to empirical anti-toxoplasmosis treatment against toxoplasmosis, lymphoma is another possible diagnosis. In South America Chagas' disease is part of the differential diagnosis. The CNS is a frequent location of lymphomas in AIDS patients. Although the life expectancy of patients with lymphoma improved since chemotherapy is combined with HAART, in most of the settings where

MSF is working intensive chemotherapy is often not possible because of haematological toxicity. CNS lymphomas may have a transient relief of symptoms when they are receiving empiric treatment for toxoplasmosis in combination with steroids.

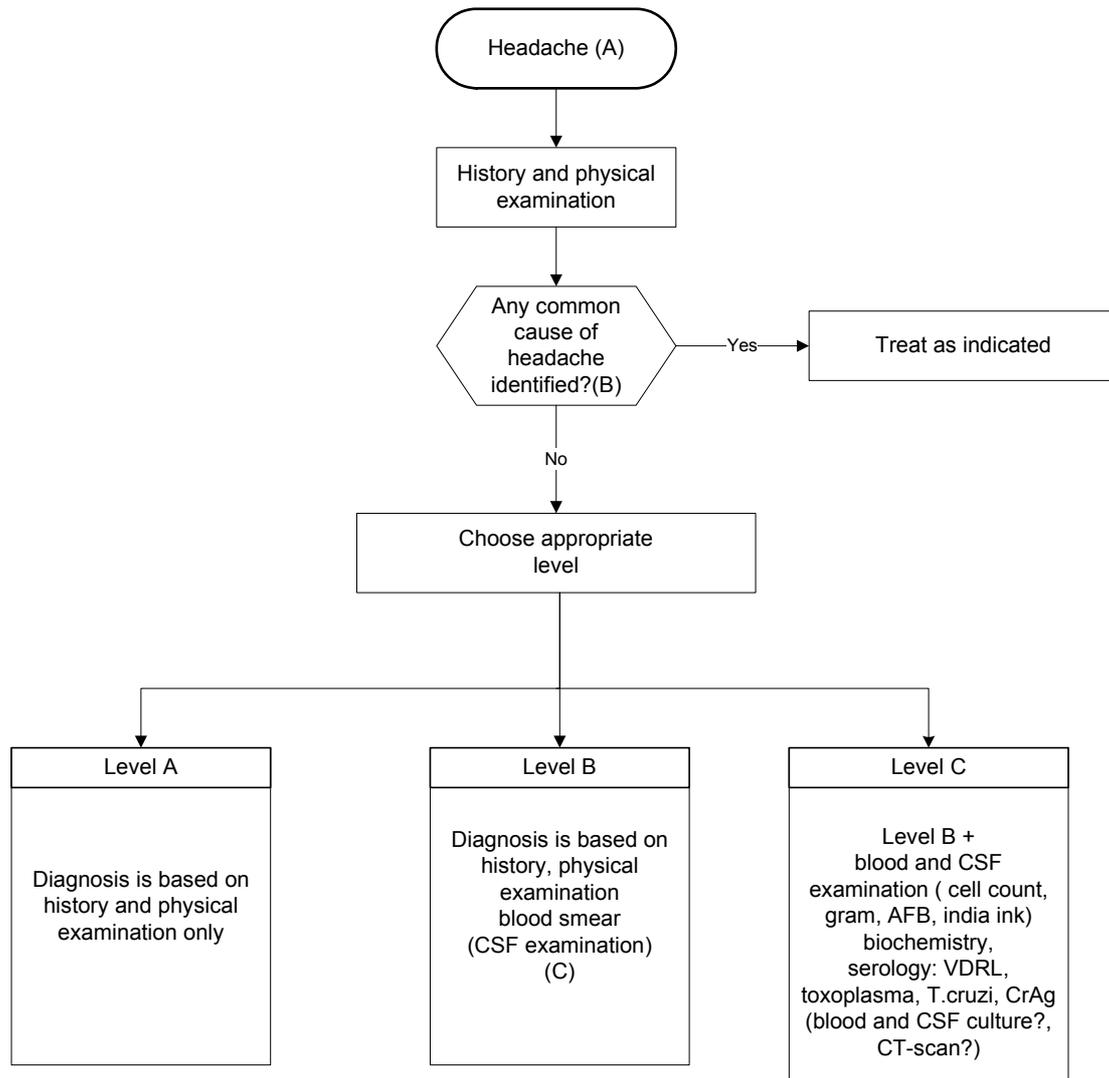
14.1.5 AZT related headache

Almost half of the patients taking AZT have headache. This occurs mainly in the first weeks of treatment and can be treated with analgesics. In case the headache is severe always bear in mind that the patient may have an underlying OI. If the headache is not improving with analgesics the patient may have problems to stay compliant with his treatment and a switch might be considered.

14.1.6 Comment

Since neurological involvement in AIDS patients can present in so many different ways and since some of the conditions can be treated, early diagnosis is important. This is true for TB meningitis, toxoplasma brain abscess and cryptococcal meningitis. The threshold for performing an LP should therefore be kept very low in AIDS patients who have headache. Even in the presence of papilloedema, an LP seems to carry no excessive risk in TB meningitis or toxoplasmosis, and is even indicated for treating intracranial hypertension in the case of cryptococcal meningitis.

14.2 Clinical management of headache in HIV-infected adults



Annotations Headache

(A) Headache in a patient with symptomatic HIV infection, often persistent and severe and rapidly increasing or not responding to common drugs used for pain relief. It can be with or without fever.

Infections

- Tuberculous meningitis
- Cryptococcal meningitis
- Toxoplasma meningo encephalitis
- Neuro-syphilis
- CMV encephalitis
- HIV meningitis
- PML
- HIV encephalopathy
- Chagas meningo-encephalitis

Malignancy

- Lymphoma; Kaposi's sarcoma

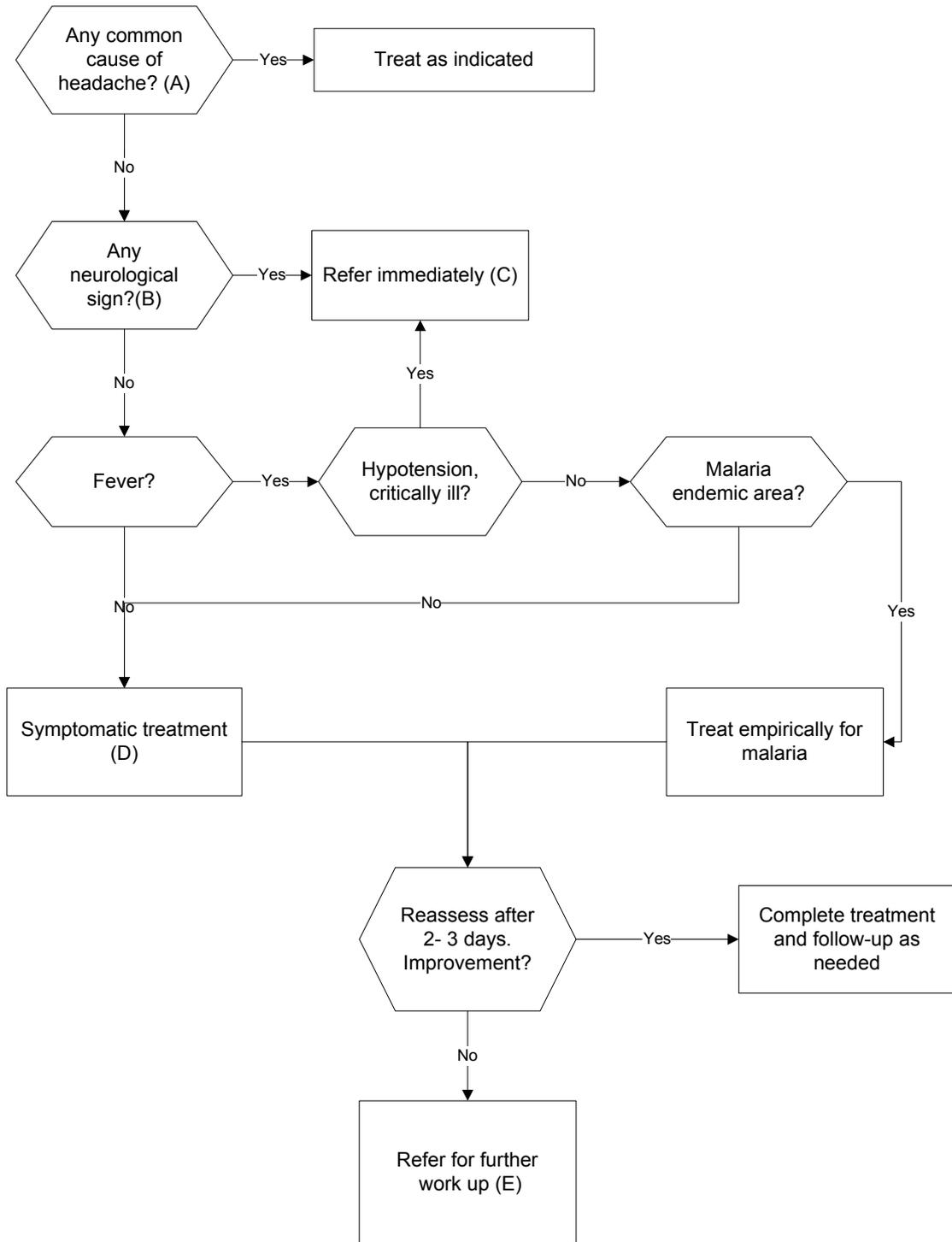
Drugs

- AZT

(B) Causes of headache not related to HIV infection: **migraine, toothache, hypertension**, etc. should be identified and treated. Other causes, such as **tension headache**, may be produced by anxiety related to the diagnosis of HIV. *See page 266.*

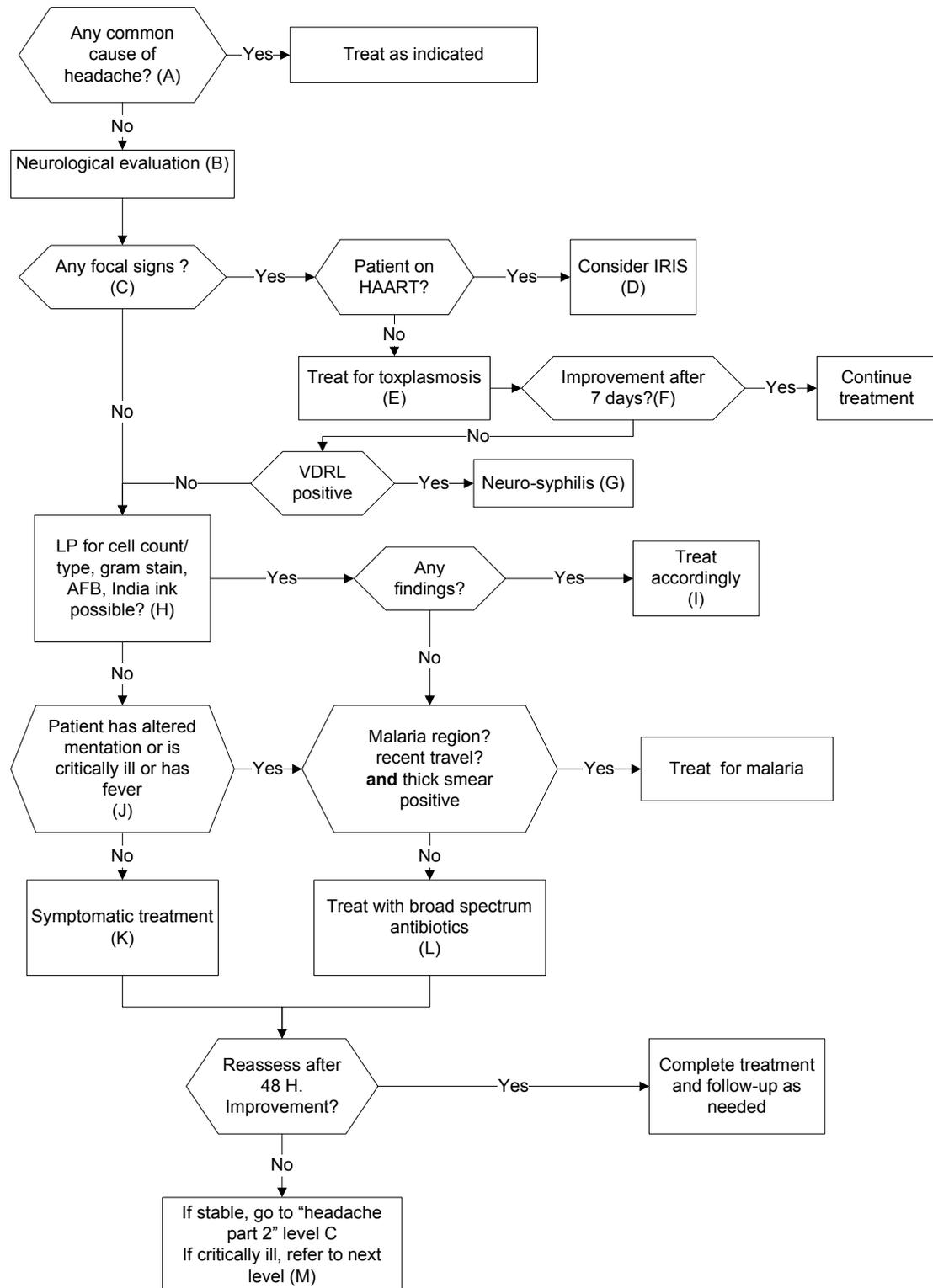
Sinusitis is a frequent HIV-related cause of headache and should be treated as usual. Infectious diseases that can lead to headache, e.g. **malaria, trypanosomiasis, typhoid fever, dengue fever, yellow fever, rickettsiosis** should also be considered.

(C) In some health centres, the health-care worker might be able to perform a lumbar puncture. If this is not the case, whenever meningitis is suspected, the patient should be referred. In most district hospitals, a lumbar puncture is possible and it is useful to identify those conditions that can be treated at level B before considering referral to a higher level.



Annotations (level A)

- (A) Causes of headache not related to HIV infection: **migraine, toothache, hypertension**, etc. should be identified and treated. **Sinusitis** is a frequent HIV-related cause of headache and should be treated as usual. Infectious diseases that are endemic in the region you are working should be considered as well: **malaria, trypanosomiasis, typhoid fever, dengue fever, yellow fever, rickettsiosis etc.**
- (B) These include:
1. Evidence of meningeal irritation or raised intracranial pressure (neck stiffness, vomiting, high blood pressure and bradycardia in the presence of fever).
 2. Seizures.
 3. Focal neurological deficits: paresis, cranial nerve palsies, movement disorders, ataxia, aphasia.
 4. Changes in mental state; including loss of concentration, personality change (mild to psychotic), confusion, cognitive impairment, dementia.
- (C) Wherever possible, further evaluation of headache, particularly in a patient with symptomatic HIV infection showing neurological signs, should be pursued to identify treatable conditions. Cerebral malaria can lead to mental changes. In areas where malaria is endemic, empirical treatment may be indicated.
- (D) As in patients without HIV-infection. Start with a simple analgesic like paracetamol; if necessary use compound analgesics containing narcotics. In palliative treatment, optimal pain relief is essential (see *Palliative care* page 267).
- (E) Many cases of cryptococcal meningitis do not have neck stiffness. Cryptococcal meningitis may present with fever and headache only.



Annotations (level B)

- (A) See page 256, annotation A.
- (B) Neurological evaluation: see page 256 annotation B.
- (C) Focal signs: hemiparesis, cranial nerve palsies, seizures, ataxia, aphasia.
- (D) If a patient recently started with HAART, IRIS is a possibility.
All of the CNS opportunistic infections can present with focal signs once started with HAART due to localised inflammatory reactions. See chapter 16. If the patient is not yet treated for an opportunistic infection follow the algorithm and try to find the diagnosis to start pathogen-specific treatment. If the patient is already treated for a CNS OI, continue the treatment. If symptoms are life threatening, add steroids during 1 month (prednisolone 40 mg/day for 2 weeks, followed by prednisolone 20 mg/day for 1 week, followed by 10 mg/day for another week). Unless the patient is seriously ill, it is best to continue HAART.
- (E) If toxoplasmosis is a frequent problem in your region it is justified to start empirical treatment against *Toxoplasma gondii* immediately. However, in regions where toxoplasmosis is not very frequent[†], a few days of observation might be incorporated if patients have isolated hemiplegia, without fever or signs of raised intracranial pressure. Symptoms due to a cerebro-vascular accident (CVA) tend to improve spontaneously. If this is the case, start treatment with low dose aspirin 1 week after the onset of symptoms. Cranial nerve lesions are often seen in TB meningitis and this is a frequent problem in HIV patients in developing countries. Therefore when living in a region where toxoplasmosis is not frequent, do not hesitate to do an LP in a patient with focal neurological signs, especially in the presence of meningeal irritation. If the CSF is normal and focal neurological signs persist, the diagnosis of toxoplasmosis becomes more likely. **Treatment** consists of cotrimoxazole or, if available, the combination therapy with sulfadiazine and pyrimethamine (see page 245). The latter is more toxic and requires the addition of folinic acid. Therefore the treatment of choice at level B is cotrimoxazole.
- (F) Toxoplasmosis usually responds well to treatment within 7-10 days, and this response can be used to support the diagnosis. Full dose treatment with cotrimoxazole should be maintained for 4 weeks or for 6 weeks in the case of sulfadiazine/ pyrimethamine. If the response is good, secondary prophylaxis is needed: cotrimoxazole 960 mg daily, or pyrimethamine 25 mg daily and sulfadiazine 2-4 g daily. This may be interrupted when the CD4 is above 100-200 cells/mm³ in a patient on stable HAART. If there is

[†] Toxoplasma brain abscess is rarely seen in Southeast Asia and serological epidemiological data from Cambodia and Vietnam show that only 10% of people have antibodies against toxoplasmosis. In these low prevalence areas, an observation period is certainly indicated in a stable patient.

no response after 7 days, a diagnosis of cerebral toxoplasmosis is unlikely. Check VDRL or RPR.

