



HIV in pregnancy

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On successful completion of this module you should be able to:

- Know the global burden of HIV in pregnancy.
- Describe the screening and diagnostic measures for HIV in general and during and after pregnancy.
- Describe the interventions to prevent HIV transmission in general and in pregnancy (PMTCT).
- Describe the laboratory and clinical monitoring of HIV-positive pregnant women and HIV-exposed newborns.
- Describe the ARV regimens in general and during and after pregnancy.
- Know what complications to expect and how to manage them when a pregnant woman is on ART.
- Know the indications for stopping or substituting ARVs and how to stop or substitute ARVs in a pregnant woman with HIV.
- Identify the common HIV co-infections and measures to reduce morbidity and mortality.
- Know the key enablers for improving quality of HIV care services.

Introduction

The human immunodeficiency virus (HIV) is a ribonucleic acid (RNA) retrovirus that infects the immune cells (especially the CD4 helper T cells) of its human hosts (Chou 2012).

There are two types of HIV: HIV-1 and HIV-2. HIV-1 is responsible for most of HIV infections globally (WHO 2016).

HIV-2 infection is more common in West Africa (Chou 2012).

HIV causes a progressive reduction in the number of immune cells, and leads to Acquired Immunodeficiency Syndrome (AIDS) in most patients if left untreated (Diaz-Rossello 2008).

- AIDS is a life threatening disease characterized by severe dysfunction of the immune system with a CD4 T cell count $\leq 0.200 \times 10^9$ cells/L (200 cells/mm³) or one or more AIDS-defining opportunistic infections or neoplastic conditions (Chou 2012).

Global burden of HIV in pregnancy

HIV infection is a pandemic disease.

Globally, 36.7 million individuals were living with HIV in 2015 (UNAIDS 2016).

In 2015, 17.8 million individuals living with HIV globally were women aged 15 years and older and 1.8 million were children under 15 years of age (UNAIDS 2016).

More than 90% of HIV-positive pregnant women reside in sub-Saharan Africa (Kendall, 2014).

There were 150 000 new paediatric HIV infections in 2015, a decline of about 50% since 2010 (UNAIDS 2016).

HIV is the leading cause of death in women of reproductive age globally; responsible for one quarter of deaths during pregnancy and the six week postpartum period in sub-Saharan Africa (Kendall 2014).

In line with the Sustainable Development Goals (SDGs), the new treatment targets for 2020 is that; 90% of the people living with HIV know their HIV status, 90% of the people who know their HIV status are receiving ART and 90% of the people receiving ART have suppressed viral loads. This aims to end the AIDS epidemic as a public health threat by 2030 (WHO 2016).

Global burden of HIV in pregnancy by region

Region	People living with HIV in 2015 (all ages)	Estimated number of pregnant women living with HIV in 2015
Asia and the Pacific	5.1 million [4.4 million–5.9 million]	77 000
Eastern and southern Africa	19 million [17.7 million–20.5 million]	960 000
Eastern Europe and central Asia	1.5 million [1.4 million–1.7 million]	10 000 (2013)
Latin America and the Caribbean	2 million [1.7 million–2.3 million]	28 000
Middle East and North Africa	230 000 [160 000–330 000]	7000
Western and central Africa	6.5 million [5.3 million–7.8 million]	340 000
Western and central Europe and North America	2.4 million [2.2 million–2.7 million]	12 000 (2013)
GLOBAL	36.7 million [34.0 million–39.8 million]	1 400 000

Epidemiological definitions

Concentrated HIV epidemic:

Rapid HIV spread in one or more defined subpopulation.

HIV is not well established in the general population.

HIV prevalence is consistently above 5% in at least one defined subpopulation but is below 1% among pregnant women in urban areas.

Generalized HIV epidemic:

HIV is firmly established in the general population.

HIV prevalence consistently exceeds 1% among pregnant women.

Epidemics are mostly mixed and disproportionately affects certain (key) subpopulations.

Mixed epidemics:

HIV acquisition in one or more subpopulations and in the general population.

One or more concentrated epidemics within a generalized epidemic.

Low-level epidemic:

Prevalence of HIV infection has not consistently exceeded 1% in the general population nationally or 5% in any subpopulation. (WHO 2013)

High-prevalence settings: HIV prevalence greater than 5% in the population tested.

Low-prevalence settings: HIV prevalence less than 5% in the population tested. (WHO 2016).

HIV testing and counselling

40% of individuals living with HIV globally do not know their HIV status (UNAIDS 2016).

In 2013, 54% of pregnant women in low- and middle-income countries did not get an HIV test done (UNAIDS 2014).

HIV testing and counselling is a gateway to HIV treatment, care and prevention.

HIV testing services (HTS) should be provided using a validated national testing algorithm.

The quality assurance of both testing and counselling is essential. (WHO 2013).

HIV testing and counselling should be voluntary, and observe the five C's of consent, confidentiality, counselling, correct test results and connections to care, treatment and prevention services.

Depending on the local context and the epidemic type, strategies for testing and counselling should be mixed, equitable, accessible to all and cost-effective. (WHO, 2016).

HIV testing and counselling

Generalized HIV epidemic

- Offer provider-initiated testing and counselling (PITC) to all clients and in all services.
- Provide community based HIV testing services with linkage to prevention, treatment and care services in addition to routine PITC for all populations, particularly key populations.

Concentrated HIV epidemic

- Offer PITC to clients in clinical settings who present with symptoms or medical conditions that could indicate HIV infection.
- Provide community-based HIV testing services, with linkage to prevention, treatment and care, in addition to PITC for key populations.

All epidemic types

- Consider PITC for malnutrition clinics, STI, hepatitis and TB services, ANC settings and health services for key populations.

Diagnosis and screening for HIV in pregnancy

Tests for HIV diagnosis in pregnant women include:

- Standard tests - the enzyme immunoassay (enzyme-linked immunosorbent assay (ELISA)) and Western blot protocol is highly (>99%) sensitive and specific.
- Rapid HIV tests- similar accuracy and provide results within hours without requiring a return visit, greater sensitivity with blood-based tests than tests using oral fluids (AHMAC 2012).

HIV testing services in all settings should use combinations of RDTs (rapid diagnostic tests) or combinations of RDTs/ enzyme immunoassays (EIAs)/supplemental assays rather than EIA/Western blot combinations.

All people who are diagnosed to be HIV positive should be retested prior to enrolment in HIV care and/or treatment in order to verify their serostatus. (WHO 2016).

Diagnosis and screening for HIV in pregnancy

In high-prevalence settings

- Provide PITC for women as a routine component of the package of care in all antenatal, childbirth, postpartum and paediatric care settings.
- Retest all HIV-negative pregnant women in the third trimester, postpartum and/or during labour, because of the high risk of acquiring HIV during pregnancy.
- Retest lactating mothers who are HIV negative periodically throughout the period of breastfeeding. (WHO 2016).

In low-prevalence settings

- Consider PITC for pregnant women in antenatal care as a key component of the effort:
 - to eliminate mother-to-child transmission of HIV
 - to integrate HIV testing with other key testing (e.g. viral hepatitis, syphilis etc.)
 - to retest HIV negative pregnant women who are in a serodiscordant couple, from a key population group or have known ongoing HIV risk (WHO 2016).

Diagnosis and screening for HIV in pregnancy

For couples and partners

- Offer voluntary HIV testing services with support for mutual disclosure to couples and partners in antenatal care settings.
- Encourage partner testing when pregnant women test HIV negative in high prevalence settings, as incident HIV in pregnancy and during the postpartum period is associated with a high risk of mother-to-child transmission.

In all settings, the goal should be to test pregnant woman at the first antenatal care visit in order to maximize the benefit of early ART. (WHO 2016).

Where feasible, women at high and ongoing risk for HIV infection should be retested in each trimester (SOGC 2014).



Diagnosis and screening for HIV in pregnancy

Settings	HIV positive result	Inconclusive result (Retest after 14 days)	HIV Negative result
High-prevalence settings	If two sequential reactive tests	Reactive Assay 1, Non-reactive Assay 2 Reactive Assay 3 Retest after 14 days	Reactive Assay 1 Non-reactive Assay 2 Non-reactive Assay 3
Low-prevalence settings	If three sequential reactive tests	Scenario 1 Reactive Assay 1 (if fourth-generation assay (antibody/antigen [Ab/Ag])) Non-reactive Assay 2 (if Ab-only assay) Scenario 2 Reactive Assay 1 Reactive Assay 2 Non-reactive Assay 3	Reactive Assay 1 Non-reactive Assay 2

In prevention of mother-to-child transmission (PMTCT) services, if it is not feasible to retest at a different site, a different provider should conduct retesting on a new specimen. If the HIV status is the same upon retesting, the person’s HIV-positive status is confirmed. If the status is not the same upon retesting, refer the person or their specimen to a higher facility for additional testing.

Testing in HIV-exposed infants

In 2014, only 50% of all HIV-exposed infants were tested by the second month of age.

