وزارة الصحة
Ministry of Health

Saudi Guidelines for HIV Treatment

Developed by The Saudi AIDS National Program (NAP).

How to Cite the Saudi Guidelines for HIV Treatment:

Saudi Ministry of health, The Saudi AIDS National Program (NAP) (2024). Saudi Guidelines for HIV Treatment (3rd ed.). Retrieved from https://www.moh.gov.sa/

3rd edition
2024

Copyright

Published by The Saudi AIDS National Program (NAP).

First Edition: 2015
Third Edition: 2024

ISBN:

The Saudi AIDS National Program (NAP).
Digital City
Riyadh, Saudi Arabia
https://www.moh.gov.sa/

Foreword

We are proud to present this comprehensive resource, developed by The Saudi AIDS National Program (NAP).

The journey of creating these guidelines has been both challenging and rewarding. Our primary goal has always been to provide a clear, concise, and up-to-date resource for healthcare professionals involved in the treatment and care of individuals living with HIV.

In this third edition, The Saudi AIDS National Program (NAP) has updated the guidelines to reflect the latest research and advancements in antiretroviral therapy. Also, the guidelines focus has been expanded to include new sections on prevention, diagnosis, and management of HIV-related complications.

We believe that these guidelines will serve as a valuable tool for healthcare professionals, enabling them to provide the highest standard of care for their patients. We also hope that it will contribute to the ongoing global effort to end the HIV epidemic.

We would like to express our gratitude to all those who contributed their time, expertise, and passion to the development of these guidelines. Your dedication is truly appreciated.

Finally, we would like to thank the individuals living with HIV, whose courage and resilience inspire us every day. This book is dedicated to you.

Authors And Editors

Lead Authors

Dr. Abdullah M. Assiri
Consultant of Infectious Diseases, Assistant Deputy for Preventive Health, IHR NFP
MOH, Riyadh, Saudi Arabia

Dr. Haleema A. Alserehi
Consultant of Infectious Diseases, Director General, Communicable Diseases Control Department
MOH, Riyadh, Saudi Arabia

Dr. Sanaa S. Alrehily
Consultant of Infectious Diseases, Head of The Saudi National AIDS Program
MOH, Riyadh, Saudi Arabia

Contributing Authors

Dr. Mohammad M. Alhazmi
Consultant Physician Infectious Diseases, King Fahad Central Hospital (KFCH)
Jazan, Saudi Arabia

Dr. Ebrahim S. Mahmoud
Consultant of Infectious Disease King Faisal Specialist Hospital and Research Center (KFSH&RC)
Madinah, Saudi Arabia

Dr. Aynaa Alsharidi
HIV, Transplant and Infectious Diseases Consultant, King Saud University Medical City (KSUMC)
Riyadh, Saudi Arabia

Dr. Alaa Alali
Consultant Internal Medicine and Infectious Diseases, King Saud Medical City (KSMC)
Riyadh, Saudi Arabia

Dr. Batool Ali
Adult Infectious Disease Consultant, East Jeddah Hospital
Jeddah, Saudi Arabia

Dr. Ali Albarrak
Consultant Internal Medicine and Infectious Diseases at Prince Sultan Military Medical City (PSMMC), Director General Assistant for Health Affairs, Health Service Directorate, MOD
Riyadh, Saudi Arabia

Dr. Sami Al Hajjar
Professor of Pediatrics-Infectious Diseases, Section-head Infectious Disease at King Faisal Specialist Hospital and Research Center (KFSH&RC)
Riyadh, Saudi Arabia

Dr. Khalid Alanbari
Medical Specialist (Sexual and Reproductive health, HIV and STIs)
MOH, Riyadh, Saudi Arabia

Dr. Ahmed Fadeel
Public Health Physician/Epidemiologist, Saudi National
AIDS Program
MOH, Riyadh, Saudi Arabia

Editors

Dr. Mohammad Chakroun
Head of The Infectious Diseases Department at Teaching Hospital and Professor in The Faculty of Medicine of Monastir
Tunisia

Dr. Pedro Cahn
Professor of Infectious Diseases at The Buenos Aires University Medical School
Argentina

Dr. Esteban Martinez
Senior Consultant and Associate Professor of Medicine, Infectious Diseases Unit Hospital Clinic and University of Barcelona
Spain

Dedication

This book is dedicated to all the healthcare professionals who work tirelessly to improve the lives of individuals living with HIV. Your dedication, compassion, and commitment inspire us every day.

We also dedicate this book to the individuals and families affected by HIV. Your strength and resilience are a testament to the human spirit. We hope that these guidelines will contribute to improving your quality of life and advancing the care you receive.

Finally, we dedicate this work to the memory of those we have lost to this disease. Your lives continue to motivate us in our pursuit of a world free from HIV.

Table of Contents

Introduction

The Saudi AIDS National Program (NAP), established in 1994, is the official health entity dedicated to managing HIV/STIs services. It also establishes the appropriate legislation and regulation that support infected individuals and prevent further transmission in the community.

These guidelines outline the Ministry of Health's response to HIV and AIDS in Saudi Arabia. They present and consolidate a range of evidence-based recommendations and health intervention guidance to have the best possible impact on HIV. Relevant existing, updated, and new recommendations are included.

The standardized guidelines address clinical and operational aspects of using antiretroviral (ARV) medicines for HIV treatment and prevention. These treatment guidelines are intended for use by all HIV clinicians and healthcare providers across the kingdom.

Major changes in these guidelines include an updated initial ARV therapy according to the most recent literature, in addition to updated and simplified information on the adverse effects of antiretroviral therapy (ART), ART in special groups, and updated content on HIV co-infections and opportunistic infections (OI). Every other part of this guideline has been reviewed and updated accordingly.

A group of highly qualified Infectious Diseases Specialists from multiple healthcare sectors in the kingdom has contributed to this edition.

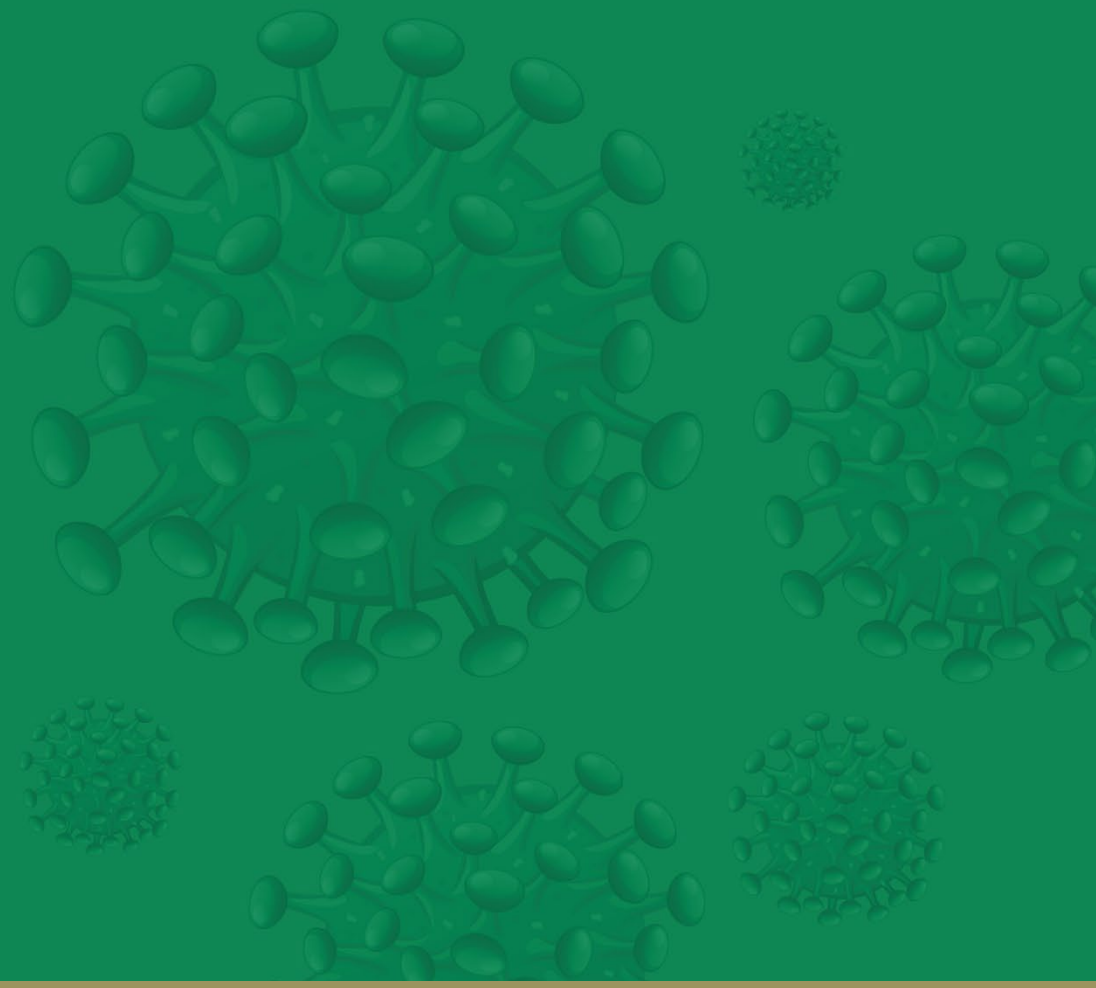
The National AIDS Program is committed to working with its partners to ensure that the right interventions are carried out for People Living with HIV (PLWH) in Saudi Arabia and will continue to assess and address their needs.

Abbreviations and Acronyms

Abbreviation	Full Form
ADI	Antibody Differentiation Immunoassay
AHI	Acute HIV Infection
AIDS	Acquired Immune Deficiency Syndrome
ANC	Antenatal Care
ARV	Antiretroviral
ARVS	Acute Retroviral Syndrome
ART	Antiretroviral Therapy
ATT	Anti-Tuberculosis Treatment
BCG	Bacille Calmette-Guerin
BMI	Body Mass Index
CBC	Complete Blood Count
CD4	Cluster of Differentiation 4
CDC	Center for Disease Control
CMV	Cytomegalovirus
CNS	Central Nervous System
HAV	Hepatitis A Virus
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HCWs	Health Care Workers
HIV	Human Immunodeficiency Virus
HIV/AIDS XDR	Extensive Drug Resistance
HIVDR	HIV Drug Resistance
HR	Isoniazid, Rifampicin
HTC	HIV Testing and Counseling
HSV	Herpes Simplex Virus
INH	Isoniazid
INSTIs	Integrase Strand Transfer Inhibitors
WB	Western Blot
HAV	Hepatitis A Virus

CHAPTER 01

INITIAL ANTIRETROVIRAL THERAPY



Summary of Investigations for HIV Positive Naïve Patients

Table 1.1 Summary of Investigations for HIV-Positive Naïve Patients

Investigation	Entry into Care	ART Initiation/ Modification	4-8 Weeks After ART Initiation /Modification	Every 3 -6 Months	Treatment Failure	Clinically Indicated
Confirmation of HIV antibody positivity HIV 1/2 confirmatory assay	√					
CD4 and CD8 percent and absolute, CD4/CD8 ratio	√	√		√	√	√
HIV viral load	√	√	√	√	√	√
CBC with differential	√	√	√	√		√
Random or fasting glucose	√	√	√	√		√
ALT, AST, total bilirubin	√	√	√	√		√
Basic metabolic panel	√			√		√
Lipid profile	√	√	√			√
Genotypic resistance testing	√	√			√	√
HLA-B*5701 testing		√				
Hepatitis B serology (HBsAb, HBsAg, HBcAb total)	√	√				√
Hepatitis C screening (HCV antibody or, if indicated, HCV RNA)	√					√
Urinalysis	√					√
Pregnancy test	√	√				√

Assessment of HIV Naive Patients at the Initial Presentation for Medical Care and Follow-Up Visits

Table 1.2 Medical History of HIV Naive Patients at the Initial Presentation

History	First visit	Prior to ART *
History of presenting illness including constitutional symptoms, fever, weight loss, candida infections, cough, sputum, hemoptysis, lymphadenopathy, diarrhea, etc.	Yes	Yes
Past Medical History of Concomitant illness including Tuberculosis, IHD, DM, Hypertension, Hyperlipidemia, Malignancy, Renal & Bone Diseases	Yes	
Cardiovascular disease risk assessment (Framingham score)	Yes	Complete the risk assessment
Marital status, Partner status and disclosure. Family size and pregnancy intention.	Yes Yes	Partner status and disclosure Discuss Conception issues when appropriate
Sexual history and safe sex practices.	Yes	Yes + Safe sex education
- Number and gender of sex partner/s. - Duration of the relationship/s.	Yes	Yes
Kind of sexual contact (vaginal, anal, oral).	Yes	Yes
History of STIs	Yes	Yes
Lifestyles and habits including Smoking.	Yes	Address the risk of smoking on IHD.
Drug Abuse, Ethanol use, and/or Gat chewing.		Address the risk of Ethanol and drug abuse and the DDI with ART. Consider Psychiatrist evaluation

History	First visit	Prior to ART *
Daily activities, exercise, and dietary habits.	Yes	Lifestyle modifications
Employment Status, average income. Need for financial support, complete the required forms for socio economic governmental and NGO programs (social security system, comprehensive rehabilitation centers, etc..).	Yes Yes	Complete the required forms
Psychological/ Social history	Yes	
Education level of the patient Knowledge about HIV/AIDS	Yes Yes	Provides appropriate information sources, trusted web sites and/or booklets
Medication history including drugs that have significant interactions with ART (anti TB, Metformin, cholesterol lowering drugs, Anti-depressants, NSAIDs, etc	Yes	Review Drug-Drug interactions with the clinical pharmacist and/or Liverpool HIV drug interaction website
Vaccination status including HBV, Covid-19, HPV, HAV vaccination#.	Yes	---
Family history of premature IHD, Hypertension, DM and renal disease	Yes	---

* (we recommend early initiation of ART either in the same visit of within 1 week whenever possible, however if the delay is mandatory due to co infection or lack of follow up for more than 1 month then these items may need to be repeated)

There are other recommended vaccinations! Refer to the specific chapter.

Physical Examination of HIV Naive Patients at the Initial Presentation

Table 1.3 Physical Examination of HIV Naive Patients at the Initial Presentation

Physical Examination	First visit	Prior to ART *
General examination of the patient including nutrition status, Height, Weight, Body Mass Index, Blood Pressure, Respiratory rate, Pulse Rate Fever, and Pulse Oximetry on room air	Yes	Complete the examination in the first follow up visit Repeat physical examination if ART initiation is delayed > 4 weeks
Lymphadenopathy	Yes	
Examination of the oral cavity	Yes	
Skin examination	Yes	
Genital and anal inspection	Yes	
Chest examination.	Yes	
CVS, and Abdominal examination.	Yes	
CNS including fundoscopy examination	Yes	
Evaluation of Neurocognitive impairment (questionnaire)	Yes	Assess compliance and the need for family support
Neuro psychiatric evaluation, depression	Yes*	

* In specific persons with risk or prior diagnosis of psychiatric illness or current neuropsychiatric symptoms/signs

Investigation of HIV Naive Patients at the Initial Presentation

Table 1.4 Investigations of the HIV status

Investigations of the HIV status	First visit	Prior to ART
HIV ELISA	Yes	No
Confirmation of HIV antibody positivity HIV 1/2 Confirmatory Assays	Yes	No
Plasma PCR for HIV 1 Viral load assessment	Yes	Repeat only if the ART initiation is delayed > 3 months
HIV genotyping and resistance testing	Yes	

Table 1.5 Immunology Investigations

Immunology investigations	First visit	Prior to ART
CD4 absolute count and %.	Yes	Only if more than 3 months from the first visit
CD8 absolute count and %.	Yes	
CD4 / CD8 ratio	Yes	
HLA B5701	Yes	No

Investigation of HIV naive persons with HIV at the initial presentation for co-morbid diseases

Table 1.6 Investigation of HIV naive persons with HIV at the initial presentation for co-morbid diseases

Investigations for co-morbidities	First visit	Prior to ART
CBC, Diff	Yes	
Renal profile	Yes	
Hepatic profile	Yes	
Lipid profile	Yes	

Investigations for co-morbidities	First visit	Prior to ART
Bone profile, serum calcium level, PO4	Yes	Repeat if clinically indicated or if ART initiation is delayed more than 3 months or in case of abnormal initial test
Fasting blood glucose	Yes	
HBA1C *	Yes*	
Urine microscopic examination	Yes	
e GFR	Yes	
Vitamin D level #	Yes#	
ECG	Yes	

* Only in specific persons: prior diabetes diagnosis, fasting blood glucose above 126 mg/Dl.
# Only in specific persons: >50 years and low bone mineral density (DXA).

Investigation of HIV naive patients at the initial presentation for co-infections

Table 1.7 Investigation of HIV naive patients at the initial presentation for co-infections

Investigations for co- infections	First visit	ART Initiation or Modification
HB S Ag, HB S Ab	Yes	In patients not immune to HBV, consider retesting if switching to a regimen that does not contain TDF or TAF. Prescribe HBV vaccination.
HCV antibodies	Yes	No
HAV IgG	Yes	No
Tuberculosis investigations CXR (PA, Lateral and lordotic view) HRCT if abnormal or inconclusive CXR PPD skin test if CD4 >200 cells/mm IQRA or TB Quanti Ferron test if CD4 is < 200 or AIDS defining illness	Yes	Repeat if history of recent TB exposure

Investigations for co- infections	First visit	ART Initiation or Modification
Syphilis serology VDRL or RPR	Yes	TPHA if positive
Toxoplasma serology	Yes	No
CMV IgG and IgM	Yes	No
Varicella zoster virus serology if no clear history of past infection or previous vaccination	If available	
Cryptococcus antigens (if CD4 count is less than 100)	If available	

*(we recommend early initiation of ART either in the same visit of within 2 weeks whenever possible, however if the delay is mandatory due to co infection or lack of follow up for more than 1 month then some test may need to be repeated)

Follow up investigations for HIV positive naive patients on Anti-retroviral therapy

Regular follow-up of all HIV patients in regional HIV specialized centers is crucial to ensure linkage to care, safety of ART (Anti-Retroviral Therapy) medications, HIV suppression, and immunological recovery.

The first follow-up visit is recommended at 2 - 6 weeks to evaluate patient compliance, side effects of medications, clinical and virological response. Subsequent clinical visits intervals will be dictated by the patient's comorbidities, psychosocial status, and treatment response. HIV positive patients who are stable, with an undetectable HIV viral load and no comorbid illness, can be seen regularly at 6-month intervals (i.e., 2-OPD visits annually).

An early follow-up evaluation at 4 – 6 weeks is mandatory in patients with poor compliance, medication side effects, introduction of any new treatment with potential drug-drug interactions with present ART, uncontrolled HIV viral load, and if ART medications are changed or dose adjustment for any of the medications.

Management of HIV patients is a multidisciplinary effort involving multiple specialties including infectious diseases physicians, nurses, clinical pharmacists, psychotherapists, social workers, and others.

Table 1.8 Follow up investigations for HIV positive naive patients on Anti-retroviral therapy

Follow up investigations	Entry Into Care	ART Initiation or Modification	Frequency
CBC, Diff, Blood Glucose, Renal and Hepatic profiles. LDH	√	√	Every 3 – 6 months
Lipid profiles	√	√	Every 6 -12 months More frequent evaluation if hyperlipemia exist or use of cholesterol lowering drug
Random or Fasting Glucose #	√	√	
Bone profile, serum calcium, PO4 *	√*	√	Every 6 – 12 months
e GFR	√	√	Every 6 – 12 months
Urinalysis or Urine Microscopy	√	√	- When ART is initiated or changed, and at least annually in stable HIV-infected patients. - Assessed before initiating TAF- or TDF TAF- or TDF containing regimens and monitored during treatment with these regimens. - More frequent monitoring may be appropriate for patients with additional kidney disease risk factors.

Follow up investigations	Entry Into Care	ART Initiation or Modification	Frequency
HIV Viral Load (PCR)	-	√	Every 6 months. More frequent monitoring of HIV viral load is required in the following patients: • at the initiation of ART (4 - 12 weeks) • in virological failures and when ART is changed (4 – 12 weeks) • during pregnancy (2 -3 times during pregnancy, at least once in the last trimester)
HIV Genotyping and resistance testing	√	-	At virological failures (if viral load is > 1,000 copies/ml)
CD4 count, CD8 count, CD4/CD8 ratio	-	√	Every 6-12 months Annual CD4 count if CD4 is > 350 and no change in ART therapy
HLA B5701	-	√	Only once at presentation it should be done prior to initiation of Abacavir or any Abacavir containing regimens if not done at presentation.
HCV screening (HCV antibody or, if indicated, HCV RNA)	√	√	Annual screening in high-risk patients like IV drug user and MSM Assess HCV PCR if acute infection is suspected
Hepatitis B Serology (HBsAb, HBsAg, HBcAb total)	√	√	In patients not immune to HBV consider retesting if switching to a regimen that does not contain TDF or TAF
HBV PCR	-	-	If HBsAg is positive, start HBV treatment and follow HBV PCR every 6 months

Follow up investigations	Entry Into Care	ART Initiation or Modification	Frequency
Vitamin D3 level	-	-	Every 2 years Annually if low level Osteopenia or osteoporosis Tenofovir TDF containing ART regimen or clinically indicated
Cervical PAP smear	-	-	Every 1 – 3 years
Anoscopy and Rectal PAP if history of anal sex	-	-	Every 1 – 3 years
ECG	-	-	Annually (Depending on personal history or current symptoms/signs)
CXR	-	-	If history of TB or Pneumonia
Tuberculosis investigation by either PPD Skin test or IGRA CXR +/- HRCT	-	-	If history of TB exposure
Sputum for TB PCR by GenXpert Sputum AFB	-	-	If clinically indicated
Ultrasound abdomen	-	-	Annually in HIV/HBV or HIV/HCV co-infected patients
DEXA scan	-	-	Consider in high-risk patient >50 years (all, at least once in life) or <50 with early menopause, cumulative steroid use >3 months, or history of low impact fracture! No need for TDF use if none of the previous. Repeat every 3 - 5 years according to the risk factors for osteoporosis

Follow up investigations	Entry Into Care	ART Initiation or Modification	Frequency
Partner education and assessment for HIV risk	√	-	In the second visit and every year if HIV negative

If random glucose is abnormal, fasting glucose should be obtained. HbA1C is no longer recommended for diagnosis of diabetes in people with HIV on ART
* Only in those persons at risk of bone fractures: >50 years and low bone mineral density (DXA).

Anti-Retroviral Treatment of HIV naive patients

Antiretroviral therapy (ART) is recommended for all individuals living with HIV, irrespective of their CD4 count and HIV Viral load. In line with most international guidelines, ART should be initiated for all individuals living with HIV as soon as possible after the diagnosis of HIV infection is confirmed. Exceptions include certain clinical situations, such as co-infections with tuberculosis or cryptococcosis, which necessitate a delay in ART initiation.

The urgency to start early ART is greater in patients with lower CD4 counts, discordant couples, and pregnant women who are HIV-positive. Initiating ART treatment in the same clinical visit once HIV diagnosis is confirmed is encouraged to improve linkage to care and prevent delays in therapy initiation. If the HIV PCR and CD4 results are not available, the use of a high genetic barrier regimen is recommended.

Evaluating patient readiness to start treatment and compliance are important predictors of linkage to care and HIV treatment success. In a patient who is willing to start treatment and educated about the importance of adherence to therapy, immediate initiation of ART should be considered once the HIV infection is confirmed.

The timing of antiretroviral therapy in HIV/TB co-infected patients depends on the clinical status, site of TB infection, CD4 count, and the risk of other opportunistic infections. In patients with HIV/TB co-infection, it is recommended to start early ART, i.e., within 2 weeks of initiating anti-tuberculous medications in those with a CD4 count of <50 cells/mm3 when TB meningitis is not suspected, and within 8 weeks of starting anti-TB treatment in those with higher CD4 cell counts. Corticosteroids should be considered as adjuvant treatment for TB meningitis.

Genotypic resistance testing is recommended upon the diagnosis of every patient prior to initiation of ART. However, HIV genotyping and resistance testing are not universally available in all HIV treatment centers. In the absence of HIV genotyping and sensitivity testing, starting ART with high genetic barriers (e.g., BIC or DTG-based or DRV/c-based regimens) is recommended.

All people living with HIV (PLHIV) should have an HIV Viral Load (VL) test before starting ART. This test should be repeated at 4-6 weeks and after 3 months to ensure virological suppression. If complete suppression is not achieved at 6 months despite good patient compliance, urgent HIV genotyping and modification of antiretroviral therapy should be undertaken. Monotherapy is not recommended for any PLHIV under any circumstances. Dual therapy for a naïve HIV-positive patient may be used in highly selected patients, those with a low HIV viral load of <500,000, no HBV or TB co-infection, and not pregnant. Obtaining the

results of HIV PCR, HIV genotyping at least for M184V, CD4 count, HBsAg are mandatory before initiation of dual therapy.

Triple therapy with 2 NRTI and an integrase inhibitor is the preferred antiretroviral therapy for naïve HIV-positive patients.

These guidelines are based on recommendations from the updated guidelines of EACS, DHHS, IAS-USA, BHIVA, and WHO, as well as results of recent important randomized controlled clinical trials.

Preferred Anti-Retroviral Treatment regimens for HIV positive naïve patients

Table 1.9 Preferred Anti-Retroviral Treatment regimens for HIV positive naïve patients

	Preferred ART regimens	Tablets burden/day	Remarks
Initial Regimens for Most PLWH*			
INSTI + Two NRTIs	TAF 25 mg/FTC 200 mg/ BIC 50 mg One tablet daily	STR	
	ABC 600 mg/3TC 300 mg /DTG 50 mg One tablet daily	STR	If HLA B5701 is negative Not recommended for HIV/HBV co infection or unknown HBV status.
	Dolutegravir (DTG) 50 mg One tablet daily **+** (TAF 25 mg **or** TDF 245 mg) **+** (FTC 200 mg One tablet daily **or** 3TC 300 mg)		• HLA B5701 is mandatory before ABC use • Not recommended for HIV/HBV co infection unknown HBV status. • TDF is preferred over TAF in HIV/TB coinfection on Rifampicin • The dose of DTG is 50 mg BID with Rifampicin and it is not recommended for patients < 30 kg body weight
INSTI + One NRTI	DTG/3TC		• is not recommended if HIV RNA is >500,000 copies/mL • Do not use in the setting of HBV coinfection or unknown HBV status.

	Preferred ART regimens	Tablets burden/day	Remarks
Initial Regimens for PLWH in Certain Clinical Situations, if some regimens are not available or not clinically suitable			
INSTI + Two NRTI	TAF 10 mg / FTC 200 mg / EVG 150 mg / Cobi 150 mg One tablet daily	STR	Not recommended in pregnancy. Food improves absorption of these regimens.
	TAF 25 mg/ FTC 200 mg One tablet daily + Raltegravir (RAL) 600 mg (2 tablets) once daily		Low genetic barrier than DTG/BIC
	TDF 245 mg/ FTC 200 mg One tablet daily + Raltegravir (RAL) 400 mg twice daily		The dose of RAL is 800 mg BID with Rifampicin
NNRTI + Two NRTI	Doravirine/TDF/3TC or Doravirine + TAF/FTC	STR	
	Efavirenz+ (TAF **or** TDF) + (FTC **or** 3TC)		
	RPV/ (TAF **or** TDF)/FTC		Not recommended if HIV Viral load is > 100,000 copies/ml and/or CD4 count < 200 cells/µL RPV-containing regimens should be taken with ≥390 calories of food.
Boosted PI + Two NRTI	(Darunavir /Cobicistat **or** Darunavir /Ritonavir) + ABC/3TC	STR (DRV/C/TAF/FTC)	HLA B5701 is mandatory before ABC use Not recommended for: • HIV/HBV and HIV/TB coinfection on Rifampicin • High risk patients for IHD • Pregnant women
	(Atazanavir/Cobicistat **or** Atazanavir/Ritonavir) + (TDF **or** TAF) + (FTC **or** 3TC)	STR ATV/c/TAF/FTC is	Not recommended of HIV/TB coinfected patients on Rifampicin

	Preferred ART regimens	Tablets burden/day	Remarks
	DRV/r **or** c + TAF **or** TDF + 3TC **or** FTC		• Previous use of CAB-LA as PrEP. • INSTI genotypic resistance test is necessary because CAB-LA may be associated with resistance to INSTIs.