(G) Treatment of neuro-syphilis: see page 250.

(H) If your patient has signs of advanced HIV disease, an LP should be performed in the presence of headache and unexplained fever, or confusion, even when there are no signs of meningeal irritation. MSF experience in South East Asia has shown that LP seldom causes problems, not even in patients with focal signs. In cryptococcal meningitis, raised intracranial pressure is caused by an alteration of reabsorption of CSF and not by a mass effect. Papilloedema is frequently present and is an indication to perform repeated spinal taps to decrease the intracranial pressure, to reduce complications and to improve survival. At level B, a CSF examination should consist of determining cell count, cell type, Gram stain, AFB stain and India ink to detect diseases that can be treated at level B.

(I) When the CSF contains **neutrophils and bacteria** the treatment consists of Benzylpenicillin 12-24 million IU daily by IV injections divided into 4 doses, or chloramphenicol 2-4 g daily by IV injection in 4 divided doses. Treat for a minimum of 7 days or for 5 days after the patient becomes afebrile. If no improvement, refer to a hospital where ceftriaxone is available. (If there is data available for your region confirming a problem of penicillin-resistant *Streptococcus pneumoniae*, the first-line treatment for bacterial meningitis should be ceftriaxone or chloramphenicol). When the CSF contains **lymphocytes** and India ink stain is negative, the differential diagnosis between viral and tuberculous meningitis is sometimes difficult. The onset of headache in viral meningitis is more rapid, while TB meningitis tends to have a protracted slow onset over several weeks. Biochemistry of the CSF is helpful, if available. A VDRL should also be done to exclude neuro-syphilis because this can also present with mononuclear pleocytosis in the CSF. Neuro-syphilis is seldom seen, but **VDRL** serology is an easy and sensitive test. VDRL on CSF is very specific and confirms the diagnosis of neuro-syphilis.

If biochemistry is not available, try to find other clinical and laboratory signs that point in the direction of tuberculous meningitis: evidence of pulmonary or extra-pulmonary TB (pericardial effusion, pleural effusion, abdominal lymph nodes, miliary TB?). Cranial nerve palsies are particularly suggestive of tuberculous meningitis. For the treatment see page 249. In severe cases, with impaired consciousness or focal signs always combine with steroids.

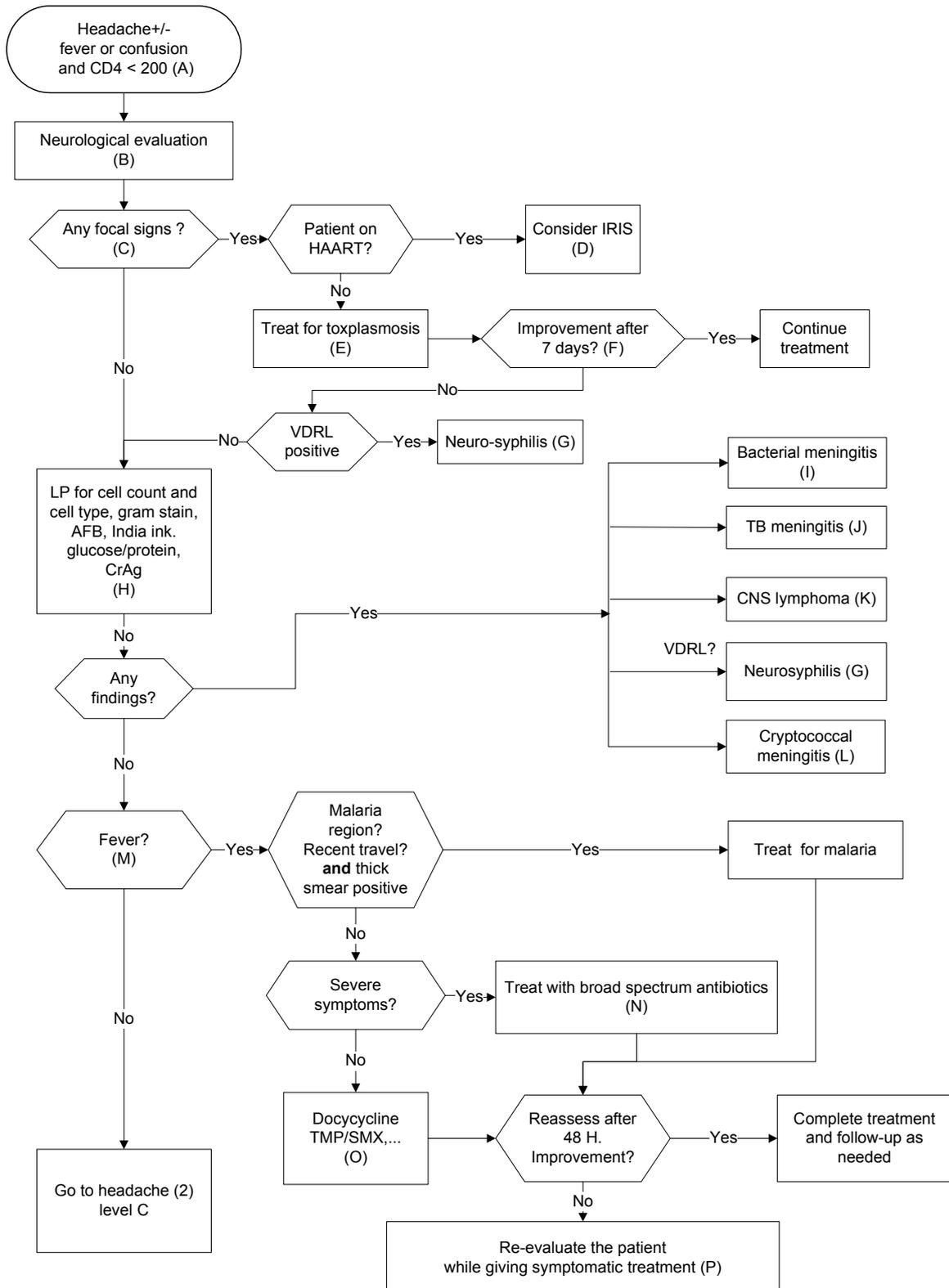
When the CSF shows **India ink** positive yeasts, the diagnosis of Cryptococcal meningitis is made (see page 239).

(J) If an LP is not possible and the patient has altered mental state or is critically ill, it is probably best to refer him. However in areas where malaria is endemic you might want to exclude this first.

- (K) In a patient who has only headache without fever or alarm signs, give symptomatic treatment: paracetamol, NSAID, see stepwise analgesia page 267. If symptoms worsen despite treatment, reassess the patient and consider referral.
- (L) In case the patient is seriously ill (hypotension, fever, tachycardia, or relative bradycardia) consider a septicaemia. The most frequent bacterial infections that can lead to septicaemias in HIV patients in Africa are *S.pneumoniae*, non-typhi salmonella infections, *Mycobacterium tuberculosis* and *Staphylococcus aureus*. Give broad-spectrum antibiotics: chloramphenicol 4 g daily IV in 4 divided doses, or amoxicillin 2 g 3 x daily IV + gentamycin 4 mg/kg IV once daily. (Depending on sensitivity of salmonella for beta-lactams in your area, for these severe infections it is justified to use ceftriaxone 2 g IV or ciprofloxacin 400 mg 2 x daily IV (750 mg 2 x daily PO). Continue PO as soon as possible. When a patient presents with headache and fever but is not severely ill, the choice of the antibiotic depends on prior treatment and on other symptoms. In the case of abdominal pain, treat as typhoid fever (ciprofloxacin, ofloxacin, amoxicillin). Doxycycline would cover rickettsial diseases and staphylococcal infections, and also has an anti-malaria effect. If the patient did not yet take antibiotics, co-trimoxazole is a broad-spectrum antibiotic that can be started on an empirical base and that also has some anti-malaria effect.
- (M) Fever that continues despite broad-spectrum antibiotics raises the possibility of blood-borne infection with *M. tuberculosis* or invasive fungal infections (*P. marneffeii* in Southeast Asia). Refer the patient to a higher level for further work-up. In case of signs of gait disturbance, behavioural changes, dementia, ataxia in the presence of a normal CSF, the diagnosis of PML and HIV encephalopathy or HIV dementia is possible in advanced AIDS. When an OI can be reasonably excluded (see chapter 16) an AZT containing HAART regimen should be started which may help in 50% of patients. However, be watchful for worsening symptoms due to IRIS. See also page 266, annotation B.

Headache (1)

Level C



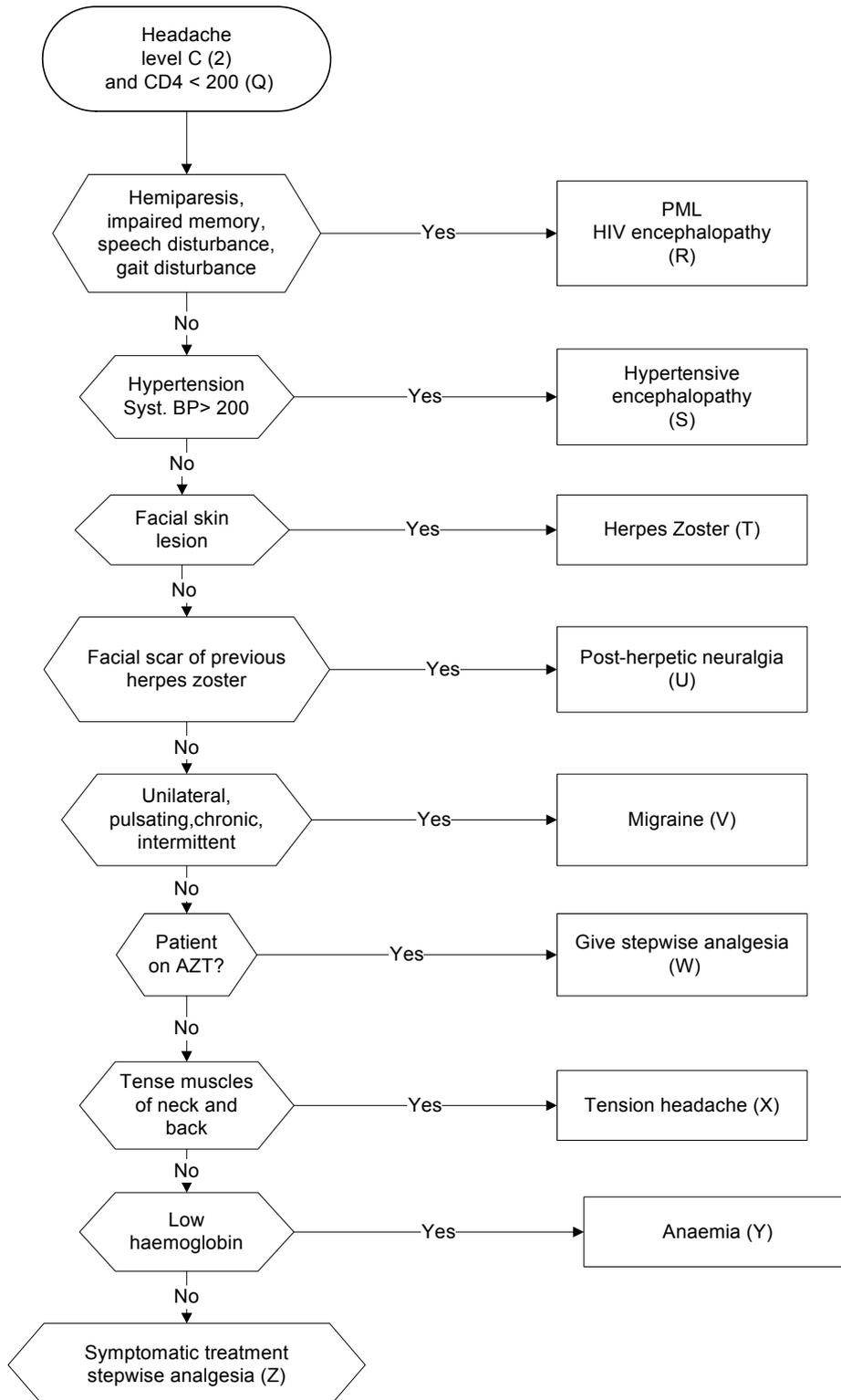
Annotations (level C)

- (A) At this level, the CD4 count is taken into account to assess the likelihood of an OI. In patients with low CD4 count the pre-test probability of an OI is so high that this is the most probable cause of headache, even in the absence of fever.
- (B) Neurological evaluation: see page 256 annotation B.
- (C) Focal signs
Hemiparesis, cranial nerve palsies, seizures, ataxia, aphasia.
- (D) IRIS is a possibility if a patient started recently with HAART (between 1 week to 6 months) See annotation B page 258.
- (E) If toxoplasmosis is a frequent problem in your region, it is justifiable to start empirical treatment against *Toxoplasma gondii* immediately. If you can do toxoplasma antibody tests, it may guide you in the decision to treat for toxoplasmosis or consider another diagnosis. See annotation E page 258. Treatment consists of combination therapy with sulfadiazine and pyrimethamine, or with cotrimoxazole (see page 245).
- (F) Toxoplasmosis usually responds well to treatment within 7-10 days, and this response can be used to support the diagnosis. Full dose treatment with cotrimoxazole should be maintained for 4 weeks or for 6 weeks in the case of sulfadiazine/ pyrimethamine. If the response is good, secondary prophylaxis is needed: cotrimoxazole 960 mg daily, or pyrimethamine 25 mg daily and sulfadiazine 2-4 g daily. This may be interrupted when the CD4 is above 100-200 cells/mm³ in a patient on stable HAART. If there is no response after 7 days, a diagnosis of cerebral toxoplasmosis is unlikely. Check VDRL or RPR.
- (G) See page 250.
- (H) The threshold for doing an LP should be very low in patients with headache and low CD4 counts. Examination of CSF at level C includes: opening pressure (normally: 7-18 cmH₂O), cell count and cell type, glucose and protein level, Gram stain, India ink, AFB and CRAg. Normal CSF has a protein content of 15-45 mg/dl, a glucose content of 45-80 mg/dl, and a cell count less than 5 cells/mm³ (see table page 248)
- (I) Elevated WBC count in the CSF with predominant neutrophils is suggestive of bacterial meningitis. Glucose in CSF is low and protein high. Sometimes the Gram stain shows Gram-positive or Gram-negative bacteria; this will orient the choice of the antibiotic. For empirical therapy, the first choice in bacterial meningitis is ceftriaxone 2g IV 2 x daily. When ceftriaxone is not available: benzylpenicillin 12-24 MIU daily by IV injections divided into 4 doses, or chloramphenicol 4 g daily by IV injection in 4 divided doses. Treat for a minimum of 7 days or for 5 days after the

patient becomes afebrile. If there is a high percentage of penicillin-resistant *Streptococcus pneumoniae*, use chloramphenicol.

