Introduction

The Government of Ukraine and the Ukrainian Ministry of Health (MoH) are actively pursuing the UNAIDS 90-90-90 targets, which were introduced in 2014. To reach these goals, in 2017 the Ukrainian MoH revised its National AIDS Program and set up 90-90-90 targets. To achieve these targets, the MoH developed ambitious strategies to improve HIV services including decentralization of HIV care and treatment sites, ART optimization, test and start strategy (rapid initiation of ART), index testing, improving linkage to care, updating patient pathways, optimizing provider-initiated HIV testing, and updating first-line and second-line ART therapy.

This Current Management of HIV: Clinical Handbook for HIV Service Providers in Ukraine has been developed to be used as a point-of-care reference tool and resource for clinicians to improve HIV services at the individual patient level. The objective of this handbook is to create a quick reference resource that streamlines the management of infants, children, adolescents, and adults living with HIV, including breastfeeding and pregnant women. This HIV resource is comprised of 9 chapters with 3 appendices highlighting the key areas of prevention, screening and diagnosis, education and adherence counseling, laboratory monitoring, ART optimization and readiness, management of common coinfections, opportunistic infections, vaccinations, immune reconstitution inflammatory syndrome, ARV drug-drug interactions, and ARV side effects.

The recommendations in this handbook come directly from sources included in Annex 4 of Order 1422 of the Methodology for Development and Implementation of Evidence-based Medical Care Standards, including: the World Health Organization, the US Centers for Disease Control and Prevention, and Up-to-Date.
Acknowledgments

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Chapter 1
HIV Prevention, Screening, and Diagnosis
Chapter 1: HIV Prevention, Screening and Diagnosis

1.1 HIV Prevention

- HIV prevention is a key component in successful HIV programs. In addition to treatment as prevention (TaSP), pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP), combination prevention programs involving biomedical, behavioral, and structural interventions are important.
- HIV positive persons who take ART daily as prescribed and achieve and maintain an undetectable viral load (ie viral load <200 copies/mL) have effectively no risk of sexually transmitting the virus to a HIV-negative partner.

1.2 Pre-Exposure Prophylaxis (PrEP)

Background:

- PrEP is the use of oral ARV drugs before HIV exposure by people who are not infected with HIV but who are at high risk of acquiring HIV. PrEP works to block the acquisition of HIV.
- WHO recommends PrEP for those people who are at “substantial risk” including serodiscordant couples where the positive partner is not virally suppressed, men who have sex with men (MSM), and transgender people in many settings, heterosexual men and women who have sexual partners with undiagnosed or untreated HIV infection, commercial sex workers, and injection drug users.

Before initiating PrEP: Laboratory Testing Prior to PrEP Initiation

- Document negative HIV test immediately before starting PrEP medication and every 3 months while PrEP is taken.
- If patient has symptoms consistent with acute HIV infection or has had a high risk HIV exposure in the prior 4 weeks, check a HIV RNA viral load if possible.
- Confirm that the patient has an ongoing high risk of acquiring HIV.
- Confirm that the estimated glomerular filtration rate is >60 ml/min/1.73m2 before starting PrEP and every 3 months during the first year on PrEP. If renal function remains normal, then annual testing can commence.
• Screening for STI’s are recommended every 3 months for high risk patients including screenings for syphilis, gonorrhea, and chlamydia.

• Check Hepatitis B serologies: since medications used for PrEP also are active against Hepatitis B, withdrawal of active therapy against HBV can lead to Hepatitis B clinical relapse. PrEP should still be provided to a person with HBV infection, however when considering discontinuing PrEP for a client with HBV infection a consultation with the relevant specialist is recommended.

• Pregnancy test for women of child bearing age. Pregnancy is not a contraindication to PrEP but pregnant women should receive counseling on the potential risks and benefits of ARV exposure during pregnancy.

Table 1: Monitoring Patients During Administration of Pre-Exposure Prophylaxis (PrEP) Against HIV

<table>
<thead>
<tr>
<th>1 month after starting PrEP</th>
<th>3 months after starting PrEP</th>
<th>Every 3 months thereafter</th>
<th>After discontinuing PrEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluate and support PrEP adherence</td>
<td>Evaluate and support PrEP medication adherence</td>
<td>Evaluate and support PrEP medication adherence</td>
<td>Perform HIV test</td>
</tr>
<tr>
<td>Assess risk behaviors and provide risk-reduction counseling and condoms</td>
<td>Assess risk behaviors and provide risk-reduction counseling and condoms</td>
<td>Assess risk behaviors and provide risk-reduction counseling and condoms</td>
<td>If the patient has chronic HBV infection, the decision to switch to an alternative agent or to monitor for HBV flare would be discussed with a provider experienced in the management of HBV</td>
</tr>
<tr>
<td>Evaluate for side effects</td>
<td>Perform HIV testing</td>
<td>Perform HIV testing</td>
<td></td>
</tr>
<tr>
<td>Check serum creatinine</td>
<td>Monitor creatinine in patients every 3 months during first year. If normal Cr after 1 year, then check Cr yearly.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for STIs in high-risk patients</td>
<td>Test for STIs in high-risk patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assess pregnancy status</td>
<td>Assess pregnancy status</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Treatment Regimen:**

- **Preferred Regimen:**
  - Tenofovir disoproxil fumarate-emtricitabine (TDF-FTC) one tab once daily.
  - In general, prescribe up to 90-day supply renewable after HIV testing confirms the patient remains uninfected after 90 days.
  - Provide counseling on PrEP medication adherence, risk reduction strategies and condom use.
  - Provide counseling on common side effects, such as nausea and headaches, and reassure patients these side effects usually resolve after continued use for a few weeks.
  - Patients should be educated on the signs and symptoms of acute HIV infection (fever, lymphadenopathy, maculopapular rashes, nausea, malaise) and should seek medical attention if such signs/symptoms occur.

**Risk of Drug Resistance:**

- Patients who have poor adherence to PrEP may become HIV-infected while on PrEP, however ARV drug resistance is very rare and standard 1st line therapy should be started as soon as possible after diagnosis of HIV.

1.3 Post-Exposure Prophylaxis (PEP)

**Background:**

- PEP should be offered to and initiated as soon as possible (but no later than 72 hours) in all individuals with a potential exposure for HIV infection.
- Exposures that may warrant PEP include but are not limited to:
  - Exposure to bodily fluids including blood, cerebral spinal fluid, amniotic fluid, peritoneal fluid, synovial fluid, bloodstained saliva, breast milk, genital secretions, pleural and pericardial fluid.
- Exposures that do not require PEP include:
  - When the exposed individual is already HIV positive.
  - When the source is confirmed to be HIV negative.
  - Exposure to bodily fluids that are not high risk such as tears, sweat, urine, and non-blood stained saliva.
  - When the exposure is on intact skin.
**Treatment Recommendations:**

**Post-Exposure Prophylaxis ARV Regimens for Adults and Adolescents**
- PEP should consist of three drugs:
  - DTG+TDF+3TC is the preferred regimen for PEP
  - If DGT is contraindicated or not available, RAL, ATV/r, or LPV/r can be used as alternative options.

**Post-Exposure Prophylaxis ARV Regimens for Children <10 Years**
- DTG+AZT+3TC is the preferred regimen for PEP for children aged 10 years and younger.
  - ABC can be considered as an alternative to AZT.
  - RAL, ATV/r, and LPV/r can be used as alternative third drug options if pediatric formulations of DTG are not available.

**Duration of PEP Therapy:**
- A 28-day course of ARVs is recommended for PEP along with adherence counseling.

**1.4 Prevention of Mother-to-Child Transmission (PMTCT)**

**Background:**
- PMTCT refers to interventions aimed at preventing transmission from an HIV infected mother to her infant during pregnancy, labor, delivery, and breastfeeding.
- HIV testing is recommended for all pregnant women and they should be tested twice during pregnancy: immediately upon enrolment into antenatal care clinic and again during the third trimester if the initial HIV test was negative.
- If a woman was not tested in the antenatal setting, they should be tested immediately with a rapid HIV test when they present in labor.
Preconception Counseling and Care for HIV-Infected Women of Childbearing Age

- Clinicians should discuss reproductive desires of all HIV-infected women of childbearing age during clinic visits throughout the course of their care.
- All HIV-infected women who are considering pregnancy should be on ART and have an undetectable HIV viral load prior to conception.
- Contraception can be used while on ART. Possible drug-drug interactions between hormonal contraceptives and ART can occur; thus patient’s clinical status should be monitored closely.

ART for Pregnant HIV-infected Women/ Women of Child-Bearing Age

- ART should be initiated as soon as possible in all pregnant and breast-feeding women with HIV regardless of CD4 count or WHO clinical stage.
- If a woman is on ART and she becomes pregnant, she can generally continue same ART regimen.
- A long-acting reversible contraceptive such as an injectable, implant, or intrauterine device (IUD), is recommended prior to hospital discharge or during first post-partum checkup if desired by the patient. If a long-acting reversible contraceptive is not desired, Depo-Provera is an option to be given as a contraceptive to avoid unplanned pregnancy in the interim.

1.4.1 First-Line ART for Pregnant Women\textsuperscript{3,16}

<table>
<thead>
<tr>
<th>Preferred first-line regimen</th>
<th>Alternative first-line regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF + 3TC (or FTC) + DTG\textsuperscript{a}</td>
<td>ABC + FTC (or 3TC) + DTG</td>
</tr>
<tr>
<td></td>
<td>TDF + FTC (or 3TC) + ATV/r</td>
</tr>
<tr>
<td></td>
<td>ABC + FTC (or 3TC) + ATV/r</td>
</tr>
<tr>
<td></td>
<td>TDF + FTC (or 3TC) + EFV\textsuperscript{b}</td>
</tr>
</tbody>
</table>

\textsuperscript{a} DTG can be prescribed for adult women and adolescent girls of childbearing age or potential who wish to become pregnant or who are not otherwise using or accessing consistent and effective contraception if they have been fully informed of the potential increase in the risk of neural tube defects (at conception and until the end of the first trimester). If women identify pregnancy after the first trimester, DTG should be initiated or continued for the duration of the pregnancy.

\textsuperscript{b} EFV-based ART should not be used in settings with national estimates of pretreatment resistance to EFV of 10% or higher.
1.4.2 Dolutegravir and Pregnancy\textsuperscript{3,4}

Interim Recommendations Regarding the Use of Dolutegravir in Pregnancy

- DTG use around the time of conception may be associated with a very small increased risk of neural tube defects (NTD) in the fetus compared to other ARVs (1 NTD in 1,000 pregnancies in the general population, with a potential increase to 3 NTDs in 1,000 pregnancies with DTG), however this potential increased risk has not been confirmed.

- The benefits of DTG (greater maternal viral suppression, fewer maternal deaths, fewer sexual transmissions of HIV, fewer mother-to-child transmissions of HIV), likely outweigh the risks (such as DTG-associated weight gain, or the potential increased risk of NTDs).

- DTG can be prescribed for adult women and adolescent girls of childbearing age or potential who wish to become pregnant or who are not otherwise using or accessing consistent and effective contraception if they have been fully informed of the potential increase in the risk of neural tube defects (at conception and until the end of the first trimester).

- Women who make an informed choice not to use DTG should be offered a PI/r-based regimen or EFV-based regimen instead (note: EFV-based ART should not be used in settings with national estimates of pretreatment resistance to EFV of 10% or higher).

- If women identify pregnancy after the first trimester, DTG is the preferred integrase inhibitor and should be initiated or continued for the duration of the pregnancy and beyond.

- Pregnant women who are taking DTG should not stop their ARV therapy and should speak with their health provider for additional guidance.

- For pregnant women who are receiving dolutegravir and who present to care during the first trimester, clinicians should provide counseling about the risks and benefits of continuing dolutegravir or switching to another ARV regimen. Providers should review the following considerations with their patients:
  - Depending on the current gestational age (if > 12 weeks), the additional potential risk of NTDs developing during the remaining time in first trimester may be small.
  - Changes in ART, even in the first trimester, are often associated with viral rebound that may increase the risk of perinatal HIV transmission.
When dolutegravir use is continued after delivery, clinicians should recommend the use of postpartum contraception if the woman is amenable to contraception.

Table 2: Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Neonatal ARV prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk of Perinatal HIV Transmission</td>
<td>• Mothers who received ART during pregnancy with sustained viral suppression near delivery</td>
<td>• AZT for 4 weeks</td>
</tr>
<tr>
<td>Higher Risk of Perinatal HIV Transmission</td>
<td>• Mothers who received neither antepartum or intrapartum ARV drugs</td>
<td>• 2-drug prophylaxis with 6 weeks AZT and 3 doses of NVP (given within 48 hours of birth, 48 hours after 1st dose, and 96 hours after 2nd dose) or • Empiric ARV with either AZT, 3TC, and NVP or AZT, 3TC, and RAL from birth to age 6 weeks</td>
</tr>
<tr>
<td>Presumed Newborn HIV Exposure</td>
<td>• Mothers with unknown HIV status who test HIV positive at delivery or postpartum or whose newborns have a positive HIV antibody test</td>
<td>• ARV management as above for higher risk of perinatal HIV transmission • Infant ARVs should be discontinued immediately if supplemental testing confirms that the mother does not have HIV</td>
</tr>
<tr>
<td>Newborn with HIV</td>
<td>• Positive newborn HIV virologic test/NAT</td>
<td>• 3-drug ARV regimen using treatment dosages (AZT/3TC/RAL or AZT/3TC/NVP)</td>
</tr>
</tbody>
</table>
Diagnosis of HIV Infection in Infants and Children\textsuperscript{1,3}

- Virologic assays such as HIV DNA proviral nucleic acid tests (NATs), should be used to diagnose HIV in infants and children <18 months with perinatal and postnatal HIV exposure; HIV antibody tests should not be used.

- If NAT result is positive, start ARVs immediately and collect second blood specimen to repeat NAT test for confirmation testing.

- Although a variety of causes may result in a false-positive NAT test result, most infants with false-positive test results have low levels of viremia; however, guidance is limited on how to interpret low levels of viremia detected in early infant diagnostic assays.

- An indeterminate range of viral copies should be used to improve the accuracy of all nucleic acid-based early infant diagnosis assays. An indeterminate range is a range of viral copy equivalents that would be too low to be accurately diagnosed as HIV infected.

- The indeterminate range suggested is currently estimated to be approximately equivalent to a cycle threshold of 33 amplification cycles on the Roche COBAS\textsuperscript{®} Ampliprep/COBAS\textsuperscript{®} TaqMan\textsuperscript{®} HIV-1 Qualitative Test v2.0 assay.

- Virologic assays are recommended for all infants with perinatal exposure at the following ages:
  - 14-21 days
  - 1-2 months
  - 4-6 months
  - For infants at higher risk of perinatal HIV transmission, additional virologic testing is recommended at birth and at 2 to 4 weeks after cessation of ARV prophylaxis.

- Definitive exclusion of HIV infection in non-breastfed infants is based on two or more negative virologic tests, with one obtained at age ≥1 month and one at age ≥4 months, or two negative HIV antibody tests from separate specimens obtained at age ≥18 months.

- Since children aged 18 to 24 months with perinatal HIV exposure occasionally have residual maternal HIV antibodies, definitive exclusion or confirmation of HIV infection in children in this age group who are HIV antibody-positive should be based on an HIV NAT.
1.5 HIV Screening and Testing Guidelines

- HIV Testing Services (HTS) is composed of the following successive steps:
  1. Providing Pre-test counseling/informing (individual, group, or partner)
  2. Administering a rapid HIV test (RT)
  3. Interpreting the test result
  4. Providing post-test counseling
  5. Linking to prevention, treatment and/or clinical services
  6. Eliciting (exposed) partners and children of HIV-positive people to offer HTS (i.e., index testing)
  7. Conducting quality assurance to ensure correct results

- Key principles for all HTS models are the Five C’s (consent, confidentiality, counseling, correct test results, and connection to care and treatment).

- HIV testing services (HTS) should be offered for all clients and in all services. See Table 3 below for frequency of testing recommended by population group.

Table 3: Recommended Frequency of HTS by Population Group and Expected HIV Prevalence

<table>
<thead>
<tr>
<th>Groups and categories</th>
<th>Recommended HTS frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expected HIV prevalence ≥ 5 %</td>
<td></td>
</tr>
<tr>
<td>Key populations at increased risk for HIV:</td>
<td>• At every initial visit and in 4 weeks if risk behavior took place during the last 3 months before applying for HTS;</td>
</tr>
<tr>
<td>✓ People who inject drugs</td>
<td>• Further on not less than once in 6 months in case of negative HIV test result</td>
</tr>
<tr>
<td>✓ Men who have sex with men</td>
<td></td>
</tr>
<tr>
<td>✓ Commercial sex workers</td>
<td></td>
</tr>
<tr>
<td>✓ Transgender people</td>
<td></td>
</tr>
<tr>
<td>✓ People in prisons and other closed settings or those released during the last 6 months</td>
<td></td>
</tr>
<tr>
<td>✓ Sex partners of key population representatives</td>
<td></td>
</tr>
<tr>
<td>People with risk behavior who do not belong to key populations</td>
<td></td>
</tr>
<tr>
<td>Sex partners of HIV-infected persons</td>
<td>• At every initial visit and every 3-6 months in case of negative HIV test result</td>
</tr>
<tr>
<td>Groups and categories</td>
<td>Recommended HTS frequency</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Expected HIV prevalence &lt; 5 %</td>
<td></td>
</tr>
<tr>
<td>Persons who receive PrEP</td>
<td>• At every initial visit and not less than once in three months in case of negative HIV test result</td>
</tr>
<tr>
<td>Homeless, migrants and internally displaced persons</td>
<td>• At every initial visit and not less than once in 12 months in case of negative HIV test result</td>
</tr>
<tr>
<td>Persons expecting PEP prescription</td>
<td>• When applying for medical assistance and further on in 6 weeks, 3 and 6 months after risk exposure</td>
</tr>
<tr>
<td>Persons who suffered from sexual violence</td>
<td></td>
</tr>
<tr>
<td>Health workers and other persons who had risk contact with blood and/or other potentially hazardous human biological fluids, instruments, equipment and objects contaminated with biological fluids</td>
<td></td>
</tr>
<tr>
<td>Donors of blood and its components, other biological fluids, cells, tissues and organs</td>
<td>• According to regulatory and legal requirements</td>
</tr>
<tr>
<td>Children born to HIV-infected mothers</td>
<td>• According to regulatory and legal requirements</td>
</tr>
<tr>
<td>Family members of an HIV-infected person except sex partners</td>
<td>• At every visit when there is no confirmed information that a person is in care for HIV infection</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>• According to regulatory and legal requirements</td>
</tr>
<tr>
<td>Sex partners of pregnant women</td>
<td>• Once during pregnancy of a woman</td>
</tr>
<tr>
<td>Women, couples and partners planning pregnancy</td>
<td>• Once when applying and not less than once in 12 months with negative result of preliminary HIV testing</td>
</tr>
<tr>
<td>All patients before prescribing immunosuppressive therapy</td>
<td>• Once at initial application</td>
</tr>
<tr>
<td>Persons not producing the expected treatment results for a long time, or when it is impossible to make a diagnosis</td>
<td>• Once at initial application</td>
</tr>
</tbody>
</table>
Pre-Test Counseling/Informing $^{1,5}$

- Pre-test information session for people receiving HIV testing should include:
  - Reasons the person may benefit from testing.
  - Test results are confidential and only shared with providers.
  - Client has the right to refuse to be tested and refusal will not affect access to other services; informed consent is needed for testing.
  - Services available in the case of a positive (or negative) HIV diagnosis; including the availability and importance of ART for HIV diagnosed individuals.
  - Brief description of HIV prevention options.
  - If HIV positive, encourage disclosure to the person’s sexual and needle-sharing partners; as well as the importance of testing for those individuals and biological children.
  - Potential risk to the client, especially for those whose sexual or other behavior is stigmatized.