* PLWH who have a history of CAB-LA (Long-acting Cabotegravir, IM injectable PrEP) need an INSTI genotypic resistance testing before starting and INSTI-based regimen.

Antiretroviral in special groups

Table 1.10 Antiretroviral in special groups

Clinical / Laboratory finding	Recommendation	Notes
HLA B5701 positive	**AVOID** Abacavir and Abacavir containing regimens	Hypersensitivity reactions to Abacavir (potentially fatal reaction).
HIV Viral Load > 100,000 copies/ml	**AVOID** - RPV-based regimens - ABC/3TC with EFV or ATV/r - DRV/r plus RAL	High rates of HIV virological failure
HIV RNA >500,000 copies/mL	**Do Not Use** the Following Regimens: - RPV-based regimens - ABC/3TC with EFV or ATV/r - DRV/r plus RAL - DTG/3TC	For DTG/3TC, limited data are available in patients with viral loads above this threshold.
CD4 count < 200 cells/mm^3	**AVOID** - RPV-based regimens - DRV/r plus RAL	Virological Failure
An ARV regimen should be started before HIV drug resistance results are available (e.g., in a person with acute HIV) or when ART is being initiated rapidly	**AVOID** NNRTI-based regimens and DTG/3TC. **AVOID** ABC. **RECOMMENDED** ARV Regimens in Persons Without Exposure to - CABLA PrEP - BIC/TAF/FTC - DTG plus (TAF or TDF)a plus (3TC or FTC) - DRV/r or DRV/c) plus (TAF or TDF) a plus (3TC or FTC) **Recommended ARV Regimen in Persons on CAB-LA PrEP Prior to HIV Acquisition** - (DRV/r or DRV/c) plus (TAF or TDF)[a] plus (3TC or FTC)	**Do not use DTG/ABC/3TC if:** - the patient is HLA-B*5701 positives. **DTG/3TC is not recommended if:** - HIV RNA is >500,000 copies/mL. **Do not use DTG/ABC/3TC or DTG/3TC in:** - the setting of HBV coinfection or unknown HBV status. **Do not use RPV-based regimens if:** - HIV RNA is >100,000 copies/mL and CD4 count is <200 cells/mm3.
Active HIV/HBV co infection	Use 3TC/FTC + TAF or TDF containing regimens If both TAF and TDF are contraindicated add Entecavir to FTC or 3TC containing regimens	Lamivudine use alone is associated with HBV mutant strains.
HIV/ TB co infection	- TDF based regimen is preferred over	Rifamycin antibiotics are

Clinical / Laboratory finding	Recommendation	Notes
	Tenofovir Alafenamide (TAF) and TAF containing regimens due to DDI with Rifampicin - ART regimens containing either Ritonavir or Cobicistat are not recommended with Rifampicin - The dose of Integrase inhibitor (only for DTG or RAL) is doubled with Rifampicin (Raltegravir is doubled to 800 mg BID, the dose of Dolutegravir is increased to 50 mg bid). - EFV 600 mg once daily (in combination with either ABC/3TC or TDF/FTC) can be used without dose adjustment	inducers of CYP3A4 and UGT1A1 enzymes, causing significant decreases in concentrations of PIs, INSTIs, and RPV
Sustained virologic suppression (<50 copies/ml for 6 months) with no history of virologic failure, and no known resistance to CAB or RPV. (Patient must not have a history of Hepatitis B or C or hepatic disorders).	**Cabotegravir + Rilpivirine (Cabenuva).** (Long-acting injection once every month Or once every two months according to drug dosing.) Given as 2 separate injections in separate ventrogluteal sites: *** CAB 400-mg/2-mL vial and RPV 600-mg/2-mL vial (Every 4 weeks).* *** CAB 600-mg/3-mL vial and RPV 900-mg/3-mL vial (Every 2 months).*	Patients need to be monitored for 10 – 15 minutes for post-injection reactions.
Renal Disease	AVOID use of Tenofovir DF if e GFR is < 60 mL/min/1.73m^2, also if eGFR decreases more than 3-5 mL/min per year with eGFR ≥60 mL/min. And Tenofovir Alafenamide TAF if e GFR is < 30 mL/min/1.73m^2	
Osteoporosis	AVOID Tenofovir DF	
Previous use of CAB-LA Cabotegravir (IM injectable PrEP).	**Avoid INSTI-based regimens, unless an INSTI genotype shows no resistance mutations.** **Recommended Regimen Pending INSTI Genotype Results** - (DRV/r or DRV/c) plus (TAF or TDF)a plus (3TC or FTC)	Mutations conferring resistance to INSTIs have been seen in association with CAB-LA PrEP. CAB-LA has a very long half-life, and drug exposure may persist at levels suboptimal to prevent infection and may select for resistant virus.
CrCL <60 ml/min (CKD).	**AVOID:**	TDF is associated with renal

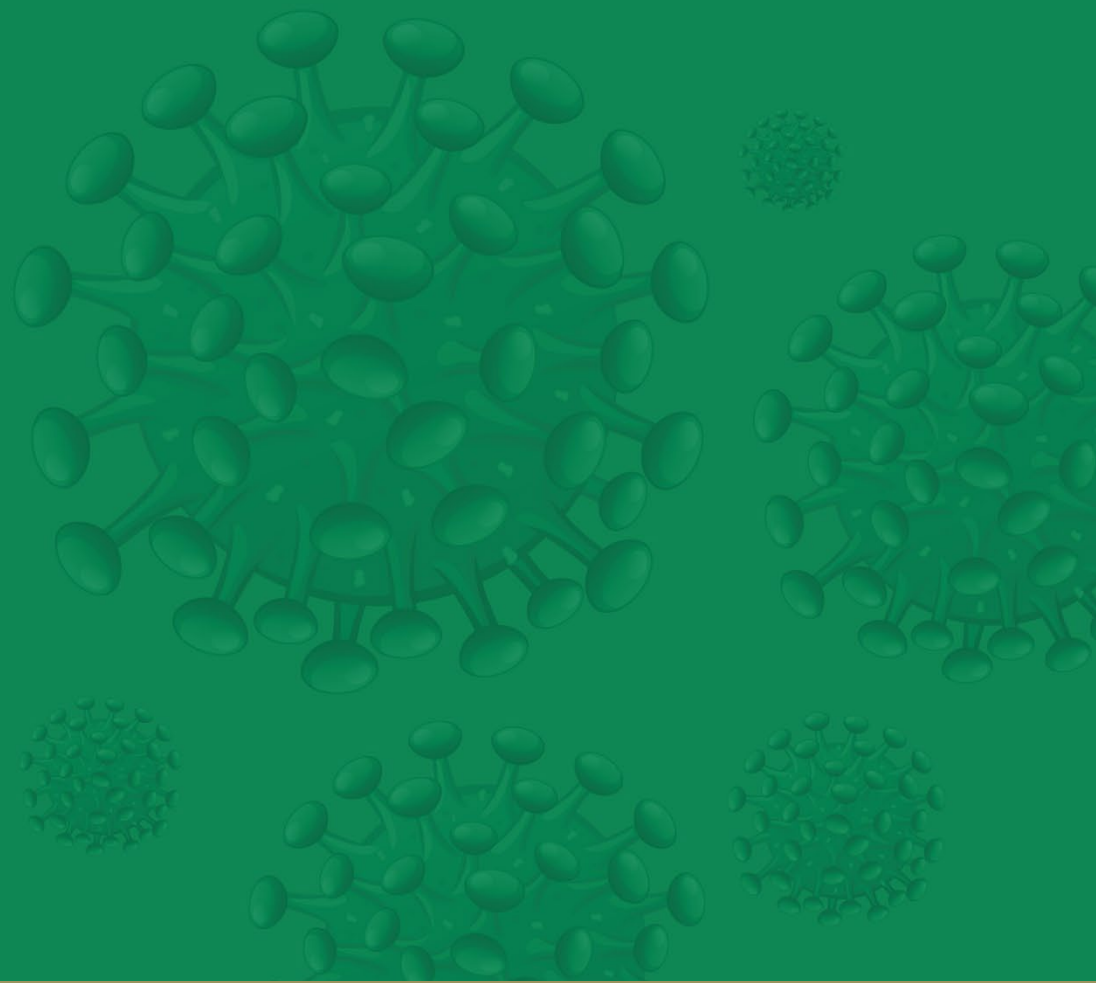
Clinical / Laboratory finding	Recommendation	Notes
	- TDF. - ATV. Recommended ARTs: - **ABC** (if HLA-B*5701 is negative). - **TAF** (if CrCl >30 ml/min or if the patient is on chronic hemodialysis). **ART Options When ABC, TAF, or TDF Cannot Be Used** (For patients with HBV coinfection, consult Hepatitis B Virus/HIV Coinfection for HBV treatment options.) - **DTG/3TC** (if viral load is < 500,000 copies/ml). - **DRV/r** plus **3TC** - **DRV/r** + **RAL** (if CD4 is >200 cells/mm3 and viral load <100,000 copies/ml).	dysfunction. ATV is associated with CKD (chronic kidney disease). LVP/r or ATV/r combined to TDF may decrease eGFR; close monitoring of renal function is needed when TDF is combined to LPV/r or ATV/r. TDF has a higher impact on renal functions than TAF. If HIV RNA is >100,000 copies/mL, do not use ABC/3TC plus EFV or ATV/r.
Food effects.	**ART regimens that should be taken with food:** - ATV/r or ATV/c- based regimens. - DRV/r or DRV/c- based regimens. - EVGc/TAF/FTC[a]. - EVGc/TDF/FTC[a]. - RPV-based regimens.	
	ART that can be taken with no regard to food: - BIC. - DOR. - DTG-based regimens. - RAL-based regimens.	

[a] TAF and TDF are two FDA-approved forms of TFV. TAF has fewer bone and kidney toxicities than TDF, whereas TDF is associated with lower lipid levels. Safety, cost, and access are among the factors to consider when choosing between these drugs.

Key: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; BMD = bone mineral density; CAB-LA = cabotegravir long acting; CD4 = CD4 T lymphocyte; CNS = central nervous system; CrCl = creatinine clearance; CV = cardiovascular; CYP = cytochrome P; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ESRD = end stage renal disease; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDA = Food and Drug Administration; FPV = fosamprenavir; FTC = emtricitabine; HBV = hepatitis B virus; HCV = hepatitis C virus; HLA = human leukocyte antigen; IDV = indinavir; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PI/c = cobicistat-boosted protease inhibitor; PI/r = ritonavir-boosted protease inhibitor; PrEP = pre-exposure prophylaxis; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; STR = single-tablet regimen; TAF = tenofovir alafenamide; TB = tuberculosis; TDF = tenofovir disoproxil fumarate; TFV = tenofovir; UGT = uridine diphosphate glucuronosyltransferase

CHAPTER 02

MANAGEMENT OF TREATMENT-EXPERIENCED PATIENTS



Virologic Response Definitions

The following definitions are used in this section to describe the different levels of virologic response to Antiretroviral Therapy (ART):

- **Virologic Suppression**: Two consecutive HIV-1 RNA measurements <50 copies/mL while prescribed ART.
- **Virologic Failure**: Two consecutive HIV-1 RNA measurements ≥200 copies/mL.
- **Persistent Low-Level Viremia**: Two or more consecutive HIV-1 RNA measurements 50-999 copies/mL at least 30 days apart without progression to higher than 1,000 copies/mL or return to viral suppression.
- **Virologic Rebound**: After virologic suppression, confirmed HIV-RNA level ≥200 copies/mL.
- **Virologic Blip**: After achieving viral suppression, any HIV-1 RNA 50-999 copies/mL that is immediately preceded and followed by an HIV-1 RNA <50 copies/mL without a change in ART.

Management of Treatment-Experienced Patients

1. Treatment-Experienced Patients with Undetectable Plasma Viral Load

These are patients who have suppressed the virus for more than six months. There are multiple options to approach them:

i. Continue their current regimens as long as they are tolerating their medications and they don't have any toxicities that stem from antiretroviral.

ii. Switching the regimen: There are many indications to switch an Antiretroviral (ARV) for patients who have been previously stable on their regimens; they include:

   A. Toxicity from ARV.
   B. Simplification.
   C. Convenience.
   D. Drug-drug interactions.
   E. Improving adherence.
   F. Pregnancy.
   G. Management of co-infection.
   H. Cost.

Before switching, a recent viral load should be drawn and counseling is done. There are a variety of options to be given; patients can be switched to Nucleoside Reverse Transcriptase Inhibitors (NRTI)-based, Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)-based (in the form of rilpivirine or doravirine) or Protease Inhibitors (PI)-based regimen (in the form of Darunavir). After switching a patient's regimen, blood work with HIV RNA should be done within 6-8 weeks to ensure maintaining virologic suppression.

2. Treatment-Experienced Patients with Detectable Virus

These are patients who have detectable virus despite being on an ARV regimen; virological failure is defined as HIV RNA more than 200 copies/mL on two occasions separated by at least three months.

It is of paramount importance to revise prior ART history and do genotype testing (should be done when Viral Load (VL) is more than 1000 copies/mL) before choosing the next regimen; this should be done while on ARV or within 2 to 4 weeks of discontinuing the regimen to avoid the possibility of reverting to wild-type virus.

If there is no access to genotype testing, the patient should be referred to a specialized center to treat these patients; in case a referral will take a long time, it is preferred to keep a patient on a holding regimen i.e., twice-daily Dolutegravir/Bictegravir (DTG/BIC) (which is available only in a combination pill with Emtricitabine/Tenofovir Alafenamide (FTC/TAF)) and/or boosted Darunavir (DRV), and stop all other drugs in particular those with low genetic barrier like NNRTI-based regimens and Integrase Strand Transfer Inhibitor (INSTI)-based regimen (excluding Dolutegravir) to prevent the accumulation of further mutations.

Approach to First Line Failure

Use either PI plus two NRTI or PI plus INSTI. The typically used PI in this instance is darunavir; this is used as 800 mg once daily unless there are documented mutations (Several major mutations are required) to darunavir in which case 600 mg twice a day is recommended.

Approach to Second Line Failure

If the genotype test yields PI susceptibility, then use either PI plus two NRTI or PI plus INSTI. In case of lack of PI susceptibility, use 2-3 fully active drugs that preferably include an active PI and high genetic barrier NRTI i.e., Dolutegravir. If the patient was previously exposed to INSTIs, DTG should be prescribed twice daily.

Multidrug Resistance Without Fully Active Commonly Used ARV Drug Options

Consensus on the optimal management of these patients is lacking. If neither a fully active boosted PI nor a second-generation INSTI (e.g., DTG or BIC) is available, the new regimen should include at least two, and preferably three, fully active agents. If less than three fully active drugs are available, the regimen should include as many fully active drugs as possible, along with potentially partially active agents (BII).

If resistance to NNRTIs, T-20, MVC, BIC, DTG, EVG, or RAL are identified, there is rarely a reason to continue using these drugs, because there is little evidence that keeping them in the regimen helps delay disease progression (BII).

Adding a single, fully active ARV drug to the regimen is not recommended because of the risk of rapid development of resistance (BII).

Patients with ongoing detectable viremia who lack sufficient treatment options to construct a fully suppressive regimen may be candidates for the first-in-class CD4 post-attachment inhibitor Ibalizumab (IBA), the gp120-directed attachment inhibitor Fostemsavir (FTR), and/or the long-acting capsid inhibitor Lenacapavir (LEN);

- **Ibalizumab (IBA)** is a long-acting CD4 post-attachment inhibitor that is given intravenously every 2 weeks.
- **Fostemsavir (FTR)** is a gp120 attachment inhibitor that is given orally twice daily.
- **Lenacapavir (LEN)** is a long-acting HIV capsid inhibitor that can be given by one of two initiation schemes (oral plus subcutaneous [SQ] dosing), followed by SQ injections every 6 months.

Antiretroviral Therapy-Experienced Patients with Suspected Drug Resistance Who Present with Limited Information (Incomplete or No Self-Reported History, Medical Records, or Drug-Resistance Test Results):

One strategy is to restart the most recent Antiretroviral (ARV) regimen and assess drug resistance in 2 to 4 weeks to guide the selection of the next regimen. Another strategy is to start two or three drugs that are predicted to be fully active based on the patient's treatment history. If no ARV history is available, a clinician may consider using agents with a high barrier to resistance—such as twice-daily Dolutegravir (DTG), Bictegravir (BIC) (which is available only in a combination pill with Emtricitabine/Tenofovir Alafenamide (FTC/TAF)), and/or boosted Darunavir (DRV)—as part of the regimen. Regardless of which strategy is employed, patients should be closely monitored for virologic response (e.g., HIV viral load testing approximately 4 to 8 weeks after reinitiation of therapy), with prompt drug-resistance testing performed if virologic response is inadequate.

Antiretroviral Therapy Goals and Presence of Viremia While on Antiretroviral Therapy

A persistent HIV-RNA level ≥200 copies/mL is often associated with evidence of viral evolution and accumulation of drug-resistance mutations. This association is particularly common when the HIV-RNA level is >500 copies/mL. Therefore, patients who have a persistent HIV-RNA level ≥200 copies/mL are considered to be experiencing virologic failure.

Causes of Virologic Failure

Virologic failure can occur for many reasons. Data from patient cohorts in the earlier era of combination Antiretroviral Therapy (ART) suggested that suboptimal adherence and drug intolerance/toxicity are key contributors to virologic failure and regimen discontinuations. The presence of preexisting (transmitted) drug resistance also may lead to virologic failure. Virologic failure may be associated with a variety of factors, including the following:

Patient/Adherence-Related Factors:

- Comorbidities that may affect adherence (e.g., active substance use, mental health disorders, neurocognitive impairment)
- Unstable housing and other psychosocial factors
- Missed clinic appointments
- Interruption of, or intermittent access to, ART
- Cost and affordability of ARV drugs (i.e., factors that may affect the ability to access or continue therapy)
- Adverse drug effects
- High pill burden and/or dosing frequency

HIV-Related Factors:

- Presence of transmitted or acquired drug-resistant virus that may or may not be documented by current or past drug-resistance test results
- Prior ARV treatment failure
- Innate drug resistance to prescribed ARV drugs
- Higher pre-treatment HIV-RNA level (some regimens may be less effective at higher levels)

Antiretroviral Regimen-Related Factors:

- Suboptimal pharmacokinetics (PKs) (e.g., variable absorption, metabolism, or penetration into reservoirs)
- Suboptimal virologic potency
- Low barrier to resistance
- Reduced efficacy due to prior exposure to suboptimal regimens (e.g., monotherapy, dual-nucleoside reverse transcriptase inhibitor [NRTI] therapy, or the sequential introduction of drugs)
- Food requirements
- Drug–drug interactions with concomitant medications, which may reduce concentrations of the ARV drugs
- Prescription (prescribing or dispensing) errors

Antiretroviral Options for Patients with Virologic Failure

Designing a new regimen for patients who are experiencing treatment failure should always be guided by ARV history and results from current and past resistance testing. This table summarizes the text above and displays the most common or likely clinical scenarios seen in patients with virologic failure. For more detailed descriptions, please refer to the texts above and/or consult an expert in HIV drug resistance to assist in the design of a new regimen. It is also crucial to provide continuous adherence support to all patients before and after regimen changes.

Table 2.1 Antiretroviral Options for Patients with Virologic Failure

Clinical Scenario	Type of Failing Regimen	Resistance Considerations	New Regimen Options[a,b]	Goal
First Regimen Failure	NNRTI plus two NRTIs	Most likely resistant to NNRTI +/- 3TC or FTC (i.e., NNRTI mutations +/- M184V/I).[b] Additional NRTI mutations may also be present.	DTG (or BIC) plus two NRTIs (preferably at least one fully active*) **(AI);** *or* Boosted PI plus two NRTIs (preferably at least one fully active) **(AI);** *or* Boosted PI plus INSTI (**CI or AIII**)[c]	Resuppression
	Boosted PI plus two NRTIs	Most likely no resistance, or resistance only to 3TC or FTC (i.e., M184V/I, without resistance to other NRTIs)[b]	DTG, or BIC, plus two NRTIs (preferably at least one fully active; *or* Continue same regimen **(AII);** *or* Another boosted PI plus INSTI **(CI or AIII)** [c]**;** *or* Another boosted PI plus two NRTIs (at least one fully active*) **(AIII)**	Resuppression
	INSTI plus two NRTIs	If failure on DTG or BIC, typically no INSTI resistance. Can have 3TC or FTC resistance (i.e., only M184V/I, usually without resistance to other NRTIs)[b]	Boosted PI plus two NRTIs (preferably at least one fully active*) **(AIII);** *or* DTG, or likely BIC, plus two NRTIs (preferably at least one fully active*) **(AIII);** *or* Boosted PI plus DTG **(AIII)**	Resuppression

Clinical Scenario	Type of Failing Regimen	Resistance Considerations	New Regimen Options[a,b]	Goal
		If failure on EVG or RAL, often have INSTI resistance, but potentially susceptible to DTG. Can have 3TC or FTC resistance	Boosted PI plus two NRTIs (preferably at least one fully active*) **(AIII);** *or* DTG[d] twice daily or possibly BIC (if HIV is sensitive) plus two fully active NRTIs **(BIII);** *or* DTG[d] twice daily or possibly BIC (if HIV is sensitive) plus a boosted PI **(AIII)**	Resuppression
Second Regimen Failure and Beyond	Drug resistance with fully active treatment options— 1. Boosted PI, but not second-generation INSTI, fully active 2. Second-generation INSTI, but not boosted PI, fully active 3. Both PI and INSTI fully active	Use past and current genotypic- +/– phenotypic-resistance testing and ART history when designing new regimen.	1. Boosted PI with two NRTIs (preferably at least one fully active) 2. DTG or BIC with two NRTIs (preferably at least one fully active) 3. The two options above or boosted PI with INSTI	Resuppression
	Multiple or extensive drug resistance with few treatment options (e.g., fully active boosted PI or second-generation INSTI unavailable)	Use past and current genotypic- and phenotypic-resistance testing to guide therapy. Confirm with a viral tropism assay when use of MVC is considered.	The new regimen should include at least two, and preferably three, fully active agents, including those with novel mechanisms of action (e.g., IBA or FTR). If <3 fully active drugs, include as many fully active drugs as possible, along with potentially partially active drugs. Consider enrollment into clinical trials or	Resuppression, if possible, otherwise, keep viral load as low as possible and CD4 count as high as possible. Keeping 3TC is advised as it impacts viral replication capacity

Clinical Scenario	Type of Failing Regimen	Resistance Considerations	New Regimen Options[a,b]	Goal
			expanded access programs for investigational agents if available. Discontinuation of all ARV drugs **is not recommended.**	
ART-Experienced Patients with Suspected Drug Resistance and Limited or Incomplete ARV and Resistance History	ART regimen unknown	Obtain medical records, if possible. Resistance testing may be helpful in identifying drug-resistance mutations, even if the patient has been off ART. Keep in mind that resistance mutations may not be detected in the absence of drug pressure.	Consider restarting the old regimen with careful monitoring of virologic response and early resistance testing, if inadequate virologic suppression. If no ARV history is available, consider initiating a regimen with drugs with high genetic barriers to resistance (e.g., DTG, BIC, and/or boosted DRV) with careful monitoring of virologic response and early resistance testing, if inadequate virologic suppression.	Resuppression

a. When switching an ARV regimen in a patient with HBV/HIV coinfection, ARV drugs that are active against HBV should be continued as part of the new regimen. Discontinuation of these drugs may lead to the reactivation of HBV, which may result in serious hepatocellular damage.

b. If other NRTI resistance mutations are present, use resistance test results to guide NRTI usage in the new regimen.

c. CI for LPV/r + RAL; AIII for other boosted PIs (e.g., DRV) or INSTIs (e.g., DTG).

d. Response to DTG depends on the type and number of INSTI mutations.

Key: 3TC = lamivudine; ART = antiretroviral therapy; ARV = antiretroviral; BIC = bictegravir; CD4 = CD4 T lymphocyte; DRV = darunavir; DTG = dolutegravir; EVG = elvitegravir; FTC = emtricitabine; FTR = fostemsavir; HBV = hepatitis B virus; IBA = ibalizumab; INSTI = integrase strand transfer inhibitor; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NTD = neural tube defect; PI = protease inhibitor; RAL = raltegravir

References

1. Kieffer, T. L., Finucane, M. M., Nettles, R. E., et al. (2004). Genotypic analysis of HIV-1 drug resistance at the limit of detection: virus production without evolution in treated adults with undetectable HIV loads. *J Infect Dis, 189*(8), 1452-1465.
2. Nettles, R. E., Kieffer, T. L., Kwon, P., et al. (2005). Intermittent HIV-1 viremia (blips) and drug resistance in patients receiving HAART. *JAMA, 293*(7), 817-829.
3. Lima, V., Harrigan, R., & Montaner, J. S. (2009). Increased reporting of detectable plasma HIV-1 RNA levels at the critical threshold of 50 copies per milliliter with the Taqman assay in comparison to the Amplicor assay. *J Acquir Immune Defic Syndr, 51*(1), 3-6.
4. Gatanaga, H., Tsukada, K., Honda, H., et al. (2009). Detection of HIV type 1 load by the Roche Cobas TaqMan assay in patients with viral loads previously undetectable by the Roche Cobas Amplicor Monitor. *Clin Infect Dis, 48*(2), 260-262.
5. Willig, J. H., Nevin, C. R., Raper, J. L., et al. (2010). Cost ramifications of increased reporting of detectable plasma HIV-1 RNA levels by the Roche COBAS AmpliPrep/COBAS TaqMan HIV-1 version 1.0 viral load test. *J Acquir Immune Defic Syndr, 54*(4), 442-444.
6. Antiretroviral Therapy Cohort C. (2015). Impact of low-level viremia on clinical and virological outcomes in treated HIV-1-infected patients. *AIDS, 29*(3), 373-383.
7. Boillat-Blanco, N., Darling, K. E., Schoni-Affolter, F., et al. (2014). Virological outcome and management of persistent low-level viraemia in HIV-1-infected patients: 11 years of the Swiss HIV Cohort Study. *Antivir Ther*.
8. Eron, J. J., Cooper, D. A., Steigbigel, R. T., et al. (2013). Efficacy and safety of raltegravir for treatment of HIV for 5 years in the BENCHMRK studies: final results of two randomised, placebo-controlled trials. *Lancet Infect Dis, 13*(7), 587-596.
9. Laprise, C., de Pokomandy, A., Baril, J. G., Dufresne, S., & Trottier, H. (2013). Virologic failure following persistent low-level viremia in a cohort of HIV-positive patients: results from 12 years of observation. *Clin Infect Dis, 57*(10), 1489-1496.
10. Taiwo, B., Gallien, S., Aga, S., et al. (2010). HIV drug resistance evolution during persistent near-target viral suppression. *Antiviral Therapy, 15*, A38.
11. Aleman, S., Soderbarg, K., Visco-Comandini, U., Sitbon, G., & Sonnerborg, A. (2002). Drug resistance at low viraemia in HIV-1-infected patients with antiretroviral combination therapy. *AIDS, 16*(7), 1039-1044.
12. Karlsson, A. C., Younger, S. R., Martin, J. N., et al. (2004). Immunologic and virologic evolution during periods of intermittent and persistent low-level viremia. *AIDS, 18*(7), 981-989.
13. d'Arminio Monforte, A., Lepri, A. C., Rezza, G., et al. (2000). Insights into the reasons for discontinuation of the first highly active antiretroviral therapy (HAART) regimen in a cohort of antiretroviral naive patients. I.CO.N.A. Study Group. Italian Cohort of Antiretroviral-Naive Patients. *AIDS, 14*(5), 499-507.
14. Mocroft, A., Youle, M., Moore, A., et al. (2001). Reasons for modification and discontinuation of antiretrovirals: results from a single treatment centre. *AIDS, 15*(2), 185-194.
15. Paredes, R., Lalama, C. M., Ribaudo, H. J., et al. (2010). Pre-existing minority drug-resistant HIV-1 variants, adherence, and risk of antiretroviral treatment failure. *J Infect Dis, 201*(5), 662-671.
16. Cooper, D. A., Steigbigel, R. T., Gatell, J. M., et al. (2008). Subgroup and resistance analyses of raltegravir for resistant HIV-1 infection. *N Engl J Med, 359*(4), 355-365.
17. Lazzarin, A., Clotet, B., Cooper, D., et al. (2003). Efficacy of enfuvirtide in patients infected with drug-resistant HIV-1 in Europe and Australia. *N Engl J Med, 348*(22), 2186-2195.
18. Lalezari, J. P., Henry, K., O'Hearn, M., et al. (2003). Enfuvirtide, an HIV-1 fusion inhibitor, for drug-resistant HIV infection in North and South America. *N Engl J Med, 348*(22), 2175-2185.
19. Reynes, J., Arasteh, K., Clotet, B., et al. (2007). TORO: ninety-six-week virologic and immunologic response and safety evaluation of enfuvirtide with an optimized background of antiretrovirals. *AIDS Patient Care STDS, 21*(8), 533-543.