- (J) In the presence of a lymphocytic pleocytosis in the CSF, the differential diagnosis between viral meningitis and TB meningitis is facilitated by the duration of the history, the biochemistry of the CSF and the presence of other signs or symptoms of TB (see annotation (I) page 259). For TB meningitis, a short-course chemotherapy containing rifampicin and INH with a 7-month continuation phase with daily rifampicin and INH is recommended. Always associate with pyridoxine 10-20 mg daily or 250 mg weekly. In severe cases, add prednisolone. Neuro-syphilis can also present with lymphocytic pleocytosis in CSF. VDRL on CSF is a specific test.
- (K) CNS lymphoma: non-Hodgkin lymphoma is one of the most common malignancies associated with HIV-infection. As chemotherapy is often not available the prognosis is poor.
- (L) A positive Indian ink or a positive CRAg in the CSF in a patient that is not yet treated is diagnostic for Cryptococcal meningitis. Treatment consists of amphotericin B and fluconazole (see page 239).
- (M) If the result of the CSF is normal, the next step is to exclude febrile conditions that can present with headache and signs of meningeal irritation such as malaria, typhoid fever, scrub typhus, etc.
- (N) The most frequent bacterial infections that can lead to septicaemias in HIV patients in developing countries are *S.pneumoniae*, non typhi salmonella infections, *Mycobacterium tuberculosis* and *Staphylococcus aureus*. If possible, take blood cultures to document the cause of septicaemia and to obtain information on antimicrobial sensitivity of the different pathogens in your situation. Chloramphenicol 4 g daily IV in 4 divided doses, or amoxicillin 2 g 3 x daily IV + gentamycin 4 mg/kg once daily IV or ofloxacin 400 mg 2 x daily or ciprofloxacin 500 mg 2 x daily, or ceftriaxone 2 gr IV once daily, if available. Continue PO as soon as possible.
- (O) A patient presenting with headache and fever, but not severely ill. The choice of antibiotic depends on prior treatment and on other symptoms. In the case of abdominal pain, treat as for typhoid fever (ciprofloxacin, ofloxacin, amoxicillin). Doxycycline would cover rickettsial diseases and staphylococcal infections. It also has an anti-malaria effect. If the patient did not yet take antibiotics, co-trimoxazole is a broad-spectrum antibiotic that can be started on an empirical basis and has some anti-malaria effect as well.
- (P) Fever and headache that continue despite broad-spectrum antibiotics raises the possibility of blood-borne infection with *M.tuberculosis* or invasive fungal infections (*P.marneffeii* in Southeast Asia). Re-examine the patient and see if there are other associated signs that may offer diagnostic clues: skin (TB, mycosis, Kaposi's sarcoma), lymph nodes (TB,

lymphoma etc.), abnormal chest X-ray, abscesses (staphylococcal, Nocardia, TB, etc).



Annotations (level C)

- (Q) At this point we are dealing with a patient, who may have focal signs, but treatment with anti-toxoplasmosis drugs didn't succeed, the VDRL is negative, and an LP didn't yield a diagnosis. Or a patient without focal signs, whose LP is negative and who doesn't have fever.
- (R) In patients with low CD4 count, hemiplegia or cognitive deterioration can be due to HIV encephalopathy and PML. About 50% of patients may respond to HAART. Patients with PML may have worsening symptoms with HAART due to IRIS, but there is no other treatment available.
- (S) Treat with anti-hypertensive drugs, preferably a beta-blocker or ace-inhibitor. Calcium-antagonists have significant drug-interactions with protease inhibitors and NNRTI.
- (T) Herpes zoster on head and face: Gentian violet or polyvidone 10% 2 x daily, Vitamin B complex 3 x daily for 2 weeks. Acyclovir 800 mg 5 x daily for 7 days. Provide stepwise analgesia and associate carbamazepine or amitryptillin for two weeks if pain not controlled.
- (U) Post-herpetic neuralgia: provide stepwise analgesia (see page 267), combined with carbamazepine or clomipramine or amitryptillin.
- (V) NSAID. In case of frequent attacks: low dose beta-blocking agent as prevention (atenolol 25 mg daily, propanolol 10 mg 3 x daily). Never use ergotamine derivates in patients taking antiviral drugs. There are significant interactions with NNRTI and PI which can lead to life-threatening complications (ergotism, gangrene).
- (W) Patients who are on an AZT containing HAART regimen may experience headache. Usually it is mild and can be treated with NSAID or paracetamol.
- (X) Make sure that CSF examination is normal. Diazepam at bedtime, massage of back and neck muscles.
- (Y) In patients with low CD4 count anaemia is almost invariably present. Always consider OI first before ascribing headache to anaemia.
- (Z) See stepwise analgesia page 267.

14.3 Symptomatic and palliative care

WHO has published an excellent document on cancer pain relief.³⁹⁷ This booklet should be available in all MSF missions involved in clinical care. Also the green guide of MSF contains a chapter on management of pain. As a basis for the palliative care sections we also used a comprehensive guide on symptomatic care for PLHA from a Canadian group.¹⁸¹

14.3.1 Headache

Aetiology: always exclude treatable condition by following the algorithms. If symptomatic treatment, try to give doses that relieve all pain as much as possible.

1. Provide stepwise analgesia (see below).
2. NSAID may reduce meningismus.
3. Corticosteroids may reduce oedema around space occupying lesions. They also have an anti-emetic effect. (1 mg dexamethasone = 7 mg prednisolone).
 - prednisone 10-80 mg 4 x daily
 - dexamethasone 1-8 mg 4 x daily.
4. Chiropractic manipulation may relieve headache of cervical or muskuloskeletal origin.
5. Massage therapy.
6. Relaxation therapy.

Provide stepwise analgesia (see also green guide MSF)

Step	Type of drug	Recommended drug	Maximum dose
1. Mild pain	Non opioid	- Aspirin PO Paracetamol PO, NSAID Indometacin 25 mg 4 x daily (or ibuprofen 400 mg 4 x daily)	4 g daily in 4-6 doses 6 g daily in 4-6 doses 200 mg daily 3 g daily
2. Moderate pain	Weak opioid	Add a weak opioid Codeine phosphate 30 mg Tramadol 50-100 mg 2-4 x daily	240 mg daily in 4-6 doses 400 mg daily
3. Severe pain	Strong opioid	Replace the weak opioid with a strong opioid Morphine every 4 hours [‡] Pethidine Buprenorphine: 0.3 mg 3 x daily	No maximum 1 mg every 8 hours

Use analgesics in incremental steps (3)

Dosing:

- Use the least invasive route of administration, oral if possible.
- Provide "around-the-clock-dosing" for constant pain at rest. Never provide pain relief only when the patient asks for it (PRN dosing) in palliative care. It takes time before the patient receives the medication and before it is absorbed and effective.
- Provide breakthrough dosing for intermittent pain, e.g. while moving.
- Add recurring breakthrough doses to the routine dose; do not hesitate to give enough.
- Consider continuous parenteral infusion, preferably sc, only when the person:
 - is unable to swallow
 - has intractable nausea
 - has severe diarrhoea
 - has too much medication to swallow.
- When changing the route of administration from PO to parenteral, decrease the dose by 50%.

[‡] The initial dose depends on what the patient took before. Sometimes 5 mg every 4 hours is enough to control the pain. Increase the dose stepwise: 5, 10, 15, 20, 30, 40, 50, 60, 100 mg. Over 100 mg increase in steps of 20-30 mg. If supplemental doses are necessary, give 50% of the dose after 2 hours.

- If a patient is on continuous infusion, provide breakthrough dosing by adding 1/2 of a normal hourly dose every 30 minutes.
- Respect maximum dosing for NSAID, paracetamol and codeine. There is no maximum standard dose for morphine.
- The sustained release form (MS-Contin®) is not appropriate for AIDS patients because of malabsorption problems due to HIV enteropathy and frequent diarrhoea.
- Buprenorphine: sublingual form is useful in patients who cannot swallow.

Side effects

Anticipate and educate about potential side effects: constipation, nausea, dry mouth, sedation, confusion, urinary retention, twitches/jerks, myoclonus.

Adjuvant drugs

1. To treat adverse effects of analgesics:

- nausea/vomiting (opioid-induced): anti-emetic: haloperidol, chlorpromazine, metoclopramide.
- constipation: in PLHA who suffer from untreatable chronic diarrhoea, this side effect is sometimes desired. If there is a problem of constipation, laxatives: Senna tablets 2 x daily is a good starting dose.

2. To enhance pain relief:

- Corticosteroids: they are useful for relieving pain associated with nerve compression or spinal cord compression, and headache from raised intracranial pressure.

3. To treat concomitant psychological disturbances such as insomnia, depression:

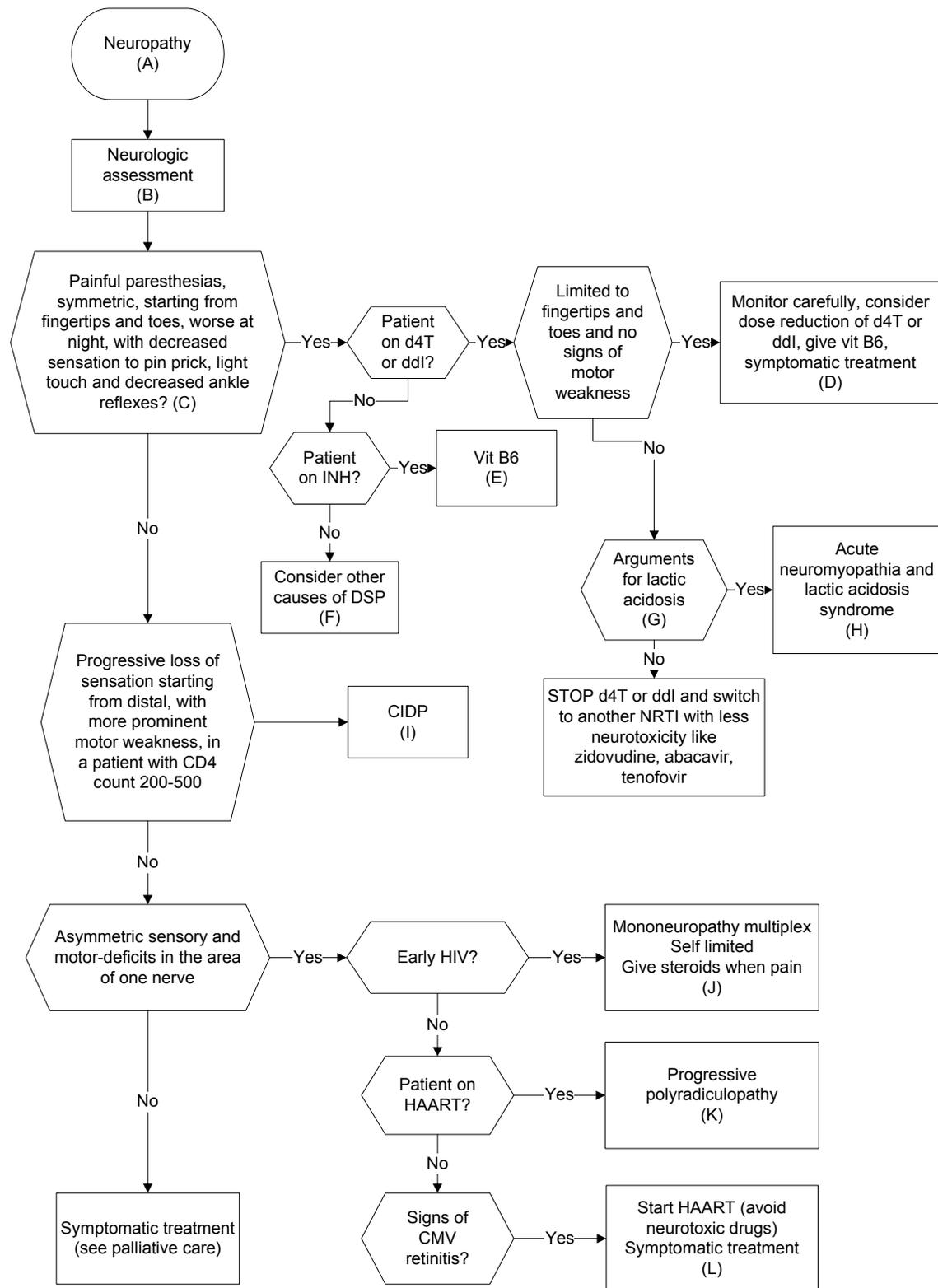
- psychotropic drugs: some have an analgesic effect (amitriptylin for neuropathic pain); others counteract side effects (haloperidol for opioid induced vomiting). For other patients, an anxiolytic drug such as diazepam is necessary. Diazepam is also useful for muscle spasms.

14.3.2 Neuropathic pain

See page 234.

- 1. Pain due to nerve compression:** irritation that may evolve into nerve damage. Sharp pain, stabbing, "shooting electrical feeling", e.g. trigeminal neuralgia. There is usually a normal cutaneous sensation. Provide stepwise analgesia and associate carbamazepine: The starting dose is 100 mg 2 x daily. This can be increased slowly, at a rate of 200 mg every few days. Sometimes nerve compression pain only responds to treatment when corticosteroids are added. However, these should be given with caution in HIV patients because of additional immunosuppression. **In terminal AIDS care, there should be no hesitation about using corticosteroids.**
- 2. Pain due to nerve damage:** infiltration, e.g. tumour invasion or drugs, e.g. d4T or INH. Burning, tingling, pins and needles. Altered skin sensation: hyperalgesia (skin is painful on light touch, e.g. patient cannot support bed sheets) or hypoalgesia, numbness. Provide stepwise analgesia and associate TCA's (tricyclic antidepressants). TCA's enhance the analgesic effect of opioids. Amitriptylin at a dose as low as 10 mg may be appropriate for some patients, but most can take 25-50 mg. The dose can be gradually increased (every 3-4 days), as rapidly as can be tolerated in terms of postural hypotension, sedation and dry mouth. The total daily dose should be given at bedtime because of the sedative effect. Maximum dosage: 200 mg daily. The effect of TCA's is usually disappointing in HIV-related neuropathy in the absence of HAART.

Figure 2: Management of neuropathy



Annotations Neuropathy

- (A) Neuropathy can present in many ways: decreased sensation, painful paresthesias, burning sensation, shooting pain, weakness, hyperalgesia,...
- (B) It is important to perform a thorough neurological examination and history taking. Drug intake? Acute or sub-acute? Sensory and/or motor deficits? Pain or dysesthesia? Related with the start of HAART?
- (C) This presentation is typically for distal symmetrical polyneuropathy (DSPN), the most frequent neuropathy in HIV patients. Several causes are possible: drugs as d4T, INH, HIV itself, CMV, herpes, syphilis, ...
- (D) If a patient was on 40 mg d4T you can reduce the dose to 30 mg. The patient has to be monitored frequently, because neurologic damage can be irreversible. Try vit B6 to alleviate nutritional deficiencies. Pain treatment, especially NSAID, and amitriptyline or carbamazepine at night can reduce the pain (see above).
- (E) HIV patients who are treated with INH should always receive pyridoxine 10-50 mg/day to avoid neuropathy. If despite this preventive measures DSPN develops give higher doses of pyridoxine (100-200 mg/day)
- (F) Other causes are viral infections (CMV, herpes, varicella zoster,...) or syphilis. In the absence of CMV retinitis, CMV disease is less likely. Intravenous ganciclovir is not available and HAART should be considered. If the VDRL is positive, the patient should be treated as neurosyphilis.
- (G) Lactic acidosis should be considered in a patient with fatigue, vague abdominal discomfort, tachypnea, especially when taking d4T or ddl.
- (H) Acute neuromyopathia syndrome: see page 237
- (I) Usually happens in patients with higher CD4 count, not yet on HAART. It is caused by HIV itself. May resemble Guillain-Barré syndrome and steroids can help. If HAART is started, avoid neurotoxic drugs.
- (J) Bell's palsy in early HIV is a typical example. It is usually self-limiting and doesn't need treatment. In case of pain, which is a sign of vasculitis, steroids are useful.
- (K) In a patient on HAART, this asymmetric, flaccid paresis, with sometimes sphincter dysfunction, is not due to drugs as in DSPN, but to IRIS on CMV or Herpes. In that case steroids can be tried, and HAART should continue.
- (L) If the patient has low CD4 count and is not yet on HAART, CMV is a likely diagnosis, especially when also eye problems are present. When anti-CMV treatment is not available, HAART should be started; however the patient should be warned against worsening eye problems and neuropathic pain.



15 KAPOSI'S SARCOMA

15.1 Epidemiology and Pathogenesis

Kaposi's sarcoma (KS) is a multifocal neoplasm involving skin and mucous membranes. Lungs, gastrointestinal tract and lymph nodes can be affected as well. KS is a stage IV defining event, and is caused by human herpes virus 8 (HHV-8) or Kaposi Sarcoma Herpes Virus (KSHV).

KS is the most frequently seen malignancy in AIDS patients. Before the era of HAART, 15% of HIV patients in US presented with KS as the primary AIDS defining event.³⁹⁸ Over the past 2 decades, some African countries with a high HIV prevalence have seen a 20-fold increase in the incidence of KS, and it has become the most common cancer in men.^{399,400} Nevertheless, the incidence of KS varies from country to country and among different risk groups.^{398,401} In South East Asia for example, AIDS KS is a very rare event.³⁰⁶

HAART has caused a sharp decline in the incidence of KS.^{402,403} This decline in incidence is due to the immune restoration following HAART, and there are indications that this coincides with immunological control of KSHV.⁴⁰⁴ HAART has improved life expectancy of HIV patients in resource-poor countries and we are more and more confronted with the question on what to do with KS.

15.2 Clinical presentation and diagnosis

Clinical manifestations of AIDS KS vary from macular skin lesions to papules and nodular tumours, to life-threatening visceral involvement of lungs and gastrointestinal tract, leading to lymphatic obstruction and respiratory failure.³⁹⁸

KS is often accompanied or preceded by local lymphoedema.

Gastro-intestinal lesions are often asymptomatic, but can cause ulceration and bleeding.

Pulmonary KS is rapidly fatal when left untreated. Patients present with dyspnoea without fever, sometimes with haemoptysis. Visceral involvement is most of the time concomitant with skin lesions.