Access to early infant diagnosis (EID) for all HIV-exposed infants is important to link perinatally infected infants to services, initiate ART timely and reduce mortality.

Serological testing cannot be used to diagnose HIV in children up to 18 months of age because maternal HIV antibody transmitted via the placenta persist in the child up to this age.

In the first year of life, HIV infection can be definitively confirmed only with virological testing. (WHO 2016).

Virological testing detects:

- 1) the presence of viral nucleic acid (HIV DNA, RNA or total nucleic acid). This is called nucleic acid testing (NAT) and may be qualitative or quantitative. For example, polymerase chain reaction (PCR)-based HIV DNA and HIV RNA assays, or
- 2) viral products such as ultrasensitive p24 antigen (Us p24 Ag). (WHO 2010, WHO 2016).

Recommended assays for virological testings (WHO 2016)

Assay	Specimen type
HIV DNA	Whole blood specimen or DBS (dried blood spot)
HIV RNA	Plasma or DBS
Us (ultrasensitive) p24Ag	Plasma or DBS

Testing in HIV-exposed infants

. Recommendations:

- Early infant HIV testing can be performed using nucleic acid testing (NAT) technologies that are developed and validated for use at or near to the point of care (*conditional recommendation, low-quality evidence*).
- Offer HIV testing to all children with a parent living with HIV and, link to services for treatment or prevention, if found to be either infected or at high risk of infection through breastfeeding.
- Consider NAT at birth to identify HIV infection in HIV exposed infants. Infants with positive results are likely infected in utero.
- Test all HIV-exposed infants using HIV virological testing at 4–6 weeks of age or at the earliest opportunity thereafter.
- Do HIV virological testing to diagnose HIV infection in infants and children below 18 months of age.
- Do rapid diagnostic tests (RDTs) for HIV serology at 9 months to rule out HIV infection in asymptomatic HIV-exposed infants. If the infant is still breastfeeding, retest at 18 months or at least 3 months after cessation of breastfeeding.
- Do RDTs for HIV serology to diagnose HIV infection in children older than 18 months and have not been breastfed for at least 3 months.

Testing in HIV-exposed infants

Recommendations cont'd.

- Do HIV serological testing for all infants with signs or symptoms suggestive of HIV infection and, if positive (reactive), perform virological testing.
- Ascertain HIV exposure status in all infants with unknown or uncertain HIV exposure using RDTs for HIV serology in infants less than 4 months of age or by performing HIV serological testing in the mother for infants and children 4–18 months of age.
- Infants who are first identified as HIV-exposed postpartum have a high cumulative risk of already having acquired HIV by the time prophylaxis is initiated. Perform an HIV PCR test around the time of initiating prophylaxis, to minimize the risk of development of resistance due to extended prophylaxis in infected infants and to help promote linkage to timely initiation of ART.
- Results from virological testing in infants should not be delayed and should be made available as soon as possible.
- Electronic communication can be considered to transfer test results and reduce delays in acting on the results of early infant diagnosis and other essential laboratory tests.

Use of RDT for HIV serology based on age, exposure status and breastfeeding practice

Age group	Known HIV exposed	Unknown HIV exposure status and breastfeeding	Unknown HIV exposure status and not breastfeeding (Not breastfed for at least 12 weeks before testing)
0–4 months	Not useful, as exposure is known and RDT cannot determine infection status.	Test mother If mother is not available, RDT in the child can reliably assess exposure.	Test mother If mother is not available, RDT in the child reliably determines exposure.
5–8 months	Not useful, as exposure is known and RDT cannot determine infection status at this age.	Test mother If mother is not available, a positive RDT establishes exposure, but a negative RDT does not fully rule it out. Infants with positive RDT will still need NAT to confirm infection. Infants with negative RDT who are still breastfeeding will need NAT at the end of breastfeeding. If sick and mother is not available, perform NAT directly to assess HIV infection status.	Test mother If mother is not available, RDT for the child does not fully rule out exposure. If sick and mother is not available, perform NAT directly to assess HIV infection status.
9–18 months	RDT useful to rule out established HIV infection. Infants with positive RDT will still need NAT to confirm infection. Infants with negative RDT who are still breastfeeding will need NAT at the end of breastfeeding.	Test mother If mother is not available, a positive RDT establishes exposure, but a negative RDT does not fully rule it out. Infants with positive RDT will still need NAT to confirm infection. RDT is useful to rule out established HIV infection. Infants with positive RDT will still need NAT to confirm infection. Infants with negative RDT who are still breastfeeding will need NAT at the end of breastfeeding. If sick and mother is not available, perform NAT directly to assess HIV infection status (Consider initiating ART for presumed HIV infection if there is high degree of suspicion while waiting for NAT results, especially if RDT positive).	Test mother If mother is not available, RDT in the child does not fully rule out exposure. RDT is useful to rule out established HIV infection. • Infants with positive RDT will still need NAT to confirm infection. • Infants with negative RDT who are not breastfeeding can be considered uninfected. If sick and mother is not available, perform NAT directly to assess HIV infection status.
>18 months	Serological testing (including RDT) is recommended to assess HIV infection status unless still breastfed. If still breastfed, serological testing (including RDT) should be provided 3 months after cessation of breastfeeding.		

Prevention of HIV transmission in pregnancy

Prevention of HIV transmission in pregnancy involves:

1. The prevention of HIV transmission in the general population- to prevent pregnant women from being infected with HIV and reduce the risk of HIV transmission from a pregnant woman to her partner.
2. Prevention of mother-to-child transmission (PMTCT)- to reduce the risk of HIV transmission from a pregnant woman to her baby.

A combination approach is needed for the prevention of HIV transmission in all population. This provides a means for people to access interventions that is appropriate to their specific needs at any point in time and is more impactful than single interventions.

Combination prevention programmes use a mix of biomedical (use of ARV drugs), behavioural and structural interventions.

Recommended antiretroviral drugs and adult dosages

Generic name	Dose
Nucleoside reverse-transcriptase inhibitors (NRTIs)	
Abacavir (ABC)	300 mg twice daily or 600 mg once daily
Emtricitabine (FTC)	200 mg once daily
Lamivudine (3TC)	150 mg twice daily or 300 mg once daily
Zidovudine (AZT)	250–300 mg twice daily
Nucleotide reverse-transcriptase inhibitors (NtRTIs)	
Tenofovir (TDF)	300 mg once daily
Non-nucleoside reverse-transcriptase inhibitors (NNRTIs)	
Efavirenz (EFV)	600 mg once daily
Etravirine (ETV)	200 mg twice daily
Nevirapine (NVP)	200 mg once daily for 14 days, followed by 200 mg twice daily
Proteases inhibitors (PIs)	
Atazanavir (ATV)+ (RTV) ritonavir (ATV/r)	300 mg + 100 mg once daily
Darunavir (DRV)+ ritonavir (DRV/r)	800 mg + 100 mg once daily (For individuals with no previous use of protease inhibitors) or 600mg + 100 mg twice daily (For individuals with previous use of protease inhibitors)
Lopinavir (LPV)/ritonavir (LPV/r)	400 mg/100 mg twice daily
	<p>On-going tuberculosis (TB) therapy</p> <ul style="list-style-type: none"> In the presence of rifabutin, no dose adjustment required. In the presence of rifampicin, adjusted dose of LPV/r (LPV 800 mg + RTV 200 mg twice daily or LPV 400 mg + RTV 400 mg twice daily) or Saquinavir/ritonavir (SQV/r) (SQV 400 mg + RTV 400 mg twice daily), with close monitoring.
Integrase strand transfer inhibitors (INSTIs)	
Dolutegravir (DTG)	50 mg once daily
Raltegravir (RAL)	400 mg twice daily

1. Prevention of HIV transmission in the general population using ARV drugs

Oral pre-exposure prophylaxis of HIV (PrEP)

The daily use of ARV drugs by HIV-uninfected people to prevent the acquisition of HIV.

Recommendations:

- Offer PrEP containing TDF (TDF or the combination of TDF + FTC) as an additional prevention choice for people at substantial risk of HIV infection (HIV incidence around 3 per 100 person-years or higher in the absence of PrEP) as part of combination HIV prevention approaches (*strong recommendation, high-quality evidence*).
- Do HIV testing before PrEP is offered and regularly (e.g. every three months) while PrEP is taken.
- Do creatinine testing before starting PrEP and quarterly during PrEP use for the first 12 months, then annually thereafter.
- Test for hepatitis B surface antigen (HBsAg) and regularly screen for and manage STI.
- Provide support for adherence, contraception services, safer conception management and links to antenatal care.

Thresholds for offering PrEP depends on several factors, including epidemiological context or trends, available resources and the relative costs, feasibility and demand for PrEP.

Further research is needed to fully evaluate PrEP use during pregnancy and breastfeeding. Discuss the risks and benefits of and alternatives to continuing to use PrEP during pregnancy and breastfeeding with each person.