20. Clotet, B., Bellos, N., Molina, J. M., et al. (2007). Efficacy and safety of darunavir-ritonavir at week 48 in treatment-experienced patients with HIV-1 infection in POWER 1 and 2: a pooled subgroup analysis of data from two randomised trials. *Lancet, 369*(9568), 1169-1178.
21. Steigbigel, R. T., Cooper, D. A., Kumar, P. N., et al. (2008). Raltegravir with optimized background therapy for resistant HIV-1 infection. *N Engl J Med, 359*(4), 339-354.
22. Katlama, C., Haubrich, R., Lalezari, J., et al. (2009). Efficacy and safety of etravirine in treatment-experienced, HIV-1 patients: pooled 48 week analysis of two randomized, controlled trials. *AIDS, 23*(17), 2289-2300.
23. Gulick, R. M., Lalezari, J., Goodrich, J., et al. (2008). Maraviroc for previously treated patients with R5 HIV-1 infection. *N Engl J Med, 359*(14), 1429-1441.
24. Fatkenheuer, G., Nelson, M., Lazzarin, A., et al. (2008). Subgroup analyses of maraviroc in previously treated R5 HIV-1 infection. *N Engl J Med, 359*(14), 1442-1455.
25. Cahn, P., Pozniak, A. L., Mingrone, H., et al. (2013). Dolutegravir versus raltegravir in antiretroviral-experienced, integrase-inhibitor-naive adults with HIV: week 48 results from the randomised, double-blind, non-inferiority SAILING study. *Lancet, 382*(9893), 700-708.
26. Hicks, C. B., Cahn, P., Cooper, D. A., et al. (2006). Durable efficacy of tipranavir-ritonavir in combination with an optimised background regimen of antiretroviral drugs for treatment-experienced HIV-1-infected patients at 48 weeks in the Randomized Evaluation of Strategic Intervention in multi-drug reSistant patients with Tipranavir (RESIST) studies: an analysis of combined data from two randomised open-label trials. *Lancet, 368*(9534), 466-475.
27. Molina, J. M., Lamarca, A., Andrade-Villanueva, J., & et al. (2012). Efficacy and safety of once daily elvitegravir versus twice daily raltegravir in treatment-experienced patients with HIV-1 receiving a ritonavir-boosted protease inhibitor: randomised, double-blind, phase 3, non-inferiority study. *Lancet Infect Dis, 12*(1), 27-35.
28. Reece, R., Delong, A., Matthew, D., Tashima, K., & Kantor, R. (2018). Accumulated pre-switch resistance to more recently introduced one-pill-once-a-day antiretroviral regimens impacts HIV-1 virologic outcome. *J Clin Virol, 105*, 11-17.
29. Lawrence, J., Mayers, D. L., Hullsiek, K. H., & et al. (2003). Structured treatment interruption in patients with multidrug-resistant human immunodeficiency virus. *N Engl J Med, 349*(9), 837-846.
30. Deeks, S. G., Wrin, T., Liegler, T., & et al. (2001). Virologic and immunologic consequences of discontinuing combination antiretroviral-drug therapy in HIV-infected patients with detectable viremia. *N Engl J Med, 344*(7), 472-480.
31. Cahn, P., Andrade-Villanueva, J., Arribas, J. R., & et al. (2014). Dual therapy with lopinavir and ritonavir plus lamivudine versus triple therapy with lopinavir and ritonavir plus two nucleoside reverse transcriptase inhibitors in antiretroviral-therapy-naive adults with HIV-1 infection: 48 week results of the randomised, open label, non-inferiority GARDEL trial. *Lancet Infect Dis, 14*(7), 572-580.
32. Raffi, F., Babiker, A. G., Richert, L., & et al. (2014). Ritonavir-boosted darunavir combined with raltegravir or tenofovir-emtricitabine in antiretroviral-naive adults infected with HIV-1: 96 week results from the NEAT001/ANRS143 randomised non-inferiority trial. *Lancet, 384*(9958), 1942-1951.
33. Paton, N. I., Kityo, C., Hoppe, A., & et al. (2014). Assessment of second-line antiretroviral regimens for HIV therapy in Africa. *N Engl J Med, 371*(3), 234-247.
34. Boyd, M. A., Kumarasamy, N., Moore, C. L., & et al. (2013). Ritonavir-boosted lopinavir plus nucleoside or nucleotide reverse transcriptase inhibitors versus ritonavir-boosted lopinavir plus raltegravir for treatment of HIV-1 infection in adults with virological failure of a standard first-line ART regimen (SECOND-LINE): a randomised, open-label, non-inferiority study. *Lancet, 381*(9883), 2091-2099.
35. Paton, N. I., Musaazi, J., Kityo, C., & et al. (2021). Dolutegravir or darunavir in combination with zidovudine or tenofovir to treat HIV. *N Engl J Med, 385*(4), 330-341.
36. Paton, N. I., Musaazi, J., Kityo, C., & et al. (2022). Efficacy and safety of dolutegravir or darunavir in combination with lamivudine plus either zidovudine or tenofovir for second-line treatment of HIV infection (NADIA): week 96 results from a prospective, multicentre, open-label, factorial, randomised, non-inferiority trial. *Lancet HIV, 9*(6), e381-e393.

37. Aboud, M., Kaplan, R., Lombaard, J., & et al. (2019). Dolutegravir versus ritonavir-boosted lopinavir both with dual nucleoside reverse transcriptase inhibitor therapy in adults with HIV-1 infection in whom first-line therapy has failed (DAWNING): an open-label, non-inferiority, phase 3b trial. *Lancet Infect Dis, 19*(3), 253-264.

38. Paton, N. I., Kityo, C., Thompson, J., Nankya, I., Bagenda, L., & Hoppe, A. (2017). Nucleoside reverse-transcriptase inhibitor cross-resistance and outcomes from second-line antiretroviral therapy in the public health approach: an observational analysis within the randomised, open-label, EARNEST trial. *The Lancet, 4*(8), E341-E348.

39. La Rosa, A. M., Harrison, L. J., Taiwo, B., & et al. (2016). Raltegravir in second-line antiretroviral therapy in resource-limited settings (SELECT): a randomised, phase 3, non-inferiority study. *Lancet HIV, 3*(6), e247-258.

40. Food and Drug Administration. (2020). Tivicay package insert [package insert].

41. Food and Drug Administration. (2017). Prezista package insert [package insert].

42. Food and Drug Administration. (2019). KALETRA [package insert].

43. Deeks, S. G., Hoh, R., Neilands, T. B., & et al. (2005). Interruption of treatment with individual therapeutic drug classes in adults with multidrug-resistant HIV-1 infection. *J Infect Dis, 192*(9), 1537-1544.

44. Deeks, S. G., Lu, J., Hoh, R., & et al. (2007). Interruption of enfuvirtide in HIV-1 infected adults with incomplete viral suppression on an enfuvirtide-based regimen. *J Infect Dis, 195*(3), 387-391.

45. Wirden, M., Simon, A., Schneider, L., & et al. (2009). Raltegravir has no residual antiviral activity in vivo against HIV-1 with resistance-associated mutations to this drug. *J Antimicrob Chemother, 64*(5), 1087-1090.

46. Hosseinipour, M. C., van Oosterhout, J. J., Weigel, R., & et al. (2009). The public health approach to identify antiretroviral therapy failure: high-level nucleoside reverse transcriptase inhibitor resistance among Malawians failing first-line antiretroviral therapy. *AIDS, 23*(9), 1127-1134.

47. Castagna, A., Maggiolo, F., Penco, G., & et al. (2014). Dolutegravir in antiretroviral-experienced patients with raltegravir- and/or elvitegravir-resistant HIV-1: 24-week results of the phase III VIKING-3 study. *J Infect Dis*.

48. Bunupuradah, T., Chetchotisakd, P., Ananworanich, J., & et al. (2012). A randomized comparison of second-line lopinavir/ritonavir monotherapy versus tenofovir/lamivudine/lopinavir/ritonavir in patients failing NNRTI regimens: the HIV STAR study. *Antivir Ther, 17*(7), 1351-1361.

49. Lathouwers, E., De Meyer, S., Dierynck, I., & et al. (2011). Virological characterization of patients failing darunavir/ritonavir or lopinavir/ritonavir treatment in the ARTEMIS study: 96-week analysis. *Antivir Ther, 16*(1), 99-108.

50. Stebbing, J., Nathan, B., Jones, R., & et al. (2007). Virological failure and subsequent resistance profiles in individuals exposed to atazanavir. *AIDS, 21*(13), 1826-1828.

51. Zheng, Y., Lambert, C., Arendt, V., & Seguin-Devaux, C. (2014). Virological and immunological outcomes of elvitegravir-based regimen in a treatment-naive HIV-2-infected patient. *AIDS, 28*(15), 2329-2331. https://doi.org/10.1097/QAD.0000000000000433

52. White, K. L., Raffi, F., & Miller, M. D. (2014). Resistance analyses of integrase strand transfer inhibitors within phase 3 clinical trials of treatment-naive patients. *Viruses, 6*(7), 2858-2879. https://doi.org/10.3390/v6072858

53. Sax, P. E., Pozniak, A., Montes, M. L., et al. (2017). Coformulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380-1490): a randomised, double-blind, multicentre, phase 3, non-inferiority trial. *Lancet, 390*(10107), 2073-2082. https://doi.org/10.1016/S0140-6736(17)32299-7

54. Gallant, J., Lazzarin, A., Mills, A., et al. (2017). Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial. *Lancet, 390*(10107), 2063-2072. https://doi.org/10.1016/S0140-6736(17)32297-3

55. van Wyk, J., Orkin, C., Rubio, R., et al. (2020). Brief report: Durable suppression and low rate of virologic failure three years after switch to dolutegravir + rilpivirine two-drug regimen: 148-week results from the SWORD-1 and SWORD-2 randomized clinical trials. *J Acquir Immune Defic Syndr, 85*(3), 325-330. https://doi.org/10.1097/QAI.0000000000002455

56. Food and Drug Administration. (2022). Cabenuva [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/212888s005s006lbl.pdf

57. De Luca, A., Dunn, D., Zazzi, M., et al. (2013). Declining prevalence of HIV-1 drug resistance in antiretroviral treatment-exposed individuals in Western Europe. *J Infect Dis, 207*(8), 1216-1220. https://doi.org/10.1093/infdis/jis938

58. Paquet, A. C., Solberg, O. D., Napolitano, L. A., et al. (2014). A decade of HIV-1 drug resistance in the United States: trends and characteristics in a large protease/reverse transcriptase and co-receptor tropism database from 2003 to 2012. *Antivir Ther, 19*(4), 435-441. https://doi.org/10.3851/IMP2753

59. Murray, J. S., Elashoff, M. R., Iacono-Connors, L. C., Cvetkovich, T. A., & Struble, K. A. (1999). The use of plasma HIV RNA as a study endpoint in efficacy trials of antiretroviral drugs. *AIDS, 13*(7), 797-804. https://doi.org/10.1097/00002030-199905280-00008

60. Miller, V., Sabin, C., Hertogs, K., et al. (2000). Virological and immunological effects of treatment interruptions in HIV-1 infected patients with treatment failure. *AIDS, 14*(18), 2857-2867. https://doi.org/10.1097/00002030-200012220-00009

61. Ledergerber, B., Lundgren, J. D., Walker, A. S., et al. (2004). Predictors of trend in CD4-positive T-cell count and mortality among HIV-1-infected individuals with virological failure to all three antiretroviral-drug classes. *Lancet, 364*(9428), 51-62. https://doi.org/10.1016/S0140-6736(04)16589-6

62. Raffanti, S. P., Fusco, J. S., Sherrill, B. H., et al. (2004). Effect of persistent moderate viremia on disease progression during HIV therapy. *J Acquir Immune Defic Syndr, 37*(1), 1147-1154. https://doi.org/10.1097/01.qai.0000137371.80695.4b

63. Food and Drug Administration. (2018). Trogarzo package insert [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761065lbl.pdf

64. Food and Drug Administration. (2020). RUKOBIA [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/212950s000lbl.pdf

65. Food and Drug Administration. (2022). SUNLENCA [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215973s000lbl.pdf

66. Emu, B., Fessel, J., Schrader, S., et al. (2018). Phase 3 study of ibalizumab for multidrug-resistant HIV-1. *N Engl J Med, 379*(7), 645-654. https://doi.org/10.1056/NEJMoa1711460

67. Emu, B., Fessel, W. J., Schrader, S., et al. (2017). Forty-eight-week safety and efficacy on-treatment analysis of Ibalizumab in patients with multi-drug resistant HIV-1. *ID Week, San Diego, CA*. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5632088/

68. Kozal, M., Aberg, J., Pialoux, G., et al. (2020). Fostemsavir in adults with multidrug-resistant HIV-1 infection. *N Engl J Med, 382*(13), 1232-1243. https://doi.org/10.1056/NEJMoa1902493

69. Lataillade, M., Lalezari, J. P., Kozal, M., et al. (2020). Safety and efficacy of the HIV-1 attachment inhibitor prodrug fostemsavir in heavily treatment-experienced individuals: week 96 results of the phase 3 BRIGHTE study. *Lancet HIV, 7*(11), e740-e751. https://doi.org/10.1016/S2352-3018(20)30216-7

70. Segal-Maurer, S., DeJesus, E., Stellbrink, H. J., et al. (2022). Capsid inhibition with lenacapavir in multidrug-resistant HIV-1 infection. *N Engl J Med, 386*(19), 1793-1803. https://doi.org/10.1056/NEJMoa2114914

Optimizing Antiretroviral Therapy in The Setting of Viral Suppression

The principle of optimizing Antiretroviral (ARV) therapy is to maintain viral suppression without affecting future treatment options (AI).

In patients with resistance to Nucleoside Reverse Transcriptase Inhibitors (NRTIs), regimen optimization includes two NRTIs: Tenofovir Alafenamide or Tenofovir Disproxil Fumarate plus Emtricitabine (FTC) or Lamivudine (3TC) with a fully active, high resistance barrier drug such as Dolutegravir, boosted Darunavir (BIII), or Bictegravir (CIII).

It is critical to review the full history of the patient before choosing a new ARV regimen. This includes virologic responses, previous ARV-related toxicities, and intolerances in addition to cumulative resistance test results (AI).

Patients who are engaged with their healthcare provider, virologically suppressed for 3-6 months, and commit to have frequent visits to their healthcare provider may be eligible for the optimization option of receiving a long-acting ARV regimen of the injectable Cabotegravir (CAB) and Rilpivirine (RPV) every one or two months (AI).

Patients with a history of resistance to one or more drug classes should have a consultation with an HIV specialist (AIII).

It is important to start close monitoring during the first 3 months after a regimen switch to assess tolerability, adherence, viral suppression, and safety (AIII).

Reasons to Consider Regimen Optimization in the Setting of Viral Suppression

- To reduce the pill burden and dosing frequency.
- To allow optimal use of ARV drugs during pregnancy.
- To reduce costs.
- To eliminate food or fluid requirements.
- To prevent or mitigate drug-drug interactions.
- To decrease short-term and long-term toxicity.
- To enhance drug tolerability.
- To switch to a long-acting injectable (CAB and RPV) regimen to relieve pill fatigue. It might also be to reduce potential stigma that is associated with taking daily oral medications.

General Principles of ARV Regimen Optimization

Table 2.2 General Principles of ARV Regimen Optimization

Principle	Description
1. Maintain viral suppression.	If the regimen switch results in virologic failure with the emergence of new resistance mutations, the patient may need less tolerated regimens.
2. Detailed and thorough review of both ARV treatment and drug resistance history before regimen switch.	The review of a patient's full ARV history is critical. That includes: 1. Virologic responses. 2. Cumulative resistance test results. 3. Previous ARV-associated intolerances, toxicities, and adverse reactions.
3. Optimization in people with active hepatitis B virus (HBV) coinfection.	- In patients with no documented history of or with no immunity to HBV infection, repeat HBV serology and re-vaccination should be completed before optimization with a regimen that is not active against HBV. - In patients with hepatitis B virus (HBV)/ HIV coinfection, when switching an ARV regimen, patients must continue to take the ARV drugs that are active against HBV **(AII)** or else specific anti-HBV drugs should be initiated. Patients must NOT discontinue HBV drugs as this may lead to the reactivation of HBV which, as a result, serious hepatocellular damage may occur. Using 3TC or FTC as the only drug in a regimen with HBV activity is NOT recommended **(AII)** due to a possible HBV resistance to them that may emerge.
4. Assessment for potential drug interactions.	
5. Assessment for potential or planned pregnancy.	- Women of childbearing potential should have a pregnancy test before switching ART. - If a woman living with HIV is found or planning to be pregnant, clinician should refer to the perinatal guidelines for safety and efficacy recommendations.

Principle	Description
6. Monitoring after switching ARV regimen.	- After regimen optimization, patients should be monitored and evaluated closely for 3 months to assess medication tolerance and to conduct targeted laboratory testing if the patient has preexisting laboratory abnormalities or if there are potential concerns with the new regimen.
7. Specific ARV switching considerations.	- Monotherapy as a switch strategy is **NOT** recommended because monotherapy with an INSTI or a boosted PI has been associated with unacceptable rates of virologic failure and the development of resistance **(AI)**. - The use of a two- or three-drug combination regimen is generally recommended when switching patients with viral suppression **(AI)**. - People living with HIV with no history of virologic failure or drug-resistance mutations may switch to the ARV regimens that have been proven to be highly effective in ARV naïve patients **(AI)**.
8. Optimization strategies with reliable supporting evidence for patients without known drug resistance.	
9. Multi-drug ARV therapy.	**A. Three-drug regimens:** - Within-class switches: *Usually* maintain viral suppression, provided there is no drug resistance to the new ART. Examples: ❖ From **TDF** or **ABC** to **TAF**. ❖ From **RAL** to **DTG**. ❖ From **DTG**, **EVG/c**, or **RAL** to **BIC**. ❖ From **EFV** to **RPV** or **DOR**. - Between-class switches: *Generally,* maintain viral suppression, provided there is no resistance to the other component of the regimen. Prior resistance test results will be very informative in guiding this switch. Examples: ❖ Replacing a boosted PI with an INSTI like **DTG**, **BIC**, or **EVG**. ❖ Replacing a boosted PI with **RPV** or **DOR**. ❖ Replacing an NNRTI with an INSTI. **B. Two-drug regimens:** - Effective in maintaining virologic control in patients who initiated therapy and achieved sustained virologic

Principle	Description
	suppression for at least 3 to 6 months with three drug regimens, provided their HIV is susceptible to both ARV drugs in the new regimen. However, these regimens are **NOT recommended** for patients with **HBV coinfection**, unless the patient is also on a specific anti-HBV active regimen (e.g., entecavir) **(AIII)**. Examples of successful strategies for switching from three- to two-drug regimens in people with suppressed HIV: ❖ **Dolutegravir** plus **Rilpivirine**. ❖ **Dolutegravir** plus **Lamivudine** or **Emtricitabine**. ❖ **Boosted Protease Inhibitor** plus **Lamivudine**. ❖ **Boosted Darunavir** plus **Dolutegravir**. **C. Long-acting ARV therapy:** - Parenteral ARV medications with innate or enhanced long half-lives have been evaluated for use with less than daily dosing. Long-acting is defined as any medication that is dosed once weekly or less frequently. - The injectable Cabotegravir (CAB) plus Rilpivirine (RPV) is indicated in patients with sustained (3-6 months) virologic suppression (HIV-1 RNA <50 copies/ml) on a stable **oral** ARV regimen, with no history of treatment failure, and with no known or suspected resistance to either CAB or RPV. Oral CAB and RPV is used in the event of planned missed injection. ❖ <u>Adverse events when using long-acting CAB and RPV:</u> - Injection site reactions (ISRs) were the most common adverse events which occurred at least once in more than 80% of the participants of both the ATLAS and FLAIR trials. - Hypersensitivity reactions, post-injection reactions, hepatotoxicity, anxiety disorders, and depressive disorders have been reported. ❖ <u>Practical consideration when using injectable CAB and RPV:</u> - A 23-gauge, 1½-inch IM needle is recommended for the injection, which is also provided in the product packaging. - Care should be taken to administer <u>ONLY</u> in the **Gluteal muscle**, preferably **ventrogluteal muscle**. ❖ <u>Management of missed doses of injected CAB and RPV:</u> - Recommendations differ based on the **dosing** being utilized (monthly vs. every 2 months) in addition to the **timing** of the missed dose.

Principle	Description
	- Oral-bridging therapy should be made available for planned missed doses. - Unplanned missed doses (beyond the 7-day window) should prompt reevaluation of whether the person remains an appropriate candidate for injectable therapy. - When stopping therapy, transition to a suppressive oral regimen should occur within 4 weeks of the last IM doses on **monthly** dosing and 8 weeks of the last IM doses for every 2-month dosing. ❖ HIV viral load and drug-resistance testing monitoring: HIV viral load monitoring should be performed 4 to 8 weeks after a switch to long-acting CAB and RPV. Viral load should also be checked in patients with unplanned missed visits and delayed dosing of the injection. ❖ Pregnancy consideration: Oral CAB and the long-acting injectable regimen of CAB and RPV have been classified as **NOT recommended** for use in pregnancy, because insufficient data exists. ❖ Other consideration: The injectable long-acting CAB and RPV do not have HBV activity. Additionally, specific treatment for HBV coinfection is needed.
10. Optimization strategies for patients with viral suppression and a history of limited drug resistance.	- Within-class switch from Dolutegravir to Bictegravir **(BI)**.

Principle	Description
11. Optimization strategies for patients with viral suppression and a history of Complex underlying resistance.	- Elvitegravir/Cobicistat/Tenofovir Alafenamide/Emtricitabine plus Darunavir : ❖ Switching to the combination of **EVG/c/TAF/FTC** plus **DRV** has been shown to be a potential optimization strategy in patients on complicated salvage regimens. ❖ **EVG/c/TAF/FTC** plus **DRV** would be an appropriate option for individuals who have treatment and drug resistance histories similar to those of participants included in this study. - BIC/TAF/FTC plus DRV/c.(JAC Podzamczer D)
12. Optimization strategies that are Not Recommended.	❖ Boosted protease inhibitor monotherapy. ❖ Dolutegravir monotherapy. ❖ Boosted Atazanavir plus Raltegravir. ❖ Maraviroc plus Boosted protease inhibitor ❖ Maraviroc plus Raltegravir.

References

1. World Health Organization. (2017). *Global action plan on HIV drug resistance*.
2. AIDSinfo. (2018). *Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents*.
3. International AIDS Society-USA Panel. (2008). *Antiretroviral drug resistance testing in adult HIV-1 infection: 2008 recommendations*.
4. The EuroGUidelines Group for HIV resistance. *Clinical and laboratory guidelines for the use of HIV-1 drug resistance testing as part of treatment management: Recommendations for the European setting*.
5. Aleman, S., Soderbarg, K., Visco-Comandini, U., Sitbon, G., & Sonnerborg, A. (2002). Drug resistance at low viraemia in HIV-1-infected patients with antiretroviral combination therapy. *AIDS, 16*(7), 1039-1044.
6. Karlsson, A. C., Younger, S. R., Martin, J. N., et al. (2004). Immunologic and virologic evolution during periods of intermittent and persistent low-level viremia. *AIDS, 18*(7), 981-989.
7. d'Arminio Monforte, A., Lepri, A. C., Rezza, G., et al. (2000). Insights into the reasons for discontinuation of the first highly active antiretroviral therapy (HAART) regimen in a cohort of antiretroviral naive patients. I.CO.N.A. Study Group. Italian Cohort of Antiretroviral-Naive Patients. *AIDS, 14*(5), 499-507.
8. Mocroft, A., Youle, M., Moore, A., et al. (2001). Reasons for modification and discontinuation of antiretrovirals: Results from a single treatment centre. *AIDS, 15*(2), 185-194.
9. Paredes, R., Lalama, C. M., Ribaudo, H. J., et al. (2010). Pre-existing minority drug-resistant HIV-1 variants, adherence, and risk of antiretroviral treatment failure. *Journal of Infectious Diseases, 201*(5), 662-671.
10. World Health Organization. (2021). *Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: Recommendations for a public health approach*.
11. World Health Organization. (2022). *Update on the transition to dolutegravir-based antiretroviral therapy: Report of a WHO meeting*.

HIV Infection and Adult Vaccination

Vaccines are especially critical for individuals with Human Immunodeficiency Virus (HIV) infection. Some individuals have a higher risk of acquiring certain vaccine-preventable diseases due to their work, living conditions, travel to endemic areas, exposure, or behavioral activities.

General Guidelines

- Early in the course of HIV infection or diagnosis, vaccine requirements should be assessed, and vaccination plans should be made whenever feasible.
- Serology tests should be requested to determine susceptibility to vaccine-preventable diseases.
- At every opportunity for vaccination, the need should be reviewed, and coverage should be completed.
- There is no contraindication to the use of inactivated vaccines at any time.
- If immune suppression is severe in an untreated or newly treated patient and the likelihood of exposure to the vaccine-preventable disease is low, vaccination may be deferred pending immune recovery after effective antiretroviral therapy.
- The risks and benefits of a live vaccine need to be carefully considered in consultation with an infectious disease specialist or immunologist.
- These recommendations are general statements. The need, history of side effects after previous vaccination, and contraindications of any vaccine products should be reviewed.

Table 2.3 Recommended Vaccination According to Immunological Status

Vaccine	Recommendation	
	CD4+ T cells > 200/µL	CD4+ T cells <200/µL
BCG	• Not recommended	
COVID-19	• All persons with HIV should receive a primary series regardless of their CD4 count or HIV viral load and may need extra dose if sever immune suppressed.	
Haemophilus influenza type B	• According to routine recommendations	
Hepatitis A virus	HAV susceptible with HIV infection Two-dose series of either single-antigen vaccine: • Havrix: 1.0 mL IM (0, 6–12 months); *or* • Vaqta: 1.0 mL IM (0, 6–18 months). Assess antibody response (total or IgG anti-HAV) 1–2 months after completion of the series, and if negative, revaccinate, preferably after the CD4 count is ≥200 cells/mm3. Post-exposure prophylaxis Administer HAV vaccine and HepA IgG (0.1 mg/kg) simultaneously in different anatomical sites as soon as possible within 2 weeks of exposure to HAV in people who are non-immune.	
Hepatitis B virus	**HBV susceptible and never vaccinated (i.e., anti-HBs <10 mIU/mL);** ○ Engerix-B (40 mcg) or Recombivax (20 mcg): three-dose series (0, 1, 6 months) *or* ○ Heplisav: two-dose series (0, 1 month) 20 mcg in 0.5 mL IM. Check Anti-HBs 1 to 2 months after completion of the vaccine series.Check HBsAb 4-8 weeks after last dose; • if the Anti-HBs titer is <100 mIU/mL, then vaccinate with a complete series of HepB followed by anti-HBs testing. **Post-exposure prophylaxis;** 1- previously vaccinated with complete series and have documented antibody response; no additional vaccine is needed.	