AIDS KS lesions can wax and wane related to the occurrence of other opportunistic infections (OI). Corticosteroid therapy (as used in severe PCP) has been associated with the induction of KS and with the exacerbation of pre-existing KS in HIV-infected persons.⁴⁰⁵ In such patients, KS lesions may

regress upon reduction or withdrawal of steroids.

Generally, lesions are recognised clinically and the diagnosis of KS can be confirmed by biopsy. In the early stages it may be difficult to differentiate KS from bacillary angiomatosis. The latter is caused by *Bartonella henselae* and responds to doxycycline. Other differential diagnoses include non Hodgkin lymphoma, cutaneous leishmaniasis and cutaneous fungal infections.

A chest X-ray may show reticulo-nodular infiltrates, enlargement of the mediastinal shadow and sometimes a pleural effusion.

Typical red purple lesions can be seen on bronchoscopy or endoscopy.

15.2.1 Staging/Prognosis

Staging is based on whether lesions are confined to the skin or if there is mucosal and visceral involvement (T), and whether patients have constitutional symptoms (S). See **Table 17**.

Table 17: Staging of AIDS KS (ACTG)⁴⁰⁶

Tumour (T)	T ₀ = lesions confined to skin and/or lymph nodes and /or minimal oral disease (only flat lesion)	T ₁ = tumor-associated oedema or ulceration; extensive oral KS; gastrointestinal KS; KS in other non-nodal viscera
Immunity [§] (I)	CD4 ≥ 200/mm ³	CD4 <200/mm ³
Systemic disease (S)	S ₀ = no history of OI or thrush; no “B” symptoms [¥] ; performance status ≥ 70 (Karnofsky)	S ₁ = history of OI and/or oral thrush; “B” symptoms present; performance status < 70; other HIV-related illness (eg, neurological disease, lymphoma)

[§] With HAART the CD4 count does no longer have an impact on the prognosis of patients with KS.⁴⁰⁷

[¥] “B” symptoms = unexplained fever, night sweats, >10% involuntary weight loss or diarrhoea persisting more than 2 weeks

With HAART, the natural history of KS has changed.

Several studies have shown a response rate (partial or complete) up to 90% after two years of HAART treatment.⁴⁰⁸ Complete response was more frequently observed in patients with higher increase in CD4 counts. Predictors of complete response were an increase of CD4 count > 150/μl after 12 months of HAART and T₀S₀ or T₀S₁ stage of KS at inclusion, but the initial CD4 count does not seem to predict the response of KS to HAART.^{409,410}

In AIDS-KS patients on HAART, two categories can be identified:

- a “good prognosis” category T₀S₀, T₁S₀, and T₀S₁ with a respective 3-year survival of 88%, 80% and 81%;
- a “poor prognosis” category T₁S₁ with a 3-year survival of 53% (46% if pulmonary involvement and 77% if no pulmonary involvement).³⁰⁴ This is much better than the 3-year-survival of any stage 4 disease before HAART.

Failure of KS treatment is related to failure to control HIV.

15.3 Treatment

15.3.1 When is treatment for KS indicated?

KS is an AIDS defining event and as such an indication for HAART. Some patients may obtain complete remission with HAART alone, others need chemotherapy, and the question is who and when.

HAART alone or with chemotherapy

Especially early stage AIDS KS (T₀S₀) seems to respond very well (complete remission of 80%) to HAART alone.^{409,411}

However, studies in patients with moderate to advanced KS show a better response rate when HAART is combined with chemotherapy.⁴¹² In the HAART only group 2/3 had progressive disease and needed chemotherapy, and in half of them the progression occurred in the first three months of HAART.

Cytotoxic chemotherapy is indicated in patients who have rapidly progressive cutaneous disease causing pain, oedema, and ulceration, but also in patients with visceral involvement. It is recommended to continue prophylaxis with cotrimoxazole in patients on chemotherapy.

Choice of HAART regimen

There has been considerable debate about the appropriateness of NNRTI based regimens in the treatment of KS. There is some in vitro evidence that PI have an anti-tumour effect on KS.^{413,414} The response of KS to HAART is related with immune restoration.

There is convincing evidence that a PI regimen is not better than a NNRTI regimen in patients with AIDS KS.^{304,412,415,416}

Options of chemotherapy

Gold standard

The gold standard in the western world for the treatment of systemic KS now, is **liposomal anthracyclines** (USD 11,000 per responding patient) They have superior efficacy when compared to ABV or BV).^{417,418} Response to treatment is often slow (3-6 months). Even if less toxic than bleomycin-vinca alkaloids, they are myelo-suppressive and potentially increase the risk of OI by aggravating HIV-related immune deficiency. Neutropenia and anaemia occur usually after 8-10 cycles and require dose reduction or delay in treatment.

Paclitaxel and **oral etoposide** are used as second line treatments, for patients who failed or did not tolerate liposomal anthracyclines. Response rates varied from 36 to 83% and especially etoposide, because of its oral administration, would be an ideal self-administrable drug in an out-patient setting in low resource-settings.⁴¹⁹⁻⁴²³ Different dosing schedules have been used (50 mg/day during 7 days, every 2 weeks, or 150-400 mg per week every 2 weeks, 25 mg/m² PO twice daily during 7 days every 2 weeks). However, 30-60% of patients developed grade 3 and 4 neutropenia and anaemia. This makes it a difficult to use drug in first line therapy in developing countries, because of the need for frequent monitoring, and the risk of other bacterial and fungal infections. A recent study in patients with no access to HAART in Zimbabwe showed a better quality of life and less toxicity after using oral etoposide* (100 mg/day during 7 days, once a month) then with a 3-drug combination consisting of actinomycin-D, vincristine and bleomycin, or radiotherapy or supportive care.⁴²⁴

Interferon-alpha has immune-modulatory and antiviral effects. It has good response rates in KS (up to 40%) at a dose of 8 million units SC daily, when given with antiretrovirals (ARVs). It is especially effective in patients with CD4 count > 150-200/μl and with only skin lesions.^{405,425} Interferon-alpha is not available in resource-limited settings.

Former treatment used in western countries

Several regimens have been used in the western world. Chemotherapeutic combinations of ABV (**adriamycine, bleomycin and vincristine**) or BV (**bleomycin, vincristine**) have important toxicity and response rates that vary from 70-90%.⁴²⁶ **Bleomycin alone** at the dose of 15 mg IM (or 5 mg/d IM for 3 days) every two weeks has a response rate of 10-75% and has the advantage that it is less myelosuppressive.^{426,427} Problems of pulmonary toxicity only occur at cumulative doses exceeding 400 mg or single dose of > 30 mg.⁴⁰⁵ However, relapses are very likely to occur once the drug is stopped.

Vincristine alone in a dose of max 2 mg/m²/week is rarely used anymore: the benefit is small and very careful monitoring of the IV line needs to be done to

* They received oral etoposide from Cipla to do the study.

avoid extravasations of vincristine which can lead to severe cellulites and extensive tissue necrosis.

Options for resource-limited settings

See Table 18 for an overview of the possibilities.

A recent Cochrane review⁴²⁸ on this question did not really provide an answer.

Bleomycin IM†

As it is an IM injection (15 mg stat or 5 mg/day for 3 days) every two weeks, this treatment seems feasible and affordable. The efficacy range lies between 10% - 75%. Its efficacy in combination with HAART needs to be determined.

The toxicity of bleomycin, especially pulmonary fibrosis, increases with cumulative doses, and therefore a total dose of more than 400 Units (= 400 mg) should be avoided.

Other side effects that may occur are stomatitis, chills and fever. Symptomatic treatment is indicated. Chills and fever occur usually soon after the injection and can be treated with paracetamol and promethazine. In case the reaction is severe, these drugs can be administered before the next injection.

This treatment is the best alternative in patients with neuropathy.

† For IM or SC administration, the drug is reconstituted by adding 1–5 ml of sterile water for injection, 0.9% sodium chloride injection, or bacteriostatic water for injection to the vial labeled as containing 15 Units of bleomycin to provide solutions containing 3–15 units/ml.

Table 18: Suggested chemotherapy for KS in low resource settings (adapted from Hoffman)⁴²⁹

Chemotherapy	Dose	Modality of administration	RR	Side effects
Vincristine alone	1.4 mg/m ² (max. 2 mg) 1x / week IV	slow IV bolus over 1-2 minutes or as short infusion over 10-15 minutes	CR/PR in 10-85%	Vincristine-induced neurotoxicity Necrosis in case of extravasation
Vinblastine alone	4-6 mg/m ² 1x / week IV	2-3 minutes bolus, or 10-15 minutes infusion	CR/PR in 25-85%	Vinblastine-induced myelosuppression
Vincristine/vinblastine	Vincristine 1.4 mg/m ² (max. 2 mg) and vinblastine 0.1 mg/kg IV alternating weekly	As previously described	CR/PR up to 43%	Vincristine-induced neurotoxicity and necrosis in case of extravasation Vinblastine-induced myelosuppression
Vincristine/bleomycin	Vincristine 1.4 mg/m ² (max. 2 mg) and bleomycin 10 mg/m ² every 2 weeks IV	Vincristine: as previously described Bleomycin: I.V. doses should be administered slowly (over a period of 10 minutes)	CR/PR in 60-75%	Bleomycine pulmonary fibrosis Less myelosuppressive and less vincristine-induced neurotoxicity
Bleomycin alone	15 mg single doses or 5 mg/d for 3 days every 2-3 weeks IM	IM may cause pain at injection site (see note for reconstitution of the drug)	CR/PR in 10-75%	Pulmonary fibrosis
Etoposide	50 mg PO for 7 days with intervals of 2-3 weeks between the cycles, or 100 mg PO /day during 5 days, every month	Postpone dose in case of grade 3-4 neutropenia	CR/PR in 36-85%	Myelosuppression

Vincristine

Vincristine alone at a dose of 1.4 mg/m² (max 2 mg per week) is the cheapest option so far, but needs to be given by IV infusion every week. It is usually administered as slow (1-2 minutes) push or as short (10-15 minutes) infusion. Very close supervision of the IV line is necessary because extravasation can lead to severe tissue necrosis and amputation.

The main risks with vincristine are the development of neuropathy and ileus. Preventive measures as anti-constipation methods are only partially effective. Extreme caution should be given in patients who have already an underlying neuropathy, or who are taking neurotoxic drugs (INH, d4T, ddI), and if possible, we should avoid the use of vincristine in these patients. The response rate ranges between 10-85%. As vincristine has little haematological toxicity it is the preferred regimen in patients with anaemia and neutropenia.

Vincristine/vinblastine

The use of vincristine 2 mg/vinblastine 0.1 mg/kg IV (the latter given usually as a slow 2-3 minutes push, or a bolus of 5 to 15 minute infusion) alternating weekly, may decrease the risk of neuropathy, according to some specialists. But this combination has a higher risk of haematological toxicity due to the vinblastine-induced myelosuppression. Check the full blood count before the next dose of vinblastine.

43% of patients will reach complete or partial remission.

Vincristine/bleomycin

There are no clear indications that the combination is superior to either of the drugs alone. Bleomycin 10 mg/m² and vincristine 2 mg IV every 2 weeks has shown a response rate of 60-75%. This combination is indicated in patients with pre-existing neutropenia and anemia, because they may not tolerate the combination vinblastine/vincristine.

Etoposide

Oral etoposide, wherever available, is an option for a second line treatment[‡]. Etoposide is given PO in a dose of 50 mg/day during one week, every other week, or 100 mg/day during 7 days every month. The dose has to be interrupted or decreased when grade 3 or 4 neutropenia develops. Before starting another cycle of etoposide, one should check the blood count.

In case the absolute neutrophil count (ANC) is < 500 cells/mm³, the Hb < 8 g/dl or the platelets < 50,000/mm³, the dose of etoposide should be postponed until lab values have normalised.

When the WBC count is between 2000 and 3000 cells/mm³ and the platelets between 50,000-75,000/mm³ the dose of etoposide should be reduced to 50%.

These alternative chemotherapeutic regimens (see Table 18) need to be

[‡] As an oral drug, one might consider it as a first line treatment. However, the frequent occurrence of grade 3-4 myelosuppression makes it less suitable as a first line drug.

evaluated for efficacy and feasibility in a low-resource setting, in combination with HAART.

15.3.2 Timing of HAART in patients with KS

HAART is usually not started before active OIs are treated, because the risk of mortality is linked to the OI first, because of reasons of complexity of treatment, adherence issues and possibility of cumulative drug toxicity and worsening symptoms due to immune reconstitution inflammatory syndrome.^{209,285,430,431}

However, because the response to chemotherapy is slow in KS and because it is now generally accepted that HAART is an essential part of first line KS treatment, it is good practice to start HAART soon after, or concurrent with the chemotherapy, especially in patients with advanced immune deficiency (see Table 19)

Table 19: Recommended strategy according to the KS stage and underlying conditions

Stage	Underlying condition	Regimen	Comments
T ₀ S ₀ / T ₀ S ₁	All patients	HAART alone	
T ₁ S ₀ /T ₁ S ₁	Neuropathy or patient on ddl, d4T, INH	Bleomycin alone, or etoposide	Start HAART as soon as possible
	Poor bone marrow reserve or patient on AZT [#]	Bleomycin alone or Bleomycin/vincristine	
	No neuropathy, no bone marrow suppression, no ddl, d4T or INH	Vincristine/vinblastine	

AZT should not be combined with etoposide because of an increased risk of anaemia, and ddl, d4T should not be used together with vincristine because of an increased risk of neuropathy.

In T₀S₀ and T₀S₁ chemotherapy should be reserved for patients who do not respond to HAART alone, or who develop extensive disease.

If HAART is not available, chemotherapy should only be initiated for palliation, i.e. when patients have disfiguring lesions in visible areas of the body, extensive painful skin lesions and oedema, oral lesions that cause obstruction or dysphagia, evidence of rapid tumour progression or visceral involvement. No local or systemic therapy has proven to increase survival without HAART.³⁹⁸

15.3.3 Assessment of treatment response

To describe the effect of treatment on KS lesions, 4 categories of responses are considered (AIDS Clinical Trial Group), see Table 20.⁴⁰⁶

Table 20: Categories of treatment responses in Kaposi's sarcoma

Complete Response (CR): Absence of any detectable residual lesion, including tumour-associated oedema, persisting for at least 4 weeks.

Partial Response (PR): A 50 % or greater decrease in the number and/or size of previously existing lesions lasting for at least 4 weeks without the appearance of new skin or oral lesions or new visceral sites of involvement or appearance or worsening of tumour-associated oedema or effusions, or an increase of 25% or more in the product of bi-dimensional diameters of any indicator lesion.

Stabilization: Any response not meeting the criteria for progression or CR/PR.

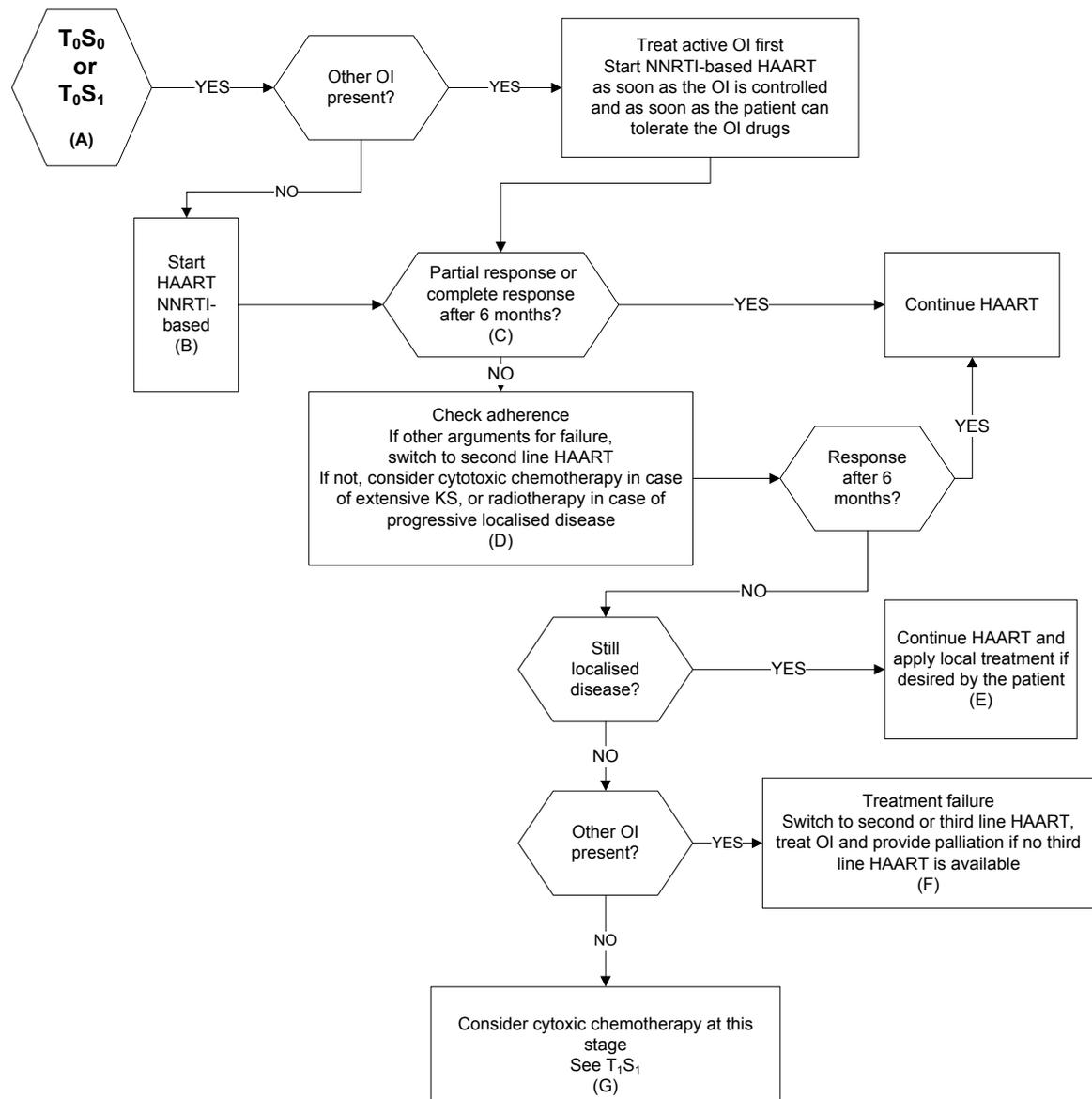
Progression: Increase of 25% or more in the size of previously existing lesions and/or the appearance of new lesions or new sites of disease and/or a change in the character of 25% or more of the skin or oral lesions from macular to plaque-like or nodular. The development of new or increasing tumour-associated oedema or effusion is also considered to represent disease progression.