1. Prevention of HIV transmission in the general population using ARV drugs

HIV post-exposure prophylaxis (PEP)

ART given for a short duration of time to lower the chances of HIV infection acquisition after potential exposure by occupational means or through sexual intercourse.

Duration of ART is 28 days with the first dose offered as early as possible within 72 hours of exposure.

Recommendations:

- Clinically assess all cases and whether exposure constitutes a significant risk. Exposures that may warrant HIV PEP include the body fluids: blood, bloodstained saliva, breast milk, genital secretions and cerebrospinal, amniotic, peritoneal, synovial, pericardial or pleural fluid.
- For HIV PEP in adults and adolescents, a regimen with two ARV drugs is effective but the preferred regimen should consist of three drugs (*conditional recommendation, very low-quality evidence*): **TDF + 3TC (or FTC) and LPV/r or ATV/r (or RAL, DRV/r, or EFV)**
- Provide enhanced adherence counselling during PEP.
- Test for active HBV infection in people started on TDF-, 3TC- or FTC-based PEP to determine the need for ongoing HBV therapy after discontinuing PEP.
- Monitor individuals with established chronic HBV infection for hepatic flare after PEP discontinuation.
- Counsel about limiting future risk if PEP is not required.
- PEP can be transitioned to PrEP after 28 days if there is continuing substantial risk.

1. Prevention of HIV transmission in the general population

Behavioural interventions

Targeted information and education:

Lowers the rate of potential transmission events using various communication approaches- school-based sex education, peer counselling and community-level and interpersonal counselling, including brief interventions to disseminate behavioural messages to discourage HIV risk behaviours and encourage protective behaviours like safer drug use, delaying sexual debut, reducing the frequency of unprotected sex with multiple partners, correct and consistent use of male and female condoms and knowledge of own and partner's HIV status.

Structural and supportive interventions:

Improve the accessibility, uptake and adherence to behavioural and biomedical interventions focusing on providing the social, legal, political and environmental enablers for HIV transmission reduction- legal and policy reform, reducing stigma and discrimination (including in the health sector), promoting gender and lesbian, gay, bisexual, transgender and intersex (LGBTI) equality and preventing gender-based and LGBTI violence, economic empowerment, access to schooling and supportive interventions to facilitate referrals, adherence, retention and community mobilization.

1. Prevention of HIV transmission in the general population

Other biomedical interventions

They reduce HIV risk practices and/or the probability of HIV transmission per contact event and include:

- Male and female condoms.
- Needle and syringe programmes.
- Opioid substitution therapy with methadone or buprenorphine- most effective in the treatment for opioid dependence.
- Voluntary medical male circumcision- provides up to 66% reduction in the risk of acquisition of HIV for men and offers significant lifetime protection.

2. Prevention of mother-to-child transmission (PMTCT)

About 220,000 infants were born with HIV in 2014 (WHO 2016).

HIV can be transmitted from mothers to their infants during pregnancy, labour, delivery and breastfeeding.

Without intervention, the risk of transmission is 15–30% in non-breastfeeding populations and 20–45% in breastfeeding mothers (WHO 2010).

In non-breastfeeding settings, up to 50% of HIV transmission from mother to child occurs late in the third trimester (from 36 weeks), during labour, or at delivery if there is no intervention (Diaz-Rossello 2008).

Providing highly effective antiretroviral therapy (ART) and antiretroviral drug (ARV) prophylaxis interventions through prevention of mother-to-child transmission of HIV (PMTCT) programmes can prevent almost all of these infections.

PMTCT can reduce the risk of mother-to-child transmission of HIV (MTCT) to less than 5% in breastfeeding populations and to less than 2% in non-breastfeeding populations (WHO 2010).

PMTCT includes all interventions to prevent transmission of HIV from a mother living with HIV to her infant during pregnancy, labour and delivery or during breastfeeding. It also improves mother's health through early initiation of ART (WHO 2013).

2. Prevention of mother-to-child transmission (PMTCT)

There are four approaches to a comprehensive PMTCT strategy:

1. Primary prevention of HIV infection among women of childbearing age.
2. Prevention of unintended pregnancies among women living with HIV.
3. Prevention of HIV transmission from women living with HIV to their infants.
4. Providing appropriate treatment, care, and support to mothers living with HIV, their children and families.

2. Prevention of mother-to-child transmission (PMTCT)

ART in pregnant and breastfeeding women

In 2015, more than 300 000 women did not receive antiretroviral medicines to prevent mother-to-child transmission (UNAIDS 2016).

Reducing maternal viral load is the most effective way to prevent mother-to-child HIV transmission.

- In all epidemic settings, ART should be initiated in **ALL** pregnant and breastfeeding women living with HIV regardless of WHO clinical stage and at any CD4 cell count and continued lifelong, that is, the “Option B+” in previous recommendations (*strong recommendation, moderate-quality evidence*).
- ART should be available in maternal and child health clinics or easily accessible in a linked model of service delivery.
- Newly diagnosed women should be counselled about the benefits of lifelong treatment as well as the importance of adherence and regular follow-up.
- Access to adolescent-friendly family planning services should be prioritized, because adolescent women are more likely to have unintentional pregnancies, detectable viral loads during pregnancy and higher mother-to-child transmission rates compared to adult mothers. (WHO 2016).

Providing lifelong ART serves the purposes of (i) improving the mother’s health; (ii) preventing mother-to-child transmission of HIV; and (iii) preventing the transmission of HIV from the mother to a sexual partner. Programmatically, it reduces loss to follow-up post delivery among women considered to be ineligible according to the previous recommendations (WHO 2016).

2. Prevention of mother-to-child transmission (PMTCT)

When to start ART in pregnant and breastfeeding women

Recommendations:

- ART should be initiated urgently in all pregnant and breastfeeding women even if they are identified late in pregnancy or postpartum. There should be a balance between accelerated ART initiation and ensuring that women are adequately prepared, have accepted lifelong ART and have access to support systems, including peer support, to promote treatment adherence.
- Implement interventions to remove barriers to ART initiation.
- Start treatment based on the woman's informed decision to initiate ART. Such rights based approach will probably result in better acceptability and improved health outcomes.
- Promote treatment literacy among all people with HIV, including information on the benefits of early treatment, the lifelong commitment required, the risks of delaying treatment and available adherence support.
- Train care providers to support shared decision-making.
- Expedite ART initiation in circumstances such as serious ill health, and for pregnant women in labour whose HIV test result is positive. (WHO 2016).
- Do not initiate ART in a pregnant woman who has substantial nausea of pregnancy until the nausea is adequately controlled. Most drugs used to stop nausea in pregnancy can be administered together with ARVs (SOGC 2014).

2. Prevention of mother-to-child transmission (PMTCT)

Factors associated with increased risk of vertical transmission from the mother to her baby

The critical determinants of transmission risk in the ART era are maternal viral load and duration of maternal ART. In the absence of ART, viral load is proportionate to the risk of mother-to-child transmission among pregnant women.

High-risk scenarios include:

- Incident HIV infection in a pregnant or breastfeeding woman (defined as new HIV diagnosis in a pregnant or breastfeeding woman with a prior negative HIV test during pregnancy).
- HIV exposure first identified at delivery or in the postpartum period in a breastfed infant.
- Pregnant women whose viral load exceeds 1000 copies/mL within four weeks prior to delivery (if viral load testing is available).
- Pregnant women on ART for less than four weeks (if viral load testing is not available).

Prolonged rupture of membranes, preterm delivery and low birth weight are no longer associated with increased risk of transmission when mothers are receiving ART.

Laboratory and clinical monitoring- general

Linkage to care and treatment

Early enrolment in care will facilitate early assessment of eligibility for ART, timely initiation of ART and access to interventions to prevent further transmission of HIV and other infections and comorbidities, and reduce loss to follow-up.

The following can facilitate linkage to care:

- Integrated services, where HIV testing, HIV prevention, treatment and care, TB and sexually transmitted infection (STI) screening and other relevant services are provided together at a single facility or site.
- Providing on-site or immediate CD4 testing with same-day results.
- Transport assistance to ART site if far from the HIV testing and counselling site.
- Community outreach workers' involvement in the identification of cases lost to follow-up.
- Peers or expert patients support.
- Use of new technologies, like mobile phone text messaging to help with disclosure, adherence and retention.
- Promoting partner testing .
- Intimate partner notification by the provider, with permission.

Laboratory and clinical monitoring- general

General care for all people infected with HIV, including pregnant women, should be adapted to the type of epidemic and includes:

- Psychosocial counselling and support.
- Disclosure and partner notification.
- Co-trimoxazole (CTX) prophylaxis.
- Tuberculosis (TB) counselling, screening and preventive therapy.
- Preventing common fungal infections.
- Treatment of STIs and supporting reproductive health needs, including prevention of and screening for cervical cancer.
- Preventing malaria (co-trimoxazole, bed-nets).
- Use of vaccines for selected vaccine-preventable diseases.
- Nutrition.
- Family planning.
- Prevention of mother-to-child transmission (PMTCT).
- Needle and syringe programmes for people who inject drugs.
- Water, sanitation and hygiene.

