HIV- INFECTION

- Human immunodeficiency virus (HIV) is a blood-borne, sexually transmissible virus (see the image below.) The virus is typically transmitted via sexual intercourse, shared intravenous drug paraphernalia, and mother-to-child transmission (MTCT), which can occur during the birth process or during breastfeeding.
- Two distinct species of HIV (HIV-1 and HIV-2) have been identified, and each is composed of multiple subtypes, or clades. Genetically, HIV-1 and HIV-2 are superficially similar, but each contains unique genes and its own distinct replication process.
- HIV-2 carries a slightly lower risk of transmission, and HIV-2 infection tends to progress more slowly to acquired immune deficiency syndrome (AIDS). This may be due to a less-aggressive infection rather than a specific property of the virus itself. Persons infected with HIV-2 tend to have a lower viral load than people with HIV-1, and a greater viral load is associated with more rapid progression to AIDS in HIV-1 infections.
- HIV produces cellular immune deficiency characterized by the depletion of helper T lymphocytes ($CD4^+$ cells). The loss of $CD4^+$ cells results in the development of opportunistic infections and neoplastic processes.
- HIV-1 and HIV-2 are retroviruses in the Retroviridae family, *Lentivirus* genus. They are enveloped, diploid, single-stranded, positive-sense RNA viruses.
- There is a specific decline in the $CD4^+$ helper T cells, resulting in inversion of the normal CD4/CD8 T-cell ratio and dysregulation of B-cell antibody production. Immune responses to certain antigens begin to decline, and the host fails to adequately respond to opportunistic infections and normally harmless commensal organisms.
- The pattern of opportunistic infections in a geographic region reflects the pathogens that are common in that area. For example, persons with AIDS in the United States tend to present with commensal organisms such as *Pneumocystis* and *Candida* species, homosexual men are more likely to develop Kaposi sarcoma because of co-infection with HHV8, and tuberculosis is common in developing countries.
- Clinical HIV infection undergoes 3 distinct phases: acute seroconversion, asymptomatic infection, and AIDS.

WHO case definition for HIV infection 2007
Adults and children 18 months or older ***HIV infection is diagnosed based on:*** ➢ positive HIV antibody testing (rapid or laboratory-based enzyme immunoassay). This is confirmed by a second HIV antibody test (rapid or laboratory-based enzyme immunoassay) relying on different antigens or of different operating characteristics; *and/or;* ➢ positive virological test for HIV or its components (HIV-RNA or HIV-DNA or ultrasensitive HIV p24 antigen) confirmed by a second virological test obtained from a separate determination.
Children younger than 18 months: ***HIV infection is diagnosed based on:*** ➢ positive virological test for HIV or its components (HIV-RNA or HIV-DNA or

ultrasensitive HIV p24 antigen) confirmed by a second virological test obtained from a separate determination taken more than four weeks after birth.
- Positive HIV antibody testing is not recommended for definitive or confirmatory diagnosis of HIV infection in children until 18 months of age.

* For the purposes of HIV case definitions for reporting and surveillance, children are defined as younger than 15 years of age and adults as 15 years or older .