Once patients respond to therapy (partial or complete response), the chemotherapy can be interrupted while immune restoration does the work, even in pulmonary KS, where the median survival before HAART was less than 4 months after diagnosis.^{398,408}

At 2-3 year follow-up, only 15% of the patients are still in need of chemotherapy.

Given the increased availability of HAART in DC, the increased disease-free survival after treatment for Kaposi's Sarcoma in the presence of HAART, and the fact that chemotherapy can be interrupted after treatment response, enthusiasm for treating KS in DC is growing.

Figure 3: Recommendations for management of AIDS KS in limited-resource settings (Part 1: T₀S₀ or T₀S₁)

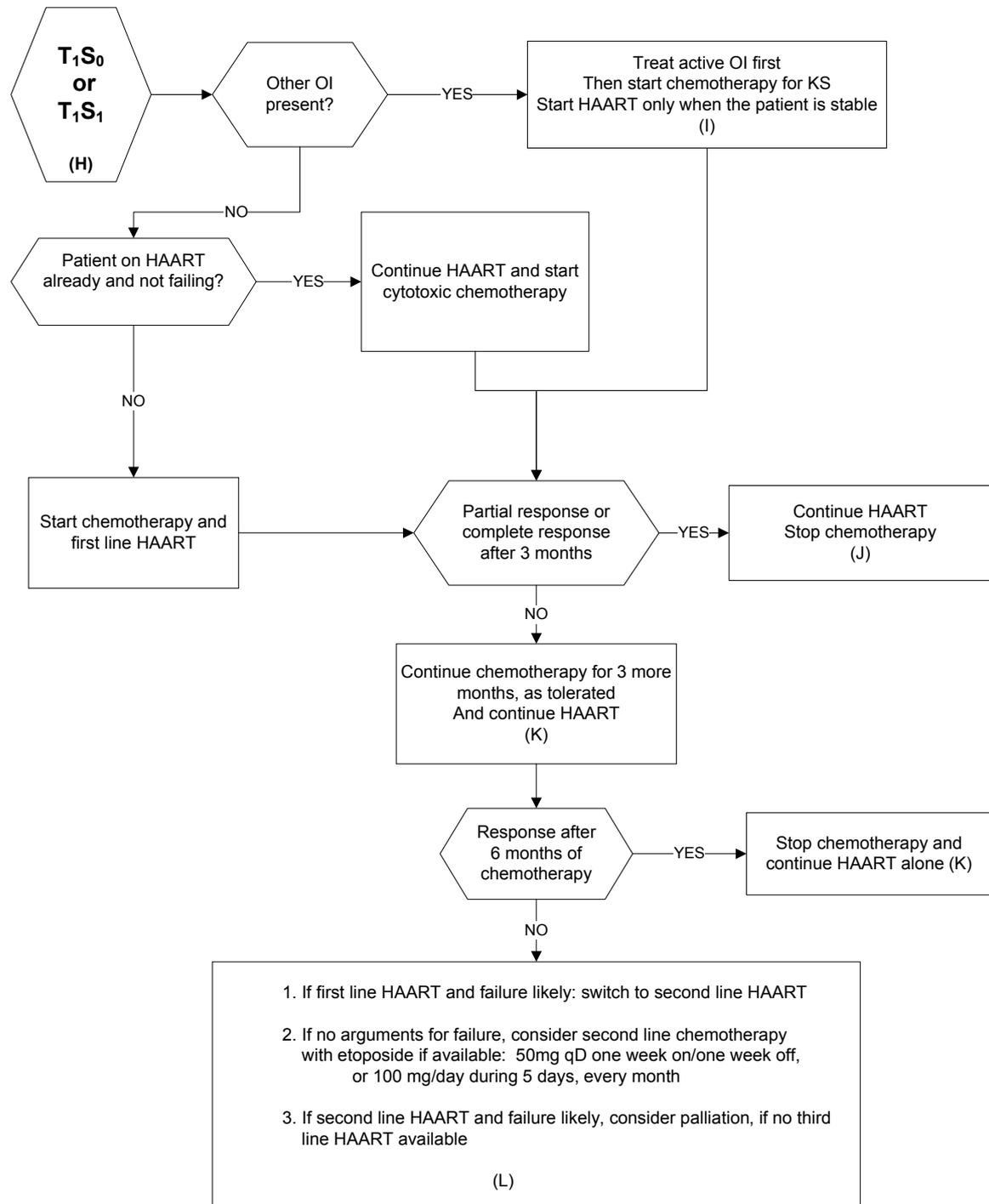


Annotations AIDS KS

- (A) In patients who present with limited disease (T_0S_0 or T_0S_1) there is no indication to start chemotherapy. These patients are likely to benefit from HAART alone. To be sure, a chest X-ray needs to be taken to exclude pulmonary KS lesions, as these may present with little symptoms. KS is a WHO stage 4 disease and following the WHO guidelines all stage 4 patients should receive HAART, regardless the CD4 count. Whenever the patient has another OI, make sure to treat first the OI, and only start HAART when the patient is stabilised and can tolerate the drugs. The presence of B-symptoms (S_1) should not be used as a criterion to start chemotherapy, as many patients with limited cutaneous disease may present with another OI causing fever and weight loss.
- (B) There is no evidence that PI-based regimens are better than NNRTI-based regimens for treatment of AIDS KS. As PI based regimens are usually reserved as second line HAART regimens in resource-poor settings, it is better to start patients with KS on the same regimen as all other patients.
- (C) A partial response is defined as no new lesions and one of the following: a > 50% decrease in the total number of lesions; or a > 50% reduction in the size of the index lesions; or marked flattening of KS lesions; or clinical complete response but with residual oedema. A clinical complete response is the absence of any residual symptom or lesion after treatment. The median time to response is 6 months.⁴³²
- (D) If, after 6 months of HAART, lesions still progress or remain stable, adherence to HAART should be checked. Failure of KS to regress under HAART is linked with virological failure to HAART. This case should be managed as a suspected treatment failure and adherence to HAART should be reinforced. If despite good adherence there are arguments to suspect treatment failure (other than KS, e.g. previous ART experience, recurrence of clinical symptoms, decrease in CD4 count), change the complete HAART regimen to a second line, PI containing regimen. If there are no other arguments for treatment failure, continue first line HAART and consider chemotherapy in case of extensive KS or radiotherapy in case of progressive localised disease. Some KS lesions may exacerbate initially due to immune restoration inflammatory syndrome (IRIS).
- (E) Local therapy for KS lesions in the mouth consists of intralesional injections with vinblastine 0.1 mg/ml (0.1 ml per 0.5 cm² of lesion). Single big lesions (> 3 cm) on the extremities respond well to radiotherapy if available. Single 8 Gray fractions result in clinically good responses.⁴³³ Radiotherapy is effective in reducing lymph oedema and pain. Smaller lesions could be treated with cryotherapy with liquid nitrogen, if available.
- (F) A patient who is developing an active OI after 12 months of HAART, is probably failing. If possible, confirm this with a viral load. The patient should be switched from first line to second line treatment, or from second line to third line treatment. In most situations there will be no third line HAART available. Treat the OI and provide palliation. Lesions of KS are painful when extensive, and tumours can cause oedema. Palliation is important. If chemotherapy is not helping, adequate pain control has to be installed. The size of tumours can be reduced by radiotherapy if available. The ulcerated KS lesions may present with an offensive smell. Metronidazole powder can be used to diminish the smell.

- (G) Although T₀S₀ and T₁S₀ have an 80% chance of a complete remission with HAART alone, some patients may require cytotoxic chemotherapy eventually, especially when progressive disease is diagnosed in patients who otherwise have no arguments for virological failure on their HAART regimen.
- (H) Cytotoxic chemotherapy should be started in combination with HAART, when patients have symptoms of severe pain, massive lymphoedema, and obstruction, difficulty to swallow or speak because of oral or pharyngeal KS. Advice on effective contraception besides condom use is needed.
- (I) Whenever the patient has another OI, make sure to treat the OI first. As soon as the patient tolerates his OI treatment, start with chemotherapy. In a resource-limited setting bleomycin 15 mg IM (or 5 mg/d IM for 3 consecutive days) every fortnight seems to be a feasible option, as is vincristine/vinblastine (See Table 18). Only start HAART when the patient is stabilised and can tolerate the drugs.
- (J) In most of the cases when a partial or complete response is obtained under HAART and chemotherapy, it is possible to interrupt the chemotherapy. The patients who have a complete response are more likely to have a good increase in CD4 count. If lesions would increase in size again later or recur, we can still restart some cycles of chemotherapy, while continuing to improve immunity by HAART.
- (K) Time to response has medians ranging from 3 to 9 months.^{411,411} In case the response after three months is not good, the patient may benefit from 3 cycles chemotherapy more.
- (L)
1. Patients who fail on chemotherapy and HAART, or who need again treatment for KS while on HAART, have a high likelihood to have a treatment failure for HIV as well. Carefully check adherence. Is there drug resistance or failure due to bad adherence? In case of failure on a first line HAART regimen, despite good adherence, it makes sense to switch to a second line treatment with PI.
 2. In case there are no arguments for treatment failure on HAART, consider second line chemotherapy. When etoposide is used, there is a high risk for pancytopenia. AZT should not be combined with etoposide and the full blood count should be checked before the etoposide is given for another week.
 3. In case the patient was already on second line HAART, and treatment failure is likely, stop chemotherapy and HAART and provide palliation. Lesions of KS are painful when extensive, and tumours can cause oedema. Palliation is important. If chemotherapy is not helping, adequate pain control has to be installed. The size of tumours can be reduced by radiotherapy if available. The ulcerated KS lesions may present with an offensive smell. Metronidazole powder can be used to diminish the smell.

Figure 4: Recommendations for management of AIDS KS in limited-resource settings (Part 2: T₁S₀ or T₁S₁)





16 OPPORTUNISTIC INFECTIONS AND HAART

16.1 Introduction

With the wide spread use of HAART the incidence of opportunistic infections (OI) in the western world has dramatically decreased.⁴³⁴ The clinical benefit of HAART in reducing the incidence of OI is especially obvious in patients with $CD4 < 200$.¹²⁴ Besides preventing OIs, HAART also helps to get rid of certain OIs, especially those for which no specific treatment is available.

Nevertheless, in our daily practice, we are still confronted with AIDS-related OIs. Patients present themselves late with an AIDS defining illness. In the first months after the initiation of HAART patients may still develop an OI, or a worsening of a pre-existing OI due to immune reactivation disease (see below). After 6 months of HAART the occurrence of an OI usually indicates treatment failure, although immune reactivation disease is still possible. TB remains common, even in the absence of treatment failure, in patients with $CD4 < 350$.

16.2 Problems with OI and HAART

In terms of patient management we can distinguish two situations in which clinical management decisions may have to be made: *before* the start of HAART and *after* the start of HAART.

16.2.1 Before the start of HAART

How to exclude an active OI before the start of HAART?

In advanced AIDS, especially in resource-poor settings, it is difficult to diagnose/exclude an acute OI in patients who have advanced AIDS.

It is, however, important to go through the process. Patients with active OIs may suffer from several complications when started on HAART in the same time: high pill burden, decreased adherence, immune reconstitution inflammatory syndrome (IRIS), drug interactions and cumulative toxicity between ART and OI drugs.

To exclude OIs before the start of HAART investigations need to be planned according to a clear strategy, so that the process is as efficient as possible. The clinical decision tree for doing this is shown on page 290 and 292.

What are important diseases in this stage that we may miss?

Cryptococcal infection in very advanced immune suppression may cause few symptoms. Physical exam may reveal typical skin lesions. Slight confusion/headache may raise suspicion of cryptococcal meningitis. The threshold for an LP and serum cryptococcal antigen detection should be very low in patients with low CD4 count (see chapter 14). In case of symptoms, Indian ink smears of skin lesions or of CSF are useful exams to do. Even a pauci symptomatic patient, but who has a CD4 count below 100 with a positive serum cryptococcal antigen test, should receive full treatment for cryptococcal disease if he was never treated for this condition before.

In advanced AIDS extra-pulmonary **tuberculosis** (TB) and disseminated TB are frequent. 50% of patients with tuberculosis in this stage have positive mycobacterial blood cultures; however, they require special media which are rarely available and final results can only be expected after 4-6 weeks. A chest X-ray may show mediastinal or hilar lymph nodes, pulmonary infiltrates or miliary lesions, but can be negative in patients with active tuberculosis. In pulmonary tuberculosis only 30-50% of patients will have a positive smear for AFB. An abdominal ultrasound can show hepato-splenomegaly and lymphadenopathy. In case of diarrhoea, AFB can be found in the stool, although the value of this finding is uncertain (see chapter 9). In case of infiltration of the liver, alkaline phosphatases can be very high (more than 600).

MAC is difficult to diagnose and is suspected in patients with very low CD4 counts (typically < 50), hepato-splenomegaly, fever, anaemia, wasting, diarrhoea and high alkaline phosphatases. The differential diagnosis with TB is very difficult in resource-poor settings, and often patients end up with combined TB and MAC treatment, when there is insufficient response to TB treatment alone. Absence of peripheral lymphadenopathy and severe anaemia and neutropenia favour the diagnosis of MAC.^{42,193}

CMV disease occurs mainly in patients with CD4 < 50. If CMV occurs in patients with CD4 > 100, it typically occurs in the first 6 months after the start of HAART.⁴³⁵

The majority of the patients will present with retinitis. Between 13-19% of the patients with CD4 < 50 may harbour CMV retinitis without symptoms. Patients may complain of decreased vision, floaters, visual distortion, light flashes, and blind spots. Redness and pain are typically absent.

Depending on the area of the retina that is involved, blindness will follow in the majority of the patients, but not all.⁴³⁶ Lesions close to or involving the fovea or optic nerve are particularly likely to cause serious visual impairment. Acute loss of vision can occur if retinitis leads to retinal detachment. Examination with an indirect ophthalmoscope reveals white, fluffy or granular retinal lesions, often located close to the retinal vessels, with or without haemorrhage. Treatment with ganciclovir is needed. Intravitreal ganciclovir may treat the retinitis, but CMV is a systemic disease. As IV ganciclovir is very expensive, it is almost nowhere available in resource-poor settings. The intra-ocular injections with ganciclovir use only a fraction of the dose needed to

treat systemic CMV disease. This reduces the cost. It is not clear whether intra-ocular injection with ganciclovir will prevent immune reactivation uveitis. If available, it seems logical to use intra-ocular injections to reduce locally the CMV antigen load in the eye. HAART should be started soon because the local treatment is not effective against systemic CMV, but HAART immune restoration is.

A significant minority of patients with CMV present with neuropathy or odynophagia.