Laboratory and clinical monitoring- pregnancy

Majority of maternal deaths among women with HIV are from non-obstetric causes, the most risk being in those with advanced disease and least time on antiretroviral therapy (ART). Improved availability of ART and early initiation will reduce maternal morbidity and mortality (Kendall 2014).

- HIV infected pregnant women should receive the minimum package of antenatal visits and pregnancy care recommended for all pregnant women following the key principles and practices of safe motherhood. Clinicians should also:
 - Provide screening for sexually transmitted infections like hepatitis B and syphilis.
 - Provide nutritional counselling, including iron and folic acid, and information on infant feeding.
 - Encourage recommended antenatal clinic visits.
 - Promote facility-based delivery by skilled birth attendants.
 - Manage pregnancy as high-risk in the late third trimester.
 - Monitor carefully for pregnancy-induced hypertension and pre-eclampsia, especially for those who initiated ART before conception.
 - Provide family planning counselling.
 - Provide support for adherence and for continuity of care throughout pregnancy and breastfeeding and for life. (WHO 2016).
 - Provide appropriate antenatal counselling for HIV-infected women already receiving ART and who become pregnant (WHO 2010).

Laboratory and clinical monitoring- pregnancy

Recommendations for clinical and laboratory monitoring of HIV-infected pregnant women should be as for non-HIV-infected pregnant women. Other monitoring for her HIV disease are as follows:

At diagnosis

Recommended:

- HIV serology.
- CD4 cell count.
- TB screening.

Desirable:

- Hepatitis B virus (HBV) serology- hepatitis B surface antigen (HBsAg).
- Hepatitis C virus (HCV) serology.
- Cryptococcus antigen if CD4 count ≤ 100 cells/mm³ (in settings with a high prevalence of cryptococcal antigenaemia (>3%)).
- Screening for sexually transmitted infections.
- Assessment for major non-communicable chronic diseases and comorbidities (WHO 2016).

HIV viral load and HIV resistance testing are recommended in resource-rich countries (BHIVA 2014; Palasanthiran 2014; SOGC 2014).

Laboratory and clinical monitoring- labour and delivery

Apart from deaths from non-obstetric causes, women with HIV suffer greater mortality due to puerperal sepsis and obstetric hemorrhage than their HIV-negative counterparts (Kendall 2014).

During labour and delivery:

- Follow universal precautions for all deliveries regardless of the HIV status of the mother- monitor labour using partograph.
- Avoid unnecessary instrumentation.
- Avoid premature rupture of membranes.
- Encourage non-invasive suction of nasogastric secretions in the newborn.
- Wash away blood in the newborn.
- Identify mothers with HIV early- offer rapid HIV testing during labour or immediate postpartum period for all mothers presenting at labour with unknown HIV status.
- Provide ARV treatment to women testing positive and their babies in line with current treatment recommendations. (WHO 2013; WHO 2016).

Laboratory and clinical monitoring- labour and delivery

During labour and delivery:

- Consider extended prophylaxis for infants of mothers who tested positive for HIV.
 - Ensure that provision of delivery care is supportive and without stigma.
 - In resource-limited settings, indication for caesarean section should be obstetric or medical and not HIV status even though it has been shown to protect against HIV transmission, especially in the absence of ARV drugs or in the case of high viral load. (WHO 2013; WHO 2016).
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- In resource-rich countries, management of labour and decisions on the mode of delivery vary and are based on whether or not the woman is on ART and her viral load (BHIVA 2014; Palasanthiran 2014; SOGC 2014).

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Laboratory and clinical monitoring- postnatal care

- Encourage all HIV infected women and women of unknown HIV status who deliver outside health facilities to visit a maternal and child health facility as soon as possible after delivery. These women should be medically assessed and HIV interventions initiated or continued as appropriate (WHO 2013).
- Provide follow-up and linkages to HIV care and treatment and postpartum care for HIV infected women and their infants.
- Initial follow up of the HIV-exposed infant should be at the first immunization visit at four to six weeks- emphasize safe feeding practices, review ARV coverage, and offer early infant diagnosis testing.
- Schedule the follow-up visit for the HIV infected mother preferably at the same time as the baby- perform a postpartum check, offer family planning counselling, review ARV regimen and provide adherence support. (WHO 2016).
- Encourage testing of previous children if their HIV status is unknown (SOGC 2014).

Laboratory and clinical monitoring- infant feeding

The decision to counsel and support mothers known to be HIV infected to either breastfeed and receive ARV interventions or to avoid breastfeeding should depend on which strategy offers their infants the greatest chance of HIV-free survival (WHO 2016a).

Mothers known to be HIV-infected:

- Should exclusively breastfeed their infants for the first 6 months of life and thereafter introduce appropriate complementary foods and continue to breastfeed.
- Should continue breastfeeding for the first 12 months of life and may continue breastfeeding for up to 24 months or longer while receiving full support for ART adherence.
- Should stop breastfeeding only once a nutritionally adequate and safe diet without breast-milk can be provided.
- Should continue to breastfeed infants who are HIV infected until 24 months or longer.

National and local health authorities should protect, promote and support breastfeeding among women living with HIV in health facilities, workplaces, communities and homes (WHO 2016b).

In other settings, it is recommended that HIV-infected mothers should not breastfeed (BHIVA 2014; Palasanthiran 2014; SOGC 2014; WHO 2016a).

Laboratory and clinical monitoring- continuum of care

Less than 30% of people diagnosed with HIV in resource-limited settings pass through the full continuum of care.

Worldwide, less than 50% of adults are retained in care four years after initiation of ART.

For pregnant women living with HIV, the transition from antenatal care and maternal, newborn and child health (MNCH) services to ART care is a potential point for loss to follow-up. (WHO 2016).

Treatment drop-out rates is high among women who are pregnant and breastfeeding, increasing the risk of transmission to their children (UNAIDS 2016).

The process of transition can be supported by community-based interventions including:

- peer support such as mothers-to-mothers programmes,
- peer adolescent support groups for adolescent pregnant women living with HIV,
- structured counselling sessions, and
- telephone reminders (WHO 2016).

Laboratory and clinical monitoring

ART initiation

The availability of laboratory monitoring is not required for initiating ART

Where feasible:

- Baseline CD4 cell count
- Haemoglobin test for AZT
- Blood pressure measurement
- Estimated glomerular filtration rate (eGFR) and serum creatinine for TDF
- Alanine aminotransferase for NVP
- Assess for the presence of chronic conditions that can influence ART management, such as hypertension and other cardiovascular diseases, diabetes, TB and depression- In addition to serum creatinine and eGFR, check serum phosphate and urine dipsticks for proteinuria and glycosuria. (WHO 2016)
- Syphilis screening
- Early infant diagnosis (EID) test. (IATT 2013)
- In defining the clinical stage of a pregnant woman, consider her expected weight gain in relation to the gestational age of the pregnancy and her potential weight loss from HIV (WHO 2010).

Laboratory and clinical monitoring

Receiving ART

Symptom-directed laboratory monitoring for safety and toxicity can be used for those receiving ART.

Recommended:

- HIV viral load- at 6 months and 12 months after initiating ART and every 12 months thereafter.
- CD4 cell count every 6 months.

Desirable:

- Serum creatinine and eGFR for TDF.

Viral load can serve as a proxy measure for the risk of transmission and effectiveness of prevention interventions at both the individual level, especially for pregnant women, and at the population level. (WHO 2016).

Recommendations for laboratory monitoring in high-income countries may differ (BHIVA 2014; Palasanthiran 2014; SOGC 2014).

Laboratory and clinical monitoring

Suspected treatment failure

Recommended:

- Serum creatinine and eGFR for TDF.

Desirable:

- HBV (HBsAg) serology, if this testing was not done or if the result was negative at baseline and the patient was not vaccinated thereafter.
- HIV/HBV coinfecting individuals who are already using TDF containing regimens and develop ART failure should continue to use TDF as an NRTI option, regardless of the selected second-line regimen.

Antiretroviral therapy (ART)

Preparation for ART initiation

- Discuss with the individuals about their willingness and readiness to initiate ART, the ARV regimen, dosage and scheduling, the likely benefits and possible adverse effects and the required follow-up and monitoring visits.
- Ensure the quality and accuracy of HIV testing. Do a retesting to confirm HIV diagnosis.
- Assess for nutritional status, comorbidities and potentially interacting medications for possible contraindications to HIV medication or dose adjustment.
- If the individual declines ART, delay initiation and offer ART at subsequent visits.
- Minimize the time between HIV diagnosis and ART initiation based on an assessment of a person's readiness.
- In cases of mental health, substance use or other problems that may jeopardise adherence, offer appropriate support, and reassess readiness for ART initiation at regular intervals.
- Provide patient information materials and link to community and peer support, and stress the importance of adherence in the success of treatment.
- Request information on any additional medication that are taken, including herbal remedies and nutritional supplements, on a regular basis.
- Provide information on condom use, safer sex and avoidance of high risk behaviours to prevent HIV transmission to others.