<table>
<tr><th rowspan="2">Vaccine</th><th colspan="2">Recommendation</th></tr>
<tr><th>CD4+ T cells > 200/µL</th><th>CD4+ T cells <200/µL</th></tr>
<tr><td></td><td colspan="2">2- Have received complete series without documentation of antibody response;

administer a single dose of HepB vaccine.

3- Not received a vaccine or have not received the complete series;

administer or complete the HepB vaccine series and administer a dose of HBIG at a separate anatomical site as soon as possible after exposure.</td></tr>
<tr><td>Human papilloma virus</td><td colspan="2">• Females <45 years and males

• Recombinant 9-valent human papillomavirus vaccine (Gardasil 9): 0.5 mL IM three-dose series (0, 1–2, and 6 months).

• Vaccination is not recommended during pregnancy.</td></tr>
<tr><td>Influenza virus</td><td colspan="2">• Annual in the fall one dose of age appropriate IIV or RIV
• LAIV is contraindicated</td></tr>
<tr><td rowspan="3">Measles, mumps, rubella viruses</td><td colspan="2">No evidence of immunity to measles, mumps, or rubella;</td></tr>
<tr><td>1 or 2 doses at least 1 month apart if;

• born in 1957 or after

• no immunity to these diseases.</td><td>• Not recommended if CD4 count <200 cells/mm^3.

• MMR vaccine is contraindicated during pregnancy</td></tr>
<tr><td colspan="2">Post-exposure prophylaxis</td></tr>
</table>

<table>
<tr><th rowspan="2">Vaccine</th><th colspan="2">Recommendation</th></tr>
<tr><th>CD4+ T cells > 200/µL</th><th>CD4+ T cells <200/µL</th></tr>
<tr><td></td><td>For measles, non-immune individuals with CD4 count >200 cells mm^3,

- Administer MMR vaccine within 72 hrs of exposure or

- IG within 6 days of exposure.

(Do not administer MMR vaccine and IG simultaneously)</td><td>Non-immune individuals with CD4 count <200 cells mm^3 or those who are pregnant, administer IG.</td></tr>
<tr><td>Meningococcal</td><td colspan="2">• ACWY conjugate vaccine, One dose
• every 5 years after completing primary schedule
• Meningococcal B:Two-dose series of Bexsero or three-dose series of Trumenba; when available.</td></tr>
<tr><td rowspan="4">Pneumococcal</td><td colspan="2">No prior pneumococcal vaccine or vaccination history unknown</td></tr>
<tr><td>Administer either of the following:
• PCV20 (Prevnar20): 0.5 mL IM x 1; or
• PCV15 (Vaxneuvance): 0.5 mL IM × 1 followed at least 8 weeks later by PPSV23 (Pneumovax): 0.5 mL IM × 1.</td><td>HIV with CD4 count <200 cells/mm^3 can be offered PPSV23 at least 8 weeks after receiving PCV15.
PPSV23 should preferably be deferred until after an individual’s CD4 count increases to >200 cells/mm^3 while on ART.</td></tr>
<tr><td colspan="2">Previously received PCV13 and PPSV23</td></tr>
<tr><td>If <65 years when received dose of PPSV23:

• Administer PCV20 0.5 mL IM x 1 at least 5 years after the last pneumococcal vaccine or

• Revaccinate the following with PPSV23 0.5 mL IM x 1;

▪ Adults aged 19–64 years if</td><td></td></tr>
</table>

<table>
<tr><th rowspan="2">Vaccine</th><th colspan="2">Recommendation</th></tr>
<tr><th>CD4+ T cells > 200/µL</th><th>CD4+ T cells <200/µL</th></tr>
<tr><td rowspan="4"></td><td>≥5 years since the first PPSV23 dose
▪ Adults aged ≥65 years if:
- Previous PPSV23 administered at age <65, and
- ≥5 years since the previous PPSV23 dose, and
- At least 8 weeks after receipt of PCV13.
If ≥65 years when received dose of PPSV23:
No further doses of PPSV23 are required.</td><td></td></tr>
<tr><td colspan="2">Previously received only PCV13</td></tr>
<tr><td>• Administer;
PCV20 0.5 mL IM x 1 at least 1 year after PCV13.

or
Initial dose of PPSV23 0.5 mL IM × 1 at least 8 weeks after PCV13.

• Revaccinate the following with PPSV23 0.5 mL IM x 1;
- Adults aged 19–64 years if
≥5 years since the first PPSV23 dose
- Adults aged ≥65 years if ≥5 years since the previous PPSV23 dose.</td><td>In patients who received PCV13 when their CD4 count was <200 cells/mm^3 and PPSV23 will be given, choose to defer PPSV23 until CD4 count is >200 cells/mm^3 to optimize vaccine efficacy .</td></tr>
<tr><td colspan="2">Previously received only PPSV23</td></tr>
<tr><td>Administer either of the following at least 1 year after last PPSV23 dose:
- PCV20: 0.5 mL IM x 1; or
- PCV15: 0.5 mL IM × 1 .</td><td></td></tr>
</table>

Vaccine	Recommendation	
	CD4+ T cells > 200/µL	CD4+ T cells <200/µL
Poliovirus	• Not routinely recommended • Use inactivated poliovirus vaccine if indicated (Three doses IPV IM at 0, 1–2 months, and third dose given 6–12 months after second dose). • Use also for household and other close contacts.	• Can Use inactivated poliovirus vaccine
Tetanus, diphtheria, and acellular pertussis (Tdap)	• According to routine recommendations (One dose Tdap (Adacel or Boostrix), then Td or Tdap every 10 years)	
Varicella virus	• Two-dose series of VAR 3 months apart If IgG antibody negative	• VAR **is contraindicated** if CD4 count <200 cells/mm^3
Zoster virus	• Age ≥18 years, regardless of past episode of herpes zoster or receipt of attenuated ZVL (Zostavax) and regardless of CD4 count; Give two-dose series of RZV (Shingrix) IM 2–6 months apart. • **Do not give** RZV (Shingrix) during an acute episode of herpes zoster.	• Consider delaying vaccination until patient is virologically suppressed on ART or wait for immune reconstitution in those who had a CD4 count <200 cells/mm^{3}to maximize immunologic response to the vaccine.
Mpox	• Administer two-dose series of JYNNEOS (0.5 mL SQ or 0.1 mL ID) given 28 days apart. • Administration of live replicating vaccinia vaccines (i.e., ACAM2000) to people with HIV is **contraindicated.**	

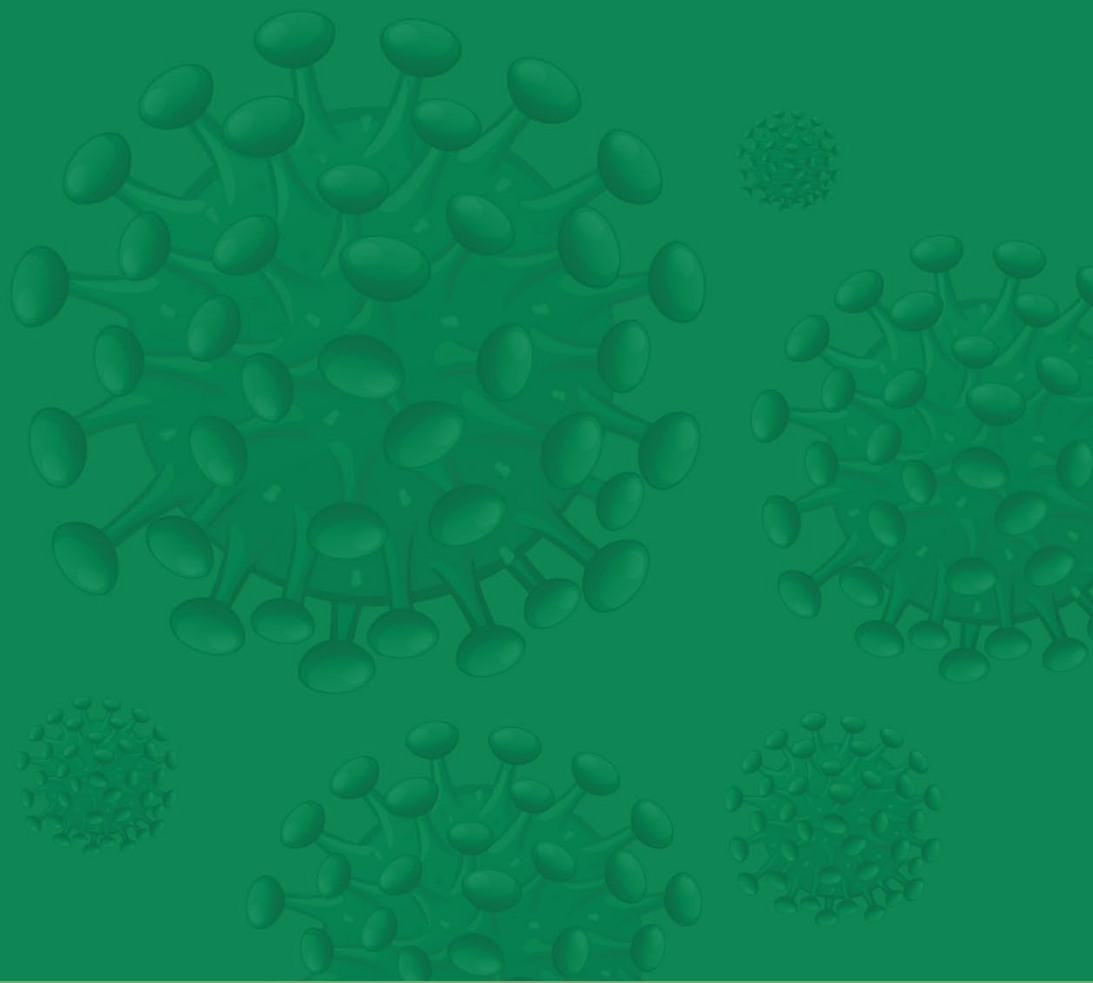
Vaccine	Travel Recommendation	
	CD4+ T cells > 200/µL	CD4+ T cells <200/µL
Initial Assessment	Review the need for vaccination; update and complete the coverage. Consider Hepatitis A, Meningococcal, and inactivated Polio vaccine	
Cholera	• Inactivated vaccine: If indicated, 2 doses	
Rabies	• If indicated: - Preexposure: three doses at 0, 7, 21-28 day. - Post exposure with rabies immunoglobulin: five doses at 0, 3,7,14, 28 days. • To check serology post vaccine , as may need boosting if continue risk of exposure	
Typhoid	• If indicated, one dose; booster in 2 years if exposure risk continues. • Inactivated vaccine safer ; Can use oral live vaccine	• If indicated, parenteral polysaccharide vaccine
Yellow fever	• If indicated, one dose.	• Not recommended

References

1. Centers for Disease Control and Prevention. (2022). Vaccines indicated for adults based on medical indications. CDC.
2. Public Health Agency of Canada. (n.d.). Canadian immunization guide. Canada.ca.
3. Crum-Cianflone, N. F., & Sullivan, E. (2017). Vaccinations for the HIV-infected adult: A review of the current recommendations, Part I. Infectious Diseases and Therapy, 6, 303–331.
4. Crum-Cianflone, N. F., & Sullivan, E. (2017). Vaccinations for the HIV-infected adult: A review of the current recommendations, Part II. Infectious Diseases and Therapy, 6, 333–361.
5. World Health Organization. (n.d.). Immunization of people living with HIV and people at risk of HIV infection. https://www.euro.who.int/__data/assets/pdf_file/0004/78502/E90840_Chapter_12.pdf%3Fua%3D1
6. World Health Organization. (2016). Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations (Updated version).
7. British HIV Association. (2015). BHIVA guidelines on the use of vaccines in HIV-positive adults.
8. Rubin, L. G., et al. (2014). 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clinical Infectious Diseases, 58(3), e44–e100. https://doi.org/10.1093/cid/cit684
9. World Health Organization. (2021). Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: Recommendations for a public health approach. https://apps.who.int/iris/handle/10665/342899

CHAPTER 03

HIV GUIDELINE FOR POST AND PRE-EXPOSURE PROPHYLAXIS



HIV Pre-Exposure Prophylaxis

Definition

Pre-exposure prophylaxis (PrEP) refers to the use of certain antiretroviral medications by individuals who are not infected with HIV but are at high, ongoing risk of HIV acquisition. This treatment begins before potential HIV exposures and continues afterward.

Recommendations

- PrEP is recommended for men who have sex with men (MSM) (strong recommendation; high quality of evidence) and transgender women (strong recommendation; moderate quality of evidence), who report condomless anal sex within the last six months and who have any of the following:
    - Infectious syphilis or rectal bacterial sexually transmitted infection (STI), particularly if diagnosed in the preceding 12 months.
    - Recurrent use of nonoccupational post-exposure prophylaxis (nPEP) (more than once).
    - Ongoing sexual relationship with an HIV-positive partner with a substantial risk of transmissible HIV.
- High-incidence risk index (HIRI)-MSM risk score ≥ 11 (See **Table 3.2**).
- PrEP is not recommended in the context of a stable, closed relationship with a single partner with no or negligible risk of having transmissible HIV (strong recommendation; moderate quality of evidence).
- PrEP may also be considered for any other person not included in the previous groups who has had repeated sexually transmitted infections (weak recommendation; moderate quality of evidence).

Heterosexual Exposure

- We recommend PrEP for the HIV-negative partner in heterosexual serodiscordant relationships reporting condomless vaginal or anal sex, where the HIV-positive partner has a substantial risk of HIV transmission and is not yet virally suppressed (see **Table 3.3**) (strong recommendation; high quality of evidence).
- PrEP may be considered for the HIV-negative partner in heterosexual serodiscordant relationships reporting condomless vaginal or anal sex, where the HIV-positive partner has a non-negligible risk of HIV transmission and is not yet virally suppressed (weak recommendation; moderate quality of evidence).

People Who Inject Drugs (PWID) Exposure

- PrEP may be considered for people who inject drugs (PWID) if they share injection drug use paraphernalia with a person with a non-negligible risk of HIV infection (weak recommendation; moderate quality of evidence).

Table 3.1 Categories of risk that a person has transmissible HIV infection

Risk Level	Examples
Substantial	HIV positive and viremic (i.e., viral load > 1,000 copies/mL). HIV status unknown, but from a population with high HIV prevalence compared with the general population (e.g., men who have sex with men, people who inject drugs).
Low but Non-Zero	HIV positive and believed to have a viral load of 200-1,000 copies/mL; with a concomitant sexually transmitted infection present at the time of exposure.
Negligible or None	Confirmed HIV negative. HIV positive with a confirmed viral load < 40 copies/mL and no known sexually transmitted infections present at the time of exposure.

Table 3.2 Risk of HIV transmission per act by exposure type from an HIV-positive source

Level	Exposure type	Estimated risk per act (%)
High	Anal (receptive)	1.38 (1.02–1.86)
	Needle sharing	0.63 (0.41–0.92)
Moderate	Anal (insertive)	0.11 (0.04–0.28)
Moderate	Vaginal (receptive)	0.08 (0.06–0.11)
	Vaginal (insertive)	0.04 (0.01–0.14)

Level	Exposure type	Estimated risk per act (%)
Low	Oral sex (giving)	Precise estimates not available
	Oral sex (receiving)	Precise estimates not available
	Oral–anal contact	Precise estimates not available
	Sharing sex toys	Precise estimates not available
	Blood on compromised skin	Precise estimates not available

Daily Oral PrEP Use Regimens

We recommend the following regimen for use as pre-exposure prophylaxis (PrEP): Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC) 300/200 mg once daily. This is a strong recommendation backed by high-quality evidence.

As an alternative, TDF/FTC 300/200 mg administered “on demand” may be considered in men who have sex with men (MSM). This involves taking two pills together 2 to 24 hours before the first sexual exposure, followed by one pill daily until 48 hours after the last sexual activity. This is a weak recommendation; however, it is supported by high-quality evidence.

F/TAF has been approved for daily PrEP use by men at sexual risk. However, F/TAF is not approved for PrEP use by women at risk through receptive vaginal sex. In such cases, F/TDF should be prescribed instead. Both F/TAF and F/TDF have equivalent high efficacy and safety as PrEP for men at sexual risk.

RECOMMENDED ORAL PrEP MEDICATIONS

Table 3.3 Recommended Oral Prep Medications

Generic Name	Trade Name	Dose	Frequency	Most Common Side Effects
F/TDF	Truvada	200 mg/300 mg	Once a day	Headache, abdominal pain, weight loss
F/TAF	Descovy	200 mg/25 mg	Once a day	Diarrhea

Initial Evaluation and Monitoring for Oral PrEP

HIV Testing at Baseline and Follow-up

For all people in whom PrEP is being considered or continued, HIV-negative status should be confirmed shortly before the initiation of PrEP and every 3 months thereafter. This confirmation should involve a laboratory-based fourth-generation assay. Confirmation of HIV status should also include evaluation for signs or symptoms suggestive of acute HIV infection within the last 12 weeks.

If acute HIV infection is suspected, additional laboratory evaluation with an HIV RNA nucleic acid amplification test (if available) or repeat fourth-generation assay 7 to 21 days later is suggested. PrEP should be deferred or suspended until results are received.

Renal Monitoring

Underlying kidney disease should be ruled out before PrEP is started, using a urinalysis and serum creatinine. The estimated glomerular filtration rate should be > 60 mL/min for use of PrEP.

Bone Health

Routine dual-energy x-ray absorptiometry to assess bone mineral density is not advised. PrEP may be considered in people with low bone mass or osteoporosis after the risks and benefits have been discussed with them.

Sexually Transmitted Infections and Viral Hepatitis

Laboratory screening for sexually transmitted infections is suggested at baseline and at each quarterly follow-up visit, with appropriate therapy for any identified infections. Hepatitis A, B,

and C serologies should be performed at baseline, with vaccination for hepatitis A and B for non-immune individuals and repeat serologic screening every 6 to 12 months for those who remain hepatitis B unvaccinated and hepatitis C uninfected.

Frequency of Follow-up

Follow-up clinical and laboratory evaluation should occur after 30 days and every three months thereafter. Each PrEP prescription should be for no more than three months, with no automatic refills.

Pregnancy Screening

Pregnancy screening in people of child-bearing potential using PrEP should occur every three months.

Counseling

PrEP clinical encounters should include assessments and counseling regarding strategies for reducing the risk of HIV infection, syndemic conditions, potential drug toxicities, and adherence to medication.

Adherence Support

Interventions to support adherence to medication should be discussed at the time that PrEP is begun, actively monitored at every follow-up patient encounter, and tailored to the individual patient. Specific interventions may include patient counseling, education, medication reminders, behavioral feedback and reinforcement, peer support, follow-up telephone calls or text messages, and minimization of out-of-pocket expenses.

PrEP DISCONTINUATION

We suggest that pre-exposure prophylaxis (PrEP) be continued for 2 days after the last HIV exposure and for daily PrEP for 7 days. Upon discontinuation of PrEP for any reason, the following should be documented in the health record:

- HIV status at the time of discontinuation;
- Reason for discontinuation; and
- Recent medication adherence and reported sexual risk behavior.

Upon PrEP discontinuation, we advise subsequent follow-up HIV testing using a laboratory-based fourth-generation assay when available, or an alternative at up to eight weeks afterwards.

Special Populations

Hepatitis B Infection

If Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC) PrEP is prescribed in a person with chronic hepatitis B infection, appropriate monitoring for hepatitis B virus should be performed in accordance with hepatitis B treatment guidelines, if necessary in consultation with a qualified practitioner with experience in treating the virus.

When considering PrEP discontinuation, the need for ongoing therapy for hepatitis B virus should be assessed. If PrEP is discontinued and no other therapy for hepatitis B virus is used, close monitoring for a flare of the condition is advised.

Pregnancy and Breastfeeding

TDF/FTC PrEP may be considered during pregnancy and breastfeeding after the benefits and risks have been discussed with the patient.

Table 3.4 Suggested Evaluation at Baseline and During Pre-Exposure Prophylaxis

Assay Type	Baseline	30 Days	Every 3 Months	Every 12 Months
Laboratory Evaluation				
HIV Testing*	X	X	X	
Hepatitis A Immunity (Hepatitis A Total Antibody)†	X			
Hepatitis B Screen (Surface Antigen, Surface Antibody, Core Antibody)†‡	X			X†
Hepatitis C Antibody	X		X*	
Screening for Gonorrhea and Chlamydia§	X		X	
Syphilis Serology§	X		X	
Complete Blood Count	X			

Assay Type	Baseline	30 Days	Every 3 Months	Every 12 Months
Creatinine	X	X	X	
Urinalysis	X			
Pregnancy Test (As Appropriate)	X		X	
Clinical Evaluation				
Symptoms of HIV Seroconversion	X	X	X	
PrEP Adherence		X	X	
Indication for PrEP	X	X	X	
Use of Other HIV and STI Prevention Strategies	X	X	X	
Presence and Management of Syndemic Conditions	X	X	X	

* If high risk, HCV antibody should be performed every 6 months. We can also consider the use of HCV/HBsAg RDT.

* Preferred HIV test is a 4th-generation antibody/antigen combo assay. Those with signs or symptoms of acute HIV should also undergo HIV RNA or pooled nucleic acid amplification test.

† Hepatitis A and/or B vaccine should be initiated in unvaccinated individuals. Those who remain non-immune to hepatitis B virus should be rescreened annually.

‡ Individuals with chronic active hepatitis B should be managed in consultation with an expert on hepatitis B virus according to Canadian guidelines.

§ Individuals who have STIs should be offered standard therapy and follow-up as per local guidelines.

Prescribing Cabotegravir PrEP Injections

Patients considering PrEP should be informed of all options approved by the Food and Drug Administration (FDA). Injections of *Cabotegravir*, a medication used for PrEP, may be particularly suitable for patients with significant renal disease, those who have had difficulty adhering to the use of oral PrEP, and those who prefer injections every two months over an oral PrEP dosing schedule. *Cabotegravir* should not be administered to individuals with a history of hypersensitivity reaction to *Cabotegravir*.

Table 3.5 Summary of Clinician Guidance for Daily Oral PrEP Use

	Sexually-Active Adults	Persons Who Inject Drugs[1]
Identifying substantial risk of acquiring HIV infection	Anal or vaginal sex in past 6 months AND any of the following: • HIV-positive sexual partner (especially if partner has an unknown or detectable viral load) • Bacterial STI in past 6 months[2] • History of inconsistent or no condom use with sexual partner(s)	HIV-positive injecting partner OR Sharing injection equipment
Clinically eligible	**ALL OF THE FOLLOWING CONDITIONS ARE MET:** • Documented negative HIV Ag/Ab test result within 1 week before initial cabotegravir injection • No signs/symptoms of acute HIV infection • No contraindicated medications or conditions	
Dosage	600 mg cabotegravir administered as one 3 ml intramuscular injection in the gluteal muscle o Initial dose o Second dose 4 weeks after first dose (month 1 follow-up visit) o Every 8 weeks thereafter (month 3,5,7, follow-up visits etc)	
Follow-up care	**At follow-up visit 1 month after first injection** • HIV Ag/Ab test and HIV-1 RNA assay **At follow-up visits every 2 months (beginning with the third injection – month 3) provide the following:** • HIV Ag/Ab test and HIV-1 RNA assay • Access to clean needles/syringes and drug treatment services for PWID **At follow-up visits every 4 months (beginning with the third injection-month 3) provide the following:**	

	Sexually-Active Adults	Persons Who Inject Drugs[1]
	• Bacterial STI screening[2] for MSM and transgender women who have sex with men2 – oral, rectal, urine, blood **At follow-up visits every 6 months (beginning with the fifth injection – month 7) provide the following:** • Bacterial STI screening[1] for all heterosexually-active women and men – [vaginal, rectal, urine - as indicated], blood **At follow-up visits at least every 12 months (after the first injection) provide the following:** • Assess desire to continue injections for PrEP • Chlamydia screening for heterosexually active women and men – vaginal, urine **At follow-up visits when discontinuing cabotegravir injections provide the following:** • Re-educate patients about the "tail" and the risks during declining CAB levels • Assess ongoing HIV risk and prevention plans • If PrEP is indicated, prescribe daily oral F/TDF or F/TAF beginning within 8 weeks after last injection • Continue follow-up visits with HIV testing quarterly for 12 months	

1. Because most PWID are also sexually active, they should be assessed for sexual risk and provided the option of CAB for PrEP when indicated
2. Sexually transmitted infection (STI): Gonorrhea, chlamydia, and syphilis for MSM and transgender women who have sex with men including those who inject drugs; Gonorrhea and syphilis for heterosexual women and men including persons who inject drugs.

Cabotegravir PrEP Drug Interactions

Table 3.6 Cabotegravir PrEP Drug Interactions

Drug	Interaction with Cabotegravir (CAB)
Rifampicin, rifapentin	**Do not co-administer with CAB** Rifampicin and rifapentine increase metabolism of CAB and may result in significantly reduced exposure to protective levels of CAB
Rifabutin	**Co-administer with caution** Rifabutin moderately increases metabolism of CAB and may result in somewhat reduced exposure to protective levels of CAB
Hormonal contraceptives	No significant effect
Feminizing hormones (Spironolactone, estrogens)	No data yet available
Carbamazepine, oxcarbazepine, phenytoin, phenobarbita	**Do not co-administer with CAB** Concern that these anticonvulsants may result in significantly reduced exposure to protective levels of CAB but strength of evidence is weak

References

1. Kuhar, D. T., Henderson, D. K., Struble, K. A., et al. (2013). Updated US Public Health Service Guidelines for the Management of Occupational Exposures to Human Immunodeficiency Virus and Recommendations for Postexposure Prophylaxis. Infection Control & Hospital Epidemiology, 34(8), 875-892. doi:10.1086/672020
2. Centers for Disease Control and Prevention. (2016). Updated guidelines for Antiretroviral postexposure prophylaxis after sexual, injection-drug use, or other nonoccupational exposure to HIV in the United States, 2016: recommendations from the U.S. Department of Health and Human Services. https://stacks.cdc.gov/view/cdc/38856
3. Cardo, D. M., Culver, D. H., Ciesielski, C. A., et al. (1997). A case-control study of HIV seroconversion in health care workers after percutaneous exposure. New England Journal of Medicine, 337(21), 1485-1490. doi:10.1056/nejm199711203372103
4. Attia, S., Egger, M., Müller, M., Zwahlen, M., & Low, N. (2009). Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis. AIDS, 23(13), 1397-1404. doi:10.1097/QCO.0b013e32832b9c7c
5. Cohen, M. S., Chen, Y. Q., McCauley, M., et al. (2011). Prevention of HIV-1 infection with early antiretroviral therapy. New England Journal of Medicine, 365(6), 493-505. doi:10.1056/nejmoa1105243
6. Rodger, A. J., et al. (2016). Sexual activity without condoms and risk of HIV transmission in serodifferent couples when the HIV-positive partner is using suppressive antiretroviral therapy. JAMA, 316(1), 1-11. doi:10.1001/jama.2016.0280

7. Patel, P., Borkoff, C. B., Brooks, J. T., et al. (2014). Estimating per-act transmission risk: a systematic review. AIDS, 28(14), 1509-1519. doi:10.1097/QCO.0000000000000326

8. Wood, E., Kerr, T., Marshall, B. D. L., et al. (2009). Longitudinal community plasma HIV-1 RNA concentrations and incidence of HIV-1 among injecting drug users: prospective cohort study. British Medical Journal, 338(7704), 1191-1194. doi:10.1136/bmj.b1143

9. Kirk, G., Galai, N., Astemborski, J., et al. (2011). Decline in community viral load strongly associated with declining HIV incidence among IDU: In: Proceedings of the 18th Conference on Retroviruses and Opportunistic Infections; 27 Feb to 2 March 2011, Boston, MA, USA; 2011.