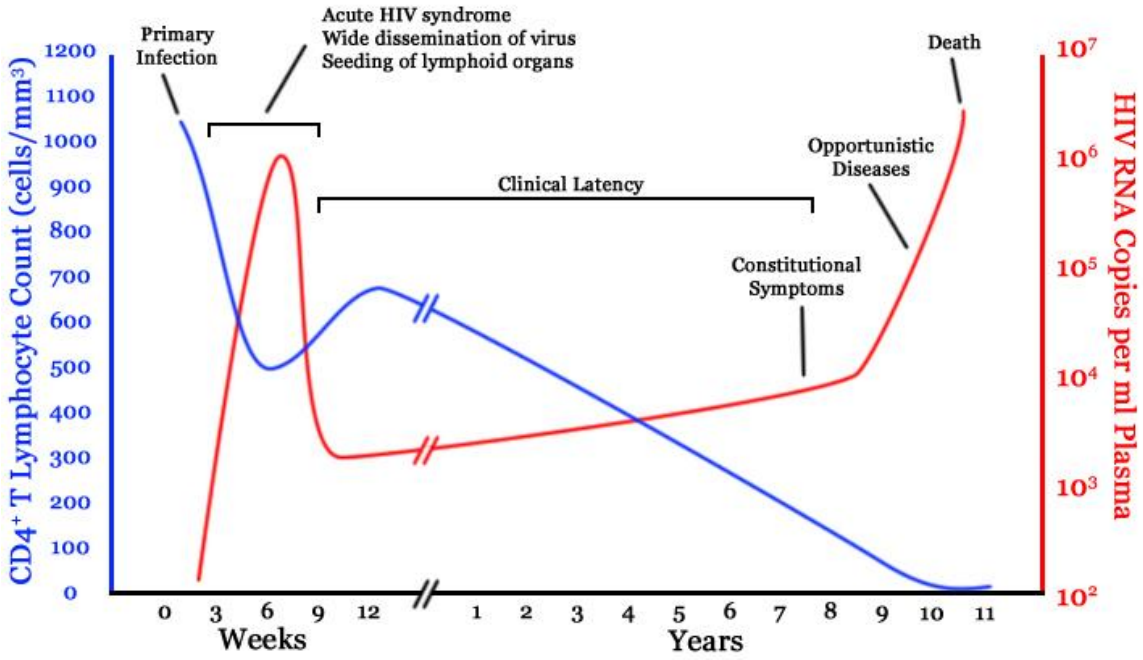
CD4+ T-cell Count

- The CD4 T-cell count is a reliable indicator of the current risk of acquiring opportunistic infections. CD4 counts vary, and serial counts are generally a better measure of any significant changes.
- The reference range for CD4 counts is 500-2000 cells/µL.
- After seroconversion, CD4 counts tend to decrease (around 700/µL on average) and continue to decline over time.
- For surveillance purposes, a CD4 count under 200/µL is considered AIDS-defining owing to the increased risk of opportunistic infections at this level.

Viral Load

- Viral load in peripheral blood is used as a surrogate marker of viral replication rate. This is a surrogate because most of the viral replication occurs in the lymph nodes rather than in the peripheral blood.
- The test is a quantitative amplification of the viral RNA using nucleic acid sequence-based amplification (NASBA), reverse-transcription polymerase chain reaction (RT-PCR), or similar technologies. Quantitative viral-load assays should not be used as a diagnostic tool because several false-positive misdiagnoses have been reported in the literature.
- The rate of progression to AIDS and death is related to the viral load, although, on an individual level, it is poorly predictive of the absolute rate of CD4 T-cell loss. Patients with viral loads greater than 30,000/µL are 18.5 times more likely to die of AIDS than those with undetectable viral loads.
- With therapy, viral loads can often be suppressed to an undetectable level (ie, < 20-75 copies/mL, depending on the assay used); this is considered optimal viral suppression. At the same time, the CD4 count rises and the risk of opportunistic infections and death is reduced. Complete inhibition of viral replication appears impossible and may be unnecessary.

Phases of HIV infection



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Primary HIV infection

There is no standard definition of primary HIV infection.
Primary HIV infection can be recognized in infants, children, adolescents and adults;
It can be:

- asymptomatic or
- be associated with features of an acute retroviral syndrome of variable severity.

Definition of Acute primary HIV infection (EACS Guidelines)

- High-risk exposure within previous 2-8 weeks,

AND

- clinical symptoms,

AND

- detectable HIV in the plasma (p24 Ag and/or HIV RNA > 10 000 c/mL)

AND

- negative or indeterminate serologic testing (negative or weakly positive ELISA, and WB ≤ 1 band)
- Recommendation: confirm HIV infection by HIV antibody test (WB) performed 2 weeks later.

Primary infection usually presents with lymphadenopathy, pharyngitis, maculopapular rash, orogenital ulcers and meningoencephalitis.
Profound transient lymphopaenia (including low CD4) can develop, and opportunistic infections may occur, but these infections should not be confused with clinical staging

events developing in established HIV infection.
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WHO immunological classification for established HIV infection				
HIV-associated immunodeficiency	**Age-related CD4 values**			
	<11 months (%CD4+)	**12–35 months (%CD4+)**	**36 –59 months (%CD4+)**	**>5 years (absolute number per mm3 or %CD4+)**
None or not significant	**[35**	**[30**	**[25**	**[500**
Mild	**30-35**	**25-30**	**20-25**	**350-499**
Advanced	**25-29**	**20-24**	**15-19**	**200-349**
Severe	**Y25**	**Y20**	**Y15**	**Y200 sau Y15%**

WHO clinical staging of HIV/AIDS for adults and adolescents with confirmed HIV infection

Clinical stage 1

- **Asymptomatic** (No HIV-related symptoms reported)
- **Persistent generalized lymphadenopathy** (Painless enlarged lymph nodes >1 cm in two or more non-contiguous sites (excluding inguinal) in the absence of known cause and persisting for 3 months or more.