First-line ART for pregnant and breastfeeding women

First-line therapy for pregnant women should:

- Be based on drugs for which adequate safety data are available,
- consist of two nucleoside reverse-transcriptase inhibitors (NRTIs) and a non-nucleoside reverse-transcriptase inhibitor (NNRTI) and
- preferably be fixed-dose combinations and once-daily regimens (*strong recommendation, moderate-quality evidence*).

Recommended first-line ART for pregnant and breastfeeding women:

TDF + 3TC (or FTC) + EFV (*strong recommendation, moderate-quality evidence*)

Rationale for recommendation

- The risk of abnormal pregnancy outcomes such as congenital anomalies, growth, bone health, low or mean birth weight, prematurity, pregnancy loss or miscarriage or other serious maternal adverse reactions, among pregnant women receiving TDF-based ART is not higher than in pregnant women receiving other triple-drug regimens without TDF.
- No increased risk in overall congenital anomalies with EFV compared to other ARVs.
- Treatment is harmonized across different populations- TB and HIV co-infection and pregnancy.

First-line ART for pregnant and breastfeeding women

Preferred first-line regimens	Alternative first-line regimens
TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP), TDF + 3TC (or FTC) + NVP (<i>strong recommendation, moderate-quality evidence</i>)

Important!

- Do not initiate TDF when the estimated glomerular filtration rate (eGFR) is <50 ml/min, or in long-term-diabetes, uncontrolled hypertension and renal failure.
- Use NVP with caution in pregnant women and women who might be pregnant due to the higher risk of hepatic and skin reactions with NVP in pregnancy and at higher CD4 counts.
- When initiating ART, escalate NVP dose with half dose for 2 weeks to avoid toxicity from high initial NVP levels.
- Countries should discontinue d4T use in first-line regimens because of its well recognized metabolic toxicities.

First-line ART regimens may differ in resource rich countries.

Postnatal infant prophylaxis

Start infant prophylaxis as soon as possible after birth or postpartum following a recognized HIV exposure.

Recommended regimen:

- Dual prophylaxis with AZT (twice daily) and NVP (once daily) for the first 6 weeks of life for infants born to mothers infected with HIV, who are at high risk of acquiring HIV, whether they are breastfed or formula fed (*strong recommendation, moderate-quality evidence*).
- Continued infant prophylaxis for an additional 6 weeks (total of 12 weeks of infant prophylaxis) using either AZT (twice daily) and NVP (once daily) or NVP alone for breastfed infants who are at high risk of acquiring HIV, including those first identified as exposed to HIV during the postpartum period (*conditional recommendation, low-quality evidence*).
- Daily NVP for six weeks for infants of mothers who are receiving ART and are breastfeeding.
- Daily NVP (or twice-daily AZT) for four to six weeks for infants receiving replacement feeding.

High-risk infants are those:

- born to women with established HIV infection who have received less than four weeks of ART at the time of delivery; OR
- born to women with established HIV infection with viral load >1000 copies/mL in the four weeks before delivery, if viral load measurement available; OR
- born to women with incident HIV infection during pregnancy or breastfeeding; OR
- identified for the first time during the postpartum period, with or without a negative HIV test prenatally.



Postnatal infant prophylaxis

Infant age	Dosing of NVP	Dosing of AZT
Birth to 6 weeks		
Birth weight 2000–2499 g	10 mg once daily (1 ml of syrup once daily)	10 mg twice daily (1 ml of syrup twice daily)
Birth weight ≥2500 g	15 mg once daily (1.5 ml of syrup once daily)	15 mg twice daily (1.5 ml of syrup twice daily)
>6 weeks to 12 weeks		
	20 mg once daily (2 ml of syrup once daily or half a 50 mg tablet once daily)	No dose established for prophylaxis; use treatment dose 60 mg twice daily 6 ml of syrup twice daily or a 60 mg tablet twice daily)
Infants weighing <2000 g and older than 35 weeks of gestational age		
	2 mg/kg per dose once daily	4 mg/kg per dose twice daily
Premature infants younger than 35 weeks of gestational age		
	Dose using expert guidance	

What to expect in the early months of ART

If adherence to ART is good:

- Clinical improvement
- Immunological improvement
- Virological suppression
- Complications like opportunistic infections (OIs)
- Early adverse drug reactions, such as drug hypersensitivity

If adherence is poor:

- Risk of early treatment failure
- Rapid development of drug resistance

The highest death rates occur in the first three months of ART.

What to expect in the early months of ART

Complications of ART:

- Opportunistic infections.
- Immune reconstitution inflammatory syndrome (IRIS).
- Adverse drug reactions like drug hypersensitivity- especially in the first three months of ART.

Risk factors for complications:

- Advanced HIV disease with severe immunodeficiency and existing co-infections and/or comorbidities.
- Severely low haemoglobin.
- Low body mass index.
- Very low CD4 counts.
- Severe malnutrition.

CD4 recovery

CD4 measurement is useful for assessing baseline risk of disease progression, especially among individuals presenting with advanced disease, in deciding when to start or stop prophylaxis for OIs and in prioritizing decisions regarding ART initiation in settings where universal treatment is not possible. It is important in the monitoring of people who are failing ART (WHO 2016).

CD4 cell counts generally rises once immune recovery starts following ART initiation.

It increases during the first year of treatment, reaches a plateau, and then further rises during the second year.

It may fail to rise significantly in individuals with persistently severe immunosuppression, especially those with a very low pre-ART CD4 cell count.

Rule out adherence problems or primary non-response to ART where CD4 recovery is poor.

Prophylaxis for OIs such as co-trimoxazole preventive therapy should continue in individuals with poor CD4 recovery. (WHO 2013).

In settings where routine viral load monitoring is available, CD4 cell count monitoring can be stopped in individuals who are stable on ART and virally suppressed (*conditional recommendation, low-quality evidence*) (WHO 2016).

Individuals who are stable on ART: on ART for at least 1 year, no current illnesses or pregnancy, good understanding of lifelong adherence and evidence of treatment success (two consecutive viral load measurements below 1000 copies/mL (WHO 2016).

Immune reconstitution inflammatory syndrome (IRIS)

A range of clinical signs and symptoms that are possibly associated with immune recovery as a result of ART.

Occurs in 10–30% of individuals initiating ART, commonly within the first 4–8 weeks after ART is initiated.

Presents as:

Paradoxical IRIS

- Opportunistic infection or tumour diagnosed before ART responding initially to treatment but then deteriorating after ART starts.
- Severe and serious and life-threatening forms seen in TB, cryptococcosis, Kaposi's sarcoma and herpes zoster.

Unmasking IRIS

- When initiating ART triggers a disease that was not clinically apparent before ART.

Consider IRIS only when the presentation cannot be explained by a new infection, expected course of a known infection or drug toxicity.

Immune reconstitution inflammatory syndrome (IRIS)

Risk factors:

- ART initiation.
- Disseminated opportunistic infections or tumours.
- A shorter duration of therapy for opportunistic infections before starting ART.

Management:

- Generally self-limiting.
- Interruption of ART is rarely indicated.
- Provide reassurance to prevent discontinuation of or poor adherence to ART.

Reduce occurrence through:

- Earlier HIV diagnosis.
- ART initiation before a decline to below 200 CD4 cells/mm³.
- Improved screening for opportunistic infections before ART, especially TB and Cryptococcus.
- Optimal management of opportunistic infections before initiating ART
- Appropriate timing of ART in individuals with opportunistic infections weighing the risk of IRIS after early initiation against high mortality with delayed initiation.

ART adherence

About a quarter of pregnant women and a higher proportion of women during the postpartum period have inadequate ART adherence.

There are significant biological, social and economic challenges during pregnancy and postpartum period that may affect treatment adherence.

ART adherence may be negatively affected by pregnancy-related conditions such as nausea and vomiting, individual factors (suboptimal understanding of HIV, ART and PMTCT, lack of partner disclosure and support, and fear of stigma and discrimination), and service delivery barriers (poor-quality clinical practices, gaps in provider knowledge and training, poor access to services and health worker attitudes).

Recommendations to improve adherence:

- Provide adherence support interventions to all people on ART. These include: peer counsellors, mobile phone text messages, reminder devices, cognitive-behavioural therapy, behavioural skills training and medication adherence training and fixed-dose combinations once-daily regimens and nutritional and financial supports.
- Additionally, for pregnant and breastfeeding women on ART, provide closer follow-up and more frequent visits, psychosocial support and counselling, especially with regard to infant feeding and postpartum care.
- Monitor adherence using viral load monitoring, pharmacy refill records, self-reporting (subject to recall bias) and pill counts.
- Use differential care models from the beginning of pregnancy until the end of the breastfeeding period.

ARV treatment failure

Art treatment failure occurs when there is viral failure. It may be due to: poor ART adherence to ART (more commonly), drug resistance, malabsorption, drug–drug interactions and other patient-, disease- and drug-associated effects.