10. Solomon, S. S., Mehta, S. H., McFall, A. M., et al. (2016). Community viral load, antiretroviral therapy coverage, and HIV incidence in India: a cross sectional, comparative study. The Lancet HIV, 3(3), e183-e190. doi:10.1016/S2368-0397(16)30010-5

11. Papenberg, J., Blais, D., Moore, D., et al. (2008). Pediatric injuries from needles discarded in the community: Epidemiology and risk of seroconversion. Pediatrics, 122(2), e487-e492. doi:10.1542/peds.2007-2957

12. Rogowska-Szadkowska, D., & Chlabicz, S. (2010). Transmission of HIV through needlestick injuries in the community setting. HIV & AIDS Review, 9(1), 37-40.

13. Osowicki, J., & Curtis, N. (2014). Question 2: A pointed question: Is a child at risk following community-acquired needlestick injury? Archives of Disease in Childhood, 99(12), 1172-1175. doi:10.1136/archdischild-2013-304909

14. Vertesi, L. (2003). Risk assessment stratification protocol (RASP) to help patients decide on the use of post-exposure prophylaxis for HIV exposure. CJEM, 5(1), 46-48. doi:10.1046/j.1480-2494.2003.00081.x

15. World Health Organization. (2022). Differentiated and simplified pre-exposure prophylaxis for HIV prevention: Update to WHO implementation guidance. Technical brief. https://www.who.int/publications/i/item/9789240053694

HIV Post-Exposure Prophylaxis (PEP)

Definition

Post-Exposure Prophylaxis (PEP) refers to the use of specific antiretroviral medications by individuals who are not infected with HIV but have been exposed to blood or body fluids from an infectious or potentially infectious source.

Potential Exposure to HIV

A potential exposure to HIV is an event where blood or other potentially infectious body fluid from an infectious or potentially infectious source comes into contact with:

- Subcutaneous tissue (via percutaneous exposure, either by a needle stick or a cut with a sharp object)
- Mucous membranes (eye, mouth, nose, vaginal, or anorectal)
- Non-intact skin, healing wound (less than 3 days old), or skin lesion causing disruption of the epidermis

Infectious Body Fluids (Capable of Transmitting HIV)

Infectious body fluids include:

- Blood
- Any body fluid visibly contaminated with blood
- Semen
- Vaginal/rectal secretions
- Cerebrospinal fluid (CSF), amniotic, pleural, pericardial, peritoneal and synovial fluids, and inflammatory exudates
- Tissue or organs (e.g., transplantation)
- Breast milk

Non-Infectious Body Fluids (Unless Bloody)

Non-infectious body fluids include:

- Stool
- Urine
- Tears
- Saliva
- Nasal secretions
- Vomitus
- Sputum
- Sweat

Infectious/Potentially Infectious Source Person

1. Source Known to be HIV Positive

- The risk of HIV transmission is directly related to the HIV viral load of the source.
- The risk is lower if the HIV-positive source is receiving effective antiretroviral therapy and has a consistently undetectable plasma viral load (less than 40 copies/mL) in at least two consecutive measurements.
- Given that this information may not be readily available in an emergency situation, to prevent delays in starting PEP, it is recommended that antiretroviral therapy should be initiated in all cases of significant exposure to infectious body fluid from an HIV-positive source. The need for continuation of PEP will be reassessed by the infectious diseases specialist in the region or by consulting the MOH hotline 937.

2. Source Known to be at High Risk of Being HIV Positive

- People who inject drugs (PWID)
- Men who have sex with men (MSM)
- Persons who have had multiple transfusions of blood or blood products (e.g., hemophiliacs) prior to November 1987
- Sexual partners of persons known to be HIV positive, or at high risk of being HIV positive.

3. Unknown Source

- Will be assessed on a case-by-case basis.
- The risk of HIV infection is negligible from an abandoned needle outside the healthcare setting when there is no history of the origin of the needle or the time of its abandonment.

Procedures for Risk Assessment

If antiretroviral therapy is indicated for PEP, it is most effective if initiated within two hours, and not more than 72 hours, after exposure. Therefore, the healthcare provider should complete a risk assessment of the exposure as soon as possible after presentation.
The risk assessment should include:

- Assessment of the exposed person
- Assessment of the event and nature of exposure
- Assessment of the source person(s)

The Risk Assessment Stratification Protocol (RASP) is a useful tool for estimating the risk of HIV infection for occupational exposures and to help guide decisions regarding the need for PEP based on the above information. PEP is generally indicated if the risk level is 1/1000 (0.1%) or greater, and not indicated if the risk level is 1/100,000 (0.001%) or less. For intermediate levels of risk, PEP may be considered on a case-by-case basis.

Assessment of Exposed Person

- Perform baseline HIV serology (HIV Ag/Ab testing) in all exposed persons not previously known to be HIV positive. If the exposed person is known to be HIV positive, PEP is not indicated.
- If the exposed person is at high risk of already being HIV positive, perform an HIV point-of-care test, if available. If the exposed person is in a high-risk group and history suggests potential acute HIV infection (symptoms suggestive of acute HIV infection within the previous 6 weeks and history of high-risk unprotected sex or needle-sharing in the previous month), a nucleic acid amplification test (NAAT) for HIV RNA is recommended in addition to the standard HIV Ag/Ab assay.
- Perform baseline complete blood count (CBC) and differential, and creatinine with estimated glomerular filtration rate (eGFR) before starting PEP. If PEP is indicated, do not delay starting PEP while waiting for lab results.
- Perform serologic tests for hepatitis B virus (HBsAg, anti-HBc total, anti-HBs) and hepatitis C virus (anti-HCV).
- Assess for other sexually transmitted infections (gonorrhea, chlamydia, syphilis), if appropriate.
- If the exposed person is female, perform a pregnancy test.

Assessment of Event/Exposure Type

Some factors which can influence the risk of transmission include:

- In percutaneous exposure (via needle or other sharp object):
    - Solid device vs. hollow needle and gauge size
    - Visible blood on device and/or device previously in source's artery or vein
    - Depth of wound
    - Use of gloves by the exposed person
- In sexual exposures:

- The presence of a sexually transmitted infection (especially genital ulcer disease) in either the source or the exposed individual
- Circumcision status for insertive male partners
- Condom use
- Degree of physical injury (e.g., mucosal or skin break) associated with the sexual act

- In other types of events (e.g., splashes):
  - Type of fluid
  - Volume of fluid
  - Duration of exposure

Table 3.7 Estimated Risk of HIV Transmission by Exposure Type from Known HIV Positive Source with Detectable Viral Load

Exposure	Estimated Risk per 10,000 Acts (95% Confidence Interval)	Estimated Risk per Act/Event
Hollow Bore Needle Stick Injury	23 (0-46)	0.23%
Needle Sharing – Injection Drug Use	63 (41-92)	0.63%
Occupational Mucous Membrane Exposure	9 (0.6-50)	0.09%
Penile-Vaginal Intercourse – Risk to Insertive Partner	4 (1-14)	0.04%
Penile-Vaginal Intercourse – Risk to Receptive Partner	8 (6-11)	0.08%
Anal Intercourse (Risk to Insertive Partner)	11 (4-28)	0.11%
Anal Intercourse (Risk to Receptive Partner)	138 (102-186)	1.38%
Oral Intercourse (Risk to Either Partner)	Low (0-4)	Low

1. The risk is probably lower with cuts or punctures involving solid objects (vs. hollow bore needle).
2. The risk is probably lower for exposures involving non-intact skin (vs. mucous membranes). Transmission risk increased by high plasma viral load or acute or late-stage HIV in the source. Transmission risk in sexual exposures increased by genital ulcer disease and decreased by male circumcision or condom use.

Assessing Source Person

1. Source Person Known to be HIV Positive

a. **HIV Positive Source Not Receiving Antiretroviral Therapy**

The risk of HIV transmission from an HIV positive source person not currently receiving antiretroviral therapy will depend on the type of exposure that has occurred. In general, significant exposures to blood or potentially infectious bodily fluids would warrant initiation of prophylaxis in this setting.

b. **HIV Positive Source Person Receiving Antiretroviral Therapy**

The risk of HIV transmission from an HIV positive source person who is receiving antiretroviral therapy is reduced, in relation to the viral load of the source. If the source's viral load is currently and consistently fully suppressed, the risk of transmission from a single sexual exposure may be negligible. Undetectable viral load in the source may also reduce the risk of HIV transmission in percutaneous exposures involving blood-to-blood contact, but the risk may still be significant in such cases; persistence of HIV in latently infected cells has been demonstrated in patients receiving antiretroviral therapy, despite absence of cell-free virus in the peripheral blood (as measured by viral load).

2. Source Known but HIV Status Unknown

a. **Source Available for HIV Testing**

- If the source person is available for interview, additional information about risk history can be obtained and permission for baseline testing can be requested to assist in determining the likelihood of HIV exposure. If available and the source person agrees, an HIV point-of-care test can be performed at this time.
- If the source person's baseline HIV test is negative, prophylaxis is not required.
- In circumstances where the source is known to be in a high-risk group and has symptoms suggestive of acute HIV infection, an HIV NAAT test should be requested, in conjunction with the standard HIV Ag/Ab assay and prophylaxis should be started or continued (if exposure type warranted initiation) until both results are confirmed to be negative.

b. **Source Not Available for HIV Testing**

- When the source is unavailable or declines HIV testing, the risk of HIV exposure can be roughly estimated using community prevalence estimates of HIV within a particular risk group, and the type of exposure that has occurred.
- Groups considered to be at potentially higher risk for HIV infection.
- Those with an exposure type associated with increased HIV transmission (see Table 1) and source belonging to a high-risk group should be offered PEP.

c. **Unknown Source**

- In settings where the source identity is unknown, HIV risk may be inferred by the potential likelihood of HIV within the risk group of the source,
- The risk of HIV infection is negligible from an abandoned needle outside the health care setting when there is no history of the origin of the needle or the time of its abandonment.
- PEP is not recommended for needle sticks from an abandoned needle.

Specimen Handling and Management of Test Results

Specimens drawn from the source (using fourth-generation HIV RDTs for rapid results) should be clearly identified on the requisition as coming from a potential HIV exposure episode so a rapid turnaround time (24-48 hours) can be achieved by the laboratory.
If the source person's HIV test result is negative or non-reactive, continued prophylaxis is not required.

Management Recommendations

A 28-day course of antiretrovirals is recommended for significant exposure to blood, or other potentially infectious body fluids of a person known to be HIV positive, or at high risk for HIV, when that exposure represents a substantial risk for transmission, and when the person seeks care within 72 hours of exposure.

Negligible Risk of HIV Transmission

Material to which exposure has occurred is a body fluid not known to transmit HIV (urine, nasal secretions, saliva, sweat, or tears if not visibly bloody) OR an event not known to transmit HIV (e.g., contact with intact skin; superficial scratches that do not bleed; bites unless there is blood in the mouth of the biter) OR Source known to be HIV negative or at low risk of HIV infection. PEP is NOT recommended.
If uncertain whether to initiate PEP, consult the regional infection control officer or call MOH 937 hotline.

Significant Risk of Transmission

- Assess baseline risk of HIV in the exposed person and perform baseline HIV Ag/Ab test.

- Baseline lab work for PEP (CBC and differential, creatinine and eGFR), viral hepatitis (HBsAg, anti-HBc total, anti-HBs, anti-HCV) if appropriate, pregnancy (if appropriate), and other sexually transmitted infections (if appropriate).
- Start PEP as soon as possible (within 72 hours, preferably within 2 hours).
- Patients must follow up with their primary care provider or designated alternate care provider (if no primary care provider is identified) as soon as possible.
- For individuals receiving 28 days of therapy, follow-up laboratory monitoring HIV serology 0,3, and 6 months (CBC and differential, creatinine, eGFR) should be completed at weeks 2 and 4 of therapy if any abnormalities were detected at baseline.

Antiretroviral Regimen for PEP

- TDFLTAF or TAF/FTC (1 tablet daily) PLUS either RAL (400 mg twice daily) OR DTG (50 mg daily).
- Alternative regimen: DRV 800 mg daily +RTV 100 mg daily +TDF/FTC 1 tablet daily OR TAF/FTC 1 tablet daily.
- A full course of PEP is 28 days.

Contraindications to Antiretroviral Therapy

- A careful medication history (including prescription and non-prescription medications, supplements and alternative therapy) should be obtained.
- Avoid or use with extreme caution in persons with chronic renal insufficiency (estimated glomerular filtration rate [eGFR] <50 mL/min).

Management of Exposures in Children

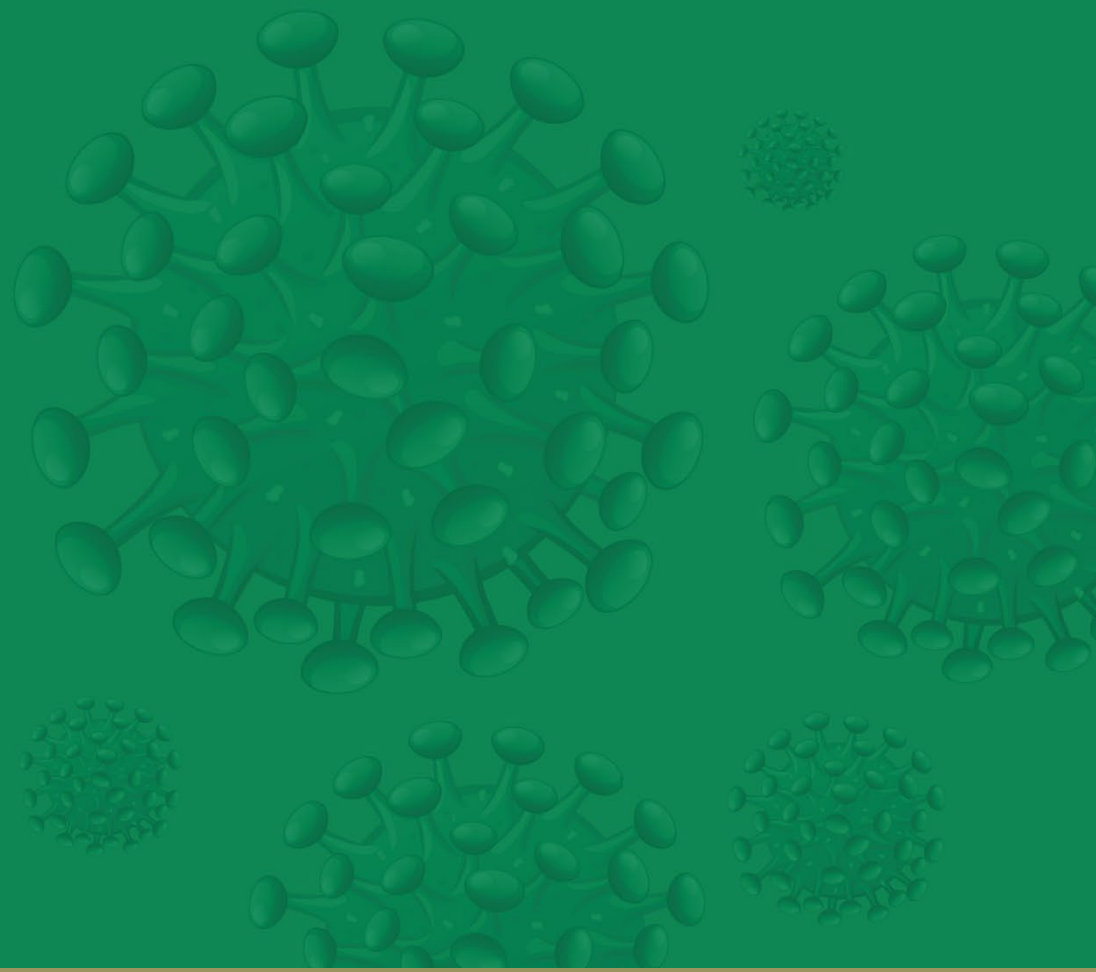
The risk of children being infected with HIV from accidental needle stick injuries, biting, or sexual assaults is very low. No data are available that show that PEP will decrease the risk of infection in children who sustain needle stick injuries or sexual assault.

PEP should be considered for children where the exposure is likely to have resulted in a transfer of potentially infectious body fluid to the recipient. In children, this would most commonly occur from blood or semen from a youth or adult who is known to be HIV positive or could potentially be HIV-positive. PEP should be considered for children sustaining sexual assault resulting in vaginal or anal penetration.

The regimen used is as in adults, with doses adjusted based on body weight.

CHAPTER 04

LIMITATIONS TO TREATMENT SAFETY AND EFFICACY



Adherence to the Continuum of Care

This section provides guidance on linking patients to care, assessing and improving retention in care, and assessing and improving adherence to Antiretroviral Therapy (ART).

Linkage-to-care and adherence to both ART and clinic appointments should be regularly assessed. An individual's barriers to adherence to ART and appointments should be assessed before initiation of ART and regularly thereafter.

Patients with ART adherence problems should be placed on regimens with high genetic barriers to resistance, such as Dolutegravir (DTG) or boosted Darunavir (DRV). Side effects, out-of-pocket costs, convenience, and patient preferences also need to be considered.

Patients having difficulties with adherence to appointments or ART should be approached in a constructive, collaborative, nonjudgmental, and problem-solving manner. The approach to improved adherence should be tailored to each person's needs.

The strategies to improve linkage to care, retention in care, adherence to appointments, and adherence to ART are as follows:

- Provide an accessible, trustworthy, nonjudgmental multidisciplinary healthcare team (care providers, nurses, social workers, case managers, pharmacists, and psychologists).
- Strengthen early linkage to care and retention in care.
- Evaluate the patient's knowledge about HIV infection, prevention, and treatment and, based on this assessment, provide HIV-related information.
- Identify facilitators, potential barriers to adherence, and necessary medication management skills both before starting ART and on an ongoing basis.
- Provide needed resources.
- Involve the patient in ARV regimen selection.
- Assess adherence at every clinic visit.
- Use positive reinforcement to foster adherence success.
- Identify the type of and reasons for poor adherence and target ways to improve adherence.
- Select from among available effective adherence and retention interventions.
- Systematically monitor retention in care.

Adverse Effects of Antiretroviral Agents

The overall benefits of viral suppression and improved immune function as a result of effective ART far outweigh the risks associated with the adverse effects of some ARV drugs.
However, adverse effects have been reported with the use of all ARV drugs and, in the earlier era of combination ART, adverse effects were among the most common reasons for switching or discontinuing therapy and for medication nonadherence. Fortunately, newer ARV regimens are associated with fewer serious and intolerable adverse effects than regimens used in the past.
Several factors may predispose individuals to adverse effects of ARV medications, such as:

- Concomitant use of medications with overlapping and additive toxicities.
- Comorbid conditions that increase the risk of or exacerbate adverse effects (e.g., alcoholism or coinfection with viral hepatitis may increase the risk of hepatotoxicity; psychiatric disorders may be exacerbated by Efavirenz [EFV], Rilpivirine [RPV], and, infrequently, by Integrase Strand Transfer Inhibitors [INSTIs]; and borderline or mild renal dysfunction increases the risk of nephrotoxicity from Tenofovir Disoproxil Fumarate [TDF]).
- Drug-drug interactions that may increase toxicities of ARV drugs or concomitant medications.
- Genetic factors that predispose patients to Abacavir (ABC) hypersensitivity reaction, EFV neuropsychiatric toxicity and QTc prolongation, and Atazanavir (ATV)-associated hyperbilirubinemia.

Table 4.1 Common adverse effects associated with ART

Adverse Effect	Drug Class				
	NRTIs	NNRTIS	PIs	INSTIs	EIs
Effects on Bone Density.	**- TDF**: Associated with a greater BMD loss than other NRTIs. Osteomalacia may be associated with renal tubulopathy and urine phosphate wasting. - **TAF**: Associated with less effect on BMD than TDF.	Decreases in BMD observed after the initiation of any ART regimen(first 48 weeks).			N/A.
Effects on Cardiac Conduction.	N/A.		**ATV/r** and **LPV/r:** PR prolongation. Risk factors include pre-existing heart disease and concomitant use of medications that may cause PR prolongation.	N/A.	**FTR:** Use with caution in patients with QTc prolongation, existing heart diseases, or concomitant use of medications that may prolong QTc interval.

Adverse Effect	Drug Class				
	NRTIs	NNRTIS	PIs	INSTIs	EIs
Bone Marrow Suppression.	**ZDV:** Associated with anemia and Neutropenia.	N/A.	N/A.	N/A.	N/A.
Cardiovascular Disease.	**ABC:** Associated with an increased risk on MI. Absolute risk greatest in patients with traditional CVD risk factors.	N/A.		N/A.	N/A.
Cholelithiasis.	N/A.	N/A.	**ATV:** Cholelithiasis and kidney stones may present concurrently.	N/A.	N/A.
DM and Insulin Resistance.	**ZDV.**	N/A.	**LPV/r**, but not with boosted DRV or ATV.	INSTI have been associated with DM*	N/A.

Adverse Effect	Drug Class				
	NRTIs	NNRTIS	PIs	INSTIs	EIs
Dyslipidemia.	**ZDV > ABC:** Associated with elevated TG and LDL. **TAF:** Elevated TG, LDL, and HDL. TDF is associated with lower lipid levels than ABC or TAF.	**EFV:** - Elevated TG. - Elevated LDL. - Elevated HDL.	All **RTV-** or **COBI-boosted PIs RTV>COBI:** Associated with elevated TG, LDL, and HDL. **LPV/r > DRV** and **ATV/r:** - Elevated TG.	**EVG/c:** - Elevated TG. - Elevated LDL. - Elevated HDL	N/A.
Gastrointestinal Effects.	**ZDV > other NRTIs:** Associated with nausea and vomiting.	N/A.	GI intolerance (e.g., diarrhea, nausea, vomiting) **LPV/r > DRV/r and ATV/r:** - Associated with diarrhea	**EVG/c:** Associated with nausea and diarrhea.	N/A.
Hepatic Effects.	**When TAF, TDF, 3TC, and FTC are withdrawn in patients with HBV/HIV coinfection or when HBV resistance develops:**	**EFV:** Most cases have an increase in transaminases . Fulminant hepatitis leading to death or hepatic failure requiring	**All PIs:** Drug-induced hepatitis and hepatic decompensation have been reported.	**DTG:** Persons with HBV or HCV coinfection may be at a higher risk of DTG-associated hepatotoxicity.	**MVC:** Hepatotoxicity with or without rash or HSRs reported. **FTR:** Transaminase

Adverse Effect	Drug Class				
	NRTIs	NNRTIS	PIs	INSTIs	EIs
	Patients with HBV/HIV coinfection may develop severe hepatic flares. **ZDV:** Steatosis.	transplantation have been reported. **NVP:** Severe hepatotoxicity associated with skin rash or hypersensitivity. A 2-week NVP dose escalation may reduce risk. Risk is greater for women with pre-NVP CD4 counts >250 cells/mm3 and men with pre-NVP CD4 counts >400 cells/mm3. **NVP** should **NEVER** be used for post-exposure prophylaxis. **EFV** and **NVP** are not recommended in patients with hepatic insufficiency (Child-Pugh class B or C).	**ATV:** Jaundice due to indirect hyperbilirubinemia.	**CAB:** (in Cabenuva IM injections) increases the risk of developing and worsening hepatic conditions.	elevation was seen more commonly in patients with HBV/HCV. Transient elevation of bilirubin has been observed in clinical trials.

Adverse Effect	Drug Class				
	NRTIs	NNRTIS	PIs	INSTIs	EIs
		RPV: (in Cabenuva IM injections) increases the risk of developing and worsening hepatic conditions.			
Hypersensitivity Reaction (HSR).	**ABC:** Contraindicated if patient is HLA-B*5701 positives. Median onset for HSR is 9 days after treatment initiation; 90% of reactions occur within 6 weeks. HSR symptoms (in order of descending frequency): Fever, rash, malaise, nausea, headache, myalgia, chills, diarrhea, vomiting, abdominal	**NVP:** Hypersensitivity syndrome of hepatotoxicity and rash that may be accompanied by fever, general malaise, fatigue, myalgia, arthralgia, blisters, oral lesions, conjunctivitis, facial edema, eosinophilia, renal dysfunction, granulocytopenia, or lymphadenopathy. Risk is greater for **ARV**-naive women with	N/A.		**MVC:** HSR reported as a part of a syndrome related to hepatotoxicity.

Adverse Effect	Drug Class				
	NRTIs	NNRTIS	PIs	INSTIs	EIs
	pain, dyspnea, arthralgia, and respiratory symptoms. Symptoms worsen with continuation of **ABC**. Patients should **NOT** be rechallenged with **ABC** if HSR is suspected, regardless of their HLA-B*5701 status.	pre-**NVP** CD4 counts >250 cells/mm3 and men with pre-**NVP** CD4 counts >400 cells/mm3. Overall, risk is higher for women than men. A 2-week dose escalation of **NVP** reduces risk.			
Rash.	**FTC:** Hyperpigmentation.	All **NNRTIs**.	**ATV**, **DRV**, and **LPV/r.**	All **INSTIs.**	**MVC, IBA, FTR.**
Lipodystrophy.	Lipoatrophy: Associated with history of exposure to **d4T** or **ZDV** (d4T > ZDV). Not reported with **ABC**, **3TC** or **FTC**, **TAF** or **TDF**.	***Lipohypertrophy:*** Trunk fat increase observed with **EFV**-, **PI**-, and **RAL**-containing regimens.			N/A.

Adverse Effect	Drug Class				
	NRTIs	NNRTIS	PIs	INSTIs	EIs
Myopathy / Elevated Creatine Phosphokinase.	**ZDV:** Myopathy.	N/A.	N/A.	**RAL** and **DTG**: (**Extremely uncommon**) Elevated CPK, rhabdomyolysis, and myopathy or myositis have been reported.	N/A.

Adverse Effect	Drug Class				
	NRTIs	NNRTIS	PIs	INSTIs	EIs
Nervous System/ Psychiatric Effects.	History of exposure to **ddI**, **ddC**, or **d4T**: Peripheral neuropathy (can be irreversible).	Neuropsychiatric events : **EFV > RPV, DOR, ETR.** **EFV:** Somnolence, insomnia, abnormal dreams, dizziness, impaired concentration, depression, psychosis, suicidal ideation, ataxia, encephalopathy. Some symptoms may subside or diminish after 2–4 weeks. Bedtime dosing and taking without food may reduce symptoms. Risk factors include psychiatric illness, concomitant use of agents with neuropsychiatric effects, and genetic factors.	N/A.	All **INSTIs:** - Insomnia. - Depression. - Suicidality, have been reported with INSTI use, primarily in patients with pre- existing psychiatric conditions.	N/A.

Adverse Effect	Drug Class				
	NRTIs	NNRTIS	PIs	INSTIs	EIs
		RPV:(uncommon) Depression, suicidality, sleep disturbances. **DOR:** Sleep disorders and disturbances, dizziness, altered sensorium; depression and suicidality and self-harm.			

Adverse Effect	Drug Class				
	NRTIs	NNRTIS	PIs	INSTIs	EIs
Injection Site Reaction.	N/A.	**RPV IM injection: (Cabenuva)** Reported in >80% of patients; reactions may include: - Localized pain/discomfort (most common). - Nodules. - Induration. - Swelling. - Erythema. - Hematoma.	N/A.	**CAB IM injection: (Cabenuva)** Reported in >80% of patients; reactions may include: - Localized pain/discomfort (most common). - Nodules. - Induration. - Swelling. - Erythema. - Hematoma..	**T-20 SQ injection (Enfuvirtide):** Reported in almost all patients; reactions may include: - Pain. - Tenderness. - Nodules. - Induration. - Ecchymosis. - Erythema.