Guidelines to exclude OIs before the start of HAART

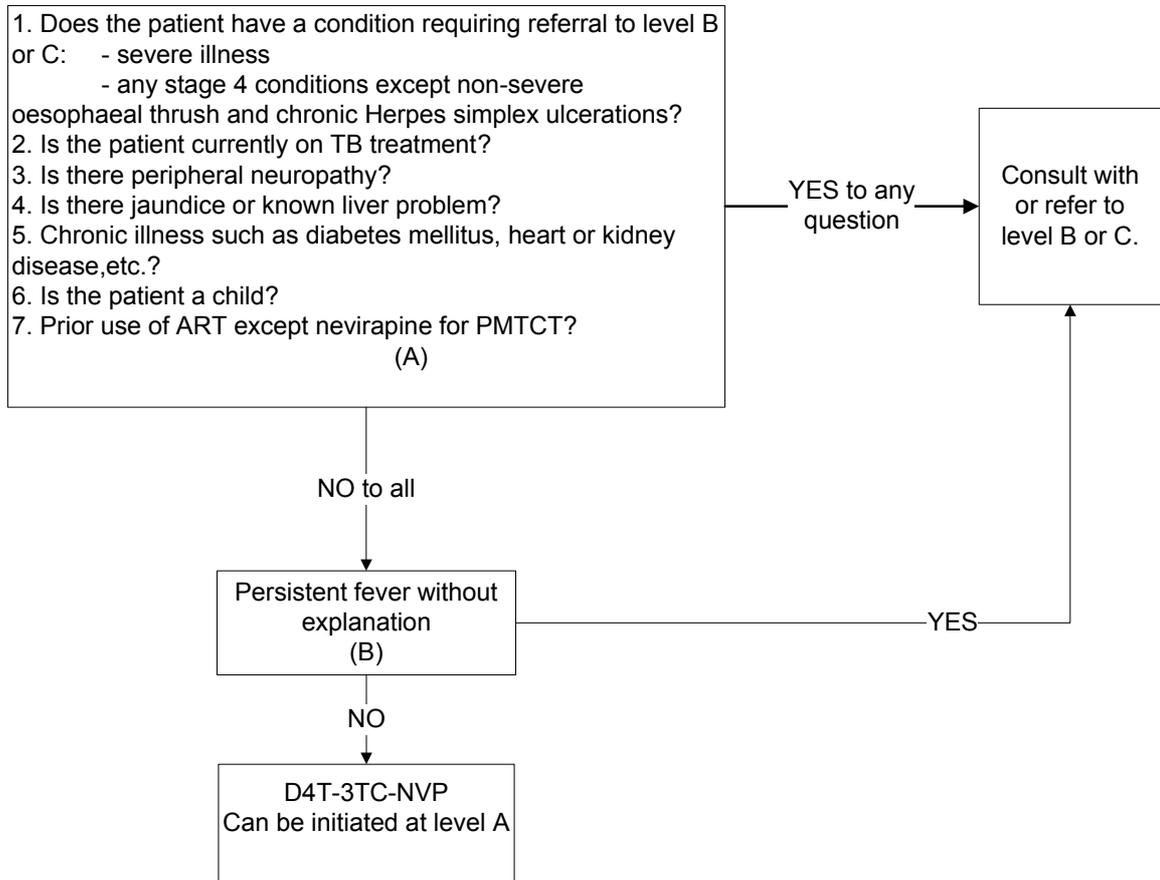
At “**level A**” diagnostic capacity is very low. Here it is important to identify those patients that can be started on ART without further consultation with a medical doctor.

The WHO’s IMAI (Integrated Management of Adults and Adolescent Illness)* guidelines provide tools and standard training packages to teach first-level facility health workers to prescribe HAART in a safe way.⁴³⁷ One of these tools is a simple table to help the nurse decide whether ARV therapy can be started at health centre level or not. In **Figure 5** this table is included in a clinical decision tree, indicating when referral to level B or C is needed. In Figure 6 we propose an algorithm to guide physicians at level B and C with excluding to a certain degree of certainty active OIs before the start of HAART.

* <http://www.who.int/3by5/publications/documents/imai/en/>

Figure 5: Exclude OI before the start of HAART

Level A

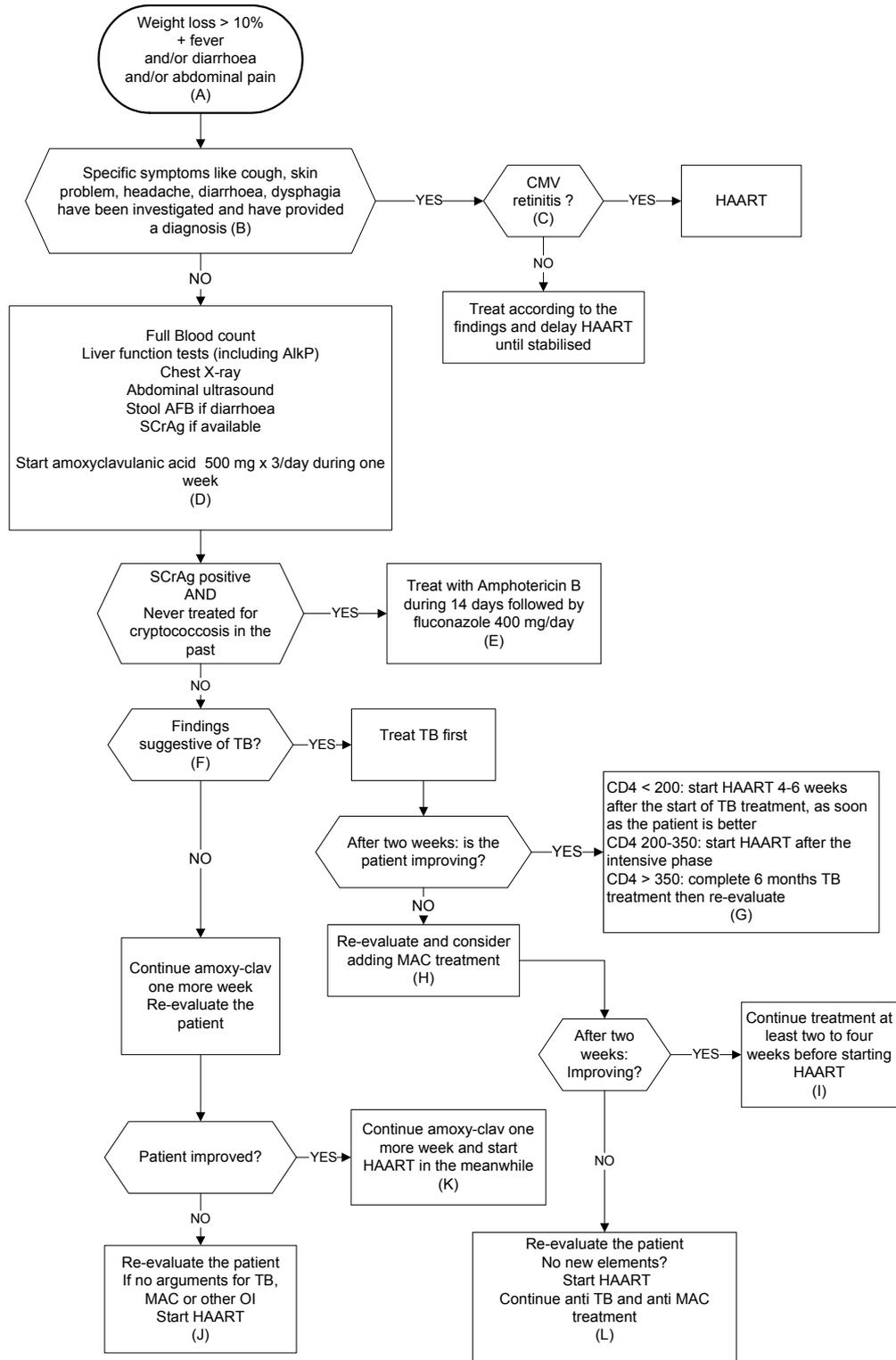


Annotations (level A)

- (A) In a patient who is HIV-positive, and who meets the medical criteria to start HAART, the IMAI guidelines recommend to check 7 conditions before a health care worker at the health centre level could initiate ART. If they are all absent the risk of having problems with the start of first line HAART is small. In case the patient has oesophageal thrush or chronic herpes simplex ulcerations, it is better to first treat this condition, however, after treatment there is no particular risk to start these patients on HAART in the health centre, on the condition that the answer to the 7 questions is negative. Patients who were treated in the past for cryptococcal meningitis or toxoplasmosis and who are now stable can start with HAART in the health centre. Patients who have been diagnosed with HIV encephalopathy and who are stable can start as well. Careful monitoring is needed in these patients.
- (B) In a patient with chronic unexplained fever, even without severe symptoms it is recommended to refer the patient for a diagnostic work up.

Figure 6: Exclude OI before the start of HAART

Level B and C



Annotations (level B and C)

- (A) End stage patients with wasting (including fever and diarrhoea) and often abdominal pain. Often these patients have gone through extensive diagnostic work-up without finding an obvious diagnosis, and we are in doubt whether to start HAART or not.
- (B) To make sure that every effort has been made to exclude obvious opportunistic infections, we first check whether any specific symptom like headache, eye problems, abdominal pain, diarrhoea and cough and even skin diseases have not provided a diagnosis.
- (C) Patients with proven CMV retinitis should not undergo the whole diagnostic process unless there are clear indications of another concomitant disease. CMV can cause diarrhoea, weight loss, anaemia abdominal lymph nodes. Intra-ocular ganciclovir could be considered, together with or before the start of HAART (see page 299).
- (D) If different symptom related algorithms do not provide a diagnosis, a clear strategy has to be followed in order not to delay effective HAART without reason. Some of the patients may have salmonella or another gram negative septicaemia. Prolonged treatment is necessary to avoid recurrence. Start with amoxycyclavulanic acid while waiting the results of the investigations that remains to be done. Do not give ciprofloxacin or macrolides, because at this point TB and MAC or not excluded, and these drugs have antimycobacterial activity which might improve the symptoms, and therefore delay the initiation of appropriate antituberculous treatment.¹⁴⁷ Moreover, monotherapy with these agents induces resistance in TB and MAC. Patients who have already received adequate antibiotics in the past weeks should be excluded from this empiric treatment.
- (E) If a patient is end stage and has a positive SCrAg while he never received a treatment for cryptococcosis and is therefore not on secondary prophylaxis, it may be wise to first start amphotericin B followed by fluconazole 400 mg daily for at least 10 weeks before considering HAART (see chapter 14). If a patient is on secondary prophylaxis for cryptococcosis the presence of a SCrAg has no meaning. HAART should be started but the patient should be watched carefully for the development of IRIS.
- (F) Findings suggestive of TB include: abdominal lymphadenopathies, abnormal chest X-ray, sputum AFB (+), anaemia and increased alkaline phosphatase. In case of unexplained abdominal pain, weight loss and fever in advanced AIDS, it is justified to start TB treatment. In some of these patients AFB on stool can be positive, however, there is discussion on the utility of this exam. If the patient has TB usually an improvement is seen within two weeks. Start of HAART can now be considered.

- (G) Following the WHO guidelines of 2003, HAART should be started early in patients who have a low CD4 count. The reason to start HAART during the intensive phase of TB treatment in patients with low CD4 counts is the high mortality observed in this group of patients due to other AIDS related illnesses, when treated with TB drugs alone.
- (H) In patients with CD4 < 50 it is difficult to make the differential diagnosis between TB and MAC. If the patient is not improving with anti-TB treatment, add azithromycin 600 mg daily to the treatment and maintain ethambutol 15mg/kg in the TB regimen. TB treatment will be completed as usual. This strategy may have to be adapted if MAC is a very rare disease in your region. Other considerations are MDR TB, or another undiagnosed infection.
- (I) If the patient was improving under MAC treatment, continue this treatment. Do not start HAART until the patient has clinically improved and is tolerating his OI treatment (wait at least one month). If a patient is treated for MAC, ethambutol and azithromycin is needed for 12 months. Afterwards, maintenance therapy with azithromycin 1200 mg/week needs to be given until the CD4 count is above 100 (and after a complete year anti-MAC treatment) and only when the patient is clinically well. MAC can give late IRIS.
- (J) If the patient is not improving after two weeks of amoxycyclavulanic acid, re-evaluate the situation. Are there any new symptoms that might merit investigation? Cough, headache, abdominal lymph nodes bigger than 1.5 cm? AFB in the stool are not diagnostic for TB, however, in an AIDS patient who also has splenic or liver lesions, this may indicate TB or MAC. If no arguments for an active OI are found at all, start HAART. This patient should be watched carefully because he is at a high risk to develop an IRIS if he has an unrecognised OI.
- (K) Start HAART but follow-up closely for the occurrence of IRIS. Continue amoxycyclavulanic acid to complete 3 weeks.
- (L) These are very complicated patients to manage. One might be inclined to stop the TB and MAC drugs, because they didn't seem to have an effect so far. The problem is that response to treatment, especially MAC, may only become apparent after several weeks of treatment. When we start HAART in patients with MAC or TB, severe IRIS can develop, especially when not treated.

When to start HAART in the setting of an acute OI?

The next complex decision to make is, once we have diagnosed an OI, what is a good time to introduce HAART. WHO has issued clear guidelines for tuberculosis, but these need still to be validated. For other OIs there are no randomised controlled trials that address the issue, and many guidelines depend on expert opinion.

Arguments pro early start of HAART

Patients who present with the OIs described above are in WHO stage 4, which signifies severe immune suppression and are therefore in urgent need of HAART. HAART will improve the immune system and the risk to develop a second OI will decrease. Some OIs do not have an effective treatment and only HAART through immune restoration will be able to clear the infection (cryptosporidium, microsporidium).

Arguments pro delayed start of HAART

The antiretroviral drugs and the drugs needed to treat opportunistic infections may have overlapping toxicity as well as possible drug interactions. Development of an immune reconstitution syndrome may occur. This inflammatory reaction can be life threatening especially when they present with severe pulmonary infiltrates or intracranial masses. In patients who develop high fever, dyspnoea, headache or abdominal pain it may be difficult to differentiate between the causes of such symptoms. Is it drug toxicity, IRIS or a new OI?

Some OIs frequently cause inflammatory syndromes when combined with HAART in an early stage. For some OIs, no effective treatment is available. When to start with HAART therefore depends on the type of OI (see **Table 21**). In the setting of MAC, TB, PCP and cryptococcal meningitis it is advised to wait for a response to OI treatment before starting HAART.¹²⁴ In **Table 21** we give a suggestion and also the rationale on when to start HAART in specific OIs.

If the patient has a proven OI such as TB, MAC, PCP or cryptococcal meningitis it is always necessary to treat the OI before initiating HAART. Never start HAART first, before the OI is treated.

Table 21: Approach to initiating HAART for different OIs

	Condition	Reason
Start HAART as soon as possible	Cryptosporidiosis	No effective treatment, except HAART
	Microsporidiosis	
	PML	
	CMV	Ganciclovir often not available, HAART is the only treatment. Warn patients for IRIS.
	Kaposi's sarcoma	Systemic chemotherapy only useful when combined with HAART (see chapter 15)
	Oesophageal candidiasis	Good effect of HAART in combination with specific treatment and no risk for life threatening IRIS
	Chronic herpes simplex	
Delay HAART, treat OI first	<p>Tuberculosis <i>CD4 < 200</i>: start as soon as the patient tolerates his TB treatment (4-6 weeks after the start of TB treatment) <i>350 > CD4 > 200</i>: wait until the end of the intensive phase <i>CD4 > 350</i>: wait until the end of the TB treatment and re-evaluate need for HAART then</p>	Severe IRIS Drug interactions between rifampicin and nevirapine Cumulative toxicity: hepatotoxic (INH, nevirapine), neurotoxic (INH, d4T)
	<p>PCP Start HAART after the 3 weeks of intensive treatment, when switching to cotrimoxazole secondary prevention</p>	Severe IRIS Rash: both cotrimoxazole and nevirapine can cause rash
	<p>MAC Start after one month of MAC treatment when the patient is asymptomatic and tolerates the treatment</p>	Severe IRIS Clarithromycin drug interactions
	<p>Cryptococcal meningitis Start HAART after 10 weeks of induction treatment when switching to secondary prophylaxis with fluconazole 200 mg daily. If at that moment intracranial hypertension is still present, continue regular lumbar taps, because ICH may worsen after the start of HAART.</p>	IRIS with severe inflammatory meningitis Possible drug interactions nevirapine-fluconazole (high dose)

16.2.2 Problems with OI after the start of HAART

OI in the first 6 months: IRIS or drug toxicity or new OI?

Patients still develop OIs, especially in the first 2-6 months after the start of HAART.^{291,438} Previously it was thought that these symptoms were a sign of incomplete immune restoration, but now it is considered to be a result of the response to HAART. It is important to explain this to the patient. Patients at high risk (e.g. active CMV, persistent intracranial hypertension) should be offered a well informed choice before the start of HAART. If not, the patient may be discouraged by the unexpected worsening of his condition, which may damage the relation of trust between patient and treatment program and may interfere with drug adherence.