- HTS provider should receive an informed consent under conditions of confidentiality.

- Identify belonging of a person to population or group with expected HIV incidence level “$<5\%$” or “$\geq 5\%$” through self-reporting by a person (see Table 3 for details).

- During pre-test informing it is advisable to conduct TB screening questioning.
HIV Serologic Testing

- Conduct HIV testing by a rapid test (RT) kit following national algorithm.
- Test results are assessed by two health workers independently:
  - For invalid HIV results, retest using RT of the same manufacturer.
- HIV testing involves conducting laboratory tests in several stages:
  - **Screening stage** – (detection of serological markers of HIV)
  - **Verification (confirmatory) stage** – to confirm the presence of serological markers of HIV
  - **Identification stage** – (examination when enrolling into medical care or before ART appointment to an HIV+ person)
- At each stage, both instrumental research methods and RT can be used.
- At the screening stage, medical devices with the highest rates are used, at the confirmatory stage – with the highest rates of specificity.
- Upon receipt of a positive result of the screening study, confirmatory studies are done with the use of another manufacturer’s RT (verification stage).
- According to WHO recommendations, for key populations with HIV prevalence >5%, one medical device is used at the confirmatory stage; for groups with HIV prevalence rate of <5%, two medical devices meant for the detection of antibodies to HIV 1/2. The prevalence rate for every group should be specified at the national HIV institutions.
- Upon receipt of a positive result of the first confirmatory test, a decision on further action depends on the code or cause of the person’s examination:
  1) If the person being examined belongs to the key groups with HIV prevalence >5%, the sample is considered as containing serological markers of HIV.
  2) If the person being examined belongs the population groups with HIV prevalence <5%, the sample is examined using another medical device for the detection of antibodies to HIV (second confirmatory test).
- Upon receipt of a positive result of the second confirmatory test, the sample is considered as containing serological markers of HIV:
  - When the negative result of the second confirmatory test is received, the result of the study is considered uncertain. The person is recommended to undergo a re-examination in 14 days.
At the identification stage, all persons, including children aged 18 months and older, who have a confirmation certificate of a positive result in detecting HIV serologic markers are re-examined in a HCF before being registered or before ART appointment.

- The examination is conducted using two different medical devices to detect antibodies to HIV:
  - **For instrumental methods** – medical devices used in the laboratory for confirmatory studies
  - **For RT** – the use of the same names of medical devices used in the screening and confirmation phases is allowed

---

**Figure 1: Testing Strategy for HIV Diagnosis in Low-Prevalence Settings**
Post-Test Counseling

• Post-testing counseling is conducted depending on the test result and provides for linkage of the person to other services.
• Test results and HIV status should be communicated to the person who received HTS with observance of confidentiality as to test results, personal data and other information received during HTS.
• Post-test information and counseling for people who test HIV negative should include the following:
  ■ Explanation of the test result.
  ■ Conduct post-test counseling and issue certificate according to effective legislation.
  ■ Information on methods to prevent HIV acquisition and provision of condoms.
  ■ Emphasis on the importance of knowing the status of sexual partners (and needle-sharing partners if applicable).
  ■ Advise people who test negative, but report recent risky behavior, to return in 4 weeks for repeat HIV testing; people at high risk could return every 6-12 months.
  ■ Assess for ongoing substantial risk and need for PrEP (see Section 1.2).
• Post-test information and counseling for people who test HIV positive should include the following:
  ■ Same-day referral for enrollment in HIV care, preferably by physically escorting the client to the ART site.
  ■ Arranging a specific date and time for active referral and follow-up of clients who are unable to enroll in HIV care on the day of diagnosis.
  ■ Clear information on ART, the importance of early ART initiation, and its benefits for maintaining health and reducing the risk of HIV transmission, as well as where and how to access ART.
  ■ Information on how to prevent transmission of HIV, including information on the reduced transmission risks when virally suppressed on ART.
  ■ Discussion of the risks and benefits of disclosure, particularly among couples and to partners, and couples counseling should be offered to support mutual disclosure.
  ■ Encouragement and offer of HIV testing for sexual partners, children and other family members, which can be done individually, through couples testing, index case testing, family testing or partner notification.
  ■ Assessment of the risk of suicide, depression and other mental health consequences of an HIV-positive diagnosis and referral to relevant services.
Linkage to Care/Enrollment of Persons with Positive HIV Test into Care

- Proactive approaches in linkage of a person with HIV-positive test result to care are critical components of HTS. These approaches are important for proving the best treatment results, reduction of HIV transmission, morbidity and mortality associated with HIV.

- Active referral approach should be undertaken for newly diagnosed HIV-infected persons. Every possible effort should be taken to enroll HIV-infected patients on the same day as HIV diagnosis was confirmed to institute rapid ART initiation. When same-day enrollment into HIV care is not possible, HIV-infected persons should be provided with a specified date and time for HIV-associated services at a healthcare facility and be enrolled within 14 days after positive HIV test result confirmation.

Index Testing/Engaging Partners of HIV-Positive People to HTS

- The overarching goal of index testing (IT) is to connect the partners and children of recently diagnosed HIV-positive individuals to HIV testing and care. All persons age 15 or older (or mature minors) who test positive for HIV should be asked about their sex partners and needle sharing partners and be screened for IT eligibility.

- The goal of IT is to ensure that all partners of newly diagnosed persons are tested for HIV.

- Notification of partners or disclosure of HIV status to a partner is a voluntary process.

- A member of the patient’s HIV care team (infectionist, nurse, psychologist, social worker, etc) should request information about current and former intimate sexual partners, and on partners of shared drug injections for their engagement in HTS if agreed upon by the HIV-infected person.

- It is inadmissible to notify partners and disclose HIV status of an HIV-infected person to his/her partner without obtaining informed consent on notifying partners from the HIV-infected person.
There are two approaches to Index Testing:

1. **Passive Approach** – a patient reveals their status to their partner themselves.
2. **Active Approach** – notifying a partner with the support of the HIV testing provider.

Below is a table highlighting partner notification by HTS provider approach and a passive approach.

<table>
<thead>
<tr>
<th>Active approach: partner notification assisted by HTS provider</th>
<th>Passive approach to partner notification</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTS provider offers counseling support and actively assists HIV-positive person in disclosing HIV status to a partner and in engaging a partner in HTS by any communication means.</td>
<td>HTS provider counsels an HIV-infected person on HIV and encourages him/her to disclose HIV status to partners for their further engagement in HTS.</td>
</tr>
<tr>
<td>HTS provider personally or using communication means notifies partner of HIV-positive person on a risk of possible HIV infection and offers him/her HTS without disclosing personal information about HIV-infected person.</td>
<td>HTS provider gives an HIV-infected person a card or other information about facilities providing HTS (HCF, NGOs) and encourages him/her to disclose HIV status to partners for their further engagement in HTS using the provided addresses.</td>
</tr>
</tbody>
</table>
Chapter 2
HIV Education and Adherence Counseling
Chapter 2: HIV Education and Adherence Counseling

2.1. Preparing People Living with HIV for ART

- Before starting ART, clinicians should have detailed discussion with patients about the readiness and willingness of the patient to initiate ART.

- Advise patients on the reasons why it is important to start ART ideally on the same day of diagnosis or within 1 week of diagnosis:
  - ART is now recommended for all people living with HIV (PLHIV) regardless of CD4 count, including people who do not feel sick
  - The sooner you start treatment the healthier you will remain and the less likely you are to develop infections, wasting, and other illnesses such as cancer and heart disease
  - In the past, we delayed ART initiation because of cost, toxicity of the medicines, and a lack of information about when we should start ART. Today we know PLHIV do better by starting ART immediately, including living longer, and we have newer, better medicines that have few side effects and are simple to take
  - Treatment also makes you less likely to pass HIV to your sexual partner, drug-sharing partners, unborn or breastfeeding baby
  - Treatment can be started right away, even today, for most people

- If the patient has mental health or substance abuse issues, the patient should be referred to appropriate support services.

- People starting ART should be advised that if they develop side effects from the medications, these are generally temporary, and if they persist, substitutions can be made to the ART regimen.

- Drug-drug interactions can occur with ART; therefore, it is important to inform the patient to discuss any other medications he/she may be taking, including over-the-counter medications, herbal and natural supplements.

- Clinicians should provide counseling and advice on safe sex practices and avoidance of other high-risk activities such as sharing injecting needles and equipment.

- Within the first three months of ART initiation, it is important to instruct the patient that opportunistic infections, immune reconstitution syndrome, and adverse drug reactions can occur, especially when patients have advanced HIV, existing coinfections, and severe malnutrition.

- Poor adherence within the first three months of ART initiation is associated with early treatment failure and development of drug resistance.
Table 4: Pre-ART Assessment

<table>
<thead>
<tr>
<th>Does the patient want to start ART?</th>
</tr>
</thead>
<tbody>
<tr>
<td>• After discussing:</td>
</tr>
<tr>
<td>■ Benefits of ART and positive impact of the treatment on the life duration and quality, as well as ART benefits for HIV transmission prevention</td>
</tr>
<tr>
<td>■ Safety, tolerability and convenience of modern ART regimens</td>
</tr>
<tr>
<td>■ Assess readiness for ART including assessment of substance abuse or mental illness</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Are there any medical contraindications to immediate ART?</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Symptoms of meningitis: further evaluation/investigations before ART initiation</td>
</tr>
<tr>
<td>• Symptoms of TB using the TB screening tool: further evaluation/investigations before ART initiation (if symptom screen negative than ART can be started even before chest x-ray or other TB investigation results)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Are there any contraindications to the preferred first-line regimen (DTG+TDF+3TC (or FTC))?</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Early pregnancy or intending to become pregnant (may require a pregnancy test): can still prescribe DTG based on patient preference; does not prevent same-day ART initiation, can start with EFV- and ATV/r-based regimen if woman chooses not to use DTG</td>
</tr>
<tr>
<td>• Known or suspected renal failure</td>
</tr>
<tr>
<td>■ Known renal failure: initiate ABC instead of TDF</td>
</tr>
<tr>
<td>■ Suspected renal failure: wait for Cr results before determining regimen</td>
</tr>
<tr>
<td>■ All others: start TDF-containing regimen; modify as needed once Cr results are available</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Opportunistic Infection Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>If there are indications prescribe opportunistic infections prophylaxis according to national standards:</td>
</tr>
<tr>
<td>1. Co-trimoxazole 960 mg/day is prescribed:</td>
</tr>
<tr>
<td>■ to all patients with advanced HIV infection (WHO III or IV clinical stage, or with CD4 &lt; 350 cells/ml);</td>
</tr>
<tr>
<td>■ to all patients with active TB regardless CD4 count.</td>
</tr>
<tr>
<td>Prophylaxis may be discontinued for clinically stable patients with the signs of immune system recovery and/or viral suppression associated with ART</td>
</tr>
<tr>
<td>2. Isoniazide 300 mg/day, for 6 months or other combination according to national standards</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Order baseline investigations but do not delay ART for the results</th>
</tr>
</thead>
</table>
2.2 Key Messages for Adherence

- Adherence to ART is the primary determinant of viral suppression and the risk of transmission, disease progression and death.
- Individual factors affecting adherence may include forgetting doses, being away from home, changes in daily routine, depression or other illness and substance or alcohol use.
- Adherence to ART may also be challenging in the absence of supportive environments for people living with HIV and in the presence of HIV-related stigma and discrimination.
- Medication-related factors may include adverse events and the complexity of dosing regimens, such as those for children.
- Effective monitoring of adherence can be accomplished through the following approaches:
  - Viral load monitoring
  - Reviewing pharmacy refill records
  - Pill counts
  - Self-reporting
- The following interventions can improve adherence and viral suppression:
  - Peer counselors
  - Mobile phone text messages
  - Reminder devices
  - Fixed-dose combinations and once-daily regimens
  - Behavioral skills training and medication adherence training
  - Cognitive-behavioral therapy
2.3 Adherence Counseling Protocol

### HIV education

- Ask the patient what they know about HIV
- Ask the patient what they know about treatment for HIV
- Correct/clarify as needed, ensuring you cover:
  - Modes of transmission and importance of testing partners/children
  - HIV effect on the immune system and health
  - HIV viral load and its relationship to health and to HIV transmission
  - Goals of ART
  - Relationship between adherence and viral suppression, treatment failure, and drug resistance
  - Consequences of drug resistance
- Ensure the patient understands by asking them to explain it back to you

### Barriers to adherence

- Ask the patient what they think will be most difficult about taking ART every day
- Discuss common reasons patients have trouble with excellent adherence and identify which may be most relevant for them, including:

<table>
<thead>
<tr>
<th>Patient Factors</th>
<th>Provider/System Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>■ Stigma and non-disclosure (having to hide their ARV pill-taking)</td>
<td>■ Side effects (many patients have side effects when they first start their ART, including nausea, headaches, and difficulty sleeping. These side effects almost always resolve with continued use)</td>
</tr>
<tr>
<td>■ Lack of support systems</td>
<td>■ Pill burden</td>
</tr>
<tr>
<td>■ Alcohol or drug use</td>
<td>■ Poor patient-provider relationship</td>
</tr>
<tr>
<td>■ Depression or other psychiatric illness</td>
<td>■ Inadequate HIV education</td>
</tr>
<tr>
<td>■ Cognitive disorders</td>
<td>■ Cost of care (direct and indirect)</td>
</tr>
<tr>
<td>■ Change in daily routine</td>
<td>■ ARV supply-chain limitations (stock-outs, or low stock levels resulting in small refill quantities)</td>
</tr>
<tr>
<td>■ Chaotic lifestyle; no consistent daily routine</td>
<td></td>
</tr>
<tr>
<td>■ Forgetting to take pills</td>
<td></td>
</tr>
<tr>
<td>■ Feeling better so does not think the ART is needed any more</td>
<td></td>
</tr>
<tr>
<td>■ Feeling too sick to take ART</td>
<td></td>
</tr>
<tr>
<td>■ Age (adolescents - impulsive, more susceptible to social pressure; children – caregiver dependent)</td>
<td></td>
</tr>
</tbody>
</table>
**Individualized adherence plan**

- Ask the patient what they can do to ensure excellent adherence
- Ensure the adherence plan incorporates details of the patient’s specific ART regimen:
  - Number of pills, frequency, food requirements/restrictions
  - Common side effects
  - Important drug interactions
- Work with the patient to make an individualized adherence plan, which may include:
  - Disclosing their HIV status to a close friend or family member who can help support their treatment; bringing their treatment buddy to clinic with them or to a session with a social worker to learn more about HIV
  - Disclosing their HIV status to household members so they do not have to hide pill-taking
  - Combining pill taking with an activity in their daily routine
  - Keeping the ARVs in a place that they are likely to see every day
  - Setting a daily alarm on their phone/watch/clock
  - Connecting with an NGO/social worker for additional counseling/education/support
  - Getting treatment for alcohol or drug use
  - Getting treatment for depression or other psychiatric illness
- Discuss what to do if:
  - Develops side effects
    - Discuss common and serious adverse events for their specific regimen
    - Encourage patient to return to clinic for any side effects rather than stopping ART
  - Forgets to take a dose: take it late rather than skipping the dose completely
  - Travels without their ART: go to the nearest AIDS center or call clinic for guidance
- Ask the patient to summarize their individualized adherence plan

**Ongoing support at subsequent visits**

- Review the patient’s HIV knowledge
- Review the patient’s motivation to take ART
- Elicit any concerns the patient may have about their ART, side effects, visit schedule, or health
- Review the ART dosing schedule and ask about any missed pills
- Explore barriers to adherence that were previously identified or new ones that have developed
- Explore any recent or expected changes in their life or daily routine
- Discuss their individualized adherence plan and if any changes are required
# Chapter 3: Laboratory Monitoring

## 3.1 Laboratory Tests for Initial Assessment and Monitoring

<table>
<thead>
<tr>
<th>Phase of HIV management</th>
<th>Recommended</th>
<th>Desirable (if feasible)</th>
</tr>
</thead>
</table>
| **HIV diagnosis**       | • HIV testing (serology for adults and children 18 months or older; EID for children younger than 18 months)  
                            • CD4 cell count  
                            • TB symptom screening | • HBV (HBsAg) serology\(^a\)  
                            • HCV serology  
                            • Cryptococcus antigen if CD4 cell count ≤100 cells/mm\(^3\)\(^b\)  
                            • Screening for STIs  
                            • Pregnancy test to assess if ART initiation should be prioritized to prevent HIV transmission to the child  
                            • Assessment for major noncommunicable chronic diseases and comorbidities\(^c\) |
| **ART initiation**      |             | • Haemoglobin test for starting AZT\(^d\)  
                            • Pregnancy test  
                            • Blood pressure measurement  
                            • Serum creatinine and estimated glomerular filtration rate (eGFR) for starting TDF\(^e\)  
                            • Baseline CD4 cell count |
| **Receiving ART**       | • HIV viral load (at 6 months and 12 months after initiating ART and every 12 months thereafter)  
                            • CD4 cell count every 6 months until patients are stable on ART | • Serum creatinine and eGFR for TDF\(^c\)  
                            • Pregnancy test, especially for women of childbearing age not receiving family planning |
| **Suspected treatment failure** | • Serum creatinine and eGFR for TDF\(^c\)  
                            • Pregnancy test, especially for women of childbearing age not receiving family planning | • HBV (HBsAg) serology\(^a\)\(^f\) (before switching ART regimen if this testing was not done or if the result was negative at baseline and the patient was not vaccinated thereafter) |

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\(^a\) If feasible, HBsAg testing should be performed at baseline to identify people with HIV and HBV coinfection and who should therefore initiate TDF-containing ART.

\(^b\) Can be considered in settings with a high prevalence of cryptococcal antigenemia (>3%).

\(^c\) Consider assessing for the presence of chronic conditions that can influence ART management, such as hypertension and other cardiovascular diseases, diabetes and TB according to the WHO Package of Essential NCD interventions (PEN), mental health Gap Action Program (mhGAP) or national standard protocols. Monitoring may include a range of tests, including serum creatinine and estimated glomerular filtration rate (eGFR), serum phosphate and urine dipsticks for proteinuria and glycosuria.

\(^d\) Among children and adults with a high risk of adverse events associated with AZT (low CD4 or low BMI).

\(^e\) Among people with a high risk of adverse events associated with TDF: underlying renal disease, older age group, low body mass index (BMI), diabetes, hypertension and concomitant use of a boosted PI or potential nephrotoxic drugs.