Do viral load to diagnosis or confirm ARV treatment failure. It is an early and more accurate indicator of treatment failure. It informs of the need to switch from first-line to second-line drugs (see next slide), thus, reducing the accumulation of drug resistance mutations and improving clinical outcomes (*strong recommendation, low-quality evidence*).

Measuring viral load can also help to distinguish between treatment failure and nonadherence. Around 70% of patients on first-line ART who have a first high viral load will resuppress following an adherence intervention, indicating non-adherence as the reason for the high viral load in the majority of cases.

If viral load testing is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure, using targeted viral load testing to confirm virological failure where possible.

Immunological and clinical criteria, however, have poor sensitivity and specificity to detect treatment failure, particularly at higher CD4 cell counts.

Clinical failure

Occurrence of new or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage 4 condition) after 6 months of effective treatment.

Clinical failure should be differentiated from immune reconstitution inflammatory syndrome (IRIS) occurring after initiating ART.

Occurrence of WHO clinical stage 3 conditions like pulmonary TB and severe bacterial infections may indicate treatment failure in adults.

Clinical criteria have low sensitivity and positive predictive value for identifying individuals with virological failure.

Immunological failure

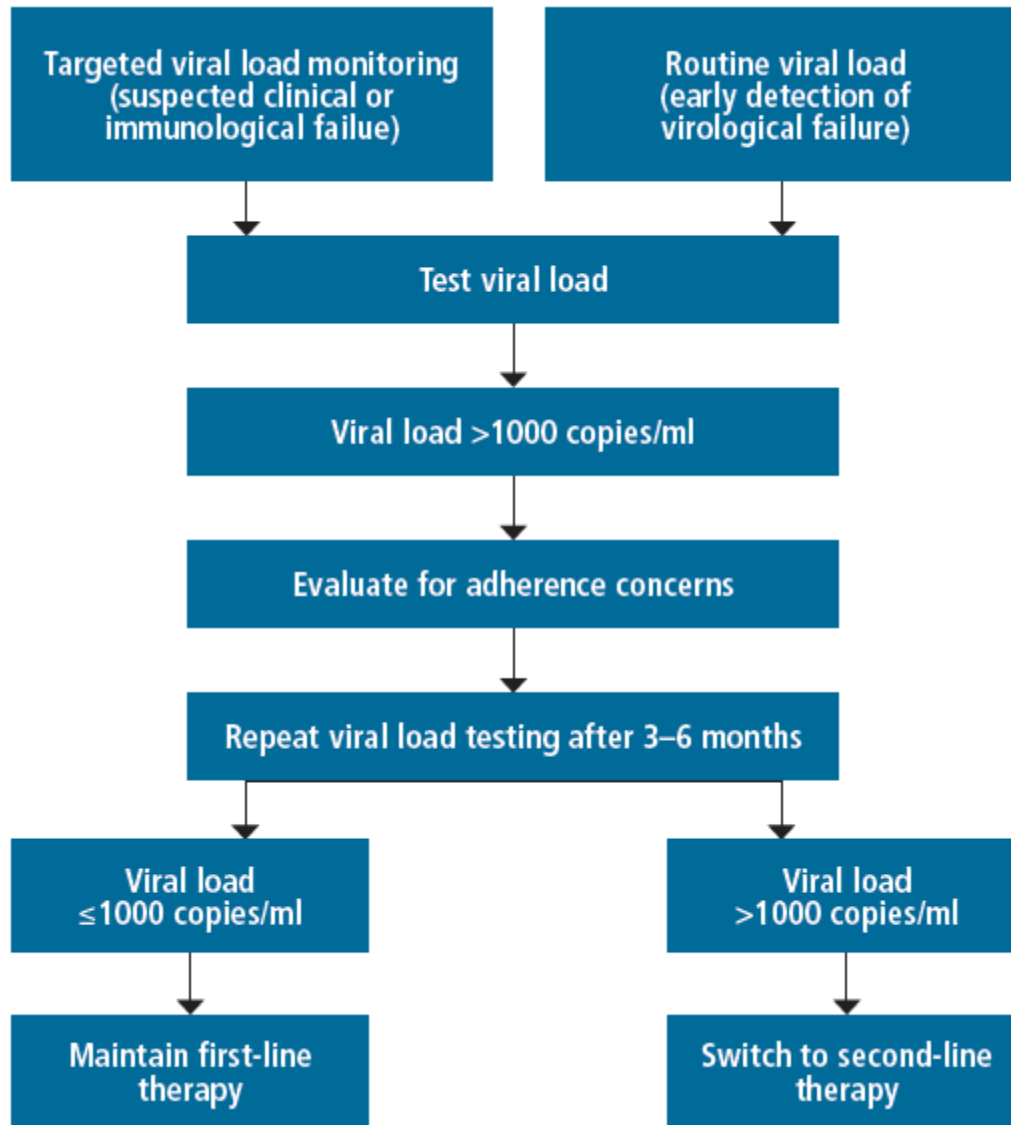
CD4 count at or below 250 cells/mm³ following clinical failure or persistent CD4 levels below 100 cells/mm³.

There should be no concomitant or recent infection to cause a transient decline in the CD4 cell count.

Immunological criteria have low sensitivity and positive predictive value for identifying individuals with virological failure (WHO 2016).

Pregnancy related haemodilution causes a drop in the absolute CD4 count in pregnancy. A decrease in the absolute CD4 count from the pre-pregnancy value should thus be interpreted with caution. CD4 cell count may rise by 50-100 cells/mm³ after delivery (WHO 2010).

Viral load testing strategy



Virological failure

Viral failure is a persistently detectable viral load above 1000 copies/ml measured on two consecutive occasions within a three-month interval and with adherence support between measurements, after at least six months of using ARV drugs.

Plasma specimens are preferred for viral load testing.

Dried blood spot specimens using venous or capillary whole blood are recommended for use in settings where logistical, infrastructural or operational barriers prevent routine viral load monitoring using plasma specimens.

A threshold of 1000 copies/mL can be used to determine viral failure when using dried blood spot samples, as defined for testing in plasma.

Second-line ART

Second-line ART should consist of two nucleoside reverse-transcriptase inhibitors (NRTIs) + a ritonavir-boosted protease inhibitor (PI).

- 2 NRTIs + ATV/r or LPV/r (If ABC+ 3TC or TDF + 3TC (or FTC) was used in the first-line failing regimen, AZT + 3TC should be used in second-line and vice versa).

That is,

TDF + 3TC (or FTC) + ATV/r or LPV/r (If d4T or AZT was used in the first line regimen) OR

AZT + 3TC + ATV/r or LPV/r (if TDF or ABC was used in first-line ART).

- NRTI backbones as a fixed-dose combination is preferably (*strong recommendation, moderate-quality evidence*).
- Heat-stable fixed-dose combinations of boosted PIs (ATV/r and LPV/r) are the preferred options (*strong recommendation, moderate-quality evidence*).
- A heat-stable fixed-dose combination of DRV/r can be used as an alternative boosted PI option, that is, 2 NRTIs + DRV/r (*conditional recommendation, low-quality evidence*).

Second-line ART

HIV and TB coinfection

- If rifabutin is available use standard PI-containing regimens as recommended for adults and adolescents for second line.
- If rifabutin is not available use same NRTI backbones as recommended for adults and adolescents plus double-dose LPV/r (that is, LPV/r 800 mg/200 mg twice daily). As alternatives, standard LPV/r and RTV-boosted saquinavir (SQV/r) doses with an adjusted dose of RTV (that is, LPV 400 mg/ RTV 400 mg or SQV 400 mg /RTV 400 mg twice daily) can be used.

HIV and HBV coinfection

- AZT + TDF + 3TC (or FTC) + (ATV/r or LPV/r)

Third-line ART

The failure of second-line ART is diagnosed based on the same criteria used for diagnosing the failure of first-line ART. Mortality is high among people for whom second-line ART had failed. Countries should develop policies for third-line ART.

Recommendations:

- Third-line regimens should include new drugs with minimal risk of cross-resistance to previously used regimens, such as integrase inhibitors and second-generation NNRTIs and PIs (*conditional recommendation, low-quality evidence*).
- Salvage regimens with DRV/r, etravirine (ETV) and RAL with or without previously used ARVs that potentially maintained residual virological activity, particularly from the NRTI class can be used as: **DRV/r + DTG (or RAL) ± 1–2 NRTIs**
- In PI-experienced patients, the recommended DRV/r dose should be 600 mg/100 mg twice daily.
- Patients on a failing second-line regimen with no new ARV options should continue with a tolerated regimen (*conditional recommendation, very low-quality evidence*).

Available data on third-line ART for pregnant women are limited. The safety of DTG use in pregnancy in particular is not well established, as there are no published safety or efficacy data on the outcomes of treating women with DTG during pregnancy. Furthermore, calcium or iron supplements frequently used during pregnancy could significantly reduce DTG drug levels. In the absence of well-controlled studies in pregnant women, DTG and RAL should be used only if the perceived benefits outweigh the risk.