Adverse Effect	Drug Class				
	NRTIs	NNRTIS	PIs	INSTIs	EIs
Renal Effects/ Urolithiasis.	**TDF:** ↑ SCr, proteinuria, hypophosphate-mia, urinary phosphate wasting, glycosuria, hypokalemia, and non-anion gap metabolic acidosis. Concurrent use of **TDF** with **COBI**- or **RTV**-containing regimens appears to increase risk. **TAF:** Less impact on renal biomarkers and lower rates of proteinuria than **TDF**.	**RPV:** Inhibits Cr secretion without reducing renal glomerular function.	**ATV:** Stone or crystal formation. Adequate hydration may reduce risk. **COBI** (as a boosting agent for **DRV** or **ATV**): Inhibits Cr secretion without reducing renal glomerular function.	**DTG, COBI** (as a Boosting agent for **EVG**), and **BIC**: Inhibits Cr secretion without reducing renal glomerular function.	**IBA:** SCr abnormalities ≥ Grade 3 reported in 10% of trial participants. **FTR:** SCr > 1.8 x ULN seen in 19% in a clinical trial, but primarily with underlying renal disease or other drugs known to affect creatinine.
Lactic Acidosis.	Reported with older **NRTIs**, **d4T**, **ZDV**, and **ddI**, but not	N/A.	N/A.	N/A.	N/A.

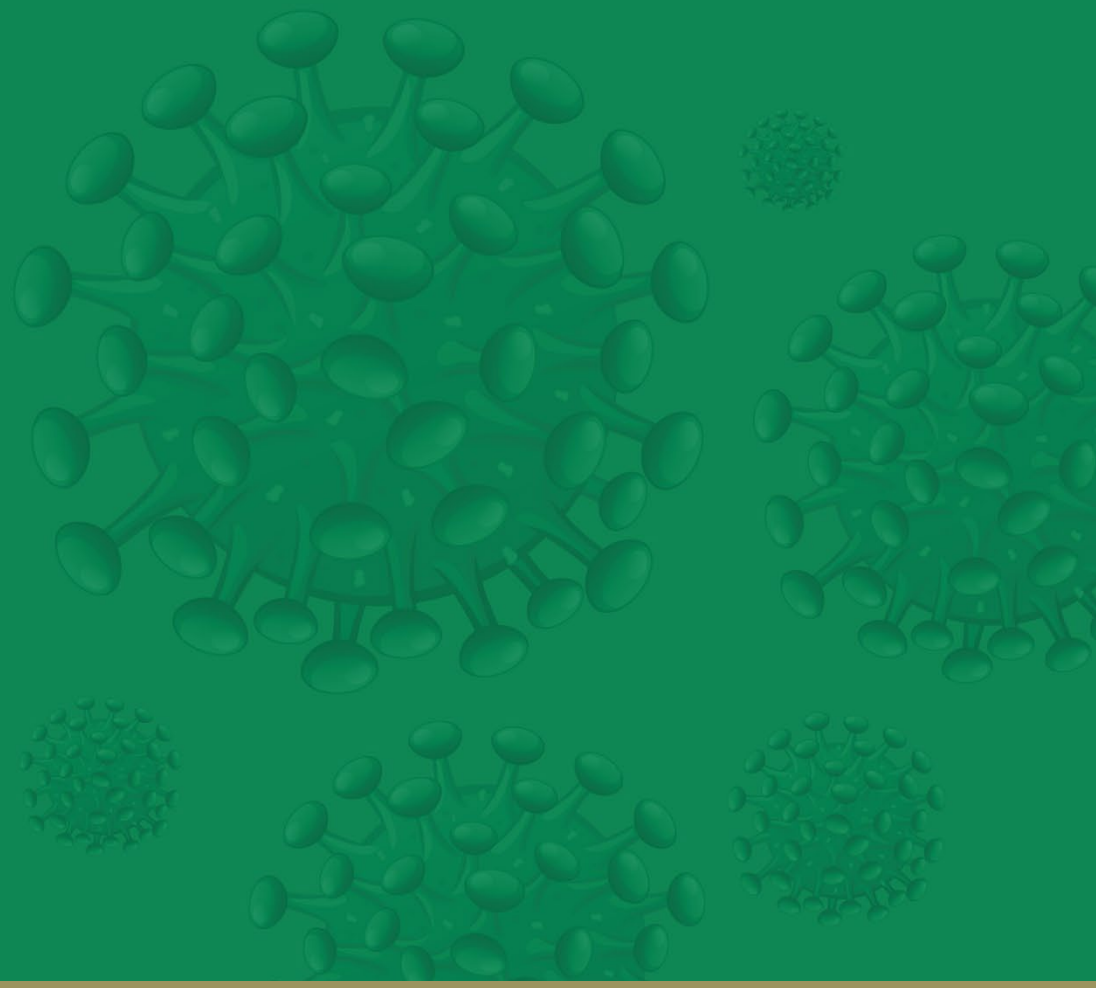
Adverse Effect	Drug Class				
	NRTIs	NNRTIS	PIs	INSTIs	EIs
	with **ABC**, **3TC**, **FTC**, **TAF**, or **TDF**.				
Weight Gain.	Weight gain has been related to the initiation of ART and subsequent viral suppression. INSTIs seem to have greater association to weight gain than other drug classes. TDF (vs TAF) and EFV (vs other 3rd drugs) have a suppressive weight impact.				N/A.

*Asundi et al. AIDS Res Hum Retrovir 2022; Rebeiro et al Clin Infect Dis 2021.

Key: 3TC = lamivudine; ABC = abacavir; ART= antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/r = atazanavir/ritonavir; BIC = bictegravir; BMD = bone mineral density; CAB = cabotegravir; CD4 = CD4 T lymphocyte; CI = capsid inhibitor; CNS = central nervous system; COBI = cobicistat; CPK = creatine phosphokinase; Cr = creatinine; CVD = cardiovascular disease; d4T = stavudine; ddC = zalcitabine; ddI = didanosine; DLV = delavirdine; DOR = doravirine; DRV = darunavir; DRV/r = darunavir/ritonavir; DTG = dolutegravir; ECG = electrocardiogram; EFV = efavirenz; EI = entry inhibitor; ETR = etravirine; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FPV = fosamprenavir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; FTR = fostemsavir; GI = gastrointestinal; HBV = hepatitis B virus; HCV = hepatitis C virus; HDL = high-density lipoprotein; HSR = hypersensitivity reaction; IBA = ibalizumab; IDV = indinavir; IM = intramuscular; INSTI = integrase strand transfer inhibitor; LDL = low-density lipoprotein; LEN = lenacapavir; LPV/r = lopinavir/ritonavir; MI = myocardial infarction; MVC = maraviroc; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SCr = serum creatinine; SQ = subcutaneous; SQV = saquinavir; SQV/r = saquinavir/ritonavir; T-20 = enfuvirtide; TAF = tenofovir alafenamide; TC = total cholesterol; TDF = tenofovir disoproxil fumarate; TG = triglycerides; TPV = tipranavir; TPV/r = tipranavir/ritonavir; ULN = upper limit of normal; ZDV = zidovudine

CHAPTER 05

HIV CO-INFECTIONS



HIV Co-Infections

Definition

- **Coinfection**: This is the simultaneous infection of a host by multiple pathogen species.
- Some coinfections commonly seen in people infected with HIV include HIV/Hepatitis B Virus (HBV), HIV/Hepatitis C Virus (HCV), and HIV/Tuberculosis (TB) coinfections.

HIV/Hepatitis B Virus (HBV) Co-infection

Introduction

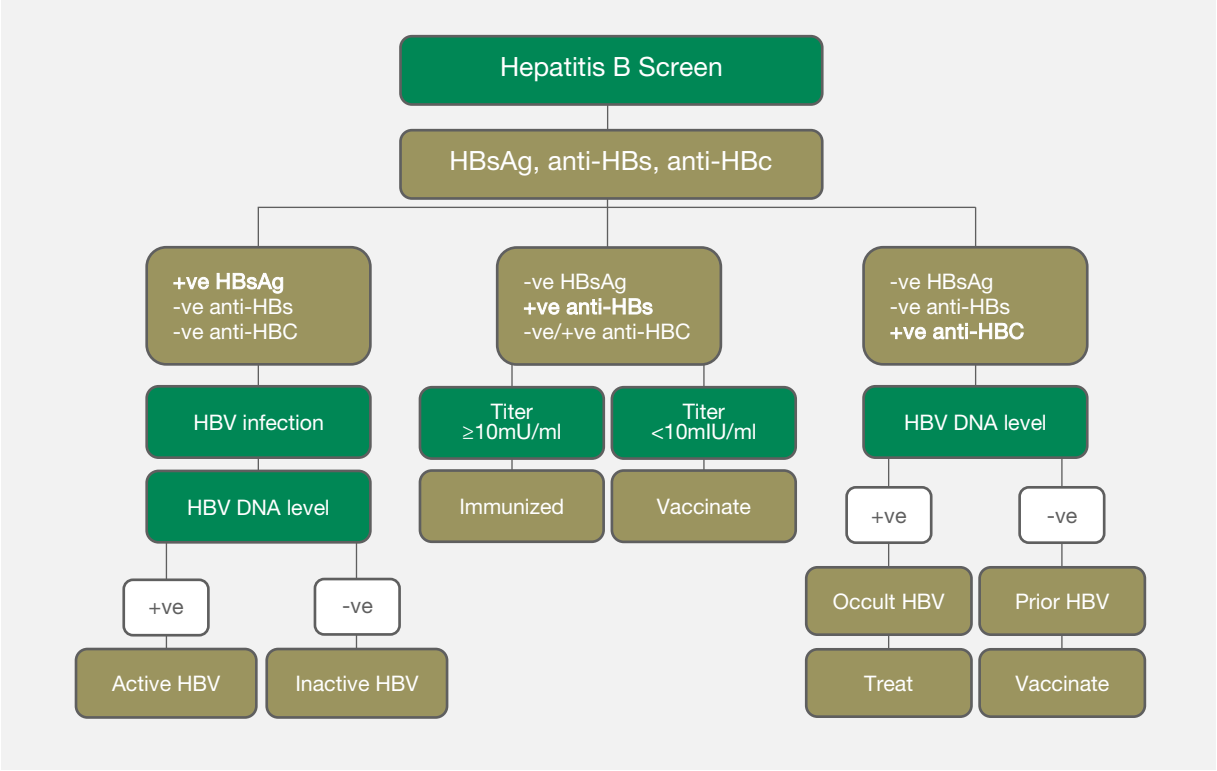
- Approximately 5%–10% of HIV-infected persons also have chronic HBV infection, defined as testing positive for Hepatitis B Surface Antigen (HBsAg) for more than 6 months.
- The progression of chronic HBV to cirrhosis, end-stage liver disease, and/or hepatocellular carcinoma is more rapid in HIV-infected persons than in persons with chronic HBV alone.
- The era of potent Antiretroviral Therapy (ART) to treat HIV infection has led to declining rates of opportunistic infections and the ability to focus on other causes of morbidity in HIV-infected individuals, such as end-stage liver disease secondary to chronic HBV infection.
- The treatment and prevention of HBV infection has taken on great significance in light of the negative impact HIV has on the natural history of chronic HBV infection.
- Vaccination is the main prevention method against hepatitis B infection. The hepatitis B vaccines currently available are inexpensive, safe, and effective. They protect against hepatitis B in more than 95% of healthy infants, children, and young adults.
- Since 1982, over a billion doses of hepatitis B vaccine have been used worldwide. In many countries, where 8%–15% of children used to become chronically infected with the hepatitis B virus, vaccination has reduced the rate of chronic infection to less than 1% among immunized children.

Diagnosis of HBV Infection in People Living With HIV (PLWH)

- All newly diagnosed HIV-infected patients should be periodically screened for HBV infection (AI).
- Annual HBV screening is preferred for patients at high risk of HBV (AI).

- The serology test should include Hepatitis B Surface Antigen (HBsAg), Hepatitis B Core Antibody (anti-HBc), and Hepatitis B Surface Antibody (anti-HBs).
- In case of negative HBsAg but positive anti-HBc, testing for HBV DNA level is recommended to rule out occult HBV infection which can be found in HIV-infected persons (BI). The significance of occult HBV infection in PLWH is unclear but has been associated with Hepatitis C Virus (HCV) coinfection, higher prevalence of advanced fibrosis, and HBV flare-up after initiation of ART.
- All patients with chronic HBV should be screened for HCV coinfection (AI).
- All patients with a reactive Hepatitis B Virus Surface Antigen should undergo Hepatitis D Virus (HDV) screening.
- All patients with chronic HBV and men who have sex with men should be assessed for Hepatitis A Virus (HAV) immunity (anti-HAV antibody) and vaccinated if non-immune (AIII).

Fig 5.1 Hepatitis B Virus Diagnosis Algorithm



HBsAg=hepatitis B surface antigen; anti-HBc=hepatitis B core antibody; anti-HBs=hepatitis B surface antibody; HBV= hepatitis B virus

Treatment of HBV Infection in People Living With HIV (PLWH)

All adults coinfected with HBV/HIV should be treated with Antiretroviral Therapy (ART) regardless of CD4 cell count or HBV DNA level to reduce HBV-associated morbidities and mortality (AII). Tenofovir (TFV), Emtricitabine (FTC), and Lamivudine (3TC) are Nucleoside Reverse Transcriptase Inhibitors (NRTIs) that act on both HIV and HBV viruses. All patients coinfected with HBV/HIV should receive ART that includes two drugs with activity against HBV. Hence, 3TC or FTC should not be used as monotherapy against HBV infection in PLWH to avoid HBV-resistance mutations (AII). The recommended combination backbone therapies are Tenofovir Alafenamide (TAF) or Tenofovir Disoproxil Fumarate (TDF) plus 3TC or FTC (AI). However, tenofovir-emtricitabine fixed combination regimens are the best options in HBV/HIV coinfection for many reasons, including having a high genetic barrier for the development of resistance mutations. A baseline HBV resistance panel is indicated if a patient had experienced a prior 3TC or FTC containing regimen.

Either TDF or TAF-based ART regimens can be used to treat HBV/HIV coinfection. Both can be an option in patients with Creatinine Clearance (CrCl) ≥ 60 mL/min. However, a TAF-based regimen is preferred in patients with CrCl of 30 to 59 mL/min and/or the presence of underlying metabolic bone disease.

Alternatively, if TAF or TDF plus 3TC or FTC combination therapy cannot be used, or if the HBV antiviral prophylaxis is indicated in a patient with positive anti-HBc on immunosuppressive like anti-CD20 antibodies, Entecavir can be used in addition to a fully suppressive ART regimen (AII). Entecavir use in patients who are not suppressed on ART can induce HIV-resistance, selectively for the M184 mutation. Conversely, Pegylated Interferon-Alfa-2a monotherapy can be used in HBV/HIV coinfected patients who are not receiving ART, however, with caution due to the limited safety data that support its use in HBV/HIV coinfection. Additionally, TFV, FTC, 3TC, and Telbivudine should not be used as monotherapy in the absence of fully suppressive ART to avoid HIV-resistance mutations.

Follow-Up of Patients with HBV/HIV Coinfection

- Patients coinfected with HBV/HIV should continue HBV therapy indefinitely (CIII).
- Patients started on HIV/HBV combination therapy need HBV DNA level done every 3–6 months until it is suppressed (AI).
- Treatment success is defined as an undetectable HBV DNA level at 24 weeks of therapy. Complete virological response is defined as loss of Hepatitis B Surface Antigen (HBsAg) and undetectable HBV DNA level.

- Patients should be monitored for drug-related adverse effects like renal toxicity with Tenofovir Disoproxil Fumarate (TDF), lactic acidosis with Entecavir, and neuropsychiatric disorders with Interferon.
- All patients started on Antiretroviral Therapy (ART) should be monitored with liver function tests in the first 8 weeks due to the risk of either HBV flare-up or Immune Reconstitution Inflammatory Syndrome (IRIS) (AI).
- IRIS diagnosis can be challenging and difficult to differentiate from drug-induced hepatotoxicity, the presence of other coinfections e.g., Hepatitis A Virus (HAV), Hepatitis D Virus (HDV), Cytomegalovirus (CMV) infections, HBV reactivation, and existing HBV resistance. In this case, an expert hepatologist needs to be involved for further testing e.g., liver biopsy if needed.
- If ART must be changed for any reason including emerged HIV resistance, anti-HBV drug should be continued as long as HBV DNA is already suppressed (AI).
- Virological breakthroughs are defined as a >1 log10 increase in HBV DNA level from nadir. Primary nonresponse is defined as failure to achieve >1 log10 decline of HBV DNA level after 12 weeks of therapy. In both case scenarios, compliance to therapy and/or HBV resistance mutations should be addressed.
- All patients must be evaluated for liver disease stage i.e., fibrosis and cirrhosis stages (AI).
- Hepatocellular Carcinoma (HCC) screening with liver ultrasound and alpha-fetoprotein blood level every 6 months is indicated in all cirrhotic HBV co-infected People Living With HIV (PLWH) (even if HBV is suppressed). In non-cirrhotic, HCC screening is indicated in the background of family history of HCC, ethnicity (Asians, Africans), HDV co-infection, and age > 45 years.

HBV Infection Prevention in PLWH

- All PLWH who are at risk of acquiring HBV infection should receive HBV vaccination (AII).
- Patients' response to vaccination can be affected by many factors, mainly, patients CD4 cell counts and HIV RNA level. For better antibodies response, it is recommended to initiate vaccination series when CD4 ≥ 200 cells/mm3 and undetectable RNA level is achieved.
- Baseline serology screening should include Hepatitis B Surface Antigen (HBsAg), Hepatitis B Surface Antibody (anti-HBs), and Hepatitis B Core Antibody (anti-HBc).

- The recommended vaccines which are registered at Saudi Food & Drug Authority (SFDA) are 3-dose (Engerix-B or Recombivax HB) series at 0, 1, 6 months' intervals, or 3-dose series HepA-HepB (Twinrix) at 0, 1, 6 months' intervals.
- PLWH with positive anti-HBc alone could have occult HBV infection and need HBV DNA level to be done. If HBV DNA level is undetectable, HBV vaccination is recommended. Patients who did not have an anti-HBs titer of > 100 mIU/mL 4 weeks after a single dose of HBV vaccine should be further vaccinated with a reinforced triple double-dose scheme. This particular recommendation is based on the ANRS study which showed that patients with anti-HBs titers of ≥ 100 mIU/mL at week 4 maintained anti-HBs titer of ≥ 10 mIU/ml at 18 months compared with 23% of the patients with a titer between 10 and 100 mIU/mL (P = .001).

References:

1. Ministry of health Statistic reports. Last access June 1, 2022. https://www.moh.gov.sa/en/Ministry/Statistics/book/Pages/default.aspx
2. Alhuraiji A, Alaraj A, Alghamdi S, et al. Viral hepatitis B and C in HIV-infected patients in Saudi Arabia. Ann Saudi Med. 2014; 34 (3): 207–10.
3. Al-Mughales JA. Co-infection assessment in HBV, HCV, and HIV patients in western Saudi Arabia. J Med Virol. 2016; 88 (9): 1545–51.
4. Thio CL, Seaberg EC, Skolasky R Jr,et al; Multicenter AIDS Cohort Study. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). Lancet. 2002; 360 (9349): 1921-6.
5. Palacios R, Mata R, Hidalgo A, et al; Grupo HEPAVIR de SAEI. Very low prevalence and no clinical significance of occult hepatitis B in a cohort of HIV-infected patients with isolated anti-HBc seropositivity: the BHOI study. HIV Clin Trials. 2008; 9 (5): 337-40.
6. Shire NJ, Rouster SD, Rajicic N, Sherman KE. Occult hepatitis B in HIV-infected patients. J Acquir Immune Defic Syndr. 2004; 36 (3):869-75.
7. Neau D, Winnock M, Jouvencel AC, et al; Groupe d'Epidemiologie Clinique du SIDA en Aquitaine. Occult hepatitis B virus infection in HIV-infected patients with isolated antibodies to hepatitis B core antigen: Aquitaine cohort, 2002-2003. Clin Infect Dis. 2005; 40 (5): 750-3.
8. Witt MD, Lewis RJ, Rieg G, et al. Predictors of the isolated hepatitis B core antibody pattern in HIV-infected and -uninfected men in the multicenter AIDS cohort study. Clin Infect Dis. 2013; 56 (4): 606-12.
9. Bhattacharya D, Tseng CH, Tate JP, et al. Isolated Hepatitis B Core Antibody is Associated with Advanced Hepatic Fibrosis in HIV/HCV Infection but Not in HIV Infection Alone. J Acquir Immune Defic Syndr. 2016; 72 (1): e14-7.
10. Filippini P, Coppola N, Pisapia R, et al. Impact of occult hepatitis B virus infection in HIV patients naive for antiretroviral therapy. AIDS. 2006; 20 (9): 1253-60.
11. Norah A. Terrault, Anna S.F. Lok, Brian J. McMahon, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018; 67 (4): 1560-99.
12. Price H, Dunn D, Pillay D, et al. Suppression of HBV by tenofovir in HBV/HIV coinfected patients: a systematic review and meta-analysis. PLoS One. 2013; 8 (7): e68152.

13. Martín-Carbonero L, Teixeira T, Poveda E, et al. Clinical and virological outcomes in HIV-infected patients with chronic hepatitis B on long-term nucleos(t)ide analogues. AIDS. 2011; 25 (1): 73-9

14. Dore GJ, Cooper DA, Barrett C, et al. Dual efficacy of lamivudine treatment in human immunodeficiency virus/hepatitis B virus-coinfected persons in a randomized, controlled study (CAESAR). The CAESAR Coordinating Committee. J Infect Dis. 1999; 180: 607–13.

15. Dore GJ, Cooper DA, Pozniak AL, et al. Efficacy of tenofovir disoproxil fumarate in antiretroviral therapy-naive and -experienced patients coinfected with HIV-1 and hepatitis B virus. J Infect Dis. 2004; 189: 1185-92.

16. Matthews GV, Seaberg E, Dore GJ, et al. Combination HBV therapy is linked to greater HBV DNA suppression in a cohort of lamivudine-experienced HIV/HBV coinfected individuals. AIDS. 2009; 23 (13): 1707-15.

17. Nunez M, Perez-Olmeda M, Diaz B, et al. Activity of tenofovir on hepatitis B virus replication in HIV-co-infected patients failing or partially responding to lamivudine. chronic hepatitis B on long-term nucleos(t)ide analogues. AIDS. 2011 Jan; 25(1):73-9.

18. Benhamou Y, Tubiana R, Thibault V. Tenofovir disoproxil fumarate in patients with HIV and lamivudine-resistant hepatitis B virus. N Engl J Med. 2003; 348 (2): 177-78.

19. Buti M, Gane E, Seto WK, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of patients with HBeAg-negative chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. Lancet Gastroenterol Hepatol. 2016; 1 (3): 196-206.

20. Chan HL, Fung S, Seto WK, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of HBeAg-positive chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. Lancet Gastroenterol Hepatol. 2016; 1 (3): 185-95

21. Gallant J, Brunetta J, Crofoot G, et all. Efficacy and Safety of Switching to a Single-Tablet Regimen of Elvitegravir Cobicistat/Emtricitabine Tenofovir Alafenamide in HIV- 1/Hepatitis B Coinfected. Adults J Acquir Immune Defic Syndr.2016; 73: 294–98.

22. European Association For The Study Of The Liver. EASL Clinical Practice Guidelines: Management of chronic hepatitis B virus infection. J Hepatol. 2012; 57 (1): 167-85.

23. Peter R. Galle, Alejandro Forner, Josep M. Llovet, et al. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol. 2018; 69 (1): 182-236.

24. Centers for Disease Control and Prevention. Adult Immunization Schedule. Recommendations for Age 19 Years or older, United States, 2022. https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fvaccines%2Fschedules%2Fhcp%2Fadult.html#notes

25. Fonseca MO, Pang LW, de Paula Cavalheiro N, et al. Randomized trial of recombinant hepatitis B vaccine in HIV-infected adult patients comparing a standard dose to a double dose. Vaccine. 2005; 23 (22): 2902-8.

26. Overton ET, Sungkanuparph S, Powderly WG, et al. Undetectable plasma HIV RNA load predicts success after hepatitis B vaccination in HIV-infected persons. Clin Infect Dis. 2005; 41 (7): 1045-8.

27. Piroth L, Launay O, Michel ML, et al. ANRS HB EP03 CISOVAC Study Group. Vaccination Against Hepatitis B Virus (HBV) in HIV-1-Infected Patients With Isolated Anti-HBV Core Antibody: The ANRS HB EP03 CISOVAC Prospective Study. J Infect Dis. 2016; 213 (11):1735-42.

HIV/Hepatitis C Virus (HCV) Co-Infection

Introduction

HIV/HCV co-infection is associated with a higher rate of chronic liver disease and decompensated liver cirrhosis than seen in HCV mono-infection. However, currently available oral, direct-acting antivirals (DAAs) for HCV treatment can achieve a sustained viral suppression (SVR) and cure in more than 95% of co-infected patients. This will play a major role in decreasing chronic liver disease in HIV-infected patients.

Diagnosis of HCV Infection in PLWH

All newly diagnosed HIV-infected patients should be periodically screened for HCV infection using an HCV antibodies (anti-HCV) test (AI). An annual HCV screen is preferred for patients at high risk of HCV infection (AI). Persons with positive anti-HCV should have an HCV RNA level and genotype assay done (AII). If acute HCV infection is suspected, anti-HCV should be repeated after 3 months to assess for HCV spontaneous clearance (AIII). Despite the fact that the HCV infection course can follow the same natural immune response in both PLWH and HCV mono-infected persons, spontaneous clearance of HCV infection is rare in PLWH and affected by many risk factors. All patients with acute and chronic HCV infection should be screened for HBV co-infection (AII). All patients with acute HCV or men who have sex with men with chronic HCV infection should be assessed for hepatitis A virus (HAV) immunity (anti-HAV antibody) and vaccinated if non-immune (AII).

Treatment of HCV Infection in PLWH

All HCV/HIV co-infected adults should be treated with ART regardless of CD4 cell counts (AI). ART regimens recommended for patients with HCV/HIV co-infection are the same for patients without HCV infection (AI). However, special precautions should be considered for the potential drug-drug interactions between ART and HCV DAAs. A significant drug interaction might indicate ART regimen modification. Two electronic resources can be helpful to guide for the use of ART with HCV DAAs; Liverpool HIV Drug Interaction Database and HIV/HCV Drug Therapy Guide. After making ART modification to be compatible with the proposed HCV DAA regimen, allow at least weeks' washout period before initiation of the DAAs. Some of ART medications have long half-life and needs few days to be cleared from the blood circulation. This technique has to be also applied when switching back to the original ART regimen after completing DAA therapy; at least 2 weeks' period should be allowed for washing out the DAAs from the blood. On the other hand, selection of HCV DAAs and duration of

therapy, which ranges between 8 - 24 weeks, are depending on the baseline HCV RNA level, HCV genotype and liver disease stage.

There is no consensus for the best and cost-effective approach in managing patients with acute HCV infection in the era of DAA therapy. However, in PLWH, it is preferred to treat acute HCV infection with DAAs rather than waiting for possible spontaneous HCV clearance to happen (BI). This approach is supported by many factors including the low possibility of spontaneous HCV clearance to occur in HIV-infected persons. Additionally, early DAA therapy is recommended to decrease prevalence and incidence of HCV infection, mainly, among high-risk behavior groups like men who have sex with men. Furthermore, treating HCV infection in its acute phase might shorten duration of DAA therapy.