\(^f\) For HIV/HBV coinfected individuals who are already using TDF-containing regimens and develop ART failure, this NRTI (or TAF) should be maintained regardless of the selected second-line regimen.
Chapter 4
Antiretroviral Therapy (ART)
Chapter 4: Antiretroviral Therapy (ART)

4.1 When to Start ART\textsuperscript{1,6}

- ART is recommended for all adults, pregnant women, adolescents, children and infants regardless of WHO clinical stage or CD4 count.
- Untreated HIV infection is be associated with the development of several non-AIDS-defining conditions, including cardiovascular, kidney and liver disease, several types of cancer and neurocognitive disorders; initiating ART earlier reduces such events and improves survival.
- ART substantially reduces sexual transmission in heterosexual and homosexual discordant couples.
- Rapid ART initiation (including starting ART on the same day as HIV diagnosis), can improve patient outcomes, including uptake of ART, viral suppression, retention in care and mortality.
- Rapid ART initiation should be offered to all people living with HIV who do not have symptoms of TB or cryptococcal meningitis. Rapid initiation is defined as starting ART within 7 days of HIV diagnosis.
- ART initiation should be offered on the same day to people who are ready to start.
- Laboratory tests should be collected during the first clinical visit, but results of the laboratory tests are not needed to initiate ART. These labs should be followed up and if there are any abnormalities (i.e. chronic kidney injury), ART regimen can be modified.
- Screening for symptoms of TB should be performed during the first clinical visit and should include completing the TB screening questionnaire and examination. ART can be started after TB-screening measures are completed. If patient does not have TB symptoms, a CXR is not needed to start ART but should be offered during the month after ART initiation.
- ART initiation may be delayed for patients with newly diagnosed TB or cryptococcal meningitis.
  - Patients with newly diagnosed TB: ART initiation is dependent on CD4 count:
    - With CD4 \leq 50 cells/mcl, start ART within the first two weeks after TB treatment initiation
    - With CD4 > 50 cells/mcl, ART should be started within 8 weeks after TB treatment initiation
    - With TB meningitis, ART should be delayed for up to 8 weeks after TB treatment initiation, regardless of CD4 cell count
Patients with newly diagnosed cryptococcal meningitis: ART should be delayed for 4-6 weeks from the time treatment with antifungal therapy was initiated.

### 4.2 First-Line ART for Adolescents and Adults\(^3,16\)

**Table 5: Preferred and Alternative First-Line Regimens for Adults and Adolescents**

<table>
<thead>
<tr>
<th>Preferred first-line regimen</th>
<th>Alternative first-line regimen(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF + 3TC(^b) + DTG(^a)</td>
<td>ABC + 3TC(^b) + DTG(^a)</td>
</tr>
<tr>
<td></td>
<td>TDF + 3TC(^b) + ATV/r</td>
</tr>
<tr>
<td></td>
<td>ABC + 3TC(^b) + ATV/r</td>
</tr>
<tr>
<td></td>
<td>TDF + 3TC(^b) + EFV(^d)</td>
</tr>
</tbody>
</table>

\(^a\) DTG can be prescribed for adult women and adolescent girls of childbearing age or potential who wish to become pregnant or who are not otherwise using or accessing consistent and effective contraception if they have been fully informed of the potential increase in the risk of neural tube defects (at conception and until the end of the first trimester). If women identify pregnancy after the first trimester, DTG should be initiated or continued for the duration of the pregnancy (see Section 1.4 PMTCT).

\(^b\) FTC can replace 3TC.

\(^c\) Alternative ARVs for patients with contraindications or treatment-limiting adverse events to any component of the recommended first-line regimen.

\(^d\) EFV-based ART should not be used in settings with national estimates of pretreatment resistance to EFV of 10% or higher.

**Table 6: Selection of Alternative First-Line ARVs**

<table>
<thead>
<tr>
<th>Recommended first-line ARV</th>
<th>Reason for not using recommended ARV</th>
<th>Preferred alternative ARV</th>
</tr>
</thead>
</table>
| DTG                        | • Woman or adolescent girl of childbearing potential who chooses not to use DTG\(^a\)  
                           | • Develops significant insomnia that persists with continued use and does not respond to conventional management | EFV or ATV/r (if known psychiatric illness then use ATV/r instead of EFV) |
| TDF                        | • Pre-existing renal disease (with eGFR < 60 ml/min)\(^b\)  
                           | • Develops renal impairment while on TDF (with eGFR < 60 ml/min)\(^b\)  
                           | • High risk for osteoporotic fractures | ABC (if HLA-B*57:01 positive or at high risk for cardiovascular disease then use DTG+3TC dual therapy instead of ABC\(^c\)) |
DTG can be prescribed for adult women and adolescent girls of childbearing age or potential who wish to become pregnant or who are not otherwise using or accessing consistent and effective contraception if they have been fully informed of the potential increase in the risk of neural tube defects (at conception and until the end of the first trimester). If women identify pregnancy after the first trimester, DTG should be initiated or continued for the duration of the pregnancy (see Section 1.4 PMTCT).

TDF + 3TC (or FTC) should be used despite renal impairment (with renal dose adjustments) for patients who have HIV/HBV co-infection and do not have other options for treatment of HBV.

DTG + 3TC dual therapy as an alternative when TDF, TAF or ABC cannot be used is a recommendation from United States DHHS guidelines, rather than using AZT.

### Table 7: DTG Prescribing Information

#### Recommended dosing of DTG

- DTG 50 mg once daily, preferably as a morning dose
- For patients taking rifampicin: increase dose to DTG 50 mg twice daily until 1-2 weeks after completion of TB treatment, then reduce to DTG 50 mg once daily again
- For patients with suspected or confirmed INSTI resistance (e.g. patients with prior history of failing a RAL-based regimen): use DTG 50 mg twice daily
- DTG can be taken with or without food

#### Common side effects of DTG

- The most common side effects of DTG are headache, nausea and diarrhea. These side effects are usually mild and usually resolve after continued use for 1-2 weeks. It is critical to inform patients about these potential side effects and their temporary nature, and encourage them to continue their ART and consult a healthcare worker if concerned
- Some patients on DTG are more likely to develop insomnia. This may be reduced by taking DTG as a morning dose, or by taking DTG with a low-fat meal or on an empty stomach
- All adverse events should be reported through the national pharmacovigilance mechanism

#### Pregnancy safety of DTG

- DTG use around the time of conception may be associated with a very small increased risk of neural tube defects (NTD) in the fetus compared to other ARVs (1 NTD in 1,000 pregnancies in the general population, with a potential increase to 3 NTDs in 1,000 pregnancies with DTG), however this potential increased risk has not been confirmed
- The benefits of DTG (greater maternal viral suppression, fewer maternal deaths, fewer sexual transmissions of HIV, fewer mother-to-child transmissions of HIV), likely outweigh the risks (such as DTG-associated weight gain, or the potential increased risk of NTDs)
- DTG is safe during pregnancy if initiated after 8 weeks gestational age (although women need to be counseled on the risk of becoming pregnant again while on DTG)
Important Drug Interactions with DTG

- All patients on DTG should be educated on important drug interactions, particularly with TB treatment and with over-the-counter antacids and mineral supplements.
- All patients should be asked if they are taking any medications or supplements prescribed by other physicians or purchased over-the-counter.
- Always check for potential drug interactions using the package insert or web-based interaction tool (e.g. www.hiv-druginteractions.org).
- See Appendix B for a list of common and important ARV drug interactions.

Contraindications for use of DTG

- DTG is contraindicated for any patient with a history to hypersensitivity reaction to DTG.
- DTG is not currently recommended for patients with end-stage renal disease or end-stage liver disease because it has not been evaluated in these populations.

### Common drug-drug interactions with Dolutegravir

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interaction</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampicin</td>
<td>Decreases DTG levels</td>
<td>Increase DTG to 50 mg twice daily</td>
</tr>
<tr>
<td>Carbamazepine, Phenytoin, Phenobarbital</td>
<td>Decreases DTG levels</td>
<td>Use an alternative anticonvulsant; if must be used together then increase DTG to 50 mg twice daily</td>
</tr>
<tr>
<td>Mineral supplements and antacids containing cations (e.g. calcium, iron, zinc, magnesium, aluminum), including prenatal vitamins</td>
<td>Decreases DTG absorption</td>
<td>Administer DTG at least 2 hours before or 6 hours after taking any of these supplements; if DTG is taken with a meal then dose separation is not required for calcium, iron, or prenatal vitamins</td>
</tr>
<tr>
<td>Metformin</td>
<td>Increases metformin levels; no effect on DTG metabolism</td>
<td>Decrease dosage of metformin by approximately 50% and monitor glycemic control; limit total daily metformin dose to 1,000 mg</td>
</tr>
<tr>
<td>Efavirenz, Etravirine, Nevirapine</td>
<td>Decreases DTG levels</td>
<td>Avoid combination; if must be used together then increase DTG to 50 mg twice daily</td>
</tr>
<tr>
<td>Other anti-TB drugs (including Rifabutin, Bedaquiline, Delamanid)</td>
<td>No interactions</td>
<td></td>
</tr>
<tr>
<td>Methadone, Buprenorphine</td>
<td>No interactions</td>
<td></td>
</tr>
</tbody>
</table>

Chapter 4
Table 8: ATV/r Prescribing Information

<table>
<thead>
<tr>
<th>Recommended dosing of ATV/r</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ATV 300 mg plus RTV 100 mg once daily</td>
</tr>
<tr>
<td>• ATV/r should be taken with food</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Common side effects of ATV/r</th>
</tr>
</thead>
<tbody>
<tr>
<td>• The most common side effects of ATV/r are nausea, headache and fever. These side effects are usually mild and usually resolve after continued use for 1-2 weeks. It is critical to inform patients about these potential side effects and their temporary nature, and encourage them to continue their ART and consult a healthcare worker if concerned</td>
</tr>
<tr>
<td>• Some patients on ATV/r are more likely to develop diarrhea. Symptoms can be improved using the following stepwise approach, while ruling out infectious or other causes:</td>
</tr>
<tr>
<td>■ Take ATV/r with a meal</td>
</tr>
<tr>
<td>■ Add bulk to the stool with oral fiber supplements (e.g. oat bran, psyllium)</td>
</tr>
<tr>
<td>■ Loperamide 1-2 tabs taken 1 hour before ATV/r</td>
</tr>
<tr>
<td>■ Calcium carbonate 500 mg twice daily</td>
</tr>
<tr>
<td>■ If diarrhea does not improve with conservative management and infectious causes have been treated or ruled out then consider switching to an ART regimen that does not contain RTV</td>
</tr>
<tr>
<td>• Increased serum unconjugated bilirubin is common among patients taking ATV/r, and up to 10% of patients may develop clinical jaundice. This is not associated with liver injury and does not require ART regimen modification unless the cosmetic concerns are affecting adherence. The increased bilirubin is reversible upon discontinuation of ATV/r</td>
</tr>
<tr>
<td>• All adverse events should be reported through the national pharmacovigilance mechanism</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pregnancy safety of ATV/r</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ATV/r is considered safe during pregnancy, and is one of the preferred ARV options in the US and European perinatal ARV guidelines</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Important drug interactions with ATV/r</th>
</tr>
</thead>
<tbody>
<tr>
<td>• All patients on ATV/r should be educated on important drug interactions, particularly with TB treatment and with drugs that alter stomach acidity</td>
</tr>
<tr>
<td>• All patients should be asked if they are taking any medications or supplements prescribed by other physicians or purchased over-the-counter</td>
</tr>
<tr>
<td>• ATV/r cannot be co-administered with rifampicin. For patients requiring TB treatment while on ATV/r then use rifabutin at 150 mg daily. If rifabutin is not available then switch to an alternative ARV to co-administer with rifampicin</td>
</tr>
</tbody>
</table>
ATV/r requires an acidic stomach environment for absorption
- ATV/r should be administered 2 hours before or 12 hours after taking a proton pump inhibitor (PPI) or histamine-2 receptor antagonist (H2 blocker)
- ATV/r should be administered 2 hours before or 1 hour after an antacid
- For patients expected to require long-term use of PPI or H2 blocker, consider an alternative ARV
- ATV/r, like all boosted protease inhibitors, has multiple other drug interactions
- Always check for potential drug interactions using the package insert or web-based interaction tool (e.g. www.hiv-druginteractions.org)
- See Appendix B for a list of common and important ARV drug interactions

Contraindications for use of ATV/r

- ATV/r is contraindicated for any patient with a history to hypersensitivity reaction to ATV or RTV

4.3 ART for Infants and Children

Table 9: Preferred and Alternative First-Line ART for Neonates, Infants, and Children

<table>
<thead>
<tr>
<th>Age/weight category</th>
<th>Preferred first-line regimen</th>
<th>Alternative first-line regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth – 4 weeks</td>
<td>AZT + 3TC + RAL(^a)</td>
<td>AZT + 3TC + NVP</td>
</tr>
<tr>
<td>&gt; 4 weeks but &lt; 20 kg</td>
<td>ABC + 3TC + LPV/r(^a)</td>
<td>AZT + 3TC + LPV/r</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ABC (or AZT) + 3TC + RAL</td>
</tr>
<tr>
<td>20 - 30 kg</td>
<td>ABC + 3TC + DTG(^b)</td>
<td>ABC + 3TC + LPV/r</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ABC + 3TC + RAL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ABC (or AZT) + 3TC + EFV</td>
</tr>
<tr>
<td>≥ 30 kg</td>
<td>TDF + 3TC (or FTC) + DTG(^b,c)</td>
<td>ABC + 3TC (or FTC) + DTG</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TDF (or ABC) + 3TC (or FTC) + LPV/r</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TDF (or ABC) + 3TC (or FTC) + EFV</td>
</tr>
</tbody>
</table>

\(^a\) DTG will become the preferred ARV once appropriate weight-based formulations are available.

\(^b\) Adult formulation of DTG (50mg once daily) can be used for children 20 kg and above.

\(^c\) Adult formulation of TDF (300mg once daily) can be used for children 30 kg and above.
4.4 Monitoring Response of ART and Detection of Treatment Failure¹

- Monitoring people on ART is important to ensure successful treatment, identify adherence problems and determine whether ART regimens should be switched in case of treatment failure.
- Routine viral load monitoring can be carried out at 6 months, at 12 months and then every 12 months thereafter if the patient is stable on ART, to synchronize with routine monitoring and evaluation reporting.
- Viral failure is defined by a persistently detectable viral load exceeding 1000 copies/mL (that is, two consecutive viral load measurements within a 3-month interval with adherence support between measurements) after at least 6 months of starting a new ART regimen.

4.4.1 Assessment and Management of Causes of Detectable Viral Load (VL)¹

- Inadequate adherence is the primary reason for having a detectable VL after at least 6 months on ART. Several methods should be used to assess adherence for patients with detectable VL:

<table>
<thead>
<tr>
<th>Adherence assessment strategy</th>
<th>Description</th>
</tr>
</thead>
</table>
| Self-Report                  | • In a non-judgmental way, ask the patient how often they miss a dose of ART, e.g.  
  ■ “It can be hard to take ARVs every day. In the past month, how many times do you think you missed a dose of your ARVs?”  
  • A standardized questionnaire can be used to assess self-reported adherence |
| Pill Count                   | • Ask the patient to bring all their pills with them to clinic visits  
  • Compare the number of pills that are remaining with the number of pills expected based on the previous prescription date and amount prescribed  
  • Excess pills are assumed to be missed doses |
| Pharmacy Refill Record       | • Compare drug pick-up date with the expected date of pick-up based on the previous prescription  
  • It is assumed that any days late for drug pick-up are equivalent to the number of days that ART was not taken |
4.4.2 Common causes of Poor Adherence

- In a non-judgmental way, ask the patient what makes it difficult for them to take their ARVs every day.
- Explore common reasons for poor adherence and identify which are relevant, including:

<table>
<thead>
<tr>
<th>Patient factors</th>
<th>Provider/system factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stigma and non-disclosure (having to hide their ARV pill-taking)</td>
<td>Side effects</td>
</tr>
<tr>
<td>Alcohol or drug use</td>
<td>Pill burden</td>
</tr>
<tr>
<td>Depression or other psychiatric illness</td>
<td>Poor patient-provider relationship</td>
</tr>
<tr>
<td>Cognitive disorders</td>
<td>Inadequate HIV education</td>
</tr>
<tr>
<td>Change in daily routine</td>
<td>Cost of care (direct and indirect)</td>
</tr>
<tr>
<td>Chaotic schedule; no consistent daily routine</td>
<td>ARV supply-chain limitations (stock-outs, or low stock levels resulting in small refill quantities)</td>
</tr>
<tr>
<td>Forgetting to take pills</td>
<td></td>
</tr>
<tr>
<td>Feeling better so does not think the ART is needed any more</td>
<td></td>
</tr>
<tr>
<td>Age (adolescents – impulsive, more susceptible to social pressure; children – caregiver dependent)</td>
<td></td>
</tr>
<tr>
<td>Side effects</td>
<td></td>
</tr>
<tr>
<td>Pill burden</td>
<td></td>
</tr>
<tr>
<td>Poor patient-provider relationship</td>
<td></td>
</tr>
<tr>
<td>Inadequate HIV education</td>
<td></td>
</tr>
<tr>
<td>Cost of care (direct and indirect)</td>
<td></td>
</tr>
<tr>
<td>ARV supply-chain limitations (stock-outs, or low stock levels resulting in small refill quantities)</td>
<td></td>
</tr>
</tbody>
</table>

- Assessing for other causes of High VL:
  - Rarely, patients have detectable VL even when adherence is perfect, for example:
    - Drug-drug interactions which lower the plasma levels of ARVs (e.g. PI/r or INSTI with rifampin; INSTI with antacids or mineral supplements; ATV/r with medications that reduce stomach acidity).
    - Impaired absorption (e.g. chronic severe diarrhea or vomiting after taking ARVs; not following food restrictions/requirements for certain ARVs).
    - Inadequate dosing (e.g. dose adjustments not being made as children grow, or incorrect dose prescribed or dispensed).
    - Transmitted drug resistance (particularly for NNRTI-based regimens).
4.4.3 Management of Patients with Detectable Viral Load

- Most patients with detectible HIV VL on first-line ART may continue treatment without changes to second-line, because they will re-suppress once adherence issues or other reasons for a detectable VL have been addressed.
- Identify the root cause/s of poor adherence or other reason/s for detectable VL:
  - Assess adherence and implement interventions to address poor adherence (i.e. stigma, side effects, drug and alcohol abuse, depression or other mental diseases, etc.), and assess for other potential causes of detectable VL (drug interaction, absorption disorders, inadequate dosing, etc.).
- Do not change the ART regimen until these causes are addressed, and only change regimen if viral load is still high after allowing time for resuppression after addressing the root cause/s of detectable VL.
- Work with the patient to develop strategies to overcome their specific barriers to adherence or other reasons for detectable VL.
- Consider implementing daily witnessed ingestion of ARVs if possible, with a treatment buddy, family member, social worker, etc.
- Discuss the case as a multi-disciplinary team.
- Assign a case manager for the patient.
- Engage an NGO/social worker if they are not already involved.
- Discuss the implications of treatment failure with the patient.
- Discuss a plan to repeat the VL after three months of excellent adherence.