Even prior to HAART, it has been known that some infectious diseases when treated can present with a temporary worsening of symptoms also called “paradoxical reaction”, due to enhancement of cell-mediated immunity (PCP, tuberculosis, leprosy).¹⁶⁹

Since the use of antiretroviral therapy IRIS has been described in association with many concomitant infections such as mycobacterial infections (mycobacterium tuberculosis (TB), mycobacterium avium complex, leprosy), fungal infections (cryptococcal, histoplasmosis and *Pneumocystis jiroveci* infection) and viral infections (herpes simplex, herpes zoster, cytomegalovirus, progressive multifocal encephalopathy, and hepatitis B infection).^{208,439} IRIS associated with a leishmania infection, Reiter's syndrome, Guillain Barré, and several dermatological conditions, have occasionally been reported.²⁰⁸ Likewise, other clinical manifestations not clearly related to infectious agents have been described, such as Graves' disease, sarcoidosis and other auto-immune disorders. Finally, malignancies like Kaposi's sarcoma and lymphoma have been reported in the context of IRIS as well.^{285,286,430}

IRIS is more frequent in patients who are ARV naïve, who have a rapid decline in viral load and who have a short delay between the start of OI treatment and the initiation of HAART.⁴⁴⁰

IRIS can occur in two different contexts, each of which has a different pathogenesis¹⁰⁹; first, it may be an unmasking of a previous latent infection or unrecognised active infection due to enhanced immunity. Examples are: MAC/TB lymphadenitis, CMV retinitis and cryptococcal meningitis. Secondly, it may be an increased immune response to residual non-viable antigens present in tissue after successful treatment of the infection, as observed in patients who experience worsening of symptoms after an initially favourable response to OI treatment.^{441,442} Because of granulomatous inflammation, which can cause an autologous production of 1.25 (OH)₂ vit D, patients may present with hypercalcemia.^{287,381,443}

Clinical case definition

IRIS is suspected in a patient who develops symptoms of an active OI soon after the start of HAART. Around 30% of patients will develop an IRIS a few weeks after the start of HAART.⁴⁴⁴

Case definitions of IRIS are found in the literature, but there are no clear diagnostic criteria or laboratory tests to confirm the diagnosis. Most of the proposed criteria for IRIS require viral load testing or CD4 count and measurement of delayed hypersensitivity testing (DTH) to mycobacterial antigens. This definition is often not applicable in developing countries.^{156,287,444}

Breton proposed a clinical definition of possible IRIS:

*“The **diagnosis** of IRIS is considered “**possible**” when there is reappearance or worsening of previous symptoms of the OI, or if there is an appearance of new manifestations, despite effective OI treatment and after exclusion of other diagnosis “*

Shelburne defines IRIS as follows⁴⁴⁰:

- the patient should be on HAART
- there is clinical evidence of new symptoms compatible with an inflammatory process that is not the usual course of the infection (swelling of lymph nodes, fever, abdominal pain, dyspnoea, headache)
- a rise in CD4 count
- a falling viral load

In developing countries, more than half of the cases of IRIS will be due to tuberculosis. In a study in India, IRIS was defined as a new lymph node enlargement and localised tenderness or fever with no other cause identified after clinical and laboratory evaluation.⁴⁴⁵

The **management** of IRIS is challenging because of the difficulties to identify the causative agent and to differentiate this condition from side effects to HAART. This is especially the case when a patient presents with fever and liver test abnormalities. In patients on AZT who develop anaemia shortly after the start of HAART, one should not overlook the possibility of an underlying OI (MAC, TB) especially when associated with fever.

The second problem is the decision whether to start a pathogen specific treatment in addition to HAART. In the absence of an active OI, symptoms could disappear spontaneously with the continuation of HAART or with the addition of steroids. However, most of the time pathogen-specific treatment should be added, while HAART is continued. Sometimes steroids are needed (see below). The third problem with IRIS in patients who are treated for an OI is that the patient's symptoms are sometimes considered as a failure of either HAART or of the OI treatment. This is especially so because IRIS can occur as late as 3-4 years after the start of HAART.

No comparative data exist on how to manage these patients best. In Figure 7 a proposal of a flowchart is given for patients who present with fever in the first weeks after the start of HAART. Other symptoms related with IRIS (respiratory distress, lymph nodes, neuropathy and headache) are dealt with in the respective chapters.

Tuberculosis

Incidence of TB IRIS after the start of HAART varies between 11 and 45%. It usually occurs 1-6 weeks after the start of HAART, but has been described up to 658 days.⁴⁴⁰ Symptoms include new fever, worsening lymphadenopathy (peripheral and mediastinal), abscesses, pulmonary infiltrates and pleural effusions and intracranial tuberculomas. TB IRIS can be a cause of focal neurologic deficits, with up to 10% of tuberculomas increasing in size after the start of HAART.²⁰⁹

The incidence is higher in patients who have both pulmonary and extra-pulmonary TB at initial diagnosis.⁴⁴⁶

Culture and AFB smear of pus aspirated from lymph nodes may be negative. A PPD skin test becomes positive in more than 85% of patients who were anergic before the start of HAART and who developed a paradoxical reaction. This syndrome responds usually well to anti-inflammatory drugs or corticosteroids. Steroids are clinically indicated when a patient develops expanding intracranial tuberculous abscesses, respiratory distress or compression of vital structures by lymph nodes and long-lasting symptoms such as recurrent chronic abscesses.

Sub-optimal adherence to anti-tuberculosis treatment due to intolerance is frequently seen in patients co-treated with HAART.⁴⁴⁷ The occurrence of a paradoxical reaction may cause additional adherence problems. When a patient is too sick to take all drugs, it is preferable to stop the HAART and to continue the TB treatment alone, until the patient is stabilised. The problem in these patients is also to distinguish between IRIS, TB relapse, which is more frequent in advanced HIV disease, and depending on the setting the occurrence of MDR TB. In all cases of TB IRIS the adequacy of previously administered TB treatment has to be evaluated. If this was inadequate or doubtful, specific TB retreatment should be started according to National TB Guidelines. If no improvement, consider MAC treatment.

MAC

In late AIDS MAC usually presents as disseminated disease. In contrast, when MAC is associated with IRIS it presents as lymphadenitis, usually solitary and occurs in the first weeks of HAART. However, MAC-IRIS has been described up to 25 months after the start of HAART. MAC-associated IRIS should be considered in patients who develop anaemia and fever after the start of HAART.

CMV

Immune recovery uveitis (IRU), also known as immune recovery vitreitis, may occur in as many as 50% of patients who are on HAART and who were previously treated for CMV retinitis or who had subclinical CMV retinitis before the start of HAART. It is characterised by much more severe inflammatory reactions (including vitreous haze, optic disc oedema, cystoid macular

oedema, and epiretinal membrane formation).⁴³⁵

Based on the theory that IRU is caused by a vigorous immune response to CMV antigens in the eye, intraocular injections of ganciclovir could be effective in reducing the persistent antigenic load local in the eye.⁴⁴¹ HAART should be continued. It is not clear whether intra-ocular injections of ganciclovir prior to HAART may prevent the IRU.

Every patient with low CD4 counts (<50) should get an eye exam before the start of HAART and patients should be warned for the risk of developing vision problems. In patients who have already CMV retinitis, blindness may follow secondary to inflammatory changes and retinal detachments.

In case of CMV presenting with neuropathy or ophthalmopathy the correct treatment would be IV ganciclovir, which is prohibitively expensive. In the first months of HAART CMV neuropathy can worsen and present with painful radiculopathy, sometimes associated with spastic paresis. This is another manifestation of IRIS. Continue HAART, add steroids[†] to reduce the inflammation and give symptomatic relief.

Cryptococcosis

Partial immune restoration after the initiation of HAART can cause an aseptic meningitis with high intracranial pressure (ICP) in patients with a latent cryptococcal meningitis (CM) or in patients who have had a CM in the recent past and who have residual antigen in the CSF.^{169,381} Evidence of immune restoration is suggested by a sharp decrease in viral load, a significant increase in CD4 count and inflammatory changes in the CSF (WBC > 10 cell/mm³).

It can occur in patients with a CD4 > 50 cells/mm³ and is seen most frequently between 1 week and 8 months after starting HAART.

Cryptococcal meningitis is the most frequent form but other forms have been described: cutaneous and pulmonary disease, mediastinal lymphadenitis, subcutaneous abscesses.¹⁶⁹ In patients who start HAART concurrent with or soon after the start of antifungal treatment (0-2 months after the diagnosis of cryptococcal disease), IRIS occurred in 50% of the patients.³⁸¹

Most of the cases described had negative culture results and a low antigen titre, but cryptococcal yeasts were detected in biopsy material.³⁸¹ These yeasts may be dead, and a definitive diagnosis of recurrent cryptococcal disease cannot be made without fungal cultures.

Serum cryptococcal antigen titres have no value in the follow-up of patients treated for cryptococcal disease. It is not known whether the persistence of cryptococcal yeasts or a high level of serum cryptococcal antigen is predictive of IRIS due to cryptococcosis. One case study suggested that the presence of residual cryptococcal antigen in the CSF predicts the onset of clinically apparent meningitis after the start of HAART.¹⁶⁹

In order to reduce the risk of cryptococcal infection related IRIS, it is advised to start HAART only when the induction phase of the treatment is finished and the patient is on secondary prophylaxis.

[†] Prednisolone 40 mg/day for 2 weeks, followed by prednisolone 20 mg/day for 1 week, followed by 10 mg/day for another week

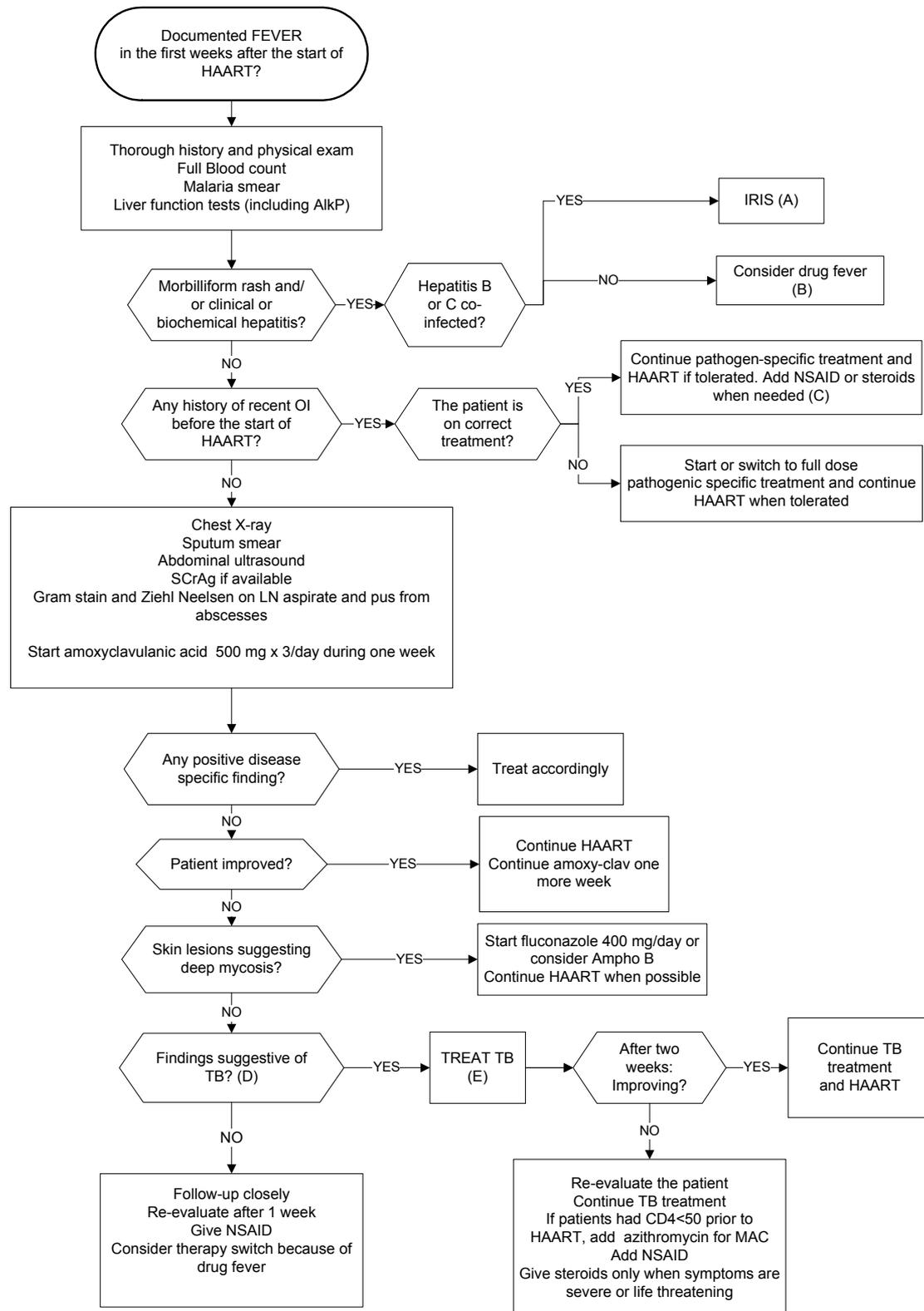
Because of the impossibility of confirming a definite diagnosis only on the basis of clinical findings and microscopy, some doctors recommend, in practice, treating all such cases as active cryptococcosis. They will restart antifungal therapy (fluconazole 400 mg daily or amphotericin B for 14 days) and repeat lumbar taps in case of meningitis. Others just add steroids and continue secondary prophylaxis. There are no studies comparing steroids with antifungal treatment in this situation.

Treatment with HAART should be continued if the patient tolerates it. Cryptococcal IRIS is often complicated by significant elevations in ICP. Repeated large volume lumbar taps are crucial in the management. In case of life threatening symptoms (severe ICP) with focal neurological lesions, steroids can be given (0.5mg/kg daily). However, there are no randomised controlled trials to prove the usefulness of this strategy.

Observational studies are necessary to determine when to start HAART after cryptococcosis is diagnosed.

Do not forget to continue secondary prophylaxis with fluconazole in patients with previous cryptococcal meningitis, until the CD4 count has been > 100 cells/mm³ on two occasions.

Figure 7: Management of fever in patients shortly after the start of HAART



Annotations Figure 7: Management of fever in patients after the start of HAART

- (A) Patients with hepatitis B or C and HIV co-infection can develop IRIS after the start of HAART. An increase in transaminases has to be interpreted in relation with the level of ALT and AST before the start of HAART (see page 304) In the presence of fever follow-up the patient closely, whenever jaundice or rash develops stop the nevirapine immediately. Some clinicians prefer the use of efavirenz in first line in patients with chronic hepatitis because of the difficulties to distinguish between liver toxicity of nevirapine or IRIS.
- (B) Drug fever can present with or without rash. When rash and fever coexist a switch of treatment has to be considered (see chapter 13). When rash, fever and hepatitis coexist it is considered to be a severe hypersensitivity reaction and an interruption of the culprit drug has to be done immediately. Stop nevirapine, continue d4T and 3TC and restart Efavirenz as soon as the rash and the fever are gone. In case the rash is still there after one week, stop all antivirals and restart a complete regimen with efavirenz when the patient has recovered from his drug fever.
- (C) Steroids are clinically indicated when a patient develops life threatening complications like compression of vital structures due to abscesses or lymph nodes and respiratory distress.
- (D) Findings suggestive of TB IRIS include: inflamed lymph nodes and abscesses, abnormal chest X-ray, weight loss while on HAART⁴⁴⁸, anaemia and increased alkaline phosphatase. In case of anaemia, fever and increased alkaline phosphatase this could also be MAC. However, in resource-poor settings the likelihood of TB is so high that it would be an error to consider MAC treatment without a full treatment for TB as well.
- (E) In patients on a first line regimen with d4T, 3TC and nevirapine a switch to efavirenz 600mg or 800 mg can be considered. However, a few studies from Thailand have shown that virological outcome was good in patients who were treated with rifampicin in combination with nevirapine based HAART (see page 306)

Hepatitis B or C

Worldwide about 10% of HIV patients are co-infected with hepatitis B and 4% with hepatitis C.

The natural history of HIV is not influenced by hepatitis B, but there is an increased risk of HAART-related hepatotoxicity.⁴⁴⁹⁻⁴⁵¹ In developing countries the bulk of hepatitis B infection is acquired perinatally. In patients infected perinatally, the rate of chronic infections is much higher (30-90% vs 15-20% in co-infected patients).^{452,453} 6-15% of patients with cirrhosis develop hepatocellular carcinoma. 15-20% of the patients who have an active chronic infection develop cirrhosis over 5 years.

Hepatitis C has a negative effect on the natural evolution of HIV. HCV infection is associated with an increased risk of progression to AIDS and

death. Patients with hepatitis C/HIV co-infection often have CD4 counts that remain low, despite good viral suppression.⁴⁵⁴ Hepatitis C infection leads to chronic hepatitis in 85% of patients and 20% of them will develop cirrhosis over the next 20 years. This evolution is even accelerated in HIV/HCV co-infected patients.

While overall survival of patients with HIV infection is increasing due to HAART, the mortality secondary to end stage liver disease is rising.⁴⁵⁵ Liver enzymes should be carefully monitored in patients under HAART and co-infected with either hepatitis B or C. Fear of starting HAART in patients with chronic hepatitis should not be exaggerated though.