Patients with HCV/HIV co-infection should be screened and treated for HBV infection (AI). HBV reactivation is associated with DAA therapy for chronic HCV infection. In such case, ART with HBV activity should be started before treating HCV infection (AIII). See “Treatment of HBV Infection in PLWH” section for detailed approach.

Follow-Up Patients with HCV/HIV Co-Infection

After starting DAA therapy, the HCV RNA level should be checked at 4, 12, and 24 weeks (AI). Consider repeating the HCV RNA level at 6 - 12 months after treatment to ensure the persistence of sustained virological response (SVR) (AII). Patients should be advised against self-discontinuation of the medications (AI). Patients should also be advised against high-risk behavior, including intravenous drug use during and after DAA therapy, to avoid re-infection with HCV (AI). Cirrhotic patients should be screened for hepatocellular carcinoma (HCC) with a liver ultrasound and alpha-fetoprotein blood level every 6 months for 5 years after clearing HCV infection (AI).

References

1. Shikha Garg, John T. Brooks, Qingwei Luo, Jacek Skarbinski. Prevalence of and Factors Associated with Hepatitis C Virus Testing and Infection Among HIV-infected Adults Receiving Medical Care in the United States. Open Forum Infec. Dis. 2014; 1 (S1): S423.
2. Ministry of health Statistic reports. Last access June 1, 2022. https://www.moh.gov.sa/en/Ministry/Statistics/book/Pages/default.aspx
3. Alzahrani AJ, Obeid OE, Al-Ali A, Imamwardi B. Detection of hepatitis C virus and human immunodeficiency virus in expatriates in Saudi Arabia by antigen-antibody combination assays. J Infect Dev Ctries. 2009; 3 (3): 235-8.
4. Alhuraiji A, Alaraj A, Alghamdi S, Alrbiaan A, Alrajhi AA. Viral hepatitis B and C in HIV-infected patients in Saudi Arabia. Ann Saudi Med. 2014; 34 (3): 207–10
5. Al-Mughales JA. Co-infection assessment in HBV, HCV, and HIV patients in western Saudi Arabia. J Med Virol. 2016; 88 (9): 1545–51.

6. CS, Baden LR, Yu E, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. Clin Infect Dis. 2001; 33(4): 562-69.
7. Greub G, Ledergerber B, Battegay M, et al. Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection: The Swiss HIV Cohort Study. Lancet. 2000; 356 (9244): 1800-5.
8. Sogni P, Gilbert C, Lacombe K, et al. All-oral Direct-acting Antiviral Regimens in HIV/Hepatitis C Virus-coinfected Patients With Cirrhosis Are Efficient and Safe: Real-life Results From the Prospective ANRS CO13-HEPAVIH Cohort. Clin Infect Dis. 2016; 63 (6): 763-70.
9. The American Association for the Study of Liver Diseases (AASLD). HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. https://www.hcvguidelines.org/
10. Aisyah DN, Shallcross L, Hully AJ, O'Brien A, Hayward A. Assessing hepatitis C spontaneous clearance and understanding associated factors-A systematic review and meta-analysis. J Viral Hepat. 2018; 25 (6): 680-98.
11. Smith DJ, Jordan AE, Frank M, Hagan H. Spontaneous viral clearance of hepatitis C virus (HCV) infection among people who inject drugs (PWID) and HIV-positive men who have sex with men (HIV+ MSM): a systematic review and meta-analysis. BMC Infect Dis. 2016; 16 (1): 471.
12. Sarkar M, Bacchetti P, Tien P, et al. Racial/ethnic differences in spontaneous HCV clearance in HIV infected and uninfected women. Dig Dis Sci. 2013; 58 (5): 1341-8.
13. Marcellin F, Demoulin B, Spire B, et al; ANRS-VESPA2 Study Group. Spontaneous and post-treatment HCV clearance: relationships with health-related quality of life in HIV infection (ANRS-VESPA2 study). Expert Rev Gastroenterol Hepatol. 2015; 9 (5): 701-13.
14. Soares J, Santos JV, Sarmento A, Costa-Pereira A. Spontaneous Viral Clearance in Sixteen HIV-Infected Patients with Chronic Hepatitis C. Intervirology. 2018; 61 (2): 64-71.
15. Fedorchenko SV, Klimenko A, Martynovich T, Liashok O, Yanchenko V. IL-28B genetic variation, gender, age, jaundice, hepatitis C virus genotype, and hepatitis B virus and HIV co-infection in spontaneous clearance of hepatitis C virus. Turk J Gastroenterol. 2019; 30 (5): 436-444.
16. Martinello, M., Hajarizadeh, B., Grebely, J. et al. Management of acute HCV infection in the era of direct-acting antiviral therapy. Nat Rev Gastroenterol Hepatol.2018; 15:412–24.
17. Boerekamps A, van den Berk GE, Lauw FN, et al. Declining Hepatitis C Virus (HCV) Incidence in Dutch Human Immunodeficiency Virus-Positive Men Who Have Sex With Men After Unrestricted Access to HCV Therapy. Clin Infect Dis. 2018; 66 (9): 1360-65.
18. Naggie S, Fierer DS, Hughes MD, et al; Acquired Immunodeficiency Syndrome Clinical Trials Group (ACTG) A5327 Study Team. Ledipasvir/Sofosbuvir for 8 Weeks to Treat Acute Hepatitis C Virus Infections in Men With Human Immunodeficiency Virus Infections: Sofosbuvir-Containing Regimens Without Interferon for Treatment of Acute HCV in HIV-1 Infected Individuals. Clin Infect Dis. 2019; 69 (3): 514-22.
19. Rockstroh JK, Bhagani S, Hyland RH, et al. Ledipasvir-sofosbuvir for 6 weeks to treat acute hepatitis C virus genotype 1 or 4 infection in patients with HIV coinfection: an open-label, single-arm trial. Lancet Gastroenterol Hepatol. 2017; 2 (5): 347-53.
20. Deterding K, Spinner CD, Schott E, et al; HepNet Acute HCV IV Study Group. Ledipasvir plus sofosbuvir fixed-dose combination for 6 weeks in patients with acute hepatitis C virus genotype 1 monoinfection (HepNet Acute HCV IV): an open-label, single-arm, phase 2 study. Lancet Infect Dis. 2017; 17 (2): 215-22.
21. Martinello M, Orkin C, Cooke G, et al. Short-Duration Pan-Genotypic Therapy With Glecaprevir/Pibrentasvir for 6 Weeks Among People With Recent Hepatitis C Viral Infection. Hepatology. 2020; 72 (1): 7-18.
22. Bersoff-Matcha SJ, Cao K, Jason M, et al. Hepatitis B Virus Reactivation Associated With Direct-Acting Antiviral Therapy for Chronic Hepatitis C Virus: A Review of Cases Reported to the U.S. Food and Drug Administration Adverse Event Reporting System. Ann Intern Med. 2017; 166 (11): 792-98.
23. Wang C, Ji D, Chen J, et al. Hepatitis due to Reactivation of Hepatitis B Virus in Endemic Areas Among Patients With Hepatitis C Treated With Direct-acting Antiviral Agents. Clin Gastroenterol Hepatol. 2017; 15 (1): 132-36.

HIV/Tuberculosis Coinfection

Definitions

- **Latent Tuberculosis Infection (LTBI):** A persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens without evidence of clinically manifested active tuberculosis (TB).
- **Active Tuberculosis Infection:** An infectious disease caused by *Mycobacterium tuberculosis* (MTB) that affects the lungs and/or other organs.
- **Immune Reconstitution Inflammatory Syndrome (IRIS):** An inflammatory disorder in patients with Acquired Immunodeficiency Syndrome (AIDS) and other infections that manifests after starting Antiretroviral Therapy (ART) and improvement of immunity.

Introduction

Globally, tuberculosis (TB) is the ninth leading cause of death worldwide and the leading cause from a single infectious agent, ranking above HIV/AIDS. According to the World Health Organization (WHO), approximately one-third of the world's population is infected with TB, with a 5% to 10% lifetime risk of progressing to active disease. People living with HIV who are coinfected with TB have a much higher risk of developing active TB than individuals who do not have HIV, and this risk increases as immune deficiency worsens.

Rates of LTBI have not been routinely reported or monitored. However, the incidence rates and prevalence of active TB are closely monitored and reported by international and local health agencies.

HIV infection has contributed significantly to the increased rates of TB in areas like Africa. HIV is the strongest risk factor for developing active TB in people with LTBI or new infection, increasing the risk up to 37 times compared to HIV-negative people. TB in people living with HIV is considered an AIDS-defining condition in developed countries. WHO classifies people living with HIV and pulmonary TB as stage 3, and people with extrapulmonary TB as stage 4 (AIDS).

Screening for HIV in patients with TB is mandated by WHO and the National Tuberculosis Program in Saudi Arabia. According to the WHO, around 3000 patients in Saudi Arabia were diagnosed with TB in 2016. Of those, 65% were known to have HIV infection. The mortality rate of HIV/TB coinfected patients reached up to 0.04 per 100,000 populations. Pulmonary disease accounted for more than 70% of total TB-infected patients.

Tuberculosis Clinical Presentations in HIV Patients

The clinical presentation, symptoms, and findings are often different in people living with HIV compared to HIV-negative individuals, which are influenced by the stage of HIV immunodeficiency.

In early stages when CD4 count is more than 350, pulmonary TB is akin to HIV-negative people. They could have chronic cough, fever, chest pain, hemoptysis, anorexia, weight loss, and night sweats.

With the progression of immunodeficiency to AIDS, patients may not have the typical manifestations of cough, hemoptysis, or cavity on chest X-ray. Around one in seven may have a normal chest X-ray. They have more extrapulmonary TB, which adds to the diagnostic challenge of identifying the infection.

Patients with advanced HIV disease could have subclinical TB that becomes unmasked after initiating ART (in what would be an IRIS). Therefore, a high clinical acumen is essential to suspect TB and search for it, prior to initiating ART.

Diagnosis of TB Infection in People Living with HIV (PLWH)

All PLWH should be screened for both active and latent TB infection (AI).

The site of TB reactivation, whether pulmonary or extrapulmonary, can be affected by the stage of HIV at presentation, non-AIDS vs AIDS, respectively. The clinical symptoms, radiological, and microbiological findings can also be affected by the patients' immunity level. Patients in the AIDS stage could present with pulmonary TB with no respiratory symptoms, a normal chest X-ray (CXR), and smear-negative but culture-positive results.

For these reasons, PLWH who present with possible pulmonary TB or even extrapulmonary TB should have a CXR, sputum acid-fast bacillus (AFB) smear, and nucleic acid amplification test (NAAT) performed, regardless of the presenting symptoms.

Treatment of Active TB Infection in People Living with HIV (PLWH)

The treatment of TB infection in PLWH is not different from that in HIV-negative individuals. However, special precautions should be considered in HIV-infected patients as follows:

1. **TB Progression and Mortality:** TB infection can rapidly progress in HIV-infected patients and is associated with a higher mortality rate, especially in the AIDS stage. For this reason, in ART-naïve patients, the timing between the initiation of Anti-Tuberculosis Therapy (ATT) and ART depends on the CD4 cell counts.

    - In patients with HIV/TB coinfection, it is recommended to start early ART, i.e., within 2 weeks of the initiation of anti-tuberculous medications, regardless of CD4 count, among people living with HIV (adults and children). ART should be

delayed at least 4 weeks (and initiated within 8 weeks) after treatment for TB meningitis is initiated. In TB-meningitis, extra caution should be taken before early ART due to a higher risk of complications and mortality with immediate ART. Corticosteroids should be considered adjuvant treatment for TB meningitis. In pregnancy, consider earlier ART to decrease the risk of mother-to-child transmission of HIV.

2. **ART and ATT Interaction:** ART significantly interacts with ATT, mainly rifamycin derivatives, which is why the ART regimen should be particularly chosen with concurrent ATT use.

    - **Nucleoside Reverse Transcriptase Inhibitors (NRTIs):** NRTIs are usually safe to be given with ATT. However, Tenofovir Alafenamide (TAF) plasma concentrations might be reduced by rifamycin. For this reason, TAF is not recommended to be given with rifamycin. In a study of healthy volunteers who were given TAF with rifampicin, intracellular tenofovir concentrations were still 4.2-fold higher than those achieved by Tenofovir Disoproxil Fumarate. Another study including TB/HIV coinfected participants is ongoing to investigate the pharmacokinetic effects of rifampin on the intracellular and plasma concentrations of TAF.
    - **Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs):** Most NNRTIs interact with rifamycin. However, Efavirenz is considered safe and one of the recommended ART options in TB/HIV coinfection.
    - **Integrase Transfer Inhibitors (INIs):** Currently, most of the recommended first-line ART options are INIs-based regimens. Raltegravir (RAL) and Dolutegravir (DTG) are considered the most compatible INIs with rifamycin use. Both DTG and RAL need dose modification with some of the rifamycin derivatives (need to double the dose. DTG must be administered at 50 mg BID, the additional tablet must be taken with a 12-hour interval from TLD or TDF/FTC+DTG. The revert to DTG 50 mg QD will be started 2 weeks after the stopping of ATT).
    - **Protease Inhibitors (PIs):** If PIs-based therapy has to be used, Rifabutin can be used with a decreased dose from 300 mg to 150 mg daily. If Rifabutin is not available, a double dose of LPV/r can be coadministered with Rifampicin with a high risk of toxicity, whereas ATV/r and DRV/r cannot be coadministered with Rifampicin.

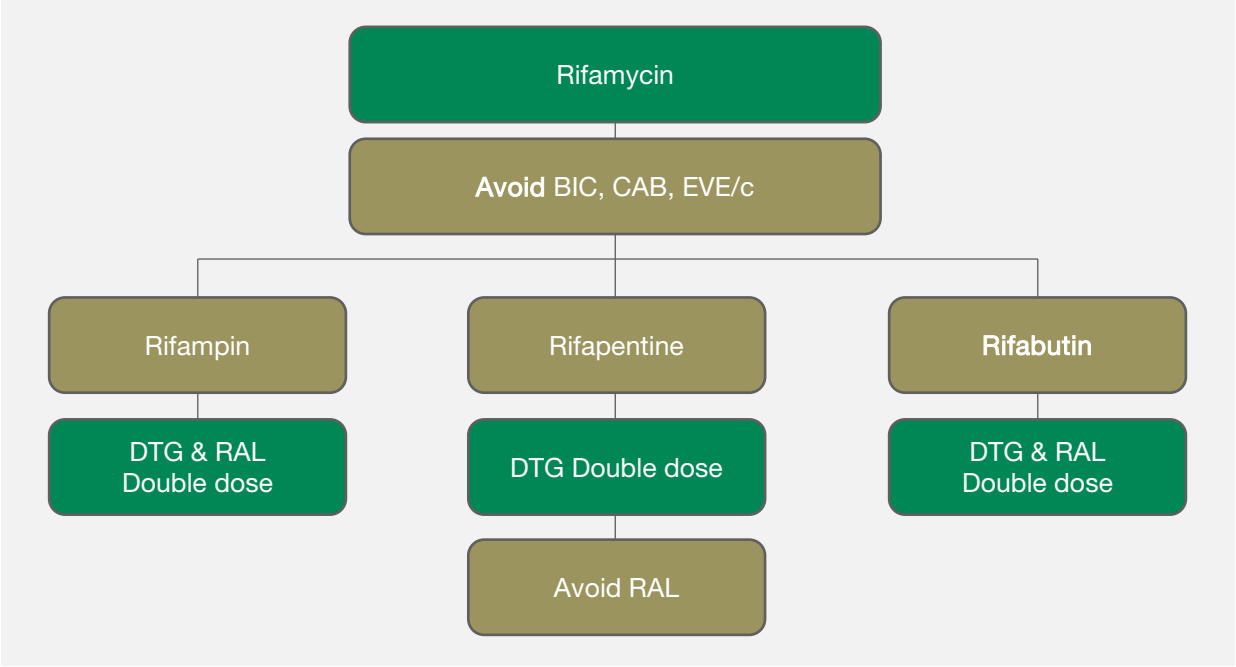
Table 5.1 Potential Drug-Drug Interactions between ART and ATT

ATT Drug	ART Class	PK effects	Recommendation
Bedaquiline	PI	↑ Bedaquiline	Avoid or monitor closely for ECG and LFT
	INI	EVG/c ↑ Bedaquiline	Avoid or monitor closely for ECG and LFT
	NNRTI	EFV & ETR ↓ Bedaquiline	Avoid (no enough data)
Rifampin	PI	↓ All PIs	Contraindicated*
	INI	↓ All INIs	Contraindicated with BIC, CAB, EVG/c Double DTG at 50 mg BID, RAL at 800 mg BID
	NNRTI	↓ RPV ↓ ETR ↓ DOR	Contraindicated
Rifapentine	PI	↓ All PIs	Contraindicated
	INI	↓ All INIs	Contraindicated with BIC, CAB, EVG/c Avoid with RAL Double DTG dose with daily Rifampin
	NNRTI	↓ RPV ↓ ETR ↓ DOR	Contraindicated with RPV & ETR Double DOR dose at 100 mg BID
Rifabutin	PI	↑ Rifabutin	Decrease Rifabutin dose at 150 mg daily or every other day
	INI	↓ BIC, CAB, EVG/c	Contraindicated
	NNRTI	↓ DOR ↓ RPV	Double DOR at 100 mg BID Double RPV (PO only) at 50 mg OD

ATT= anti-tuberculosis therapy, ART= antiretroviral therapy; BIC = bictegravir; BID= Twice daily; CAB = cabotegravir; COBI = cobicistat; DOR = doravirine; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG/c = elvitegravir/cobicistat; INI=integrase strand transfer inhibitor; NNRTI= non-nucleoside transcriptase inhibitor; OD= once daily; PI = protease inhibitor; PO = oral; RAL = raltegravir; RPV = rilpivirine;

* double dose of LPV/r can be coadministered with rifampicin with a high risk of toxicity, whereas ATV/r and DRV/r can not be coadministered with rifampicin (are contraindicated).

Fig. 5.2 Integrase Transfer Inhibitors Selection with Rifamycin Therapy.



ATT= anti-tuberculosis therapy, ART= antiretroviral therapy; BIC = bictegravir; CAB = cabotegravir; DTG = dolutegravir; EVG/c = elvitegravir/cobicistat; INI=integrase strand transfer inhibitor; RAL = raltegravir;

Tuberculosis and Immune Reconstitution Inflammatory Syndrome (IRIS)

Immune Reconstitution Inflammatory Syndrome (IRIS) refers to clinical manifestations that occur in response to the recovery of the immune system after initiating Antiretroviral Therapy (ART) in patients infected with the Human Immunodeficiency Virus (HIV). IRIS can present in two forms:

1. The development of new symptoms due to a subclinical Tuberculosis (TB) infection, also known as unmasked TB-IRIS.
2. The worsening of a TB infection, known as paradoxical TB-IRIS.

The rate of paradoxical TB-IRIS can reach up to 18%, with a mortality rate of 2%. The main risk factors for paradoxical TB-IRIS include low CD4 counts (less than 100 cells/mm3), high HIV RNA levels, immediate initiation of ART within the first month, and patients with extrapulmonary TB[26-33]. IRIS is usually a mild and self-limiting disease that requires only supportive therapy. However, in moderate or severe reactions, prednisone (1.5 mg/kg per day for 2 weeks, then 0.75 mg/kg per day for 2 weeks) can be used to reduce the need for hospitalization and therapeutic procedures, and hasten improvements in symptoms, performance, and quality of life. The use of dexamethasone is associated with a lower mortality rate if TB-IRIS involves the Central Nervous System (CNS). Antiretroviral Therapy (ART) and Anti-Tuberculosis Therapy (ATT) regimens should not be stopped in the case of IRIS (CI).

Screening for Latent TB Infection in People Living with HIV (PLWH)

- All PLWH should be screened for latent TB infection (AI).
- The Interferon-Gamma Release Assay (IGRA), such as QuantiFERON or T-SPOT, is the recommended test for adults due to its rapidity and accuracy (AI).
- The Tuberculin Skin Test (TST) is an alternative test; a result is considered positive if there is ≥ 5 mm of skin induration at 48–72 hours.
- It is preferred to conduct latent TB screening when the CD4 count is ≥ 200 cells/mm3 (AII). Patients with CD4 counts < 200 cells/mm3 may have a false-negative result[37-40]. However, the IGRA T-SPOT test is more sensitive in patients with low CD4 counts.
- All patients should undergo a chest X-ray and clinical exam to rule out signs of active TB infection (AI).

Recommended Regimens for Latent TB in PLWH

1. Isoniazid 300 mg orally daily + pyridoxine daily for 6 to 9 months[41-43].
    - Patients should be monitored for toxicity due to prolonged use and to ensure completion of therapy.

2. Rifampin 600 mg orally daily for 4 months.
    - This regimen should be avoided if there is a drug-drug interaction with ART (Table 5.1).

3. Daily isoniazid 300 mg orally + rifampin 600 mg orally + pyridoxine daily for 3 months.
    - This regimen is preferred due to its short course.
    - It should be avoided if there is a drug-drug interaction with ART.

4. Rifapentine orally once weekly + isoniazid (15 mg/kg, max 900 mg) orally once weekly + pyridoxine 50 mg orally once weekly for 12 weeks.
    - This regimen is preferred for patients due to its short course and less frequent dosing.
    - It is recommended for patients with a CD4+ count of ≥ 350 cells/mm3.
    - Patient compliance should be ensured with directly observed therapy.

References:

1. WHO. Global Tuberculosis Report, 2021. https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2021
2. Ministry of health Statistic reports. Last access June 1, 2022. https://www.moh.gov.sa/en/Ministry/Statistics/book/Pages/default.aspx
3. Al-Mozaini M, Alrahbeni T, Dirar Q, Alotibi J, Alrajhi A. HIV in the Kingdom of Saudi Arabia: Can We Change the Way We Deal with Co-Infections. Infect Drug Resist. 2021; 14: 111-17.
4. https://www.who.int/publications/i/item/9789240022232
5. Ahuja SS, Ahuja SK, Phelps KR, Thelmo W, Hill AR. Hemodynamic confirmation of septic shock in disseminated tuberculosis. Crit Care Med. 1992; 20 (6): 901-03.
6. Shafer RW, Kim DS, Weiss JP, Quale JM. Extrapulmonary tuberculosis in patients with human immunodeficiency virus infection. Medicine. 1991; 70 (6): 384-97
7. Post FA, Wood R, Pillay GP. Pulmonary tuberculosis in HIV infection: radiographic appearance is related to CD4+ T-lymphocyte count. Tuber Lung Dis. 1995; 76 (6): 518-21.
8. Perlman DC, el-Sadr WM, Nelson ET, et al. Variation of chest radiographic patterns in pulmonary tuberculosis by degree of human immunodeficiency virus-related immunosuppression. The Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA). The AIDS Clinical Trials Group (ACTG). Clin Infect Dis. 1997; 25 (2): 242 – 46.
9. Cavanaugh JS, Modi S, Musau S, et al. Comparative yield of different diagnostic tests for tuberculosis among people living with HIV in western Kenya. PLoS One. 2016; 11 (3): e0152364.
10. Henostroza G, Harris JB, Chitambi R, et al. High prevalence of tuberculosis in newly enrolled HIV patients in Zambia: need for enhanced screening approach. Int J Tuberc Lung Dis. 2016; 20 (8): 1033-39.
11. Abdool Karim SS, Naidoo K, Grobler A, et al. Integration of antiretroviral therapy with tuberculosis treatment. NEJM. 2011; 365 (16): 1492-1501.
12. Blanc FX, Sok T, Laureillard D, et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. NEJM. 2011; 365 (16): 1471-81.
13. Havlir DV, Kendall MA, Ive P, et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. NEJM. 2011; 365 (16): 1482-91.
14. Torok ME, Yen NT, Chau TT, et al. Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)-associated tuberculous meningitis. Clin Infect Dis. 2011; 52 (11): 1374-83.
15. Descovy package insert [package insert]. Gilead. http://www.gilead.com/~/media/files/pdfs/medicines/hiv/descovy/descovy_pi.pdf?la=en
16. Cerrone M, Alfarisi O, Neary M, Marzinke MA, Parsons TL, Owen A, Maartens G, Pozniak A, Flexner C, Boffito M. Rifampicin effect on intracellular and plasma pharmacokinetics of tenofovir alafenamide. J Antimicrob Chemother. 2019;74 (6): 1670-78.
17. Sokhela S. The Effect of Rifampicin on the Pharmacokinetics of Intracellular Tenofovir-diphosphate and Tenofovir When Coadministered With Tenofovir Alafenamide Fumarate During the Maintenance Phase of Tuberculosis Treatment in TB/HIV-1 Coinfected Participants (EpiTAF). https://clinicaltrials.gov/ct2/show/NCT04424264?term=tenofovir+alafenamide%2C+rifampin&cond=tuberculosis&draw=2&ra
18. Boulle A, Van Cutsem G, Cohen K, et al. Outcomes of nevirapine- and efavirenz-based antiretroviral therapy when coadministered with rifampicin-based antitubercular therapy. JAMA. 2008; 300 (5): 530-39.
19. Cohen K, Grant A, Dandara C, et al. Effect of rifampicin-based antitubercular therapy and the cytochrome P450 2B6 516G>T polymorphism on efavirenz concentrations in adults in South Africa. Antivir Ther. 2009; 14 (5): 687-95

20. Ramachandran G, Hemanth Kumar AK, Rajasekaran S, et al. CYP2B6 G516T polymorphism but not rifampin coadministration influences steady-state pharmacokinetics of efavirenz in human immunodeficiency virus-infected patients in South India. Antimicrob Agents Chemother. 2009; 53 (3):863-68.

21. Grinsztejn B, De Castro N, Arnold V, et al. Raltegravir for the treatment of patients co-infected with HIV and tuberculosis (ANRS 12 180 Reflate TB): a multicentre, phase 2, non-comparative, open-label, randomised trial. Lancet Infect Dis. 2014; 14(6): 459-67.

22. Wenning LA, Hanley WD, Brainard DM, et al. Effect of rifampin, a potent inducer of drug-metabolizing enzymes, on the pharmacokinetics of raltegravir. Antimicrob Agents Chemother. 2009; 53(7): 2852-56.

23. Dooley KE, Sayre P, Borland J, et al. Safety, tolerability, and pharmacokinetics of the HIV integrase inhibitor dolutegravir given twice daily with rifampin or once daily with rifabutin: results of a phase 1 study among healthy subjects. J Acquir Immune Defic Syndr. 2013; 62(1): 21-27.

24. Dooley KE, Kaplan R, Mwelase N, et al. Dolutegravir-based Antiretroviral Therapy for Patients Coinfected With Tuberculosis and Human Immunodeficiency Virus: A Multicenter, Noncomparative, Open-label, Randomized Trial. Clin Infect Dis. 2020; 70(4): 549-56.

25. Kendall MA, Lalloo U, Fletcher CV, et al. Safety and pharmacokinetics of double-dose lopinavir/ritonavir + rifampin versus lopinavir/ritonavir + daily rifabutin for treatment of human immunodeficiency virus-tuberculosis coinfection. Clin Infect Dis. 2021; 73(4): 706-15.

26. Namale PE, Abdullahi LH, Fine S, Kamkuemah M, Wilkinson RJ, Meintjes G. Paradoxical TB-IRIS in HIV-infected adults: a systematic review and meta-analysis. Future Microbiol. 2015; 10(6): 1077-99.

27. Narita M, Ashkin D, Hollender ES, Pitchenik AE. Paradoxical worsening of tuberculosis following antiretroviral therapy in patients with AIDS. Am J Respir Crit Care Med. 1998; 158(1): 157-61.

28. Serra FC, Hadad D, Orofino RL, et al. Immune reconstitution syndrome in patients treated for HIV and tuberculosis in Rio de Janeiro. Braz J Infect Dis. 2007; 11(5): 462-65.