4.4.4 Confirmation and Management of Treatment Failure

- After identifying and addressing reasons for detectable VL and providing enhanced adherence counseling and support, the VL should be repeated after 3 months of excellent adherence (to allow enough time for viral re-suppression).
  - If VL < 1,000 copies/ml this confirms the patient has re-suppressed and can continue their current regimen with ongoing adherence support.
  - If VL ≥ 1000 copies/ml this confirms treatment failure and the patient should be prepared for switching regimens (including drug resistance testing (DRT) if indicated). For patients with high baseline VL it may take longer than three months to re-suppress, so if there is at least a 3 log drop in VL within 3 months then continue current regimen and repeat VL in another three months.
### 4.5 Second-Line ART Regimen Selection\textsuperscript{3,16}

#### Table 10: Second and Third-Line ART Regimens for Adults and Adolescents

<table>
<thead>
<tr>
<th>Population</th>
<th>Failing first-line regimen</th>
<th>Preferred second-line regimen</th>
<th>Alternative second-line regimens</th>
<th>Possible third-line regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults/ Adolescents including women of childbearing potential or who are pregnant\textsuperscript{a}</td>
<td>TDF + 3TC + DTG\textsuperscript{a}</td>
<td>AZT\textsuperscript{b} + 3TC + ATV/r (or LPV/r)</td>
<td>AZT\textsuperscript{b} + 3TC + DRV/r</td>
<td>DRV/r\textsuperscript{c} ± DTG\textsuperscript{a,d} + 1-2 NRTIs\textsuperscript{b} (if possible, use genotype to guide regimen selection)</td>
</tr>
<tr>
<td></td>
<td>TDF + 3TC + EFV (or PI/r)</td>
<td>AZT\textsuperscript{b} + 3TC + DTG\textsuperscript{a}</td>
<td>AZT\textsuperscript{b} + 3TC + ATV/r (or LPV/r or DRV/r)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AZT + 3TC + EFV (or PI/r)</td>
<td>TDF + 3TC + DTG\textsuperscript{a}</td>
<td>TDF + 3TC + ATV/r (or LPV/r or DRV/r)</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a} Effective contraception should be offered to adult women and adolescent girls of childbearing age or potential. DTG can be prescribed for adult women and adolescent girls of childbearing age or potential who wish to become pregnant, or who are not otherwise using or accessing consistent and effective contraception if they have been fully informed of the potential increase in the risk of neural tube defects (at conception and until the end of the first trimester). If women identify pregnancy after the first trimester, DTG should be initiated or continued for the duration of the pregnancy.

\textsuperscript{b} For people with HBV co-infection, TDF should be continued in second-line to treat the HBV.

\textsuperscript{c} For PI-experienced people, the recommended DRV/r dose should be 600 mg/100 mg twice daily.

\textsuperscript{d} For INSTI-experienced people, the recommended DTG dose should be 50mg twice daily twice daily.

#### Table 11: Second-Line ART for Infants and Children

<table>
<thead>
<tr>
<th>Failing first-line regimen</th>
<th>Preferred second-line regimen</th>
<th>Alternative second-line regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZT+3TC+DTG</td>
<td>ABC\textsuperscript{a} + 3TC+ LPV/r (or ATV/r)</td>
<td>ABC\textsuperscript{a} + 3TC+ DRV/r</td>
</tr>
<tr>
<td>ABC+3TC+DTG</td>
<td>AZT+3TC+LPV/r (or ATV/r)</td>
<td>AZT+3TC+ DRV/r</td>
</tr>
<tr>
<td>ABC (or TDF) +3TC+LPV/r</td>
<td>AZT+3TC +DTG\textsuperscript{b}</td>
<td>AZT+3TC+ RAL</td>
</tr>
<tr>
<td>AZT+3TC+EFV (or NVP)</td>
<td>ABC\textsuperscript{a} +3TC+DTG\textsuperscript{b}</td>
<td>ABC\textsuperscript{a} +3TC+ LPV/r (or ATV/r)</td>
</tr>
<tr>
<td>ABC+3TC+EFV (or NVP)</td>
<td>AZT+3TC + DTG\textsuperscript{b}</td>
<td>AZT+3TC+ LPV/r (or ATV/r)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} TDF is preferred to ABC if appropriate formulations are available. Adult formulation of TDF (300mg once daily) can be used for children 30 kg and above.

\textsuperscript{b} Adult formulation of DTG (50mg once daily) can be used for children 20 kg and above. For children 15 - 20kg DTG can be used once appropriate formulations are available.
4.5.1 Counseling on Regimen Change

- Adherence issues should have been addressed before confirming treatment failure, however it is still important to discuss the following at time of switch to second-line:
  - Knowledge of HIV and ART
  - Individualized adherence plan
  - Changes in the regimen, including: the number of pills, appearance of pills, dosing frequency, food requirements/restrictions and drug interactions
  - Current pill-taking routine and any changes required with the new regimen (changing their reminder alarm for the new regimen, changing which activities in their daily routine they will combine with pill taking)
  - Common and serious side effects of any new ARV being introduced; encourage the patient to return to clinic for any side effects rather than stopping ART
  - Important drug interactions
  - Next appointment in 2-4 weeks to review adherence and side effects; sooner if any concerns
  - Viral load testing in 3-6 months to confirm viral suppression

4.6 Modifying ART for Adolescents/Adults who are Virally Suppressed

1. Reasons for Modifying ART for Patients Who are Virally Suppressed

   A) Reasons to consider regimen modification for other patients:
   - Simplify the regimen (reduce pill burden, dosing frequency, food requirements).
   - Manage current toxicity or side effects (all drug-related adverse events should be reported through the national pharmacovigilance system).
   - Prevent long-term toxicity.
   - Prevent or manage drug-drug interactions.
   - Manage comorbidities.
   - Respond to pregnancy intention.

* Section 4.6 are taken from the Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV from the United States Department of Health and Human Services. http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf.
B) High priority for proactively discussing regimen modification:
- On LPV/r-containing regimen: modify in order to improve tolerability, prevent long-term toxicity, reduce pill burden, and provide a once-daily fixed-dose combination regimen.
- On AZT-containing regimen: modify in order to prevent long-term toxicity, reduce pill burden, and provide a once-daily fixed-dose combination regimen.
- On NVP-containing regimen: modify in order to provide a once-daily regimen.

2. Selection of Modified Regimen for Virally Suppressed Adults and Adolescents on First-Line ART

<table>
<thead>
<tr>
<th>Current ARV that is being changed</th>
<th>Preferred ARV to switch to</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPV/r</td>
<td>DTG</td>
</tr>
<tr>
<td>AZT</td>
<td>TDF (if pre-existing renal disease (with eGFR &lt; 60 ml/min) and HLA*B57:01 negative then switch to ABC instead of TDF)(^a)</td>
</tr>
<tr>
<td>EFV, NVP</td>
<td>DTG</td>
</tr>
<tr>
<td>Other</td>
<td>Consult the national program</td>
</tr>
</tbody>
</table>

\(^a\) TDF + 3TC (or FTC) should be used despite renal impairment (with renal dose adjustments) for patients who have HIV/HBV co-infection and do not have other options for treatment of HBV.

3. Selection of Modified Regimen for Virally Suppressed Children on First-Line ART

<table>
<thead>
<tr>
<th>Current ARV that is being changed</th>
<th>Weight</th>
<th>Preferred ARV to switch to</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFV, NVP, or LPV/r</td>
<td>≥ 20 kg</td>
<td>DTG(^a)</td>
</tr>
<tr>
<td>ABC</td>
<td>&gt; 30 kg</td>
<td>TDF(^b)</td>
</tr>
<tr>
<td>AZT</td>
<td>20-30 kg</td>
<td>ABC</td>
</tr>
<tr>
<td></td>
<td>&gt; 30 kg</td>
<td>TDF(^b)</td>
</tr>
</tbody>
</table>

\(^a\) Adult formulation of DTG (50mg once daily) can be used for children 20 kg and above.
\(^b\) Adult formulation of TDF (300mg once daily) can be used for children 30 kg and above.
4. Counseling on Regimen Modification

Discuss the following with the patient:

- Rationale for modification.
- Changes in the regimen, including: the number of pills, appearance of pills, dosing frequency, food requirements/restrictions and drug interactions.
- Current pill-taking routine and any changes required with the new regimen (changing their reminder alarm for the new regimen, changing which activities in their daily routine they will combine with pill taking).
- Common and serious side effects of any new ARV being introduced; encourage the patient to return to clinic for any side effects rather than stopping ART.
- Important drug interactions.
- Next appointment in 2-4 weeks to review adherence and side effects; sooner if any concerns.
- Viral load testing in 4-8 weeks to confirm suppression is maintained.

4.7 Monitoring and Substitution of ART Adverse Events and Toxicities

- ARVs can cause a range of toxicities ranging from mild to life threatening. When assessing a patient for potential ARV toxicities, it is important to use both a symptom-directed approach and laboratory testing if available.
- Less than 10% of ART-naïve patients developed treatment-limiting adverse events in randomized clinical trials.
- In the event of life-threatening or severe toxicity or hypersensitivity (such as with ABC hypersensitivity reaction), ART should be discontinued until symptoms have resolved and a substitute regimen can be safely initiated.
- All adverse events should be reported through the national pharmacovigilance mechanism.
- See Appendix A for ART Adverse Events and Toxicities.7*

4.8 Important ART Drug-Drug Interactions

- See Appendix B.
- For specific interactions, can also consult University of Liverpool HIV drug-drug interaction website: https://hiv-druginteractions.org.

Chapter 5
Advanced HIV Disease
Chapter 5: Advanced HIV Disease

5.1 Definition of Advanced HIV Disease

- For adults and adolescents, and children older than five years, advanced HIV disease is defined as CD4 cell count <200 cells/mm$^3$ or WHO stage 3 or 4 event.
- All children younger than five years old with HIV are considered as having advanced HIV disease.
- Leading causes of mortality among adults with advanced HIV disease globally include tuberculosis (TB), severe bacterial infections, cryptococcal meningitis, toxoplasmosis and Pneumocystis jirovecii pneumonia.
- Among children, TB, severe bacterial infections, Pneumocystis jirovecii pneumonia, diarrhoeal diseases, malnutrition and wasting are the leading causes of death.

5.2 Role of CD4 Cell Count Testing in Identifying and Managing People with Advanced HIV Disease

- Relying on clinical staging alone risks missing substantial numbers of people living with HIV with severe immune suppression.
- Identifying people with advanced HIV disease who are eligible for elements of a package of care requires CD4 cell count testing.

5.3 Package of Care for Advanced HIV Disease

- A package of interventions including screening, treatment and/or prophylaxis for major opportunistic infections, rapid ART initiation and intensified adherence support interventions should be offered to everyone presenting with advanced HIV disease.
Table 12: Components of the Package of Care for People with Advanced HIV Disease

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Intervention</th>
<th>CD4 cell count</th>
<th>Adults</th>
<th>Adolescents</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum Xpert MTB/RIF as for test for TB diagnosis</td>
<td>Any</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Cryptococcal antigen screening</td>
<td>≤100 cells/mm³</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

| Prophylaxis                                  | Co-trimoxazole prophylaxis                        | ≤350 cells/mm³ or clinical stage 3 or 4 | Yes    | Yes         | Yes      |
|                                              | Any                                              | Any CD4 count in settings with high prevalence of malaria or severe bacterial infections |        |             |          |
|                                              | TB preventive treatment                           | Any            | Yes    | Yes         | Yes      |
|                                              | Fluconazole preemptive therapy for cryptococcal antigen—positive people without evidence of meningitis | ≤100 cells/mm³ | Yes    | Yes         | Not applicable |

| ART Initiation                              | Rapid ART initiation                              | Any            | Yes    | Yes         | Yes      |
|                                              | Defer initiation if clinical symptoms suggest TB or cryptococcal meningitis | Any            | Yes    | Yes         | Yes      |

| Adapted adherence support                    | Tailored counselling to ensure optimal adherence to the advanced disease package, including home visits if feasible | <200 cells/mm³ | Yes    | Yes         | Yes      |
Chapter 6
Management of Common Coinfections
Chapter 6: Management of Common Coinfections

6.1 Tuberculosis and Drug-Resistant Tuberculosis

**Background:**
- TB is the most common cause of death of hospitalized children and adults who have HIV.
- All people living with HIV should be screened regularly using clinical symptom-based algorithm of assessing for fever, cough of any duration, weight loss and night sweats.
- The risk of extrapulmonary TB is higher in people living with HIV, especially in those with lower CD4 cell counts. People living with HIV with extrapulmonary TB often have disseminated disease and are at high risk of rapid clinical deterioration and death.

**Diagnosis:**
- Xpert MTB/RIF and/or Xpert Ultra (if available) rather than conventional microscopy, culture, and drug susceptibility testing (DST) is recommended for initial diagnostic testing.
- Xpert MTB/RIF is preferred over conventional microscopy and culture as the initial diagnostic test for cerebrospinal fluid specimens from patients suspected of having TB meningitis.
- Xpert MTB/RIF may be used as a replacement test for usual practice (including conventional microscopy, culture or histopathology) for testing specific non-respiratory specimens (CSF, lymph nodes and other tissues biopsies) from patients suspected of having extrapulmonary TB.
- In peripheral settings where TB investigations are not available, clinical assessment and judgment should be used to provide presumptive TB treatment for select individuals who are seriously ill.
- The diagnosis of extrapulmonary TB is challenging, as disseminated TB can manifest as non-specific febrile illness.
- Extrapulmonary TB should be suspected in all HIV-positive individuals presenting with TB symptoms. Furthermore, symptoms suggesting a specific organ involvement, such as breathlessness (pleural effusion/pericarditis), abdominal pains and distension, enlarged glands in the neck or armpit (lymphadenitis) and chronic headache or altered mental status (meningitis) should prompt further investigation for extrapulmonary TB.
Timing of ART for Adults and Children with TB

- ART should be started in all TB patients living with HIV, regardless of CD4 cell count.
- TB treatment should be initiated first, followed by ART as soon as possible within the first 8 weeks of treatment.
- HIV-positive patients with CD4<50 cells/mm$^3$ should receive ART within the first two weeks of initiating TB treatment.
- Patients with TB meningitis can defer ART initiation for up to 8 weeks, irrespective of CD4 count.
- ART should be started in any child with active TB as soon as possible and within 8 weeks of following the initiation of TB treatment, regardless of CD4 cell count and clinical stage.
- ART is recommended for all patients with HIV and drug-resistant TB regardless of CD4 count and should be started within the first 8 weeks of drug-resistant TB treatment.

Table 13: Summary of Recommended ART Regimens for Adults, Pregnant or Breastfeeding Women, Adolescents and Children Who Need TB Treatment

<table>
<thead>
<tr>
<th>Population</th>
<th>Preferred first-line ART regimen</th>
<th>Preferred second-line ART regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV and TB coinfection</td>
<td>TDF+3TC (or FTC) + DTG (use DTG 50mg twice daily if using rifampicin-containing TB treatment)</td>
<td>If using rifampicin: Optimized NRTI backbone plus double-dose DTG (50mg twice daily) or double-dose LPV/r$^{a,b,c}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If using rifabutin: Optimized NRTI backbone plus DTG or boosted PI regimen at standard doses</td>
</tr>
</tbody>
</table>

$^a$ If TDF + 3TC (or FTC) was used as the NRTI backbone in the 1st line failing regimen, AZT+3TC should be used in second-line and vice-versa.

$^b$ DTG can be prescribed for adult women and adolescent girls of childbearing age or potential who wish to become pregnant, or who are not otherwise using or accessing consistent and effective contraception, if they have been fully informed of the potential increase in the risk of neural tube defects (at conception and until the end of the first trimester).

$^c$ Standard LPV dose with an adjusted dose of RTV (that is, LPV400mg/RTV 400mg twice daily) can be used as alternative options.
Table 14: Summary of Recommended ART Regimens for Children Who Need TB Treatment

<table>
<thead>
<tr>
<th>Recommended regimens for children and infants initiating ART while on TB treatment&lt;sup&gt;a,b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Younger than 3 years</strong></td>
</tr>
<tr>
<td><strong>3 years and older</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommended regimen for children and infants initiating TB treatment while receiving ART&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Child on standard NNRTI-based regimen (Two NRTIs + EFV or NVP)</strong></td>
</tr>
<tr>
<td><strong>Younger than 3 years</strong></td>
</tr>
<tr>
<td><strong>3 years and older</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommended regimen for children and infants initiating TB treatment while receiving ART&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Child on standard PI-based regimen (Two NRTIs + LPV/r)</strong></td>
</tr>
<tr>
<td><strong>Younger than 3 years</strong></td>
</tr>
<tr>
<td><strong>3 years and older</strong></td>
</tr>
</tbody>
</table>
a Ensure optimal dosing of rifampicin based on dosing guidelines.
b Substitute ARV drugs based on an age-appropriate ART regimen in line with nationally recommended first-line ART.
c Triple NRTI is only recommended for the duration of TB treatment; an age-appropriate PI- or NNRTI-based regimen should be restarted when rifampicin-based therapy ends. Based on the findings from the ARROW trial (174), this regimen should be considered as the preferred option for children younger than 3 years who are receiving an LPV/r-based regimen when starting TB treatment. The US FDA approval for the use of EFV in children 3 months to 3 years old weighing more than 3.5 kg offers a potential alternative to the triple-NRTI approach (358). An EFV-based regimen in children under 3 years is still not recommended because pharmacokinetic data are needed to ensure that the co-administration of rifampicin does not decrease drug levels below the therapeutic level. Triple NRTI should also be considered as the preferred regimen for children older than 3 years with a history of failure on an NNRTI-based regimen.
d Increase RTV until it reaches the same dose as LPV in mg, in a ratio of 1:1.
e Substitution with EFV should be considered as the preferred option (359), and EFV could be maintained after TB treatment ends to enable simplification and harmonization with the ARV drug regimens used for older children.
Algorithm for Managing People Living With HIV Who are Suspected of Having TB (Not Severely Ill Patients)¹

- HIV-positive or unknown⁸ and
- Suspected of having TB⁷ and no danger signs⁹

**Expert MTB/RIF⁴**

- Expert MTB/RIF-positive for TB
- Expert MTB/RIF-negative for TB or test not available

**First visit**

- Treat for TB⁷
- ART
- Co-trimoxazole preventive therapy

- TB likely

**Further investigations for TB⁷**

- TB unlikely

- Treat for bacterial infection⁶ and/or *Pneumocystis* pneumonia
- ART assessment⁸
- Provide co-trimoxazole preventive therapy as appropriate

**Second visit**

- No or partial response
- Response

- Further investigate for TB and other diseases⁴
- Provide isoniazid preventive therapy

---

¹ For all people with unknown HIV status, HIV testing should be performed according to national guidelines.

² Suspicion of TB is defined by the presence of any one of the following symptoms:
- For adults and adolescents living with HIV: current cough, fever, weight loss or night sweats.
- For children living with HIV: poor weight gain, fever, current cough or history of contact with a TB case.