Clinical stage 2

- **Moderate unexplained weight loss** (<10% of presumed or measured body weight)
- **Recurrent respiratory tract infections**: sinusitis, tonsillitis, otitis media and pharyngitis without features of viral infection. (current event plus one or more in last 6 month period)
- **Herpes zoster**
- **Angular cheilitis** (Splits or cracks at the angle of the mouth)
- **Recurrent oral ulceration** (Current event plus at least one previous episode in past six months.)
- **Papular pruritic eruptions**
- **Seborrhoeic dermatitis**
- **Fungal nail infections**: paronychia (painful red and swollen nail bed) or onycholysis (separation of the nail from the nail bed), proximal white subungual onchomycosis.

Clinical stage 3

- **Unexplainedi severe weight loss** (>10% of presumed or measured body weight)
- **Unexplained chronic diarrhoea** (loose or watery stools three or more times daily) for longer than one month
- **Unexplained persistent fever** (> 37.5°C intermittent or constant, for >1 month). with reported lack of response to antibiotics or antimalarial agents, with negative blood culture, negative Ziehl-Nielsen stain, negative malaria slide, normal or unchanged

chest X-ray and no other obvious focus of infection.

- **Persistent or recurring oral candidiasis**
- **Oral hairy leukoplakia** (Fine white small linear or corrugated lesions on lateral borders of the tongue that do not scrape off.)
- **Pulmonary tuberculosis** (current)
- **Severe bacterial infections** (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia, and severe pelvic inflammatory disease)
- **Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis**
- **Unexplained anaemia** (<8 g/dl), **neutropaenia** (<$0.5x10^9$) or chronic **thrombocytopaenia** (<$50x10^9$) not explained by other non-HIV conditions; not responding to standard therapy with haematinics, antimalarial agents or anthelmintic agents

Clinical stage 4

- **HIV wasting syndrome** (Unexplained involuntary weight loss >10% baseline body weight PLUS EITHER unexplained chronic diarrhoea reported for >1month; OR reports of fever or night sweats for >1 month without other cause.
- **Pneumocystis pneumonia** (Dyspnoea on exertion or nonproductive cough of recent onset (within the past three months), tachypnoea and fever; AND Chest X-ray evidence of diffuse bilateral interstitial infiltrates; AND no evidence of bacterial pneumonia; bilateral crepitations on auscultation with or without reduced air entry)
- **Recurrent severe bacterial pneumonia** (this episode plus one or more episodes in last six months).
- Chronic herpes simplex infection (orolabial, genital or anorectal of >1 month's duration or visceral at any site)
- **Oesophageal candidiasis** (or candidiasis of trachea, bronchi or lungs)
- **Extrapulmonary tuberculosis**: miliary, pleural, pericardia, peritoneal, meningitis, mediastinal or abdominal lymphadenopathy or ostetis. (Discrete peripheral lymph node *Mycobacterium* tuberculosis infection (especially cervical) is considered a less severe form of extrapulmonary tuberculosis).
- Kaposi's sarcoma (Typical gross appearance in skin or oropharynx of persistent, initially flat, patches with a pink or violaceous colour, skin lesions that usually develop into plaques or nodules.)
- **Cytomegalovirus infection** (retinitis or infection of other organs, other than liver, spleen or lymph node).
- **Central nervous system toxoplasmosis**
- **HIV encephalopathy (**Disabling cognitive and motor dysfunction interfering with activities of daily living, progressing over weeks or months in the absence of a concurrent illness or condition other than HIV infection that might explain the findings.)
- **Extrapulmonary cryptococcosis** including meningitis
- **Disseminated non-tuberculous mycobacterial infection**
- **Progressive multifocal leukoencephalopathy**
- **Chronic cryptosporidiosis** (with diarrhoea lasting more than 1month).
- **Chronic isosporiasis**
- **Disseminated mycosis** (coccidiomycosis or histoplasmosis)

- **Recurrent non-typhoidal Salmonella bacteraemia**
- **Lymphoma** (cerebral or B-cell non-Hodgkin) or other solid HIV-associated tumours
- **Invasive cervical carcinoma**
- **Atypical disseminated leishmaniasis**
- **Symptomatic HIV-associated nephropathy**
- **Symptomatic HIV-associated cardiomyopathy**

AIDS in adults and children is defined as

clinical diagnosis (presumptive or definitive) of any stage 4 condition with confirmed HIV infection:
OR
immunological diagnosis in adults and children with confirmed HIV infection and >5 years of age; first-ever documented CD4 count less than 200 per mm3 or %CD4+ <15:
OR
among children with confirmed HIV infection aged 12–35 months first ever documented %CD4 <20:
OR
among children with confirmed HIV infection and less than 12 months of age first ever documented %CD4 <25.