Although such patients have a two-fold increased risk of hepatotoxicity, (around 80%), they do not develop severe liver test abnormalities (defined as grade 3 and 4: see Table 22) and are able to continue HAART.²³⁵

Patients should be monitored closely and HAART should not be interrupted prematurely.²⁰⁹

Abnormal liver function tests in co-infected patients can have different origins.⁴⁵¹

- reactivation of hepatitis B because of worsening immunity
- improved immune response as a result of HAART (IRIS)
- hepatitis flare after withdrawal of lamivudine, or because of resistance has developed against 3TC
- hepatotoxicity due to drugs
- acute hepatitis due to another type of hepatotropic virus (HAV, HCV)

Table 22: Modified toxicity grade scale for patients with pre-existing abnormal liver function tests

Baseline values	Grade 3	Grade 4
Within normal limits	5-10x ULN	> 10 x ULN
Baseline increase in ALT, AST	3.6-5 x baseline value	> 5 times baseline value

ULN: upper limit of normal

HIV-positive patients who have chronic active hepatitis B but who do not need HAART, should not be treated with antiviral agents that are active against HIV (Lamivudine, tenofovir, FTC) because of the risk of developing resistance in HIV in a short time. Patients who need HAART should preferably be treated with regimens that are also active against hepatitis B. When alternatives are available, lamivudine should not be given as the sole treatment for hepatitis B because a high percentage of patients will develop resistant HBV in 1-3 years. Tenofovir alone or combined with 3TC can be given as part of a HAART regimen to treat co-infected patients.⁴⁵¹ The best regimen would be lamivudine + tenofovir and efavirenz.

Some patients with chronic active hepatitis will experience worsening of symptoms especially when taking ritonavir or nevirapine. This worsening may even occur when specific hepatitis B medication is included in the HAART regimen.^{456,457} HbeAg seroconversion has occurred after immune restoration

secondary to HAART.

Treating first the hepatitis C infection before starting HAART has been proposed.²⁰⁸ However, the response to such treatment is not good in patients with low CD4 counts and interferon alpha and ribavirin are often not available in resource-poor settings. In practice HAART alone is given, and this also improves the morbidity and mortality related with hepatitis C. For this reason physicians sometimes decide to start HAART earlier in patients who have chronic hepatitis C.

OI occurring after 6 months of HAART therapy: new OI, treatment failure, late IRIS?

OIs that occur after a patient has been on HAART for more than 6 months may suggest a failing HAART regimen or a late form of IRIS as has been described in TB and MAC.²⁰⁹ TB can occur at any level of CD4 count. Patients who are regularly seen in an HIV outpatient clinic, in countries with a high prevalence of TB, are frequently exposed to TB patients who have not been diagnosed yet. Such a patient may develop a new active TB, which does not imply disease progression. In the absence of a viral load it is difficult to diagnose treatment failure early. WHO criteria of failure include immunological and clinical criteria.²⁴ Recurrence of a previous OI is among the criteria of clinical failure. In the case of TB this could be a new infection. Immunological criteria, such as a return of the CD4⁺ lymphocyte count to pre-therapy baseline or below, or a more than 50% fall from peak levels, may suggest treatment failure. This is difficult to interpret in the presence of an acute infection, since intercurrent infections may cause CD4 count levels to decline.⁴⁵⁸ In the absence of viral load testing, the diagnosis of antiretroviral treatment failure can only be based on a careful assessment of the antiretroviral treatment history, on adherence to previous and the current regimens, on past and current clinical symptoms and signs and on other laboratory parameters such as haemoglobin levels, total lymphocyte and CD4 count if available.

If possible try to confirm treatment failure with a VL before switching.

<p>When an OI occurs in the first 6 months after HAART → Continue HAART and treat OI</p> <p>When an OI occurs after the first 6 months → Evaluate for treatment failure (don't forget poor adherence to HAART and to secondary prophylaxis!) and consider switch to a second line HAART Treat OI</p>
--

16.2.3 Drug interactions

There are important interactions between drugs to treat OI and HAART. Several websites can be consulted (Table 23). The drug interactions relevant for this topic of “OI and HAART” are mainly occurring with macrolides, azoles, antituberculous medication, protease inhibitors and NNRTIs. In general co-administration of interacting drugs should be avoided unless 1) strictly indicated, 2) after verification of the exact nature of the interactions and the suggested dosage adaptations and 3) under strict clinical and laboratory monitoring for efficacy and toxicity of both drugs.

An extensive list of all possible drug-drug interactions for drugs used to treat OIs can be found in the latest CDC guidelines for the treatment and prevention of OIs.¹²⁴

Table 23: Websites dealing with drug interactions

http://www.hiv-druginteractions.org/ http://www.medscape.com/px/hivscheduler http://clinicaloptions.com/hiv/ http://www.drugs.com http://hivinsite.ucsf.edu http://www.tthhivclinic.com
--

Rifampicin

The main problems occur with the simultaneous treatment of TB and HIV. Rifampicin is a strong inducer of the cytochrome P450 (especially the CYP 3A4) which lowers the concentration of PI with 75-80%. The effect is less on nevirapine and efavirenz, 37% and 22% reduction of the plasma concentration respectively. Besides drug interactions both treatments consist of a combination of 3-4 drugs, which have cumulative toxicities and which cause problems of adherence.

In their earlier guidelines the CDC stated that the use of rifampicin was contra-indicated in patients who were taking a PI or a NNRTI.

The latest CDC recommendations state that the following drugs can be used together with rifampicin.⁴⁵⁹

Single PI

Ritonavir + NRTI

Dual PI combinations

(Saquinavir 400 mg + ritonavir 400 mg twice daily + NRTI)

Lopinavir/ritonavir 3 capsules + 300 mg ritonavir twice daily + NRTI

The experience with these regimens is limited and there is an increased risk of hepatotoxicity.

Another combination recently studied (Saquinavir/rtv 1000/100 mg) twice daily in combination with rifampicin 600 mg daily caused severe hepatocellular toxicity in 40% of the patients. Roche Pharmaceuticals Ltd. has subsequently issued a warning letter that rifampicin should not be used in patients who are receiving saquinavir/ritonavir as part of their HAART.

NNRTI

Efavirenz 800 mg/day in patients > 50 kg[‡], although the dose may have to be decreased to 600 mg/day if 800 mg dose is not tolerated.⁴⁶⁰ In people with lower body weight the use of efavirenz at the normal 600 mg dose together with rifampicin does not appear to result in low efavirenz levels or HIV treatment failure.^{461,462} Efavirenz is the preferred drug to use in patients on TB treatment, certainly in men.

Nevirapine 200 mg twice daily: three small studies have proven the safety and the efficacy of nevirapine in combination with rifampicin.⁴⁶³⁻⁴⁶⁵ Larger cohort studies are needed to confirm these observations. Until then nevirapine should only be used with rifampicin if no other options exist and when clinical and laboratory monitoring of toxicity and treatment efficacy is possible.

Some questions are unsolved concerning the switch back from efavirenz to nevirapine after rifampicin is stopped.

Should we switch again? Efavirenz is more expensive, and should preferable not be given to women of child bearing age. Therefore some physicians prefer to go back to the fixed dose combination 3TC/d4T/nevirapine.

Is a lead-in dose necessary, or can we start right away with a full dose of nevirapine? As efavirenz is an inducer of the CYT P 450 it is probably safe to use immediately the 2x200 mg nevirapine dose.

The inducing effect of rifampicin is active up to 14 days after stopping the drugs.

The proposed switch is therefore:

Stop rifampicin

14 days later switch efavirenz back to nevirapine and use immediately the full dose.

On the other hand the drug company Boehringer is cautious and advises to use first a lead-in dose of nevirapine. A middle way could be to start a double dose of nevirapine in stead of efavirenz immediately after the stop of rifampicin.

[‡] A survey of the Liverpool TDM database examined 111 pts receiving EFV (600 or 800 mg) with RIF and they said that there was no significant difference between the efavirenz levels in both groups, but the levels were > 4 mg/L in patients with a weight < 60 kg. Recommended reading: <http://www.clinicaloptions.com/HIV/Treatment> Updates/Drug-Drug Interactions

Macrolides

Clarithromycin, used for the treatment of MAC, is an inhibitor and a substrate of CYP 3A4. Drug interactions occur with nevirapine, efavirenz and ritonavir containing regimens. The clinical significance is unknown, but most experts switch to azithromycin.

Erythromycin is a CYP 3A4 inhibitor. It increases by 100% the plasma levels of nevirapine. Close monitoring for nevirapine toxicity is recommended.

Fluconazole and itraconazole

Fluconazole is an inhibitor of the CYP 3A4. Fluconazole doubles nevirapine levels, leading to a significantly higher incidence of drug-related adverse events, including nevirapine-related liver toxicity.⁴⁶⁶

Experiments in rats have also shown a 7-fold increase of plasma levels of nevirapine when used with high dose fluconazole (20mg/kg).⁴⁶⁷

Fluconazole decreased glucuronidation of zidovudine, and 400 mg/day results in increased zidovudine AUC by 74%. Therefore toxicity due to AZT should be monitored.

Itraconazole is an inhibitor and a substrate of the CYP 3A4. Therefore interactions are possible with both NNRTI and PI. Drug level monitoring is recommended but not available in resource-poor settings.

Buffered didanosine formulations

Drugs that require an acid pH for absorption will have a decreased absorption when taken together with didanosine buffered formulation. Doxycycline and ciprofloxacin should be taken at least two hours separate from ddl, unless the enteric coated capsule is used.

16.2.4 Conclusion

HAART has significantly increased survival and reduced the occurrence of OI in PLHA. However, because of late presentation, especially in resource-poor settings, clinicians will still be confronted with the challenges of OI management. Atypical presentations of new OI, IRIS, and treatment failure or hypersensitivity reactions are complicating the picture. Some of these problems are more frequent in patients with low CD4 count, which represent the majority in resource-poor settings. While part of these patients can be "saved" and have a reasonable long term prognosis, an early mortality of 5-10% in the first year of treatment is observed in resource-poor settings despite intensive medical follow-up.

An individual approach to each complex patient problem is labour intensive and demands well trained experienced physicians. Unfortunately, this type of high skilled human resources is not always available.

Operational research and creative ideas are needed to organise task shifts to less experienced clinicians or nurses, in a safe way. One way is to screen out those patients that are likely to present severe problems and have them treated at the referral level. Another way is to install remote expert support systems (telephone or e-mail) to provide the necessary ongoing support after training.



17 NECESSARY DRUGS AND EQUIPMENT

17.1 Necessary drugs

Level A	Level B	Level C
ORAL DRUGS		
Actapulgite (+/- furazolidone)	Actapulgite (+/- furazolidone)	Actapulgite (+/- furazolidone)
Aluminium hydroxide	Acyclovir 200 mg/800 mg	Acyclovir 200 mg/800 mg
Amoxicillin	Albendazole	Albendazole
Antimalaria drugs	Aluminium hydroxide	Aluminium hydroxide
Aspirin	Amitriptyline	Amitriptyline
CaCO ₃	Amoxicillin	Amoxicillin
Chlorpheniramine	Amoxy-clavulanic acid	Amoxy-clavulanic acid
Codeine 30 mg	Antimalaria drugs	Antimalaria drugs
Cotrimoxazole	Aspirin	Aspirin
Loperamide	CaCO ₃	CaCO ₃
Mebendazole	Carbamazepine	Carbamazepine
Metoclopramide	Cimetidine	Chlorpheniramine
Metronidazole	Chlorpheniramine	Chlorpromazine
Morphine	(Clindamycin)	Cimetidine
NSAID	Clomipramine	Clindamycin
Oat bran	Codeine 30 mg	Codeine 30 mg
ORS	Cotrimoxazole	Cotrimoxazole
Paracetamol	Diazepam	Dapsone
Penicillin V	Doxycycline	Dexamethasone
Senna	Erythromycin	Diazepam
	Ethambutol	Doxycycline
	(Flu)cloxacillin	Ethambutol
	Fluconazole	(Etoposide)
	Griseofulvin	Etretinate
	Indometacin	Erythromycin
	INH	(Flu)cloxacillin
	Itraconazole	Fluconazole
	Ivermectin	(Folinic acid)
	(Ketoconazole)	Griseofulvin
	Loperamide	Indometacin
	Mebendazole	INH
	Metronidazole	Itraconazole
	Metoclopramide	Ivermectin
	Minocycline	Ketoconazole
	Morphine	Loperamide
	Nifedipine SL	Mebendazole
	NSAIDs	Metronidazole

Level A	Level B	Level C
ORAL DRUGS		
	Oat bran	Metoclopramide
	ORS	Minocycline
	Paracetamol	Morphine
	Paromomycin or diloxanide furoate	Nifedipine SL
	Penicillin V	Nitazoxanide
	Phenytoin	NSAID
	Praziquantel	Oat bran
	Prednisolone	ORS
	Pyrazinamide	Paracetamol
	Pyridoxine	Paromomycin or diloxanide furoate
	Quinolones	Penicillin V
	Rifampicin	Phenytoin
	Salbutamol 2.5 mg	Praziquantel
	Senna	Prednisolone
	Tetracycline 250 mg	Pyrazinamide
	Vit B complex	Pyridoxine
		(Pyrimethamine)
		Quinolones
		Rifampicin
		Salbutamol 2,5 mg
		Senna
		(Sulfadiazine
		Tetracycline 250 mg
		Tramadol
		Vit B complex

Level A	Level B	Level C
INJECTABLE DRUGS		
	Acyclovir	Acyclovir
	Aminophylline	Amikacin
	Amphotericin B	Aminophylline
	Atropin 0.5 mg/ml	Amphotericin B
	Benzathine penicillin	Atropin 0.5 mg/ml
	Benzyl penicillin	Benzathine penicillin
	Ceftriaxone	Benzyl penicillin
	Chloramphenicol	Bleomycin
	Epinephrine 1:1000	Ceftriaxone
	Fortified penicillin procaine	Chloramphenicol
	Morphine SC, IV	Clindamycin
	Parenteral fluid: normal saline with KCL Ringer Lactate	Doxorubicin
	Scopolamine	Epinephrine 1:1000
	Streptomycin	Fortified penicillin procaine
		(Ganciclovir)
		Glucantime
		Haloperidol
		Morphine SC, IV
		Parenteral fluid: Normal saline with KCL Ringer Lactate
		Scopolamine
		Streptomycin
		Vincristine

Level A	Level B	Level C
TOPICAL DRUGS		
Antiseptic mouthwashes	Antiseptic mouthwashes	Antiseptic mouthwashes
Baking soda	Baking soda	Baking soda
Benzyl benzoate	Benzyl benzoate	Benzyl benzoate
Chlorhexidine	Betamethasone 0.1%	Betamethasone 0.1%
Dry skin lotion	Chlorhexidine	Chlorhexidine
Gentian violet	Dry skin lotion	Dry skin lotion
Hydrocortisone 1% cream	Gentian violet	Gentian violet
Local anaesthetic gel	Hydrocortisone 1% cream	Hydrocortisone 1% cream
Nystatin/miconazole oral gel or gum patch	Imidazole cream	Imidazole cream
Polyvidone iodine	Ketoconazole cream	Ketoconazole cream
Urea 10% ointment	Local anaesthetic gel	Local anaesthetic gel
	Nystatin/miconazole oral gel or gum patch	Nystatin/miconazole oral gel or gum patch
	Polytar shampoo	Podophyllotoxin 0.5%
	Polyvidone iodine	Polytar shampoo
	Triamcinolone + 5% LCD	Polyvidone iodine
	Urea 10% ointment	Triamcinolone + 5% LCD
	Whitfield's ointment	Urea 10% ointment
	Zinc oxide ointment	Whitfield's
		Zinc oxide ointment

17.2 Laboratory and medical equipment

Level A	Level B	Level C
MEDICAL EQUIPMENT		
Naso-gastric feeding tube + syringes	Ultrasound	Ultrasound
	(Chest X-ray)	Chest X-ray
	Fundoscopy	Cryotherapy or electro-coagulation
	Microscope	Endoscopy (+ Biopsy)
	Naso-gastric feeding tube + syringes	Fundoscopy
	Nasopharyngeal suction	(Fluorescence microscope)
	Nebulisher (salbutamol)	Microscope
	Oxygen	Naso-gastric feeding tube + syringes
		Nasopharyngeal suction
		Nebuliser
		Oxygen

Level A	Level B	Level C
Laboratory equipment/tests		
	AFB stain	AFB stain
	Complete blood count (CBC)	Blood chemistry: liver and renal function, electrolytes
	CSF: cell type/count Gram Stain, AFB, India Ink	Blood culture
	ESR, HgB, WBC count	Complete blood count (CBC)
	Fresh examination of sputum	Cotton-blue or Wright's stain
	Gram stain	CSF culture
	KOH	CSF: cell type/count Gram Stain, AFB, India Ink + glucose and protein CRAg latex agglutination
	LN aspiration	ESR, complete blood count (CBC)
	Malaria smear	Formol-ether concentration method
	Stool microscopy: fresh and lugol wet mount	Fresh examination
	VDRL or RPR	Giemsa stain
		Gram stain
		(Histopathology)
		KOH
		LN aspiration
		LN biopsy
		Malaria smear
		Microscope
		Modified Kinyoun stain
		PCP staining
		Pleural fluid: WBC count, differential count, protein
		Stool culture
		Stool microscopy: fresh and lugol wet mount
		TB culture
		Toxoplasma serology
		Trichrome stain
		T.cruzi serology
		VDRL or RPR/TPHA



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