³ Danger signs include any one of the following: respiratory rate>30 per minute, temperature>39°C, heart rate>120 beats per minute and unable to walk unaided.

⁴ For people suspected of having extrapulmonary TB, extrapulmonary specimens should be obtained for Xpert MTB/RIF (cerebrospinal fluid, lymph nodes and other tissues: Xpert MTB/RIF has low sensitivity for pleural fluid and data are limited for stool, urine or blood).

⁵ If Xpert MTB/RIF shows rifampicin resistance, treatment for multidrug-resistant TB should be initiated. If the person is considered at low risk for rifampicin resistance, a second Xpert MTB/RIF test should be performed on a fresh specimen. Collect and refer a sample for culture and additional drug sensitivity testing.
Further investigations for TB include chest X-ray, clinical assessment and a repeat Xpert MTB/RIF using a fresh specimen. Refer a sample for TB culture where feasible. If Xpert MTB/RIF is not available, conduct acid-fast bacillus (AFB) microscopy. AFB-positive is defined as at least one positive smear, and AFB-negative as two or more negative smears. If extrapulmonary TB is suspected, extrapulmonary specimens should be obtained and sent for culture and abdominal ultrasound may be performed. These investigations may require additional visits. A urine lateral flow lipoarabinomannan (LF-LAM) assay should not be performed for people with no danger sign.

Antibiotics with broad-spectrum antibacterial activity (except fluoroquinolones) should be used.

ART should be recommended for all adults, regardless of CD4 cell count or clinical stage.

Algorithm for Managing People Living with HIV Who are Suspected of Having TB (Seriously Ill)\(^1\)

1. HIV-positive or unknown\(^a\) and
2. Seriously ill, suspected of having TB\(^b\) and danger signs\(^c\)

- Immediate referral not possible
  - Expert MTB/RIF\(^d\)
  - Parenteral antibiotics for treatment of bacterial infections\(^e\)
    - Consider treatment for *Pneumocystis* pneumonia
    - Chest X-ray if available

- Immediate referral to a higher level facility

Expert MTB/RIF-positive

- Treat for TB\(^f\)
- ART
- Co-trimoxazole preventive therapy

- Clinical worsening or no improvement after 3-5 days
  - Start presumptive TB treatment
  - ART
  - Co-trimoxazole preventive therapy
  - Further investigations for TB and other diseases\(^h\)
  - Complete the course of parenteral antibiotics

- Improvement after 3-5 days
  - TB unlikely
    - Reassess for HIV related diseases
    - ART assessment\(^i\)
    - Isoniazid preventive therapy
    - Co-trimoxazole preventive therapy
    - Complete the course of parenteral antibiotics

Expert MTB/RIF-negative\(^g\) or test available

- Complete the course of parenteral antibiotics

---

\(^a\) For all people with unknown HIV status, HIV testing should be performed according to national guidelines.

\(^b\) Suspicion of TB is defined by the presence of any one of the following symptoms:
- For adults and adolescents living with HIV: current cough, fever, weight loss or night sweats.
- For children living with HIV: poor weight gain, fever, current cough or history of contact with a TB case.
Danger signs include any one of the following: respiratory rate > 30 per minute, temperature > 39°C, heart rate > 120 beats per minute and unable to walk unaided.

For people suspected of having extrapulmonary TB, extrapulmonary specimens should be obtained for Xpert MTB/RIF (cerebrospinal fluid, lymph nodes and other tissues: Xpert MTB/RIF has low sensitivity for pleural fluid and data are limited for stool, urine or blood).

The urine lateral flow lipoarabinomannan (LF-LAM) assay may be used to assist in diagnosing active TB among seriously ill adults and children living with HIV, regardless of CD4 count.

If Xpert MTB/RIF is not available, conduct AFB microscopy. AFB-positive is defined as at least one positive smear and AFB-negative as two or more negative smears. Refer the specimen for TB culture where feasible.

Antibiotics with broad-spectrum antibacterial activity (except fluoroquinolones) should be used.

If Xpert MTB/RIF shows rifampicin resistance, treatment for multidrug-resistant TB should be initiated. If the person is considered at low risk for rifampicin resistance, a second Xpert MTB/RIF test should be performed on a fresh specimen. Collect and refer a sample for culture and additional drug sensitivity testing.

If Xpert MTB/RIF shows negative results, the test can be repeated using a fresh specimen.

Further investigations for TB include chest X-ray, clinical assessment, a repeat Xpert MTB/RIF using a fresh specimen and culture. If extrapulmonary TB is suspected, extrapulmonary specimens should be obtained and sent for culture and abdominal ultrasound may be performed.

ART should be recommended for all adults, regardless of CD4 cell count or clinical stage.

**Isoniazid Preventive Therapy (IPT)**

- Adults and adolescents living with HIV should be screened with a clinical algorithm; those who do not report any one of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have active TB and should be offered IPT.

- Adults and adolescents living with HIV who have an unknown or positive tuberculin skin test (TST) status and are unlikely to have active TB should receive at least six months of IPT as part of a comprehensive package of HIV care. IPT should be given to such individuals regardless of the degree of immunosuppression, and also to those on ART, those who have previously been treated for TB, and pregnant women.

- Children living with HIV who do not have poor weight gain, fever or current cough are unlikely to have active TB. Children living with HIV who have poor weight gain, fever or current cough or contact history with a TB case may have TB and should be evaluated for TB and other conditions. If the evaluation shows no TB, they should be offered IPT.

- Children living with HIV who are more than 12 months of age and who are unlikely to have active TB on symptom-based screening and have no contact with a TB case should receive six months of IPT (10 mg/kg/day) as part of a comprehensive package of HIV prevention and care.

- In children living with HIV who are less than 12 months of age, only those who have contact with a TB case and who are evaluated for TB (using investigations) should receive six months of IPT if the evaluation shows no TB disease.
6.2 Hepatitis B Coinfection

**Background:**
- Hepatitis B (HBV) is the most common cause of chronic liver disease worldwide.
- HBV is transmitted through sexual contact, injection drug use and perinatally.
- Patients with HIV are at an increased risk of developing chronic HBV infection.

**Clinical Manifestations:**
- Acute HBV infection is asymptomatic in ~70% of patients with <1% of patients developing fulminant hepatic failure.
- Symptoms such as fever, vomiting, right upper quadrant pain, with or without jaundice can be seen in the acute setting.
- Chronic HBV is usually asymptomatic with between 15%-40% of patients with chronic HBV developing cirrhosis, liver failure, or hepatocellular carcinoma.

**Diagnosis:**
- Check Hepatitis surface antigen (HbsAg), hepatitis B core antibody (anti-HBc), and hepatitis B surface antibody (anti-HBs).
- In acute infection, HBsAg can be detected 4 weeks (range 1–9 weeks) after exposure, while anti-HBc immunoglobulin M is usually detectable at the onset of symptoms.
- Chronic HBV infection is defined as persistent HBsAg detected on 2 occasions at least 6 months apart.
- Patients with chronic HBV infection should be further tested for HBV e-antigen (HBeAg), antibody to HBeAg (anti-HBe), and HBV DNA if available.
- Active disease, which can be HBeAg-negative or HBeAg-positive, can be distinguished from inactive disease by the presence of serum HBV DNA and persistent or fluctuating alanine transaminase (ALT) elevations.
- The presence of an isolated anti-HBc test result usually signifies infection with HBV in the past with subsequent loss of anti-HBs and occurs in 7% to 19% of patients with HIV infection. The clinical significance of isolated anti-HBc is unknown, but in individuals with HIV infection, it may indicate chronic or, more likely, resolved HBV infection.

* Section 6.2 is taken from the Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-Infected Adults and Adolescents: recommendations from the CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America.
HBV/HIV Coinfection Treatment

- HBV and HIV co-treatment is essential and recommended. Fortunately, several ARVs used for HIV also treat HBV.
- Two NRTIs are recommended for HBV treatment, but 3 drug ARV therapy is still recommended for HIV.
- Preferred regimen for co-infected HIV/HBV patients includes lamivudine (3TC) or emtricitabine (FTC), plus either tenofovir disoproxil fumareate (TDF) or tenofovir alafenamide (TAF).

<table>
<thead>
<tr>
<th>Preferred HBV coinfection treatment regimens for CrCl &gt;60mg/min</th>
<th>Preferred HBV coinfection treatment regimens for CrCl 30-59 mL/min</th>
<th>Preferred HBV coinfection treatment regimen for CrCl &lt; 30 ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF 300mg + FTC 200mg PO once daily, or</td>
<td>TAF (10 or 25mg) + FTC 200mg PO once daily</td>
<td>A fully suppressive ART regimen without tenofovir should be used, with the addition of renally dosed entecavir to the regimen, or</td>
</tr>
<tr>
<td>TAF 10 or 25mg + FTC 200mg PO once daily, or</td>
<td></td>
<td>ART with renally dosed-adjusted TDF and FTC can be used when recovery of renal function is unlikely</td>
</tr>
<tr>
<td>TDF 300mg + 3TC 300mg PO once daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAF 10 or 25mg + 3TC 300mg PO once daily</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* HIV/Hepatitis B coinfection needs to be treated with a total of 3 ARVs. The 2 drug NRTIs target Hep B infection, but HIV infection still needs to be treated with a 3-drug combination.

- Treatment with either emtricitabine or lamivudine monotherapy as the only active drug against HBV should be avoided because of high rates of HBV drug-resistance mutations.
- Tenofovir (TDF and TAF), entecavir, lamivudine, emtricitabine, and telbivudine should not be used alone in the absence of a fully suppressive ART regimen because of the development of HIV-resistance mutations.
- Patient’s receiving ART should continue HBV therapy indefinitely because relapses after response occur, particularly in those with lower CD4 cell counts.
- Discontinuation of nucleos(t)ide analogue therapy is associated with a HBV flare in approximately 30% of cases with loss of the benefit accrued from previous anti-HBV treatment and possible decompensation of liver disease.
• If anti-HBV therapy and ART must be discontinued, transaminase levels should be monitored every 6 weeks for 3 months and every 3 to 6 months thereafter. If a flare occurs, anti-HBV therapy and ART should be reinstituted and can be potentially lifesaving.

Immune Reconstitution Syndrome (IRIS)
• Any immune reconstitution can lead to a rise in serum aminotransferases, so called “hepatitis flare,” which constitutes IRIS in persons with HIV/HBV coinfection.
• IRIS may manifest when serum aminotransferase levels dramatically increase as CD4 cell counts rise within the first 6 to 12 weeks after ART is started, with signs and symptoms characteristic of acute hepatitis and without another cause for the flare.
• After introduction of ART, serum ALT levels should be monitored closely every 3-6 months if available.
• Glucocorticoids can be used for severe IRIS.

Preventing HBV Infection
Indications for HBV Vaccination:
• Patients without chronic HBV infection and without immunity to HBV (anti-HBs <10 IU/mL).
• Patients with isolated anti-HBc. Recommend one standard dose of HBV vaccine followed by anti-HBs at 1-2 months. If the titer is >100 IU/mL, no further vaccination is needed, but if the titer is <100 IU/mL, a complete series of HBV vaccine should be completed followed by anti-HBs testing.
• Early vaccination is recommended (if possible) before CD4 count falls below 350 cells/mm\(^3\), as low CD4 count at time of vaccination has been associated with poor response to the vaccine.
• However, in a patient with low baseline CD4 cell count, vaccination should not be deferred until CD4 reaches >350 cells/mm\(^3\), as some patients with CD4 <200 cells/mm\(^3\) do respond to vaccination.
Vaccination Schedule:
- HBV vaccine IM (Engerix-B® 20 mcg/mL or Recombivax HB® 10 mcg/mL) at 0, 1, and 6 months; or
- HBV vaccine IM (Engerix-B® 40 mcg/mL or Recombivax HB® 20 mcg/mL) at 0, 1, 2, and 6 months; or
- Combined HAV and HBV vaccine (Twinrix®) 1 mL IM as a 3-dose series (at 0, 1, and 6 months) or as a 4-dose series (at days 0, 7, 21 to 30, and 12 months); or
- Vaccine conjugated to CpG (Heplisav-B®) IM at 0 and 1 months— a 2-dose series can only be used when both doses given are Heplisav-B®.
- Anti-HBs should be obtained 1 to 2 months after completion of the vaccine series. Patients with anti-HBs <10 IU/mL will be considered as vaccine non-responders.

For Vaccine Non-Responders:
- Revaccinate with a second vaccine series.
- For patients with low CD4 count at the time of first vaccination series, some experts might delay revaccination until after a sustained increase in CD4 count with ART.

6.3 Hepatitis C Coinfection

Background:
- Hepatitis C virus (HCV) is a single-stranded RNA virus.
- HCV is transmitted through injection drug use, sexual intercourse, mother-to-child transmission, and through exposure to blood products.
- Can cause chronic liver disease, cirrhosis and hepatic cellular carcinoma (HCC).

Clinical Manifestations:
- Acute and chronic HCV typically cause minimal or no symptoms.
- Elevated transaminases may be the only abnormal laboratory findings during an acute or chronic infection.
- Cirrhosis develops in ~20% of patients who develop chronic HCV infection within 20 years after initial infection.

* Section 6.3 is taken from the Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-Infected Adults and Adolescents: recommendations from the CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America.
• HIV can cause an accelerated progression of liver disease to cirrhosis as well as end stage liver disease and HCC.
• HCV can also cause symptomatic vasculitis secondary to cryoglobulinemia, porphyria cutanea tarda, and renal disease due to membranoproliferative glomerulonephritis.

**Diagnosis:**
• All HIV-infected patients should undergo initial testing with an immunoassay for detection of antibody to HCV.
• In an acute HCV infection, HCV antibody testing can be negative during the window period prior to seroconversion (the window period can range from 2-12 weeks). If AST/ALT are elevated in the setting of a negative HCV antibody test, HCV RNA testing is recommended if available.
• Patients who test positive for HCV antibody should receive confirmatory testing using a sensitive quantitative assay to check HCV RNA level.

**Treatment of HIV/HCV Infection:**
• ARVs should be started on all HIV/HCV coinfected patients.
• For treatment of HCV, physicians should follow the most recent guidelines as the armamentarium of approved drugs are likely to continue to expand considerably over the next few years (for most up to date guidelines, see http://www.hcvguidelines.org).
Chapter 7
Opportunistic Infections
Prevention and Treatment
Chapter 7: Opportunistic Infections Prevention and Treatment

7.1: Prevention of Common Coinfections

7.1.1 ART as Prevention: Initiation of ART with Opportunistic Infections (OI)

- ART can prevent opportunistic infections. As CD4 decreases, the likelihood of developing an opportunistic infection increases; therefore, if a patient does not have a documented OI along with negative screening tests for OIs, rapid initiation of ART will help prevent future OIs.
- With the exception of Cryptococcal meningitis and TB meningitis, ARVs should be started within 14 days of opportunistic infection treatment initiation (see each specific OI below for specific details on ART initiation).

7.1.2 Co-Triomoxazole Prophylaxis

<table>
<thead>
<tr>
<th>Recommendations</th>
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</thead>
<tbody>
<tr>
<td>Population</td>
</tr>
<tr>
<td>Adults (including pregnant women) with HIV</td>
</tr>
<tr>
<td>Children and adolescents with HIV</td>
</tr>
<tr>
<td>HIV-exposed uninfected infants</td>
</tr>
<tr>
<td>People living with HIV and TB</td>
</tr>
</tbody>
</table>
7.1.3 Isoniazid Preventative Therapy (Adapted from WHO 2016 Consolidated HIV Guidelines)

- Refer to IPT in Section 6.1.

7.2 Cryptococcal Meningitis\textsuperscript{9,10*}

**Background:**
- Invasive fungal infections.
- Ubiquitous spores in the environment, bird droppings.
- Most cases occur CD4 <100 cells/μL.
- Although Infection begins in lungs, meningoencephalitis is the most frequently encountered manifestation.

**Clinical Manifestations:**
- Symptoms progress over couple of weeks (not days).
- Common Symptoms: progressive headache, fever, malaise, stiff neck/photophobia (~30% cases), skin rashes and coma (less common).
- Common Signs: Altered mental status, hemiparesis, psychomotor retardation, CN palsies.
- Fever and Headache and CD4 <100 should trigger Crypto workup.

**Diagnosis:**
- **Lumbar Puncture:**
  - >250 mm H2O in 60-80% of patients
  - CSF cryptococcal antigen (~95% sensitive/specific)
  - India Ink (60-80% sensitive)
  - CSF WBC usually <50 WBCs
  - Glucose commonly low, protein slightly elevated
  - 25-30% have normal CSF profile
- **Blood tests:**
  - CD4<100
  - Serum Cryptococcal antigen (CrAg) positive

\* Section 7.2 uses information from the Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-Infected Adults and Adolescents: recommendations from the CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America.
**Treatment:**

- **Preferred Induction Regimen:**
  - Amphotericin B 1.0 mg/kg/d IV + Flucytosine (5-FC) 100 mg/kg/d PO in 4 divided doses. Give pre-infusion 500-1000mL of Normal Saline prior to Amphotericin B.
  - Plus aggressive ICP management:
    - May require daily LPs (if having ongoing confusion, blurred vision, lower extremity clonus, papilledema).
    - Remove CSF that at least halves opening pressure.
    - ~20-30 ml, repeat daily until signs/symptoms improve.
    - Steroids, mannitol, and acetazolamide are not recommended.

- **Alternative Regimens:**
  - Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily + Fluconazole 1200mg po/IV qday.
  - *If side effects with Amphotericin B prior to 2 weeks of therapy, stop Amphotericin and use Fluconazole 1200mg po qday to complete 2 week course.
  - Fluconazole 1200 mg PO or IV daily alone.