WHO clinical staging of HIV/AIDS for children with confirmed HIV infection

Clinical stage 1

- **Asymptomatic**
- **Persistent generalized lymphadenopathy**

Clinical stage 2

- ***Unexplained persistent hepatosplenomegaly***
- **Papular pruritic eruptions (**Papular pruritic vesicular lesions)
- **Fungal nail infection**
- **Angular cheilitis**
- **Lineal gingival erythema**
- **Extensive wart virus infection**
- **Extensive molluscum contagiosum**
- **Recurrent oral ulcerations**
- **Unexplained persistent parotid enlargement** (Asymptomatic bilateral swelling that may spontaneously resolve and recur, in absence of other known cause, usually painless)
- **Herpes zoster**
- **Recurrent or chronic upper respiratory tract infections** (otitis media, otorrhoea, sinusitis, tonsillitis, bronchitis, pharyngitis, laryngotracheal bronchitis)

Clinical stage 3

- **Unexplainedi moderate malnutrition or wasting** not adequately responding to standard therapy (Weight loss: low weight-forage, up to −2 standard deviations from the mean, not explained by poor or inadequate feeding and or other infections, and not adequately responding to standard management.)
- **Unexplained persistent diarrhoea** (**14 days or more**) not responding to standard

treatment.

- **Unexplained persistent fever** (above 37.5°C intermittent or constant, for longer than one month)
- **Persistent oral candidiasis** (**after first 6–8 weeks of life**)
- **Oral hairy leukoplakia**
- **Acute necrotizing ulcerative gingivitis or periodontitis**
- **Lymph node tuberculosis**
- **Pulmonary tuberculosis**
- **Severe recurrent bacterial pneumonia**
- **Symptomatic lymphoid interstitial pneumonitis**
- **Chronic HIV-associated lung disease including brochiectasis**
- **Unexplained anaemia** (<8 g/dl), **neutropaenia** (<$0.5x10^9$) or chronic **thrombocytopaenia** (<$50x10^9$) not explained by other non-HIV conditions; not responding to standard therapy with haematinics, antimalarial agents or anthelmintic agents

Clinical stage 4

- **Unexplained severe wasting**, stunting or severe malnutrition not responding to standard therapy (Documented weight for height or weight for age of more than –3 standard deviations from the mean with or without oedema.)
- **Pneumocystis pneumonia**
- **Recurrent severe bacterial infections** (such as empyema, pyomyositis, bone or joint infection or meningitis **but excluding pneumonia**)
- **Chronic herpes simplex infection** (orolabial or cutaneous of more than one month's
- duration or visceral at any site)
- **Oesophageal candidiasis** (or candidiasis of trachea, bronchi or lungs)
- **Extrapulmonary tuberculosis**
- **Kaposi sarcoma**
- **Cytomegalovirus infection:** retinitis or cytomegalovirus infection affecting another organ, **with onset at age older than one month**
- **Central nervous system toxoplasmosis** (**after one month of life**)
- **Extrapulmonary cryptococcosis** (including meningitis)
- **HIV encephalopathy** (At least one of the following, progressing over at least two months in the absence of another illness:
  failure to attain, or loss of, developmental milestones or loss of intellectual ability;
  OR
  progressive impaired brain growth demonstrated by stagnation of head circumference;
  OR
  acquired symmetrical motor deficit accompanied by two or more of the following: paresis, pathological reflexes, ataxia and gait disturbances.)
- **Disseminated endemic mycosis** (coccidiomycosis or histoplasmosis)
- **Disseminated non-tuberculous mycobacterial infection**
- **Chronic cryptosporidiosis** (with diarrhoed)
- **Chronic isosporiasis**
- **Cerebral or B-cell non-Hodgkin lymphoma**
- **Progressive multifocal leukoencephalopathy**

- **Symptomatic HIV-associated nephropathy**
- **HIV-associated cardiomyopathy**

TREATMENT

The treatment of human immunodeficiency virus (HIV) disease depends on the stage of the disease and any concomitant opportunistic infections.

In general, the goal of treatment is to prevent the immune system from deteriorating to the point that opportunistic infections become more likely. Immune reconstitution syndrome is also less likely in patients whose immune systems are weakened to this point.