Management of ARV toxicities

ABC

Hypersensitivity reaction

The presence of HLA-B*5701 allele is a risk factor.

Action:

Do not use ABC in the presence of HLA-B*5701 allele.

Substitute with TDF or AZT.

ATV/r

Electrocardiographic abnormalities (PR and QRS interval prolongation), indirect hyperbilirubinaemia (clinical jaundice), Nephrolithiasis.

Actions:

- Electrocardiographic abnormalities- Use with caution in people with pre-existing conduction disease or who are on concomitant drugs that may prolong the PR or QRS intervals.
- Indirect hyperbilirubinaemia- clinically benign but potentially stigmatizing. Substitute only if adherence is compromised.
- Nephrolithiasis- History of nephrolithiasis is a risk factor. Substitute with LPV/r or DRV/r. If boosted PIs are contraindicated and NNRTIs have failed in first-line ART, consider integrase inhibitors.

Management of ARV toxicities

AZT

1. Severe anaemia, neutropaenia

Risk factor: CD4 cell count of ≤ 200 cells/ mm³

Actions:

- Substitute with TDF or ABC.
- Consider use of low-dose zidovudine

2. Myopathy, lipoatrophy, lipodystrophy and lactic acidosis or severe hepatomegaly with steatosis

Risk factor: BMI >25 (or body weight >75 kg), prolonged exposure to NRTIs

Action:

- Substitute with TDF or ABC.

DRV/r

1. Hepatotoxicity:

Risk factor: Underlying hepatic disease HBV and HCV coinfection, concomitant use of hepatotoxic drugs

2. Severe skin and hypersensitivity reactions:

Risk factor: Sulfonamide allergy

Actions:

- Substitute with ATV/r or LPV/r.
- When it is used in third-line ART, limited options are available.
- For hypersensitivity reactions, substitute with another therapeutic class

Management of ARV toxicities

DTG

Hepatotoxicity, Hypersensitivity reactions

Risk factors: Hepatitis B or C coinfection, Liver disease

Action: If DTG is used in first-line ART, substitute with another therapeutic class (EFV or boosted PIs).

EFV

1. Persistent central nervous system toxicity (such as abnormal dreams, dizziness, insomnia, depression or mental confusion)

Risk factor- Depression or other mental disorder (previous or at baseline)

2. Convulsions: Risk factor- History of seizure

3. Hepatotoxicity

Risk factor: Underlying hepatic disease, HBV and HCV coinfection, concomitant use of hepatotoxic drugs

4. Severe skin and hypersensitivity reactions: Risk factors: Unknown

5. Gynaecomastia Risk factors: Unknown

Actions:

1. The central nervous system side effects usually resolve after a few weeks, but may persist for months or not resolve at all in some cases. Either dose at night-time, use EFV at a lower dose (400 mg/day) or substitute with NVP or integrase inhibitor (DTG) if EFV 400 mg is not effective in reducing symptoms.

2. For severe hepatotoxicity or hypersensitivity reactions, substitute with another therapeutic class (integrase inhibitors or boosted PIs).

3. For gynaecomastia- Substitute with NVP or another therapeutic class (integrase inhibitors or boosted PIs).

Management of ARV toxicities

ETV

- Severe skin and hypersensitivity reactions. Risk factors are unknown.

Action: Substitute with another therapeutic class (integrase inhibitors or boosted PIs).

LPV/r

1. Electrocardiographic abnormalities (PR and QRS interval prolongation, torsades de pointes),

Risk factors: People with pre-existing conduction system disease, concomitant use of other drugs that may prolong the PR or QRS intervals, Congenital long QT syndrome, Hypokalaemia

2. Hepatotoxicity

Risk factors: Underlying hepatic disease, HBV and HCV coinfection, concomitant use of hepatotoxic drugs.

3. Pancreatitis

Risk factors: Advanced HIV disease, alcohol misuse.

4. Dyslipidaemia

Cardiovascular risk factors such as obesity and diabetes

5. Diarrhoea

Actions:

- Use with caution in individuals at risk of Electrocardiographic abnormalities.
- For hepatotoxicity, consider integrase inhibitors if LPV/r is used in second-line ART, and the person has treatment failure with NNRTI in first-line ART.
- For dyslipidaemia, substitute with another therapeutic class (integrase inhibitors).
- In cases of diarrhoea, substitute with ATV/r, DRV/r or integrase inhibitors.

Management of ARV toxicities

NVP

Hepatotoxicity, severe skin rash and hypersensitivity reaction (Stevens-Johnson syndrome).

Risk factors: Underlying hepatic disease, HBV and HCV coinfection, concomitant use of hepatotoxic drugs, high baseline CD4 cell count (CD4 count >250 cells/mm³ in women or >400 cells/mm³ in men)

Action:

- If hepatotoxicity is mild, switch to EFV.
- For severe hepatotoxicity and hypersensitivity, substitute with another therapeutic class (integrase inhibitors or boosted PIs).

RAL

1. Rhabdomyolysis, myopathy and myalgia.

Risk factors: Concomitant use of other drugs that increase the risk of myopathy and rhabdomyolysis, including statins.

2. Hepatitis and hepatic failure, severe skin rash and hypersensitivity reaction.

Risk factors: Unknown

Action: Substitute with another therapeutic class (etravirine, boosted PIs).

Management of ARV toxicities

TDF

1. Chronic kidney disease, acute kidney injury and Fanconi syndrome

Risk factors: Underlying renal disease, older age (than 50 years of age), BMI <18.5 or low body weight (<50 kg) notably in females, untreated diabetes, untreated hypertension, concomitant use of nephrotoxic drugs or a boosted PI

2. Decreases in bone mineral density

Risk factors: History of osteomalacia and pathological fracture, risk factors for osteoporosis or bone mineral density loss, Vitamin D deficiency

3. Lactic acidosis or severe hepatomegaly with steatosis

Risk factors: Prolonged exposure to nucleoside analogues, obesity, liver disease

Actions:

- Substitute with AZT or ABC.
- Do not initiate TDF at eGFR <50 mL/min, uncontrolled hypertension, untreated diabetes, or presence of renal failure.

ARVs and hormonal contraceptives

ARV drugs may increase or decrease levels of steroid hormones in hormonal contraceptives.

Drug interactions between some NNRTIs and RTV-boosted PIs and hormonal contraceptives may reduce the effectiveness of both the hormonal contraceptive and the ARV drug.

The contraceptive efficacy of injectable depot medroxyprogesterone acetate (DMPA) is NOT affected by ARV drugs and can be used without restriction.

The efficacy of long-acting progestogen-only implants may be reduced in women who are on ART containing EFV.

Women who are on ART and are using or want to use hormonal contraceptives, should consistently use condoms and other contraceptive methods to prevent HIV transmission and unintended pregnancy.

Stopping or substituting ARVs

Substituting ARVs may become necessary for drug toxicity or to avoid drug interactions.

- In general, if severe and life-threatening toxicity or hypersensitivity occurs, ART should be discontinued until symptoms have resolved and a substitution regimen can be safely initiated.
- Substitute ARVs early in cases of severe adverse drug effects to prevent harm and avoid poor adherence and subsequent drug resistance and treatment failure (WHO 2016).
- Discontinue ART in a woman who is already on ARVs and has hyperemesis of pregnancy until this is controlled (SOGC 2014).
- Resistance may develop if an NNRTI-based regimen is stopped suddenly because of the prolonged half-life of EFV and NVP. When a NNRTI is to be discontinued, prolong the use of the NRTI backbone for two to three weeks or substitute the NNRTI temporarily with a boosted PI. If the NRTI backbone included TDF, the tail may not be needed. If the NRTI backbone included AZT, the tail should be given (WHO 2013).
- If ART is not an NNRTI-based regimen, discontinue all drugs at once and restart all drugs simultaneously to reduce the risk of developing viral resistance during therapy.
- Resume ART as quickly as possible after discontinuation to reduce the risk of rebound viremia and the potentially increased risk of vertical transmission (SOGC 2014).

Co-trimoxazole (CTX) prophylaxis

To be implemented as part of the HIV care services for prevention of Pneumocystis pneumonia, toxoplasmosis and bacterial infections.

Adult dose of Co-trimoxazole: 960 mg daily.

Initiate therapy:

- At any WHO stage and CD4 count <350 cells/mm³ (CD4 threshold of <200 cells/mm³ in some countries) **OR** WHO stage 3 or 4 irrespective of CD4 level.
- In all HIV-infected patients regardless of CD4 percentage or clinical stage in settings where malaria and/or severe bacterial infections are highly prevalent.
- In all HIV-infected patients with active TB disease regardless of CD4 cell count.
- In HIV-exposed infants 4 to 6 weeks of age until HIV infection has been excluded by an age-appropriate HIV test to establish final diagnosis after complete cessation of breastfeeding. (WHO 2016).