**Table 15: Minimum Package for Preventing, Monitoring, and Managing Amphotericin B Toxicity per WHO Recommendations**

<table>
<thead>
<tr>
<th>Pre-emptive hydration and electrolyte supplementation</th>
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</thead>
<tbody>
<tr>
<td><strong>Adults and Adolescents</strong></td>
</tr>
<tr>
<td>One litre of normal saline solution with 20 mEq of potassium chloride (KCl) over two hours before each controlled infusion of amphotericin B and one to two 8-mEq KCl tablets orally twice daily. An additional 8-mEq KCl tablet twice daily may be added during the second week. If available, magnesium supplementation should also be provided (two 250-mg tablets of magnesium trisilicate or glycerophosphate twice daily, or magnesium chloride 4 mEq twice daily).</td>
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<table>
<thead>
<tr>
<th>Monitoring (adults, adolescents, and children)</th>
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<tbody>
<tr>
<td><strong>Serum Potassium</strong></td>
</tr>
<tr>
<td>Baseline and 2–3 times weekly (especially in the second week of amphotericin B administration)</td>
</tr>
<tr>
<td><strong>Serum Creatinine</strong></td>
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<tr>
<td>----------------------</td>
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<tr>
<td><strong>Hemoglobin</strong></td>
</tr>
<tr>
<td><strong>Management (adults, adolescents, and children)</strong></td>
</tr>
<tr>
<td><strong>Hypokalaemia</strong></td>
</tr>
<tr>
<td><strong>Elevated Creatinine</strong></td>
</tr>
<tr>
<td><strong>Severe Anemia</strong></td>
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**Additional notes:**
- Potassium replacement should not be given to people with pre-existing renal impairment or hyperkalaemia.
- Careful attention should be given to monitoring of intake and output of fluid and daily weight, especially among children.
- Flucytosine – because of concerns about bone marrow suppression, regular monitoring of full blood counts should be considered.
- The incidence of renal dysfunction and electrolyte disturbance is much less with liposomal amphotericin preparations, but renal function and electrolytes still need to be monitored.
**Duration of Therapy:**

- **Induction Phase:**
  - Minimum of 2 weeks. Completion occurs when substantial clinical improvement (do not check repeat CSF CrAg or serum CrAg titers)

- **Consolidation Phase:**
  - Begin after at least 2 weeks of successful induction therapy (defined as substantial clinical improvement and a negative CSF culture after repeat LP)
  - Preferred Regimen:
    - Fluconazole 400mg po or IV once daily x 8 weeks

- **Maintenance Phase:**
  - Fluconazole 200mg po once daily for at least 1 year
  - Stopping Maintenance Therapy:
    - >1 year on maintenance therapy
    - Remains asymptomatic from cryptococcal infection
    - CD4 count ≥100 cells/μL for ≥3 months and suppressed HIV RNA in response to effective ART

- **Restarting Maintenance Therapy:**
  - If CD4 count declines to ≤100 cells/μL

- **Treating Non-CNS Isolated Cryptococcal Antigenemia:**
  - Fluconazole 400mg po qday x 12 months, check CSF CrAg

**Initiation of ARVs:**

- Delayed approach is better
- Initiate ART after 4-6 weeks of treatment

### 7.3 Toxoplasma Gondii Encephalitis^9^*

**Background:**

- Caused by a protozoan *Toxoplasma gondii.*
- Primary infection occurs after eating undercooked meat containing tissue cysts or ingesting oocysts shed by cat feces or sporulated in the environment.
- Clinical disease is rare among HIV patients with CD4>200 cells/μL.
- Patients with CD4<50 cells/μL are at greatest risk.

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* Section 7.3 is taken from the Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-Infected Adults and Adolescents: recommendations from the CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America.
**Clinical Manifestations:**
- Symptoms progress over hours to days:
  - Common Symptoms:
    - Headache, confusion, fevers, seizures
  - Common Signs:
    - Altered mental status, hemiparesis, psychomotor retardation, CN palsies

**Diagnosis:**
- TE diagnosis requires:
  - Clinical syndrome + ring enhancing lesion(s) on CT or MRI + detection of organism in a clinical sample
- However, if these are not available, clinicians rely on empiric diagnosis based on clinical and radiology findings.
- Usually, anti-toxo IgG positive (sign of reactivation), IgM will likely be negative.

**Treatment:**
- *Preferred Regimen:*
  - Pyrimethamine + Sulfadiazine + Leucovorin
- *Alternative Regimens:*
  - TMP-SMX ((TMP 5 mg/kg and SMX 25 mg/kg) (IV or PO) BID.
  - Pyrimethamine + Clindamycin + Leucovorin
  - Atovaquone 1500 mg PO BID (+/- pyrimethamine or sulfadiazine)

**Duration of Therapy:**
- Treat for minimum 6 weeks:
  - Clinical response to acute therapy occurs in 90% of patients with TE within 14 days of initiation of appropriate anti-toxoplasma treatment.
  - Chronic Maintenance Therapy:
    - Pyrimethamine + sulfadiazine + leucovorin
    - Pyrimethamine + clindamycin + leucovorin
    - TMP-SMX DS 1 tab po bid or qday
    - Atovaquone 750-1500mg po BID
  - Criteria to discontinue Maintenance Phase:
    - Completion of initial therapy + Asymptomatic of signs/symptoms of TE + CD4 >200 for > 6 months on ART
• **Common Side of Effects of TE Drugs:**
  - **Sulfadiazine:**
    - Rash, fever, leukopenia, hepatitis, AKI
  - **TMP-SMX:**
    - Rash, hepatotoxicity, renal insufficiency, leukopenia/thrombocytopenia
  - **Atovaquone:**
    - Nausea, vomiting, hepatotoxicity, fever. Timing of ARV Initiation

**Initiation of ARVs:**
- Start ARVs within 2 weeks.
- IRIS < 5% of cases, no official treatment recommendations.
- Can use steroids and NSAIDs for treatment of IRIS symptoms.

### 7.4 Progressive Multifocal Leukoencephalopathy (PML)\(^9\)\(^*\)

**Background:**
- Caused by the JC virus.
- Seroprevalence ~40-70% adults.
- Reactivates with profound immunosuppression to cause PML.
- 80% cases in AIDS.
- Can occur at any CD4 count, most often CD4<100 cells/μL.

**Clinical Manifestations:**
- Symptoms progress over **weeks**, not **hours/days**.
- Manifest as acute focal neurological deficits with **steady progression of symptoms**.
- Often mistaken for evolving CVA, **progressive course is key feature**.
- Common Symptoms: Visual field loss, limb weakness, gait disturbance, cognitive dysfunction, seizures (~20%).
- Uncommon symptoms: dementia, behavior changes, encephalopathy.

\(^*\) Section 7.4 is taken from the Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-Infected Adults and Adolescents: recommendations from the CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America.
**Diagnosis:**
- Combination of clinical and neuroimaging findings:
  - **Clinical:**
    - Progression of focal deficits
  - **MRI head:**
    - White matter lesions *without* mass effect (unlike TB, PCL, Toxo)
  - If available, check CSF JCV PCR (note: can be negative if on ARVs)

**Treatment:**
- No specific therapy exists for JCV infection/PML.
- **Start ARVs immediately.**
- HIV-associated PML is often complicated by clinically significant IRIS that may require administration of corticosteroid therapy.
- Neurological deficits often persist, but some patients experience clinical improvement.

**7.5 Syphilis/Neurosyphilis**

**Background:**
- Infection caused by *Treponema pallidum* subspecies *pallidum* (T. pallidum).
- Neurosyphilis occurs at **ALL** stages of syphilis (Primary, Secondary, Latent, Tertiary).

**Clinical Manifestations:**
- **Primary Syphilis:**
  - Painless ulcer(s) that develops into a chancre at site of contact.
- **Secondary Syphilis:**
  - Occurs 2-8 weeks after primary infection.
  - Mucocutaneous lesions that are macular, maculopapular, pustular.
  - Rash involving palms/soles.
  - Fevers, malaise, arthralgia’s, lymphadenopathy, headache.
  - Lues maligna: papulapustular skin lesions that evolve into ulcerative lesion with sharp borders.
  - Condyloma lata: flat, moist, papular lesions in warm intertrigenous regions.

*Section 7.5 is taken from the Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-Infected Adults and Adolescents: recommendations from the CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America.*
• *Latent Syphilis:*
  ■ Serologic reactivity without clinical signs and symptoms of infection.

• *Neurosyphilis:*
  ■ General Paresis:
    ✦ Progressive dementing illness (months-years)
    ✦ Progressive memory loss
    ✦ Forgetfulness
    ✦ Personality changes including depression, mania, psychosis
  ■ Possible focal symptoms:
    ✦ Facial/limb hypotonia
    ✦ Tabes dorsalis (sudden pains in limbs, back, face lasts min-days)
    ✦ Dysarythmia
    ✦ Uveitis
    ✦ CVA
    ✦ Cranial nerve abnormalities
    ✦ Absent lower extremity reflexes, loss of vibratory sensation

**Diagnosis:**

• Need combination of 3 factors if possible:
  ■ Primary/Secondary/Latent: Positive reactive serum serologic tests
  ■ Neurosyphilis/CNS Infection
    ✦ Neurologic signs/symptoms
    ✦ Positive reactive serum serologic tests
    ✦ CSF test: Elevated WBC count >5, elevated protein, +CSF PCR or VDRL or RPR

**Treatment:**

• *Early-Stage (primary, secondary, early-latent):*
  ■ Single dose intramuscular injection of 2.4 million Units of benzathine penicillin G. For penicillin allergic patients, can give doxycycline 100mg po bid for 14 days.

• *Late-Latent:*
  ■ 3 weekly intramuscular injections of 2.4 million units of benzathine penicillin G. If allergic, alternative therapy is doxycycline 100mg po bid for 28 days.

• *Neurosyphilis/Ocular/otic Syphilis:*
  ■ First-Line Regimen:
    ✦ Aqueous Crystalline Penicillin G: 24 MU/day continuous infusion for 10-14 days or 4 MU IV q4hrs for 10-14 days.
• Procaine Penicillin 2.4MU IM daily + Probenecid 500mg po every 6 hours for 10-14 days (Note: do not give probenecid with sulfa allergy).

■ Alternative Regimen:
  ♦ Ceftriaxone 2gm IV/day for 10-14 days

Note: If CSF pleocytosis was initially present, recommend repeating CSF cell count after 6 months. If CSF WBC has not decreased after 6 months, retreatment should be considered.

• Successful Syphilis treatment = 4-fold decrease in serum RPR.

Initiation of ARVs:
• If not on ARVs, initiate ARV treatment within 14 days of neurosyphilis treatment.

7.6 Pneumocystis Pneumonia

Background:
• Pneumocystis jirovecii is a ubiquitous fungus.
• Two-thirds of healthy children have antibodies to P. jirovecii by ages 2-4 years.
• Disease occurs with reactivation of latent infection and new acquisition of the infection.
• Approximately 90% of PJP cases occur in patients with CD4 counts < 200 cells/μL.

Clinical Manifestations:
• Subacute onset of progressive dyspnea, non-productive cough, fever, chest discomfort that worsens over days to weeks.
• Hypoxemia often exacerbated by walking/exercise.
• Hypoxemia ranges from mild (room air arterial oxygen [pO2] ≥70mm Hg or alveolar-arterial O2 gradient, [A-a] DO2 <35 mm Hg) to moderate ([A-a] DO2 ≥35 and <45 mm Hg) to severe ([A-a] DO2 ≥45 mm Hg).

* Section 7.6 is taken from the Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-Infected Adults and Adolescents: recommendations from the CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America.
**Diagnosis:**

- Usually have CD4<200.
- CXR: typically demonstrates diffuse, bilateral, symmetrical “ground-glass” interstitial infiltrates emanating from the hila in a butterfly pattern. However, CXR can be normal in early disease.
- CXR also can show cysts, blebs, adenopathy. Spontaneous pneumothoraces should raise suspicion of PCP in HIV-infected patients.
- If possible, histopathologic or cytopathologic demonstration of organisms in tissue, bronchoalveolar lavage (BAL) fluid, or induced sputum samples is required for a definitive diagnosis.
- Polymerase chain reaction (PCR) is an alternative method for diagnosing PCP and is very sensitive and specific for detecting Pneumocystis; however, PCR cannot distinguish colonization from disease.
- 1,3ß-D-glucan can be elevated in patients with PCP but has low specificity for establishing a PCP diagnosis, as many other fungal diseases can cause positive results.

**Treatment:**

- For Moderate to Severe PCP
  - Preferred Therapy:
    - TMP-SMX: (TMP 15–20 mg and SMX 75–100 mg)/kg/day IV given q6h or q8h; can change to PO after clinical improvement. Treat for 21 days.
    - Adjunctive corticosteroids are indicated in moderate to severe cases.
    - For Moderate to Severe PCP Based on the Following Criteria:
      - PaO2 <70 mmHg at room air, or
      - Alveolar-arterial O2 gradient ≥35 mm Hg.
  
Begin Prednisone as early as possible in treatment course.

<table>
<thead>
<tr>
<th>Prednisone</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days 1-5</td>
<td>40mg PO BID</td>
</tr>
<tr>
<td>Days 6-10</td>
<td>40mg PO daily</td>
</tr>
<tr>
<td>Days 11-21</td>
<td>20mg PO daily</td>
</tr>
</tbody>
</table>
Alternative Therapy:
- Pentamidine 4 mg/kg IV once daily infused over at least 60 minutes; may reduce the dose to 3 mg/kg IV once daily because of toxicities, or
- Primaquine 30 mg (base) PO once daily + (Clindamycin [IV 600 q6h or 900 mg q8h] or [PO 450 mg q6h or 600 mg q8h]).

For Mild to Moderate PCP
- Preferred Therapy treat for 21 days:
  - TMP-SMX: (TMP 15–20 mg/kg/day and SMX 75–100 mg/kg/day), given PO in 3 divided dose, or
  - TMP-SMX DS - 2 tablets TID.

Alternative Therapy:
- Dapsone 100 mg PO daily + TMP 15 mg/kg/day PO (3 divided doses), or
- Primaquine 30 mg (base) PO daily + Clindamycin PO (450 mg q6h or 600 mg q8h), or
- Atovaquone 750 mg PO BID with food.

Common Side Effects of Pneumocystis Pneumonia Drugs:
- Sulfadiazine:
  - Rash, fever, leukopenia, hepatitis, AKI.
- TMP-SMX: r:
  - Rash, hepatotoxicity, renal insufficiency, leukopenia/thrombocytopenia

Indications for Primary Prophylaxis
- CD4 count <200 cells/mm.³
- Preferred regimen:
  - TMP-SMX 1 DS PO daily or TMP-SMX 1 SS PO daily.
- Alternative regimens:
  - Dapsone 100 mg PO daily or Atovaquone 1500mg PO daily with food.

Indications for Discontinuing Primary Prophylaxis
- CD4 count >= 200 cells/mm³ for at least 3 months in response to ART.
- Consider if CD4 count is between 100-200 and HIV RNA remains undetectable for at least 3 months.

Initiation of ARVs:
- Start ARVs within 2 weeks of PCP treatment initiation. IRIS is uncommon in PCP infections, especially if steroids are used.
7.7 Mucocutaneous Candidiasis

**Background:**
- Majority of oropharyngeal and esophageal candidiasis are caused by *Candida albicans*.
- Commonly seen in patients with CD4 count <200 cells/mm.$^3$

**Clinical Manifestations:**
- Painless, creamy white, plaque-like lesions on the hard or soft palate, buccal or tongue surface.
- Occasionally can present with erythematous patches on upper palate.
- Esophageal candidiasis presents with burning pain and discomfort with swallowing and odynophagia.

**Diagnosis:**
- Usually made based on characteristic appearance of the lesions and response to therapy.
- Laboratory confirmation can be made by using scrapings of the white plaques and combining it with a potassium hydroxide preparation.

**Treatment:**
- **Oropharyngeal Candidiasis (Duration of Therapy: 7-14 days):**
  - Preferred Therapy
    ✦ Fluconazole 100mg po once daily, treat for 7-14 days
  - Alternative Therapy
    ✦ Clotrimazole troches 10mg PO 5 times daily or
    ✦ Itraconazole oral solution 200mg PO daily or
    ✦ Nystatin suspension 4-6 cc every 6 hours or
    ✦ Posaconazole oral suspension 400mg PO BID for 1 day, then 400 mg PO daily
- **Esophageal Candidiasis (Duration of Therapy: 14-21 days):**
  - Preferred Therapy:
    ✦ Fluconazole 100mg (up to 400mg) PO or IV daily, or
    ✦ Itraconazole oral solution 200mg PO daily.

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* Section 7.7 is taken from the Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-Infected Adults and Adolescents: recommendations from the CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America.
Alternative Therapy:
- Voriconazole 200mg PO or IV BID, or
- Isavuconazole 200mg PO as a loading dose, then 50mg PO daily, or
- Isavuconazole 400mg PO once-weekly, or
- Micafungin 150mg IV daily or Caspofungin 50mg IV daily, or
- Amphotericin B deoxycholate 0.6mg/kg IV qdaily.

Initiation of ARVs:
- There are no special considerations regarding ARV initiation; start within 14 days.

7.8 Cytomegalovirus (CMV) Encephalitis

Background:
- CMV is a double-stranded herpes virus.
- Risk factors: CD4<100, high CMV viremia, high HIV RNA (>100,000 copies/mL).
- Latent CMV infection does not equal CMV disease:
  - Latent CMV infection: + virus detection (PCR) in any body fluid regardless of symptoms/signs.
  - CMV disease: signs/symptoms of infection (fever, malaise, pancytopenia) or tissue invasive disease + signs of CMV infection.

Clinical Manifestations:
- Symptoms progress over couple of weeks (not days).
- CMV neurological diseases: dementia, ventriculoencephalitis, polyradiculomyopathies.
- Clinical Symptoms: lethargy, fever, confusion, dementia, retinitis, lower extremity weakness, absent reflexes.
- Retinitis = most common clinical manifestation:
  - Symptoms of floaters, visual field defects, scotomata.
  - 2/3 symptomatic patients have unilateral eye symptoms.

* Section 7.8 is taken from the Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-Infected Adults and Adolescents: recommendations from the CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America.  .
**Diagnosis:**
- Based on a compatible clinical syndrome and the presence of a positive CSF CMV PCR.

**Neuroimaging:**
- MRI brain with periventricular enhancement.

**Lumbar Puncture:**
- +CSF CMV PCR.
- Lymphocytic pleocytosis.
- Low-to-normal glucose, normal-to-elevated protein.

**Blood Tests:**
- CD4<100.
- Note: CMV viremia can be present in CMV disease-free patients (if latent form of infection) with low CD4 cell counts. Therefore, serologic blood tests to detect CMV by antigen, culture or PCR are not recommended for diagnosis of CMV end-organ disease because of poor positive predictive value.
- Also, a negative serum PCR assay does not rule out CMV end-organ disease.

**Treatment:**

**Induction Phase:**
- Ganciclovir 5gm/kg IV q12 + Foscarnet 90mg/kg IV q24 x 14-21 days (until significant clinical improvement, or
- Ganciclovir 5mg/kg IV q12 x 14-21 days, or

**Alternative Regimens:**
- Foscarnet 60 mg/kg IV q8h or 90 mg/kg IV q12h for 14–21 days, then 90–120 mg/kg IV q24h, or
- Cidofovir 5 mg/kg/week IV for 2 weeks, then 5 mg/kg every other week with saline hydration before and after therapy and probenecid 2 g PO 3 hours before the dose followed by 1 g PO 2 hours after the dose, and 1 g PO 8 hours after the dose (total of 4 g).

**Laboratory Monitoring:**
- Check CBC, serum electrolytes, renal function twice weekly during induction phase, once weekly during maintenance phase.
• **Maintenance Phase:**
  ■ Valganciclovir 900mg po qday and CD4>100 with undetectable VL for >3-6 months.

• **Side Effects of Anti-CMV Therapy:**
  ■ Ganciclovir/Valganciclovir:
    ✦ Neutropenia, thrombocytopenia, renal dysfunction.
  ■ Foscarnet:
    ✦ Renal dysfunction, electrolyte abnormalities (hypocalcemia, hypomagnesemia, hypokalemia), anemia, seizures.
  ■ Cidofovir:
    ✦ Renal dysfunction, neutropenia, uveitis, hypotony.

**Initiation of ARVs:**
■ If not on ARVs, initiate ARV treatment within 14 days of CMV treatment.

### 7.9 Herpes Simplex Virus (HSV) Disease and Encephalitis

**Background:**
• ~95% of HIV infected patients are seropositive for either HSV-1 or HSV-2.

**Clinical Manifestations:**
• **Oroabial Herpes**
  ■ Most common manifestation of HSV-1 infection, includes sensory prodrome around the lips followed by papules turning into vesicles with crusting.