Highly active antiretroviral therapy (HAART) is the principal method for preventing immune deterioration. In addition, prophylaxis for specific opportunistic infections is indicated in particular cases.

Successful long-term HAART results in a gradual recovery of CD4 T-cell numbers and an improvement of immune responses and T-cell repertoire (previously lost antigen responses may be restored).

Therapy initiation

1. Antiretroviral therapy should be initiated in all patients with a history of an AIDS-defining illness (see Staging) or with a CD4 count below 350 cells/µL
2. Antiretroviral therapy should be initiated regardless of CD4 count in pregnant patients, patients with HIV-associated nephropathy, and those with hepatitis B virus coinfection when treatment of hepatitis B virus infection is indicated
3. The panel was divided on the initiation of antiretroviral therapy in patients with CD4 counts between 350 and 500 cells/µL: 55% of panel members considered this a strong recommendation, while 45% considered it a moderate recommendation
4. The panel was also divided on initiation of antiretroviral therapy in patients with CD4 counts above 500 cells/µL: half of the panel members favored initiation in this setting, while the other half considered treatment initiation as optional.

Classes of antiretroviral agents include the following:

- Nucleoside reverse transcriptase inhibitors (NRTIs)
- Protease inhibitors (PIs)
- Nonnucleoside reverse transcriptase inhibitors (NNRTIs)
- Fusion inhibitors
- CCR5 co-receptor antagonists (entry inhibitors)
- HIV integrase strand transfer inhibitors

Regimen selection

- Virologic efficacy
- Toxicity
- Pill burden
- Dosing frequency
- Drug-drug interaction potential

- Drug resistance testing results
- Comorbid conditions

First approved to treat HIV	How they attack HIV
1987	NRTIs interfere with the action of an HIV protein called reverse transcriptase, which the virus needs to make new copies of itself.
1997	NNRTIs also stop HIV from replicating within cells by inhibiting the reverse transcriptase protein.
1995	PIs inhibit protease, which is another protein involved in the HIV replication process.
2003	Fusion or entry inhibitors prevent HIV from binding to or entering human immune cells.
2007	Integrase inhibitors interfere with the integrase enzyme, which HIV needs to insert its genetic material into human cells.

Approved antiretroviral drugs

Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs):

Abbreviation	Generic name	Brand name
3TC	lamivudine	Epivir
ABC	abacavir	Ziagen
AZT or ZDV	zidovudine [1]	Retrovir
d4T	stavudine [2]	Zerit
ddI	didanosine [3]	Videx EC
FTC	emtricitabine	Emtriva
TDF	tenofovir	Viread

Combination	Brand name
ABC + 3TC	Epzicom (US)
	Kivexa (Europe)
ABC + AZT + 3TC	Trizivir [4]
AZT + 3TC	Combivir
TDF + FTC	Truvada
d4T + 3TC	-

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs):

Abbreviation	Generic name	Brand name
DLV	delavirdine [5]	Rescriptor
EFV	efavirenz	Sustiva (US)
		Stocrin (Europe)
ETR	etravirine [6]	Intelence
NVP	nevirapine	Viramune
	rilpivirine [7]	Edurant

Protease Inhibitors (PIs):

Abbreviation	Generic name	Brand name
APV	amprenavir	Agenerase
FOS-APV	fosamprenavir	Lexiva (US)
		Telzir (Europe)
ATV	atazanavir [8]	Reyataz
DRV	darunavir	Prezista
IDV	indinavir	Crixivan
LPV/RTV	lopinavir + ritonavir	Kaletra [9]
		Aluvia (developing world)
NFV	nelfinavir	Viracept
RTV	ritonavir	Norvir
SQV	saquinavir	Invirase (hard gel capsule) [10]
TPV	tipranavir [11]	Aptivus

Fusion or Entry Inhibitors:

Abbreviation	Generic name	Brand Name
T-20	enfuvirtide [12]	Fuzeon
MVC	maraviroc [13]	Celsentri (Europe)
		Selzentry (US)

Integrase Inhibitors:

Abbreviation	Generic name	Brand Name
RAL	raltegravir [14]	Isentress

Treatment of primary HIV infection

• Treatment indicated if:
-- AIDS defining events
-- Confirmed CD4 < 350 c/μL at month 3 or beyond
• Treatment should be considered if:
-- Severe illness/prolonged symptoms (especially CNS symptoms)
• If treatment of PHI is considered, patient should be preferably recruited into a clinical trial
• Treatment optional, if based only on theoretical considerations.
In most situations, wait till month 6 (with CD4 and plasma HIV-RNA monitoring) and follow criteria for initiation of treatment in chronic HIV infection. Some experts recommend treatment as a tool for prevention of HIV transmission.
• Duration of treatment should be lifelong.
• Maintain closer follow-up in case of treatment interruption