Discontinue therapy:

- In individuals with HIV who are clinically stable on ART (including pregnant women), with evidence of immune recovery and viral suppression. However, **continue therapy** in settings with a high prevalence of malaria and/or severe bacterial infections. (WHO 2016).
- In individuals with Stevens-Johnson syndrome, severe liver disease, severe anaemia, severe pancytopenia.
- Contraindications to CTX: severe allergy to sulfa drugs; severe liver disease, severe renal disease and glucose-6-phosphate dehydrogenase (G6PD) deficiency. (WHO 2013).

Monitoring: Do toxicity monitoring for adverse reactions, particularly in the context of chronic CTX prophylaxis use (WHO 2016).

Co-infection with Tuberculosis (TB)

TB is the most common cause of death in hospitalized adults and children living with HIV, accounting for about a third of all mortality (WHO 2016).

The risk of active TB is about 10 times higher in HIV-infected pregnant women than in HIV-uninfected women.

Active TB accounts for up to 15% of maternal mortality in some settings.

TB in pregnant women is also associated with prematurity, low birthweight, and perinatal tuberculosis. (WHO 2010).

The following *Three I's* strategy should be implemented:

- intensified TB case-finding- Routinely screen for TB using an algorithm containing (fever, cough of any duration, weight loss and night sweats).
- isoniazid preventive therapy (IPT)- Offer IPT if none of the symptoms of active TB is reported.
- infection control at all clinical encounters

The timely initiation of ART and implementation of the “Three I’s” for HIV/TB are critical to prevent TB and mortality from HIV-associated TB. (WHO 2013).

Co-infection with Tuberculosis (TB)

Isoniazid preventive therapy (IPT): Use of IPT and ART have both TB prevention and mortality benefits.

Dose: Isoniazid 300 mg

Duration: Minimum of six months, as part of a comprehensive package of HIV.

Contraindications: Active hepatitis (acute or chronic), regular and heavy alcohol consumption and symptoms of peripheral neuropathy.

Past history of TB is not a contraindication for starting IPT.

Timing of ART

- Early initiation of ART for patients with HIV-associated TB is critical in reducing morbidity and mortality.
- For individuals with TB, start antituberculosis treatment first, then initiate ART as soon as clinically possible within the first 8 weeks of treatment.
- HIV-positive TB patients with profound immunosuppression (e.g. CD4 counts less than 50 cells/mm³) should receive ART within the first two weeks of initiating TB treatment.

Co-infection with Hepatitis B and C

Chronic hepatitis B virus (HBV) infection affects 5–20% of the 33 million people living with HIV worldwide.

Hepatitis C (HCV) affects 5–15% of individuals living with HIV- up to 90% among people who inject drugs.

The burden of co-infection is highest in low- and middle-income countries, particularly in South-East Asia and sub-Saharan Africa for HBV.

There is increasing morbidity and mortality from viral hepatitis among people living with HIV, including those on ART.

A comprehensive approach includes prevention, hepatitis B and HCV screening, HBV vaccination and treatment and care for people with HIV co-infected with HBV and/or HCV. (WHO 2016).

Recommendations:

Offer routine testing for HBV and HCV infections to all women living with HIV who are recognized to be IDUs.

Counsel all pregnant women with HIV/HBV coinfection about signs and symptoms of liver toxicity. (WHO 2010).

After the first trimester, vaccinate against HBV all HCV co-infected women without immunity for HBV (BHIVA 2014).

The recommended NRTI drugs for ART – TDF with 3TC or FTC – are active against HBV.

When changing ARV drugs because of HIV drug resistance or toxicity, TDF with 3TC or FTC should be continued together with the new ARV drugs to prevent HBV reactivation.

The decision to start ART among people coinfecting with HCV should follow the same principles as in HIV mono-infection. (WHO 2016).

Co-infection with Malaria

There is increased risk of more frequent and higher-density infection, severe malaria and malaria-related death in people living with HIV, depending on the malaria transmission intensity of the area.

Key interventions to control malaria

- Early diagnosis- malaria parasite testing using either microscopy or a rapid diagnostic test to confirm all suspected malaria cases.
- Prompt and effective treatment with artemisinin-based combination therapies.
- Use of insecticide-treated nets and indoor residual insecticide spraying to control the vector mosquitoes- routine use of insecticide-treated bed-nets or access to indoor residual spraying to reduce exposure to malaria in areas of stable malaria transmission.
- Use of intermittent preventive treatment during pregnancy in areas of high transmission.

Drug interactions

Do not give sulfadoxine-pyrimethamine to patients with HIV who are receiving co-trimoxazole prophylaxis to treat or prevent malaria.

Antimalarial drugs and ARV drugs may share toxicities (particularly sulfa- based drugs) and may have clinically important pharmacokinetic interactions (especially artemesinins, lumefantrine, NNRTIs and PIs).

If possible, avoid amodiaquine-containing artemisinin-based combination regimens in people with HIV receiving AZT, or EFV because of increased risk of neutropaenia in combination with AZT, and hepatotoxicity in combination with EFV.

Monitor people receiving treatment for both HIV and malaria closely for adverse drug reactions.

Co-infection with sexually transmitted infections

Sexually transmitted infections (STIs) commonly coexist with HIV.

Most are asymptomatic and can cause complications, be transmitted to sexual partners and increase HIV transmission.

HIV infection alters the natural history of STIs.

Serious clinical manifestations of HSV, human papillomavirus (HPV), syphilis and other STIs are observed among people with advanced HIV disease.

STI services should be an important part of comprehensive HIV care among adults and adolescents.

Provide routine screening, diagnosis and treatment of STIs to identify the infection, provide appropriate treatment and prevent transmission.

The dual elimination of mother-to-child transmission of HIV and syphilis is a global public health objective.

Co-infection with cervical cancer

Cervical cancer is preventable and curable if diagnosed and treated early.

Higher risk of pre-cancer and invasive cervical cancer among women living with HIV.

The risk and persistence of human papillomavirus (HPV) infection increases with low CD4 count and high HIV viral load.

Invasive cervical cancer is a WHO HIV clinical stage 4 condition.

Cervical cancer screening leads to early detection of precancerous and cancerous cervical lesions that will prevent serious morbidity and mortality.

Screen all women with HIV for cervical cancer regardless of age.

Follow up women living with HIV closely for evidence of pre-cancerous changes in the cervix, regardless of their ART status or CD4 count and viral load.

Provide immediate management for pre-cancerous and cancerous lesions.

HIV testing should not be a prerequisite before routine HPV immunization.

Vaccinations

Immunizations are an important component of the HIV care package.

Vaccines usually have better safety and efficacy among people with HIV who are receiving ART and those without significant immunosuppression (CD4 count >200 cells/mm³).

Individuals with more severe immunosuppression may be at higher risk of complications from live attenuated vaccines. Inactivated vaccines are safe, but less effective in this group, requiring supplemental doses or revaccination after ART-induced immune reconstitution.

Assess people living with HIV for eligibility for vaccination at all stages of care.

Offer routine vaccination according to recommended national immunization schedules.

Transient but clinically insignificant increases in plasma HIV-RNA load may occur after the administration of several vaccines.

Further information on WHO recommended routine immunizations and their safety in pregnant or breastfeeding women can be found at the following link:

www.who.int/immunization/policy/immunization_tables/en/index.html.

Improving quality of HIV care services

HIV programmes should:

- Provide people-centred care that:
 - is focused and organized around the health needs, preferences and expectations of people and communities,
 - upholds individual dignity and respect, especially for vulnerable populations, and
 - engages and supports people and families to be actively involved in their own care through informed decision-making.
- Provide safe, acceptable, appropriate and timely clinical and non-clinical services, with the aim to reduce morbidity and mortality associated with HIV infection, and to improve health outcomes and quality of life in general.
- Promote efficient and effective use of resources.

Key enablers of quality HIV care services

1. Incorporate HIV care quality in the national policy and programme framework.
2. Define package of HIV care services to offer, including for which population and at what level of the health-care delivery system.
3. Integrate quality assurance and quality improvement in the management and delivery of HIV care services at health facilities and community levels.
4. Engage the community for strengthening the quality of HIV care services, advocacy and demand creation; and community literacy on quality.

You have completed the module HIV infection in pregnancy and should now be able to:

- Know the global burden of HIV in pregnancy.
- Describe the screening and diagnostic measures for HIV in general and during and after pregnancy.
- Describe the interventions to prevent HIV transmission in general and in pregnancy (PMTCT).
- Describe the laboratory and clinical monitoring of HIV-positive pregnant women and HIV-exposed newborns.
- Describe the ARV regimens in general and during and after pregnancy.
- Know what complications to expect and how to manage them when a pregnant woman is on ART.
- Know the indications for stopping or substituting ARVs and how to stop or substitute ARVs in a pregnant woman with HIV.
- Identify the common HIV co-infections and measures to reduce morbidity and mortality.
- Know the key enablers for improving quality of HIV care services.

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