• **Genital Herpes**
  ■ Can be caused by HSV-1 or HSV-2. Symptoms similar as above with sensory prodrome of pain and pruritus in the genital region followed by formation of papules, vesicles, ulcers, and crusting.
  ■ HSV-1 and HSV-2 are indistinguishable from one another on exam.

• **HSV Encephalitis**
  ■ Fever with 1-2 week history of behavior changes, decreased need for sleep, inflated self-esteem, impaired memory, loss of emotional control, aphasia, dysphagia, focal seizures.

* Section 7.9 is taken from the Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-Infected Adults and Adolescents: recommendations from the CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America.
• **Possible Focal Symptoms:**
  - Upward gaze palsy or facial numbness (symptoms of brainstem encephalitis).
  - Focal cranial nerve abnormalities, hemiparesis.

**Diagnosis:**

• **HSV Mucocutaneous Infections:**
  - Since it is difficult to diagnose mucosal infections accurately by clinical examination, a laboratory diagnosis is recommended.
  - Viral culture and HSV DNA polymerase chain reaction (PCR) are the preferred diagnostic tests.

• **HSV Encephalitis**
  - Clinical Manifestations + Neuroimaging + Laboratory tests (if possible, see below).
    ✦ Neuroimaging:
      ❖ Temporal lobe abnormalities.
    ✦ Lumbar Puncture:
      ❖ Lymphocytic pleocytosis, increased RBCs, elevated protein, HSV PCR.
    ✦ Blood tests:
      ❖ Serum HSV1-2 IgG+. Most patients will have reactivation disease with +IgG.

**Treatment:**

• **HSV Mucocutaneous Lesions:**
  - Initial and Recurrent Infections.

• **Treatment Duration 5-10 Days.**
  - Valacyclovir 1gm PO BID, or
  - Famciclovir 500mg PO BID, or
  - Acyclovir 400mg TID
  - *For severe mucocutaneous infections, use Acyclovir 5mg/kg IV q8, once lesions begin to improve, then change to above therapy.

• **Chronic Suppressive Therapy:**
  - Suppressive therapy can be considered for patients who have severe or frequent HSV recurrences. Therapy can be continued indefinitely, but continuation should be addressed on an annual basis.
  - Suggested suppressive regimens include:
    ✦ Valacyclovir 500mg PO BID, or
    ✦ Famciclovir 500mg PO BID, or
    ✦ Acyclovir 400mg PO BID.
- **HSV Encephalitis:**
  - IV Acyclovir 10-12.5mg/kg IV q8h + IVF bolus to prevent crystalluria and renal failure.
  - Treat 14-21 days.
  - Mortality can occur up to ~20%-30% of cases even with treatment.

**Initiation of ARVs:**
- If not on ARVs, initiate ARV treatment within 14 days of HSV treatment.

### 7.10 Varicella-Zoster Virus (VZV)**

**Background:**
- Reactivation of latent VZV results in herpes zoster (shingles).
- Incidence of herpes zoster is >15-fold higher in HIV-infected adults than for age-matched controls.
- VSV reactivation in HIV patients can occur at any CD4 count, but is most common when CD4 counts are <200 cells/mm$^3$.

**Clinical Manifestations:**
- **Skin:** painful cutaneous eruption of stages of macules, papules, vesicles, pustules, and crusting that occur in a dermatomal distribution. Successive crops of new lesions occur in the presence of lesions in different stages.
- Most common sites include thoracic dermatomes (40%-50% cases), cranial nerve (20%-25%), cervical (15%-20%), lumbar (15%), and sacral (5%) dermatomes.
- Neurological syndromes including multifocal leukoencephalitis, myelitis, CNS vasculitis, ventriculitis, optic neuritis, asceptic meningitis, cranial nerve palsies, and focal brain-stem lesions can occur.
- Progressive outer retinal necrosis (PORN) and acute retinal necrosis (ARN) are caused by VZV.

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* HSV Encephalitis information taken from CDC Source: [https://www.cdc.gov/vaccines/adults/rec-vac/health-conditions/hiv.html](https://www.cdc.gov/vaccines/adults/rec-vac/health-conditions/hiv.html)

** Section 7.10 is taken from the Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-Infected Adults and Adolescents: recommendations from the CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America.
**Diagnosis:**
- Generally made on a clinical basis due to the distinctive appearance of lesions.

**Treatment:**
- **Post-Exposure Prophylaxis:**
  - Indication: Close contact with a person with herpes zoster or varicella and is susceptible to VZV.
  - Treatment: Valacyclovir 1g PO TID for 5-7 days, or Acyclovir 800 mg PO 5 times a day for 5-7 days.

- **Primary Varicella Infection:**
  - Uncomplicated Cases: Valacyclovir 1 gm PO TID for 5-7 days or Acyclovir 800mg PO 5 times a day for 5-7 days.
  - Complicated/Severe Cases: Acyclovir 10-15 mg/kg IV q8 for 7-10 days. Can change to oral antivirals after clinical improvement.

- **Herpes Zoster (Shingles):**
  - Acute localized dermatomal: Valacyclovir 1000 mg PO TID, or Famciclovir 500 mg PO TID for 7-10 days.
  - Extensive Cutaneous Involvement: Acyclovir 10-15 mg/kg IV q8 until clinical improvement, then can change to valacyclovir 1gm PO TID or Famciclovir 500 mg PO TID or acyclovir 800 mg PO 5 times daily to Complete 10-14 day course.

**Initiation of ARVs:**
- Initiate ARVs within 14 days.

### 7.11 Chronic Diarrhea*

**Background:**
- Acute and chronic diarrhea are common symptoms with advanced immunosuppression. The most common etiologies of acute and chronic diarrhea are cryptosporidiosis, cyclospora, microsporidiosis, and bacterial enteric gram negative infections, (i.e. Salmonella, E.coli, Shigellosis, Campylobacter sp).

* Section 7.11 is taken from the Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-Infected Adults and Adolescents: recommendations from the CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America.
**Clinical Manifestations:**
- *Cryptosporidiosis, cyclospora, microsporidosis:* acute or chronic watery diarrhea, with or without abdominal cramping, nausea and vomiting. Rarer symptoms such as encephalitis, acute hepatitis, respiratory diseases, and keratoconjunctivitis have been seen with a few species of microsporidiosis (i.e. *E. bieneusi, E. hellem*).
- *Enteric gram-negative infections:* present with self-limited gastroenteritis or more severe symptoms including fevers, bloody diarrhea, and sepsis.

**Diagnosis:**
- *Cryptosporidiosis, cyclospora, microsporidosis:* typically is a clinical diagnosis but special tests such as stool cultures, special gram stains, acid-fast staining, immunofluorescence, and light microscopy can be used.
- Enteric gram-negative infections: stool cultures and blood cultures (if available).

**Treatment:**
- *Cryptosporidiosis:*
  - Start ARVs if not on therapy. Aggressive oral and/or IV
    - IV rehydration and electrolyte replacement. No antibiotic therapy has been shown to be effective. Alternative therapy with Nitazoxanide 500-1000 mg PO BID x 14 days or
    - Paromomycin 500 mg PO QID 14-21 days could be considered
- *Cyclospora:*
  - Start ARVs if not on therapy. TMP-SMX (160mg/800mg) PO BID for 7-14 days
    - For sulfa allergies, try Nitazoxanide 500 mg PO once daily for 7 days or Ciprofloxacin 500 mg
    - PO BID for 7-14 days
- *Microsporidosis:*
  - Start ARVs if not on therapy. Aggressive oral and/or IV
    - IV rehydration and electrolyte replacement. No specific antibiotics have been shown to be effective. Anti-motility agents can be used for diarrhea control, if needed.
• **Enteric gram-negative infections:**
  ■ Salmonella and Shigella sp:
    ✦ Ciprofloxacin 500 mg PO BID (or other fluoroquinolone) for 7-14 days. TMP-SMX or extended spectrum cephalosporins (i.e. Ceftriaxone also may be used depending on susceptibilities for 7-14 days.
  ■ Campylobacter spp:
    ✦ Ciprofloxacin 500mg PO BID for 7-10 days, or Azithromycin 500mg PO once daily for 5 days (due to increased resistance to antibiotics, stool culture and sensitivities should be performed).

**Initiation of ARVs:**
• Initiate ARVs as soon as possible as they will help improve diarrhea symptoms.

**7.12 Kaposi Sarcoma**

**Background:**
• Kaposi Sarcoma (KS) is a vascular tumor caused by HHV-8 and is the most common malignancy in HIV-infected patients and most commonly is seen with CD4 counts under 200. However, with the introduction of ARVs, the incidence of KS has dramatically decreased. KS most commonly involves the skin (cutaneous), visceral (lymph nodes, bone marrow, oral disease), respiratory tract and GI tract.

**Clinical Manifestations:**
• **Cutaneous KS:**
  ■ Lesions often appear on face, upper and lower extremities, and abdomen and back. Lesions are nonpainful and nonpruritic. They often appear elliptical and can be purple, blacks, red, brown and pink in color.
• **Visceral Disease:**
  ■ Most common involvement is the oral cavity and lesions have characteristics similar to cutaneous lesions. Also can present as lymphadenopathy or bone marrow suppression with pancytopenia.

* Section 7.12 was taken from Groopman, J. AIDS-related Kaposi sarcoma: Staging and Treatment. UpToDate. Waltham, MA.: UpToDate; 2018. www.uptodate.com.
• **Gastrointestinal Tract:**
  ■ Symptoms including abdominal pain, weight loss, upper and lower GI bleeding, nausea and vomiting, intestinal obstruction can be seen. Often diagnosed by endoscopy when hemorrhagic nodules are seen.

• **Respiratory Tract Disease:**
  ■ Symptoms including shortness of breath, hemoptysis, chest pains, in the setting of pleural effusions, pulmonary nodules, and alveolar infiltrates are often seen.

**Diagnosis:**
• Biopsies should be taken at the concerned site (ie skin, oral mucosal, GI tract, lung/pleurocentesis) to establish a diagnosis.

**Treatment:**
• **Dependent on stage of disease:**
  ■ Overall goals include shrinkage of tumor, prevention of disease progression and symptom palliation.
  ■ Start ARVs immediately.
  ■ Approximately 50% of patients’ symptoms will improve with ARVs. However, further chemotherapy may be needed and patients should be referred to an oncologist for further treatment.

**Initiation of ARVs:**
• Initiate ARVs as soon as possible, and are indicated in virtually all patients with KS.

**7.13 Cervical Cancer**

**Background:**
• Human papillomavirus (HPV) is the main cause of cervical cancer and is detected in 99.7% of cases of cervical cancer. The two most common histologic types of cervical cancer are squamous cell (69% of cases) and adenocarcinoma (~25% of cases). Risk factor include multiple sexual partners, early onset of sexual activity, high risk sexual partner with known HPV infections, history of sexual transmitted infections, and immunosuppression. There are approximately 15 known strains of HPV to be oncogenic including HPV 16 and 18 which are present in ~70% of cases.

*Section 7.13 was taken from Frumovitz, M. Invasive cervical cancer: Epidemiology, risk factors, clinical manifestations, and diagnosis. UpToDate. Waltham, MA.: UpToDate; 2018. www.uptodate.com.*
Clinical Manifestations:
- Early cervical cancer is often asymptomatic but may have postcoital bleeding or irregular vaginal bleeding. Later stages include heavy vaginal bleeding, weight loss, pelvic and/or lower back pain; hematuria and hematochezia may be seen.

Diagnosis:
- Visual inspection and biopsy of the cervix. Diagnosis based on histologic evaluation of cervical biopsy.

Treatment:
- Depends on stage of cancer (Stage T1-T4) and whether or not metastasis is present. Referral to OB-GYN and oncologist is recommend for further treatment and workup if cervical cancer is suspected as chemotherapy and/or surgery may be warranted.

Initiation of ARVs:
- Start ARVs as soon as possible.
Chapter 8
Vaccinations
Chapter 8: Vaccinations

Vaccinations are very important for people who have HIV. Since HIV weakens the immune system it also weakens the body’s response to vaccines. Since a stronger immune system makes vaccines more effective, vaccines work better when people with HIV are on ARVs and when CD4 counts are above 200. Whenever possible, ARVs should be started prior to receiving vaccinations. Although there are no current vaccines to prevent or cure HIV, people with HIV should receive the following vaccines to help prevent the following infections:

- Hepatitis B (3 dose series)
- Human papillomavirus (HPV) (2 doses, up to age 26)
- Meningococcal (Menveo or Menactra) above 2 months of age
- PCV 13 (Prevnar 13) for infants, children and adults
- PSV 23 Pneumovax (age 2 and older)
- Tetanus, diphtheria, and pertussis (Tdap). Every 10 years a repeat vaccination against tetanus and diphtheria (Td) is recommended
- Measles, Mumps, Rubella (MMR) starting age 12 months (2 doses)
- Varicella (2 doses)

Of note, live attenuated vaccines contain a weakened form of a live virus, however these vaccines do not generally cause disease but can trigger immune responses (with fevers, arthralgias, etc.). It is recommended that patients with HIV receive live vaccines only when CD4 counts are above 200. Inactive vaccines can be given at any CD4 count, but may not be as effective if CD4 counts are below 200 and repeat vaccinations may need to be given.

* Chapter 8 information taken from CDC Source: https://www.cdc.gov/vaccines/adults/rec-vac/health-conditions/hiv.html.
### Table 16: Recommended Immunization Schedule for Adults and Adolescents with HIV Infection

<table>
<thead>
<tr>
<th>VACCINE</th>
<th>AGE</th>
<th>CD4 Cell Count (cells/pL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>13-18 years</td>
<td>19-26 years</td>
</tr>
<tr>
<td>Influenza¹</td>
<td>1 dose annually</td>
<td>1 dose annually</td>
</tr>
<tr>
<td>Tdap/Td²</td>
<td>1 dose Tdap, then Td booster every 10 yrs</td>
<td>1 dose Tdap, then Td booster every 10 yrs</td>
</tr>
<tr>
<td>MMR³</td>
<td>2 doses if CD4 cell count ≥200</td>
<td>2 doses if CD4 cell count ≥200</td>
</tr>
<tr>
<td>VAR⁴</td>
<td>2 doses if CD4 cell count ≥200</td>
<td>2 doses if CD4 cell count ≥200</td>
</tr>
<tr>
<td>HZV⁵</td>
<td>3 doses</td>
<td>3 doses</td>
</tr>
<tr>
<td>HPV⁶</td>
<td>3 doses</td>
<td>3 doses</td>
</tr>
<tr>
<td>PCV13⁷</td>
<td>1 dose</td>
<td>1 dose</td>
</tr>
<tr>
<td>PPSV23⁷</td>
<td>2 doses</td>
<td>2 doses</td>
</tr>
<tr>
<td>HepA⁸</td>
<td>2 or 3 doses depending on vaccine</td>
<td>2 or 3 doses depending on vaccine</td>
</tr>
<tr>
<td>HepB⁹</td>
<td>3 doses</td>
<td>3 doses</td>
</tr>
<tr>
<td>MenACWY¹⁰</td>
<td>2 doses, then booster every 5 yrs</td>
<td>2 doses, then booster every 5 yrs</td>
</tr>
<tr>
<td>MenB¹⁰</td>
<td>2 or 3 doses depending on vaccine</td>
<td>2 or 3 doses depending on vaccine</td>
</tr>
<tr>
<td>Hib¹¹</td>
<td>1 or 3 doses depending on indication</td>
<td>1 or 3 doses depending on indication</td>
</tr>
</tbody>
</table>

**Abbreviations Used for Vaccines**

- **MMR**: measles, mumps, and rubella vaccine (live)
- **PCV13**: 13-valent pneumococcal conjugate vaccine
- **PPSV23**: 23-valent pneumococcal polysaccharide vaccine
- **RIV**: recombinant influenza vaccine (inactivated)
- **Td**: tetanus and diphtheria toxoids
- **Tdap**: tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine
- **VAR**: varicella vaccine (live)

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*Report clinically significant postvaccination events to the Vaccine Adverse Event Reporting System (VAERS) at www.vaers.hhs.gov or by telephone, 800-822-7967.*

*All vaccines listed on this immunization schedule except herpes zoster and 23-valent pneumococcal polysaccharide vaccines are covered by the Vaccine Injury Compensation Program. Information on how to file a claim is available at www.hrsa.gov/vaccinecompensation or by telephone, 800-338-2382.*

*Table 16 taken from Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. United States Department of Health and Human Services.*
Chapter 9
Immune Reconstitution Inflammatory Syndrome (IRIS)
Chapter 9: Immune Reconstitution Inflammatory Syndrome (IRIS)\textsuperscript{15*}

**Background:**
- IRIS is an inflammatory reaction against a foreign antigen (alive or dead) in patients who have started ART. IRIS often occurs between two weeks to 3 months after ARVs are initiated when the immune system begins to strengthen. The immune system, once it regains some function, is now able to respond against the foreign antigen. Most commonly, IRIS occurs when CD4 count is $<200$ cells/μL at the time of ART initiation.