Current drug regimen recommendations

he January 2011 DHHS guidelines lists the following regimens as preferred in treatment-naive patients

- Efavirenz/tenofovir/emtricitabine (EFV/TDF/FTC)
- Ritonavir-boosted atazanavir + tenofovir/emtricitabine (ATV/r + TDF/FTC)
- Ritonavir-boosted darunavir + tenofovir/emtricitabine (DRV/r + TDF/FTC)
- Raltegravir + tenofovir/emtricitabine

The guidelines consider lopinavir/ritonavir–based regimens as alternative rather than preferred, except in pregnant women, in whom twice-daily lopinavir/ritonavir plus zidovudine/lamivudine remains preferred.

Treatment of HIV pregnant women

Pregnant women should be monitored every month and as close as possible to the predicted delivery date.

Criteria for starting ART in pregnant women (see different scenarios)	Same as for non pregnant
Objective of treatment in pregnant women	Full plasma HIV RNA suppression by third trimester and specifically at time of delivery
Resistance testing	Same as for non pregnant, i.e. before starting ART and in case of virological failure
SCENARIO	
1. Women becoming pregnant while already on ART	1. Maintain ART but switch drugs that are potentially teratogenic
2. Women becoming pregnant while treatment naive and who fulfil the criteria (CD4) for initiation of ART	2. Starting ART at beginning of 2nd trimester is optimal
3. Women becoming pregnant while treatment naive and who do not fulfil the criteria (CD4) for initiation of ART	3. Start ART at beginning of W28 of pregnancy (at the latest 12 weeks before delivery); start earlier if high plasma viral load or risk of prematurity
4. Women whose follow-up starts after W28 of pregnancy	4. Start ART immediately
Antiretroviral regimen in pregnancy	**Same as non pregnant**
	• Except avoid EFV
	• NVP not to be initiated but continuation is possible if started before pregnancy
	• Among PI/r, prefer LPV/r or SQV/r or ATV/r
	• RAL, DRV/r: little data available in pregnant women
	• ZDV should be part of the regimen if possible
Drugs contra-indicated during pregnancy	Efavirenz, ddI + d4T, triple NRTI combinations
IV zidovudine during labour	Benefit uncertain if plasma HIV RNA < 50 c/mL
Single dose nevirapine during labour	Not recommended
Caesarean section	Benefit uncertain if plasma HIV RNA < 50 c/mL at W34-36. In this case, consider vaginal delivery only

Post-exposure prophylaxis

	POST EXPOSURE PROPHYLAXIS (PEP) RECOMMENDED IF	
	Nature of exposure	**Status of source patient**
Blood	Subcutaneous or intramuscular penetration with IV or IM needle, or intravascular device	HIV + Or serostatus unknown but presence of HIV risk factors
	• Percutaneous injury with sharp instrument (lancet), IM or SC needle, suture needle • Contact > 15 min of mucous membrane or non intact skin	HIV +
Genital secretions	Anal or vaginal sex	HIV + Or serostatus unknown but presence of HIV risk factors
	Receptive oral sex with ejaculation	HIV +
Intravenous drug use	Exchange of syringe, needle, preparation material or any other material	HIV +

- Rapid testing of the source patient for HCV and HIV (if HIV status unknown) recommended
- If source patient HIV+ on ARV therapy, order resistance testing if VL detectable
- Individualise PEP according to the source's treatment history and previous resistance tests
- PEP to be started ideally < 4 hours after the exposure, and no later than 48 hours
- Duration of PEP: 4 weeks
- Standard PEP regimen: TDF/FTC (alternative: ZDV/3TC) + LPV/r tablets 400/100 mg bid
- Full sexual health screen in case of sexual exposure
- Follow-up:
  - HIV serology + HBV and HCV, pregnancy test (women) within 48 hours of exposure
  - Re-evaluation of PEP indication by HIV expert within 48-72 hours
  - Assess tolerability of PEP regimen
  - Transaminases, HCV-PCR and HCV serology at month 1 if source of exposure was HCV+ (observed or suspected)
  - Repeat HIV serology after 2 and 4 months, syphilis serology after 1 month if sexual exposure