**Diagnostic Criteria:**
- CD4 count (often less than 100 cells/μL)
- Improvement of CD4 and immunologic response to ARVs
- Symptoms not better explained by an obvious underlying infection, adverse drug reactions, drug allergy
- Clinical manifestations consistent with an inflammatory condition
- Temporal association between ART initiation and inflammatory symptoms

**Common Pathogens Associated with IRIS:**
- Mycobacterium tuberculosis
- Mycobacterium avium complex
- Cryptococcus neoformans
- Cytomegalovirus
- Hepatitis B virus
- Herpes Simplex virus
- Human herpes virus (associated with Kaposi sarcoma)

Management:
- Identify the underlying infection that the immune system is responding to:
  - If it has already been treated or is currently being treated, then evaluate for treatment failure of the underlying infection as a cause for increased symptoms
  - If the underlying infection has not been treated yet, then begin infection-specific treatment
- Continue ARVs.
- Treat the IRIS-associated inflammation:
  - Mild-moderate symptoms: nonsteroidal anti-inflammatory drugs (ibuprofen, naproxen, acetylsalicylic acid)
  - Severe symptoms: glucocorticoids (ie prednisone 0.5-1.0 mg/kg/day), with gradual taper over 4-8 weeks
    - Note: steroids should not be used for KS-associated IRIS as they may result in acute worsening of the KS
References


### Appendix A: ART Associated Adverse Events that can be Managed with Substitution of Alternative Antiretroviral Agent⁷*

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>ARV Agent(s) or Drug Class</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bone Density Effects</strong></td>
<td>TDF&lt;sup&gt;a&lt;/sup&gt; TAF or ABC&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Declines in BMD have been observed upon initiation of most ART regimens. Switching from TDF to alternative ARV agents has been shown to increase bone density, but the clinical significance of this increase remains uncertain. TAF is associated with smaller declines in BMD than TDF, and patients show improvement in BMD upon switching to TAF. The long-term impact of TAF on patients with osteopenia or osteoporosis is unknown; close clinical monitoring is recommended in this setting.</td>
</tr>
<tr>
<td><strong>Bone Marrow Suppression</strong></td>
<td>AZT TDF TAF or ABC&lt;sup&gt;b&lt;/sup&gt;</td>
<td>AZT has been associated with neutropenia and macrocytic anemia.</td>
</tr>
<tr>
<td><strong>Cardiac QTc Interval Prolongation</strong></td>
<td>EFV RPV A PI- or INSTI-based regimen</td>
<td>High EFV and RPV exposures may cause QT prolongation. Consider switching from EFV- or RPV-based regimens if patient is taking other medications with known risk of Torsades de Pointes, or in patients at higher risk of Torsades de Pointes.</td>
</tr>
<tr>
<td><strong>Cardiovascular Events</strong></td>
<td>ABC TDF TAF FTC or 3TC</td>
<td>ABC use has been associated with CV disease and cardiac events in some, but not all, observational studies. TDF has been associated with lower lipid levels than TAF.</td>
</tr>
<tr>
<td><strong>Myocardial infarction, ischemic stroke</strong></td>
<td>RTV- or COBI-boosted PI regimens EFV EVG/c</td>
<td>RAL DTG BIC and RPV have less effect on lipids than RTV- or COBI-boosted PI regimens, EFV, and EVG/c</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>ARV Agent(s) or Drug Class</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Central Nervous System, Neuropsychiatric Side Effects</strong></td>
<td>EFV, RPV</td>
<td>Switch From: ETR, PI/c, or PI/r INSTIs may be used, but monitoring is recommended (see Comments column). Switch To: INSTIs are associated with insomnia. Depression and suicidality have been infrequently reported with INSTI use, primarily in patients with pre-existing psychiatric conditions.</td>
</tr>
<tr>
<td>Dizziness, suicidal ideation, abnormal dreams, depression</td>
<td>RAL, DTG, BIC, or RPV</td>
<td>Elevated TG and LDL levels are more common with LPV/r and FPV/r than with other RTV-boosted PIs. Improvements in TG and LDL levels have been observed with switch from LPV/r to ATV or ATV/r.</td>
</tr>
<tr>
<td><strong>Dyslipidemia</strong></td>
<td>RAL, DTG, BIC, or RPV</td>
<td>Hypertriglyceridemia (with or without elevated LDL level) RTV- or COBI-boosted regimens, and EFV Elevation of TG and LDL levels is more common with LPV/r and FPV/r than with other RTV-boosted PIs. Improvements in TG and LDL levels have been observed with switch from LPV/r to ATV or ATV/r.</td>
</tr>
<tr>
<td>Gastrointestinal Effects</td>
<td>LPV/r</td>
<td>Gastrointestinal Effects Nausea, diarrhea Other RTV- or COBI-boosted regimens RAL, DTG, BIC, or NNRTIs Gastrointestinal intolerance is common with boosted PIs and is linked to the total dose of RTV. More GI toxicity is seen with LPV/r than with ATV/r or DRV/r. GI effects are often transient and do not warrant substitution unless they are persistent and intolerable.</td>
</tr>
</tbody>
</table>
| **Hypersensitivity Reaction**                                               | ABC                         | ABC TDF or TAF

NVP, EFV, ETR, RPV

Non-NNRTI ART

DTG, RAL

MVC

Non-INSTI ART

Suitable alternative ART

Reactions to NVP, ETR, RAL, DTG, and MVC may be accompanied by elevated liver transaminases. |
| **Insulin Resistance**                                                       | LPV/r, FPV/r                | LPV/r, FPV/r INSTI, NNRTI Insulin Resistance Results of switch studies have been inconsistent. Studies in HIV-negative patients suggest a direct causal effect of LPV/r (and IDV) on insulin resistance. However, traditional risk factors may be stronger risk factors for insulin resistance than the use of any PI. |
| **Jaundice and Icterus**                                                     | ATV, ATV/c, ATV/r           | ATV, ATV/c, ATV/r DRV/c, DRV/r, INSTI, or NNRTI Jaundice and Icterus Increases in unconjugated bilirubin are common with ATV and generally do not require modification of therapy unless resultant symptoms are distressing to the patient. |
| **Lipoatrophy**                                                              | d4T, AZT                    | d4T, AZT TDF, TAF, or ABC

Peripheral lipoatrophy is associated with prior thymidine analog (d4T and AZT) use. Switching from these ARVs prevents worsening lipoatrophy, but fat recovery is typically slow (may take years) and incomplete. |
<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>ARV Agent(s) or Drug Class</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipohypertrophy</td>
<td>Accumulation of visceral, truncal, dorsocervical, and breast fat has been observed during ART, particularly during use of older PI-based regimens (e.g., IDV), but whether ART directly causes fat accumulation remains unclear. There is no clinical evidence that switching to another first-line regimen will reverse weight or visceral fat gain.</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NNRTIs (especially NVP and EFV)</td>
<td>PI- or INSTI-based regimen</td>
<td>Mild rashes that develop after initiation of NNRTIs other than NVP rarely require treatment switch. When serious rash develops due to any NNRTI, switch to another drug class.</td>
</tr>
<tr>
<td>DRV/c, DRV/r</td>
<td>ATV/c, ATV/r, or another drug class (e.g., INSTI)</td>
<td>Mild rashes following DRV/r use may resolve without modification of therapy. For more severe reactions, change to an alternative boosted PI or an agent from another drug class.</td>
</tr>
<tr>
<td>Renal Effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Including proximal renal tubulopathy and elevated creatinine</td>
<td>TDF&lt;sup&gt;a&lt;/sup&gt;</td>
<td>ABC&lt;sup&gt;b&lt;/sup&gt; TAF (for patients with CrCl &gt;30 mL/min), NRTI-sparing regimens, or regimens using only 3TC or FTC as the NRTI may be considered if appropriate.</td>
</tr>
<tr>
<td>ATV/c, ATV/r, LPV/r</td>
<td>DTG, BIC, RAL, or NNRTI</td>
<td>COBI, DTG, BIC, and, to a lesser extent, RPV, can increase SCr through inhibition of creatinine secretion. This effect does not affect glomerular filtration. However, assess patient for renal dysfunction if SCr increases by &gt;0.4 mg/dL.</td>
</tr>
<tr>
<td>Stones</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephrolithiasis and cholelithiasis</td>
<td>ATV, ATV/c, ATV/r</td>
<td>DRV/c, DRV/r, INSTI, or NNRTI</td>
</tr>
</tbody>
</table>

<sup>a</sup> In patients with chronic active HBV infection, another agent that is active against HBV should be substituted for TDF.

<sup>b</sup> ABC should be used only in patients known to be HLA-B*5701 negative.

<sup>c</sup> TDF reduces ATV levels; therefore, unboosted ATV should not be coadministered with TDF.
Key to Abbreviations:
3TC = lamivudine
ABC = abacavir
ART = antiretroviral therapy
ARV = antiretroviral
ATV = atazanavir
ATV/c = atazanavir/cobicistat
ATV/r = atazanavir/ritonavir
BIC = bictegravir
BMD = bone mineral density
CD4 = CD4 T lymphocyte
CNS = central nervous system
COBI = cobicistat
CrCl = creatine clearance
CV = cardiovascular
d4T = stavudine
DOR = doravirine
DRV = darunavir
DRV/c = darunavir/cobicistat
DRV/r = darunavir/ritonavir
DTG = dolutegravir
EFV = efavirenz
ETR = etravirine
EVG/c = elvitegravir/cobicistat
FPV = fosamprenavir
FPV/r = fosamprenavir/ritonavir
FTC = emtricitabine
GI = gastrointestinal
HBV = hepatitis B virus
HSR = hypersensitivity reaction
IDV = indinavir
INSTI = integrase strand transfer inhibitor
LDL = low-density lipoprotein
LPV/r = lopinavir/ritonavir
MVC = maraviroc
NNRTI = non-nucleoside reverse transcriptase inhibitor
NRTI = nucleoside reverse transcriptase inhibitor;
NVP = nevirapine
PI = protease inhibitor
PI/c = protease inhibitor/cobicistat
PI/r = protease inhibitor/ritonavir
RAL = raltegravir
RPV = rilpivirine
RTV = ritonavir
Scr = serum creatinine
TAF = tenofovir alafenamide
TC = total cholesterol
TDF = tenofovir disoproxil fumarate
TG = triglycerides
AZT = zidovudine
## Appendix B: Key ART Drug-Drug Interactions

<table>
<thead>
<tr>
<th>ARV Drug</th>
<th>Key Interactions</th>
<th>Suggested Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZT</td>
<td>Ribavirin and pegylated interferon alpha-2a</td>
<td>Substitute AZT with TDF</td>
</tr>
<tr>
<td>TAF</td>
<td>Rifabutin, Rifapentine, rifampin</td>
<td>Coadministration is not recommended</td>
</tr>
<tr>
<td></td>
<td>Carbamazepine, phenobarbital, phenytoin</td>
<td>Coadministration is not recommended</td>
</tr>
<tr>
<td>Boosted PI (ATV/R, LPV/r)</td>
<td>Rifampicin</td>
<td>Substitute Rifampicin with Rifabutin. Adjust dose of LPV/r</td>
</tr>
<tr>
<td></td>
<td>H2 Receptor antagonists</td>
<td>Give ATV 2 hours before or 10 hours after H2 receptor antagonist</td>
</tr>
<tr>
<td></td>
<td>PPIs</td>
<td>PPIs are not recommended in PI-experienced patients</td>
</tr>
<tr>
<td></td>
<td>Lovastatin and Simvastatin</td>
<td>Use alternative cholesterol lowering agent</td>
</tr>
<tr>
<td></td>
<td>Alfuzosin, Tamsulosin, Silodosin</td>
<td>Contraindicated with PIs</td>
</tr>
<tr>
<td></td>
<td>Warfarin</td>
<td>Monitor INR closely, may need to decrease warfarin dose</td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban, Ticagrelor, Vora-paxar</td>
<td>Coadministration is not recommended</td>
</tr>
<tr>
<td></td>
<td>Amiodarone</td>
<td>Contraindicated</td>
</tr>
<tr>
<td></td>
<td>Fluticasone, Mometasone, Budesonide, Betamethasone</td>
<td>Do not coadminister unless potential benefits of inhaled/intranasal steroids outweigh the risks of adverse effects associated with corticosteroids</td>
</tr>
<tr>
<td></td>
<td>Carbamazepine, Phenobarbital, Phenytoin</td>
<td>Contraindicated</td>
</tr>
<tr>
<td></td>
<td>Hormonal contraceptives</td>
<td>Use of alternative or additional contraceptive methods</td>
</tr>
<tr>
<td></td>
<td>Methadone and Buprenorphine</td>
<td>Adjust Methadone and Buprenorphine doses</td>
</tr>
<tr>
<td></td>
<td>Astemizole and Terfenadine</td>
<td>Use alternative antihistamine</td>
</tr>
<tr>
<td></td>
<td>TDF</td>
<td>Monitor renal function</td>
</tr>
<tr>
<td></td>
<td>Simeprevir</td>
<td>Use alternative DAA</td>
</tr>
<tr>
<td></td>
<td>Ombitasvir+Paritaprevir+ Ritonavir+ Dasabuvir</td>
<td>Use alternative DAA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ARV Drug</th>
<th>Key Interactions</th>
<th>Suggested Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DTG/RAL</strong></td>
<td>Carbamazepine, Phenobarbital, Phenytoin</td>
<td>Use alternative anticonvulsant agent.</td>
</tr>
<tr>
<td></td>
<td>Polyvalent cation products (Mg, Al, Fe, Ca, Zn)</td>
<td>Use DTG at least 2 hours before or 6 hours after use of these supplements</td>
</tr>
<tr>
<td></td>
<td>St. John’s Wort</td>
<td>Do not coadminister</td>
</tr>
<tr>
<td><strong>EFV</strong></td>
<td>Methadone</td>
<td>Adjust the Methadone dose as appropriate</td>
</tr>
<tr>
<td></td>
<td>Hormonal contraceptives</td>
<td>Use alternative or additional contraceptive methods to prevent HIV transmission and unintended pregnancies as EFV may lower efficacy of some long-acting hormonal contraceptives</td>
</tr>
<tr>
<td></td>
<td>Astemizole and Terfenadine</td>
<td>Use alternative antihistamine</td>
</tr>
<tr>
<td></td>
<td>Voriconazole</td>
<td>Dose adjustment Voriconazole 400mg BID, EFV 300mg PO daily</td>
</tr>
<tr>
<td></td>
<td>Bedaquiline</td>
<td>Do not coadminister</td>
</tr>
<tr>
<td></td>
<td>Simeprevir, Elbasivir/Grazoprevi, Sofosbuvir/Velpatasvir</td>
<td>Use alternative DAA</td>
</tr>
<tr>
<td></td>
<td>Ombitasvir+Paritaprevir+Ritonavir+ Dasabuvir</td>
<td>Use alternative DAA</td>
</tr>
<tr>
<td></td>
<td>St. John’s Wort</td>
<td>Do not coadminister</td>
</tr>
<tr>
<td><strong>NVP</strong></td>
<td>Rifampicin</td>
<td>Substitute NVP with EFV</td>
</tr>
<tr>
<td></td>
<td>Methadone</td>
<td>Adjust the methadone dose as appropriate</td>
</tr>
<tr>
<td></td>
<td>Astemizole and Terfenadine</td>
<td>Use alternative antihistamine</td>
</tr>
<tr>
<td></td>
<td>Simeprevir, Sofosbuvir/ Velpatasvir/ Voxilaprevir</td>
<td>Use alternative DAA</td>
</tr>
<tr>
<td></td>
<td>Ombitasvir+Paritaprevir+Ritonavir+ Dasabuvir</td>
<td>Use alternative DAA</td>
</tr>
<tr>
<td></td>
<td>St. John’s Wort</td>
<td>Do not coadminister</td>
</tr>
</tbody>
</table>
# Appendix C: Clinical Stage of HIV Disease in Adults and Adolescents

<table>
<thead>
<tr>
<th>Symptoms, syndromes, conditions and diseases</th>
<th>ICD-10 Code</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACUTE HIV INFECTION</strong></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>Z21</td>
</tr>
<tr>
<td>Acute retroviral syndrome</td>
<td>B23.0</td>
</tr>
<tr>
<td><strong>CLINICAL STAGE I</strong></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic course</td>
<td>Z21</td>
</tr>
<tr>
<td>Persistent generalized lymphadenopathy</td>
<td>B23.1</td>
</tr>
<tr>
<td><strong>CLINICAL STAGE II</strong></td>
<td></td>
</tr>
<tr>
<td>Unexplained weight loss (≤ 10% within 6 months)</td>
<td>B22.2</td>
</tr>
<tr>
<td>Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis - 2 or more episodes within 6 months)</td>
<td>B20.1</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>B20.3</td>
</tr>
<tr>
<td>Angular cheilitis</td>
<td>B23.8</td>
</tr>
<tr>
<td>Recurrent aphthous stomatitis (two or more episodes within 6 months)</td>
<td>B23.8</td>
</tr>
<tr>
<td>Recurrent oral ulceration</td>
<td>B23.8</td>
</tr>
<tr>
<td>Papular pruritic eruption</td>
<td>B23.8</td>
</tr>
<tr>
<td>Seborrhoeic dermatitis</td>
<td>B23.8</td>
</tr>
<tr>
<td>Fungal nail infections</td>
<td>B20.5</td>
</tr>
<tr>
<td><strong>CLINICAL STAGE III</strong></td>
<td></td>
</tr>
<tr>
<td>Unexplained weight loss (over 10% within 6 months)</td>
<td>B22.2</td>
</tr>
<tr>
<td>Unexplained chronic diarrhea for longer than 1 month</td>
<td>B22.7</td>
</tr>
<tr>
<td>Unexplained persistent fever (intermittent or constant for longer than 1 month)</td>
<td>B24</td>
</tr>
<tr>
<td>Persistent oral candidiasis (thrush) (two or more episodes within 6 months)</td>
<td>B20.4</td>
</tr>
<tr>
<td>Oral hairy leukoplakia</td>
<td>B23.8</td>
</tr>
<tr>
<td>Pulmonary tuberculosis</td>
<td>B20.0</td>
</tr>
<tr>
<td>Severe bacterial infections (such as pneumonia, meningitis, empyema, pyomyositis, arthritis or osteitis, severe inflammatory small pelvis disease, etc.)</td>
<td>B20.1</td>
</tr>
<tr>
<td>Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis</td>
<td>B22.7</td>
</tr>
<tr>
<td>Unexplained anemia (≤ 80 g/L), neutropenia (≤ 0.5×10⁹/L) and/or chronic thrombocytopenia (≤ 50×10⁹/L)</td>
<td>B23.2</td>
</tr>
<tr>
<td><strong>CLINICAL STAGE IV</strong></td>
<td></td>
</tr>
<tr>
<td>HIV wasting syndrome</td>
<td>B22.2</td>
</tr>
<tr>
<td>Pneumocystis pneumonia</td>
<td>B20.6</td>
</tr>
<tr>
<td>Symptoms, syndromes, conditions and diseases</td>
<td>ICD-10 Code</td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Recurrent aphthous stomatitis (two or more episodes within one year)</td>
<td>B20.1</td>
</tr>
<tr>
<td>Chronic herpes simplex infection of more than 1 month in duration</td>
<td>B20.3</td>
</tr>
<tr>
<td>Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)</td>
<td>B20.4</td>
</tr>
<tr>
<td>Extrapulmonary tuberculosis (incl. lymph nodes)</td>
<td>B20.0</td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
<td>B21.0</td>
</tr>
<tr>
<td>Cytomegalovirus infection (retinitis or infection of other organs)</td>
<td>B20.2</td>
</tr>
<tr>
<td>CNS Toxoplasmosis</td>
<td>B20.8</td>
</tr>
<tr>
<td>HIV-associated encephalopathy</td>
<td>B22.0</td>
</tr>
<tr>
<td>Extrapulmonary cryptococcosis, including meningitis</td>
<td>B20.5</td>
</tr>
<tr>
<td>Disseminated nontuberculous mycobacterial infection</td>
<td>B20.0</td>
</tr>
<tr>
<td>Progressive multifocal leukoencephalopathy (PML)</td>
<td>B20.3</td>
</tr>
<tr>
<td>Chronic cryptosporidiosis (with diarrhea for longer than 1 month)</td>
<td>B20.8</td>
</tr>
<tr>
<td>Chronic isosporiasis</td>
<td>B20.8</td>
</tr>
<tr>
<td>Disseminated mycosis (candidiasis, coccidioidomycosis, histoplasmosis)</td>
<td>B20.4 B20.5</td>
</tr>
<tr>
<td>Lymphoma (cerebral or B-cell non-Hodgkin)</td>
<td>B21.3</td>
</tr>
<tr>
<td>Symptomatic HIV-associated nephropathy or cardiomyopathy</td>
<td>B23.8</td>
</tr>
<tr>
<td>Recurrent septicaemia (including nontyphoidal Salmonella)</td>
<td>B20.1</td>
</tr>
<tr>
<td>Invasive cervical carcinoma</td>
<td>B21.8</td>
</tr>
<tr>
<td>Atypical disseminated leishmaniasis</td>
<td>B20.8</td>
</tr>
</tbody>
</table>