29. Lawn SD, Myer L, Bekker LG, Wood R. Tuberculosis-associated immune reconstitution disease: incidence, risk factors and impact in an antiretroviral treatment service in South Africa. AIDS. 2007; 21(3): 335-41.

30. Michailidis C, Pozniak AL, Mandalia S, Basnayake S, Nelson MR, Gazzard BG. Clinical characteristics of IRIS syndrome in patients with HIV and tuberculosis. Antivir Ther. 2005; 10(3): 417-22.

31. Luetkemeyer AF, Kendall MA, Nyirenda M, et al. Tuberculosis immune reconstitution inflammatory syndrome in A5221 STRIDE: timing, severity, and implications for HIV-TB programs. J Acquir Immune Defic Syndr. 2014; 65(4): 423-28.

32. Narendran G, Andrade BB, Porter BO, et al. Paradoxical tuberculosis immune reconstitution inflammatory syndrome (TB-IRIS) in HIV patients with culture confirmed pulmonary tuberculosis in India and the potential role of IL-6 in prediction. PLoS One. 2013; 8(5): e63541.

33. Manosuthi W, Kiertiburanakul S, Phoorisri T, Sungkanuparph S. Immune reconstitution inflammatory syndrome of tuberculosis among HIV-infected patients receiving antituberculous and antiretroviral therapy. J Infect. 2006; 53(6): 357-63.

34. Breton G, Duval X, Estellat C, et al. Determinants of immune reconstitution inflammatory syndrome in HIV type 1-infected patients with tuberculosis after initiation of antiretroviral therapy. Clin Infect Dis. 2004; 39(11): 1709-12.

35. Meintjes G, Wilkinson RJ, Morroni C, et al. Randomized placebo-controlled trial of prednisone for paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome. AIDS. 2010; 24(15): 2381-90.

36. https://www.nejm.org/doi/full/10.1056/nejmoa1800762

37. Thwaites GE, Nguyen DB, Nguyen HD, Hoang TQ, Do TT, Nguyen TC, Nguyen QH, Nguyen TT, Nguyen NH, Nguyen TN, Nguyen NL, Nguyen HD, Vu NT, Cao HH, Tran TH, Pham PM, Nguyen TD, Stepniewska K, White NJ, Tran TH, Farrar JJ. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. N Engl J Med. 2004; 351(17): 1741-51.

38. Gerald H. Mazurek, John Jereb, Andrew Vernon, et al. Updated Guidelines for Using Interferon Gamma Release Assays to Detect Mycobacterium tuberculosis Infection --- United States, 2010; 59 (RR05): 1-25. CDC MMR. https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5905a1.htm?s_cid=rr5905a1_e

39. Fisk TL, Hon HM, Lennox JL, Fordham von Reyn C, Horsburgh CR Jr. Detection of latent tuberculosis among HIV-infected patients after initiation of highly active antiretroviral therapy. AIDS. 2003; 17(7): 1102-4.

40. Girardi E, Palmieri F, Zaccarelli M, Tozzi V, Trotta MP, Selva C, Narciso P, Petrosillo N, Antinori A, Ippolito G. High incidence of tuberculin skin test conversion among HIV-infected individuals who have a favourable immunological response to highly active antiretroviral therapy. AIDS. 2002; 16(14): 1976-9.

41. Cattamanchi A, Smith R, Steingart KR, Metcalfe JZ, Date A, Coleman C, Marston BJ, Huang L, Hopewell PC, Pai M. Interferon-gamma release assays for the diagnosis of latent tuberculosis infection in HIV-infected individuals: a systematic review and meta-analysis. J Acquir Immune Defic Syndr. 2011; 56(3): 230-8.

42. Gray J, Reves R, Johnson S, Belknap R. Identification of false-positive QuantiFERON-TB Gold In-Tube assays by repeat testing in HIV-infected patients at low risk for tuberculosis. Clin Infect Dis. 2012; 54(3): e20-3.

43. Temprano ANRS Study Group, Danel C, Moh R, et al. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. NEJM. 2015; 373(9): 808-22.

44. Hawken MP, Meme HK, Elliott LC, et al. Isoniazid preventive therapy for tuberculosis in HIV-1-infected adults: results of a randomized controlled trial. AIDS. 1997; 11(7): 875-82.

45. Whalen CC, Johnson JL, Okwera A, et al. A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus. Uganda-Case Western Reserve University Research Collaboration. NEJM. 1997; 337(12): 801-08.

46. Menzies D, Adjobimey M, Ruslami R, et al. Four months of rifampin or nine months of isoniazid for latent tuberculosis in adults. NEJM. 2018; 379(5): 440-53.

47. Johnson JL, Okwera A, Hom DL, et al; Uganda-Case Western Reserve University Research Collaboration. Duration of efficacy of treatment of latent tuberculosis infection in HIV-infected adults. AIDS. 2001; 15(16): 2137-47.

48. Rivero A, López-Cortés L, Castillo R, eat al; Grupo Andaluz para el estudio de las Enfermedades Infecciosas (GAEI). Randomized clinical trial investigating three chemoprophylaxis regimens for latent tuberculosis infection in HIV-infected patients. Enferm Infecc Microbiol Clin. 2007; 25(5): 305-10.

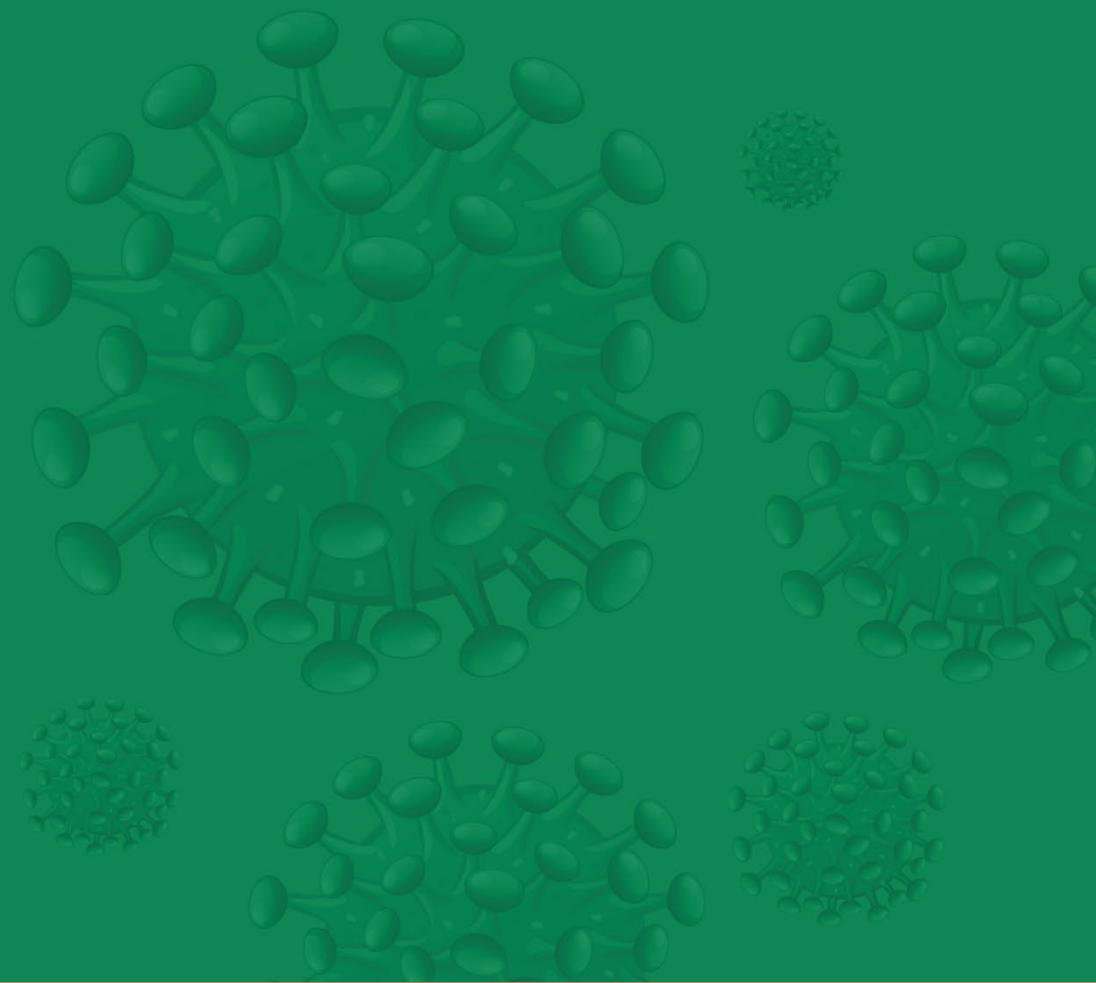
49. Sterling TR, Scott NA, Miro JM, et al; Tuberculosis Trials Consortium, the AIDS Clinical Trials Group for the PREVENT TB Trial (TBTC Study 26ACTG 5259). Three months of weekly rifapentine and isoniazid for treatment of Mycobacterium tuberculosis infection in HIV-coinfected persons. AIDS. 2016; 30(10): 1607-15.

50. Martinson NA, Barnes GL, Moulton LH, et al. New regimens to prevent tuberculosis in adults with HIV infection. NEJM. 2011; 365(1): 11-20.

51. https://www.nejm.org/doi/full/10.1056/nejmoa1800762

CHAPTER 06

GUIDELINES FOR THE PREVENTION AND TREATMENT OF OPPORTUNISTIC INFECTIONS IN ADULTS AND ADOLESCENTS WITH HIV



Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV

Introduction

Opportunistic infections (OIs) are defined as infections that are more frequent or more severe because of HIV-mediated immunosuppression.

Pneumocystis pneumonia, Toxoplasma encephalitis, Cytomegalovirus retinitis, Cryptococcal meningitis, Tuberculosis, disseminated *Mycobacterium avium complex (MAC)* disease, and *Pneumococcal* respiratory disease, as well as certain cancers such as *Kaposi sarcoma* and central nervous system lymphoma, have been hallmarks of AIDS.

These OIs, and many more, occurred on average 7 to 10 years after infection with HIV. Until effective antiretroviral therapy (ART) was developed, patients generally survived only 1 to 2 years after the initial manifestation of AIDS.

The use of chemoprophylaxis, immunization, and better strategies for managing OIs improved the quality of life and lengthened the survival of people with HIV.

Despite the availability of multiple safe, effective, and simple ART regimens that, when used widely, have led to corresponding population-level declines in the incidence of OIs, some people with HIV infection will continue to present with an OI as the sentinel event leading to a diagnosis of HIV infection or present with an OI as a complication of unsuccessful viral suppression.

Recommendations

This report addresses the following:

1. Preventing exposure to opportunistic pathogens.
2. Preventing disease.
3. Discontinuing primary prophylaxis after immune reconstitution.
4. Treating disease.
5. When to start ART in the setting of an acute OI.
6. Managing treatment failure.
7. Preventing disease recurrence (secondary prophylaxis or chronic maintenance therapy).
8. Discontinuing secondary prophylaxis or chronic maintenance therapy after immune reconstitution.

Bacterial Enteric Infections

Table 6.1a Treatment of HIV-Associated Opportunistic Infections

Treatment of AIDS-Associated Opportunistic Infections			
Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Empiric therapy pending definitive diagnosis	Diagnostic fecal specimens should be obtained before the initiation of empiric antimicrobial therapy. Reflex culture for antibiotic susceptibilities should also be done if diagnosis is made using PCR-based methods. Empiric antibiotic therapy may be indicated for: - pts with CD4 count 200–500 cells/mm^3 where diarrhea is severe enough to compromise quality of life or the ability to work **(CIII)**. -pts with CD4 count <200 cells/mm^3 or concomitant AIDS-defining illness and with clinically severe diarrhea (≥6 stools per day or bloody stool) and/or accompanying fever or chills **(AIII).** **Empiric Therapy** Ciprofloxacin 500–750 mg PO (or 400 mg IV) q 12 hours for 5 days **(AIII)** (particularly if diarrhea is not associated with international travel) Therapy should be adjusted based on the results of a diagnostic work-up. For patients with chronic diarrhea (>14 days) without severe clinical signs, empiric antibiotics therapy is not necessary. Treatment can be withheld until a diagnosis is made.	***Empiric Therapy in Patients with Marked Nausea, Vomiting, Diarrhea, Electrolyte Abnormalities, Acidosis, Blood Pressure Instability, and/or When Hospitalization Is Needed*** • Ceftriaxone 1 g IV every 24 hours **(BIII),** or • Cefotaxime 1 g IV every 8 hours **(BIII)**	Oral or IV rehydration (if indicated) should be given to patients with diarrhea (**AIII**). Anti-motility agents should be avoided if there is concern about inflammatory diarrhea, including CDI (BIII). If no clinical response is observed after 3–4 days, consider a follow up stool culture with antibiotic susceptibility testing or alternative diagnostic tests (e.g., toxin assays, molecular testing) to evaluate alternative diagnoses, antibiotic resistance, or drug–drug interactions

Treatment of AIDS-Associated Opportunistic Infections			
Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Campylobacteriosis	**For Mild Disease and if CD4 Count >200 Cells/mm³** • No therapy unless symptoms persist for more than several days **(CIII)**. **For Mild-to-Moderate Disease (If Susceptible)** • Ciprofloxacin 500–750 mg PO (or 400 mg IV) every 12 hours for 7–10 days **(BIII)**, or • Azithromycin 500 mg PO daily for 5 days **(BIII)** (Note: Not for patients with bacteremia **[AIII])** **For Campylobacter Bacteremia** • Ciprofloxacin 500–750 mg PO (or 400 mg IV) every 12 hours for ≥14 days if the isolate is sensitive **(BIII)** plus an aminoglycoside **(BIII).** **For Recurrent infections** • Duration of therapy may be extended to 2–6 weeks **(BIII).**	**For Mild-to-Moderate Disease (If Susceptible)** • Levofloxacin 750 mg (PO or IV) every 24 hours **(BIII)**, or • Moxifloxacin 400 mg (PO or IV) every 24 hours **(BIII)** • Add an aminoglycoside to fluoroquinolone in bacteremic patients **(BIII).**	Oral or IV rehydration if indicated (AIII) Anti-motility agents should be avoided (BIII). If no clinical response is observed after 5–7 days, consider a follow-up stool culture, alternative diagnosis, or antibiotic resistance. The rationale for addition of an aminoglycoside to a fluoroquinolone in bacteremic patients is to prevent emergence of quinolone resistance. Effective ART may reduce the frequency, severity, and recurrence of campylobacter infections.
Clostridium difficile infection (CDI)	Fidaxomicin 200 mg PO two times daily for 10 days **(AI).** Vancomycin 125 mg PO four times daily for 10 days **(AI).** For severe, life-threatening CDI, see text and references for additional information.	For Nonsevere CDI If Fidaxomicin or Vancomycin Access Is Limited • Metronidazole 500 mg (PO) three times daily for 10 days **(CII)**	Recurrent CDI Treatment is the same as in patients without HIV infection. Bezlotoximab **(CIII)** or fecal microbiota therapy may be successful and safe to treat recurrent CDI **(CIII).**
Salmonellosis	All people with HIV and salmonellosis should receive antimicrobial treatment due to an increase of bacteremia (by 20-fold to 100-fold) and mortality (by up to 7-fold) compared to individuals without HIV **(AIII).**		Oral or IV rehydration if indicated **(AIII).**

Treatment of AIDS-Associated Opportunistic Infections			
Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
	Ciprofloxacin 500–750 mg PO (or 400 mg IV) every 12 hours, if susceptible **(AIII)** **Duration of Therapy For Gastroenteritis Without Bacteremia** • If CD4 count ≥200 cells/mm^3: 7–14 days **(BIII)** • If CD4 count <200 cells/mm^3:2–6 weeks **(BIII).** **For Gastroenteritis with Bacteremia** • If CD4 count ≥200/mm^3: 14 days or longer duration if bacteremia persists or if the infection is complicated (e.g., if metastatic foci of infection are present) **(BIII)** • If CD4 count <200 cells/mm^3: 2–6 weeks **(BIII).** **Secondary Prophylaxis Should Be Considered** • For patients with recurrent Salmonella bacteremia **(BIII),** or • For patients with recurrent gastroenteritis (with or without bacteremia) with CD4 count <200 cells/mm^3 with severe diarrhea**(BIII).**	• Levofloxacin 750 mg (PO or IV) every 24 hours **(BIII), or** • Moxifloxacin 400 mg (PO or IV) every 24 hours **(BIII), or** • TMP 160 mg-SMX 800 mg (PO or IV) every 12 hours **(BIII), or** • Ceftriaxone 1 g IV every 24 hours **(BIII)**, or • Cefotaxime 1 g IV every 8 hours **(BIII)**.	Anti-motility agents should be avoided **(BIII).** The role of long-term secondary prophylaxis in patients with recurrent Salmonella bacteremia is not well established. Must weigh benefit against risks of long-term antibiotic exposure **(BIII).** Effective ART may reduce the frequency, severity, and recurrence of salmonella infections.

Treatment of AIDS-Associated Opportunistic Infections			
Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Shigellosis	• Ciprofloxacin 500–750 mg PO (or 400 mg IV) every 12 hours (if MIC <0.12 µg/mL **(AIII)** **Duration of Therapy** • Gastroenteritis: 7–10 days **(AIII)** • Bacteremia: ≥14 days **(BIII)** • Recurrent infections: Up to 6 weeks **(BIII)** Avoid fluoroquinolones if ciprofloxacin MIC is ≥0.12 µg/mL, even if the laboratory identifies the isolate as sensitive. Many Shigella strains resistant to fluoroquinolones exhibit resistance to other commonly used antibiotics. Thus, antibiotic sensitivity testing of Shigella isolates from HIV-infected individuals should be performed routinely.	• Levofloxacin 750 mg (PO or IV) every 24 hours **(BIII)**, **or** • Moxifloxacin 400 mg (PO or IV) every 24 hours **(BIII), or** • TMP 160 mg-SMX 800 mg (PO or IV) every 12 hours **(BIII)** **or** • Azithromycin 500 mg PO daily for 5 days **(BIII)** (Note: not recommended for patients with bacteremia [**AIII**].) Note: Azithromycin-resistant Shigella spp. has been reported in HIV-infected MSM.	Therapy may slightly shorten duration of illness and/or prevent spread of infection **(AIII)**. Given increasing antimicrobial resistance and limited data showing that antibiotic therapy limits transmission, antibiotic treatment may be withheld in patients with CD4 count >500 cells/mm3 whose diarrhea resolves prior to culture confirmation of Shigella infection **(CIII).** Oral or IV rehydration if indicated **(AIII).** Anti-motility agents should be avoided **(BIII)**. If no clinical response after 5–7 days, consider a follow-up stool culture, alternative diagnosis, or antibiotic resistance. Effective ART may decrease the risk of recurrence of Shigella infections.

Candidiasis (Mucocutaneous)

Table 6.1b Treatment of HIV-Associated Opportunistic Infections

Treatment of AIDS-Associated Opportunistic Infections			
Chemoprophylaxis to Prevent First Episode	**Preferred Therapy**	**Alternative Therapy**	**Other Comments**
Not applicable	**For Oropharyngeal Candidiasis; Initial Episodes (for 7–14 Days)** **Oral Therapy** • Fluconazole 100 mg PO daily **(AI)** **For Esophageal Candidiasis (for14–21 Days)** • Fluconazole 100 mg (up to 400 mg) PO or IV daily **(AI)**, **or** • Itraconazole oral solution 200 mg PO daily **(AI)** **For Uncomplicated Vulvo-Vaginal Candidiasis** • Oral fluconazole 150 mg for one dose **(AII)**, **or** • Topical azoles (clotrimazole, butoconazole, miconazole, tioconazole, or terconazole) for 3–7 days **(AII)** **For Severe or Recurrent Vulvovaginal Candidiasis** • Fluconazole 100–200 mg PO daily for ≥7 days (AII), or • Topical antifungal ≥7 days **(AII)**	**For Oropharyngeal Candidiasis; Initial Episodes (for 7–14 Days)** **Oral Therapy** • Itraconazole oral solution 200 mg PO daily **(BI)**, **or** • Posaconazole oral suspension 400 mg PO twice a day for 1 day, then 400 mg daily **(BI)** **Topical Therapy** • Clotrimazole troches, 10 mg PO five times daily **(BI)**, **or** • Miconazole mucoadhesive buccal 50-mg tablet; apply to mucosal surface over the canine fossa once daily (do not swallow, chew, or crush tablet) **(BI)**, **or** • Nystatin suspension 4–6 mL four times a day or 1–2 flavored pastilles four to five times daily **(BII)**. • Gentian violet (0.00165%) topical application twice daily (BI) **For Esophageal Candidiasis (for 14–21 Days)** • Voriconazole 200 mg PO or IV twice a day **(BI)**, **or** • Isavuconazole 200 mg PO as a loading	Chronic or prolonged use of azoles may promote development of resistance. Higher relapse rate for esophageal candidiasis seen with echinocandins than with fluconazole use. Suppressive therapy usually not recommended **(BIII)** unless patients have frequent or severe recurrences. **If Decision Is to Use Suppressive Therapy** *Oropharyngeal Candidiasis* • Fluconazole 100 mg PO daily or three times weekly **(BI)**, **or** Itraconazole oral solution 200 mg PO daily **(CI)** *Esophageal Candidiasis* • Fluconazole 100–200 mg PO daily **(BI)**; **or** • Posaconazole 400 mg PO twice a day **(BII)** Vulvo-Vaginal Candidiasis • Fluconazole 150 mg PO once weekly **(CII)**.

Treatment of AIDS-Associated Opportunistic Infections			
Chemoprophylaxis to Prevent First Episode	**Preferred Therapy**	**Alternative Therapy**	**Other Comments**
		dose, followed by 50 mg PO daily **(BI)**, **or** • Isavuconazole 400 mg PO as a loading dose, followed by 100 mg PO daily **(BI)**, **or** • Isavuconazole 400 mg PO once weekly **(BI), or** • Anidulafungin 100 mg IV 1 time, then 50 mg IV daily **(BI), or** • Caspofungin 50 mg IV daily **(BI)**, **or** • Micafungin 150 mg IV daily **(BI)**, **or** • Amphotericin B deoxycholate 0.6 mg/kg IV daily **(BI)**, **or** • Lipid formulation of amphotericin B 3–4 mg/kg IV daily **(BIII)** **For Uncomplicated Vulvovaginal Candidiasis** • Itraconazole oral solution 200 mg PO daily for 3–7 days **(BII).** **For Azole-Refractory *Candida glabrata* Vaginitis** • Boric acid vaginal suppository 600 mg once daily for 14 days	

Community-Acquired Pneumonia (CAP)

Table 6.1c Treatment of HIV-Associated Opportunistic Infections

Treatment of AIDS-Associated Opportunistic Infections			
Chemoprophylaxis to Prevent First Episode	**Preferred Therapy**	**Alternative Therapy**	**Other Comments**
Not applicable	Empiric antibiotic therapy should be initiated promptly for patients presenting with clinical and radiographic evidence consistent with bacterial pneumonia. The recommendations listed are suggested empiric therapy. The regimen should be modified a needed once microbiologic result are available (**BIII**). Providers must also consider the risk of opportunistic lung infections (e.g., PCP, TB), which may alter the empiric therapy. **Empiric Outpatient Therapy** • A PO beta-lactam plus a PO macrolide (azithromycin or clarithromycin) **(AII)** *Preferred Beta-Lactams* • High-dose amoxicillin or amoxicillin/clavulanate *Alternative Beta-Lactams* • Cefpodoxime or cefuroxime, or • Levofloxacin 750 mg PO once daily **(AII)**, or moxifloxacin 400 mg PO once daily **(AII)**, especially for patients with penicillin allergies	Empiric antibiotic therapy should be initiated promptly for patients presenting with clinical and radiographic evidence consistent with bacterial pneumonia. The recommendations listed are suggested empiric therapy. The regimen should be modified as needed once microbiologic results are available **(BIII).** Providers must also consider the risk of opportunistic lung infections (e.g., PCP, TB), which may alter the empiric therapy. **Empiric Outpatient Therapy** • A PO beta-lactam plus PO doxycycline **(CIII)** *Preferred Beta-Lactams* • High-dose amoxicillin or amoxicillin/clavulanate *Alternative Beta-Lactams*: • Cefpodoxime or cefuroxime. **Empiric Therapy for Hospitalized Patients with**	**Duration** For most patients, 5–7 days Patients should be afebrile for 48–72 hours and clinically stable before stopping antibiotics. Longer duration is often required if severe CAP or bacteremia is present, and particularly if due to S. pneumoniae or complicated S. aureus pneumonia. Fluoroquinolones should be used with caution in patients in whom TB is suspected but is not being treated. Empiric therapy with a macrolide alone is not routinely recommended, because of increasing pneumococcal resistance (up to 30%) **(BIII).** Patients receiving a macrolide for MAC prophylaxis may have bacterial resistance to macrolide due to chronic exposure. For patients begun on IV antibiotic therapy, switching to PO should be considered when they are

Treatment of AIDS-Associated Opportunistic Infections			
Chemoprophylaxis to Prevent First Episode	**Preferred Therapy**	**Alternative Therapy**	**Other Comments**
	Empiric Therapy for Hospitalized Patients with Non-Severe CAP • An IV beta-lactam plus a macrolide (azithromycin or clarithromycin) **(AI)** *Preferred Beta-Lactams* • Ceftriaxone, cefotaxime, or ampicillin-sulbactam • Levofloxacin 750 mg IV once daily**(AI)**, or moxifloxacin, 400 mg IV once daily **(AI),** especially for patients with penicillin allergies. **Empiric Therapy for Hospitalized Patients with Severe CAP** • An IV beta-lactam plus IV azithromycin **(AI)**, or • An IV beta-lactam plus (levofloxacin 750 mg IV once daily or moxifloxacin 400 mg IV once daily) **(AI)** Preferred Beta-Lactams • Ceftriaxone, cefotaxime, or ampicillin-sulbactam Empiric Therapy for Patients at Risk of Pseudomonas Pneumonia • An IV antipneumococcal, antipseudomonal beta-lactam plus (ciprofloxacin 400 mg IV every 8–12 hours or levofloxacin 750 mg IV once daily) **(AI)**	**Non-Severe CAP** • An IV beta-lactam plus doxycycline **(CIII)** Empiric Therapy for Hospitalized Patients with Severe CAP. **For Penicillin-Allergic Patients** • Aztreonam IV plus (levofloxacin 750 mg IV once daily or moxifloxacin 400 mg IV once daily) **(BIII)** **Empiric Therapy for Patients at Risk of Pseudomonas Pneumonia** • An IV antipneumococcal, antipseudomonal beta lactam plus an IV aminoglycoside plus azithromycin **(BII),** or • An IV antipneumococcal, antipseudomonal betalactam plus an aminoglycoside plus (levofloxacin 750 mg IV once daily or moxifloxacin 400 mg IV once daily) **(BIII)** For Penicillin-Allergic Patients	clinically improved and able to tolerate oral medications. Antibiotic chemoprophylaxis is generally, not recommended because of the potential for developing drug resistance and drug toxicities **(AI).**

Treatment of AIDS-Associated Opportunistic Infections			
Chemoprophylaxis to Prevent First Episode	**Preferred Therapy**	**Alternative Therapy**	**Other Comments**
	Preferred Beta-Lactams • Piperacillin-tazobactam, cefepime, imipenem, or meropenem **Empiric Therapy for Patients at Risk for Methicillin-Resistant Staphylococcus Aureus Pneumonia** • Add vancomycin IV or linezolid (IV or PO) to the baseline regimen **(AII).** • Addition of clindamycin to vancomycin (but not to linezolid) can be considered for severe necrotizing pneumonia to minimize bacterial toxin production **(CII)**	• Replace the beta-lactam with aztreonam **(BIII).**	

Cryptococcosis

Table 6.1d Treatment of HIV-Associated Opportunistic Infections

Treatment of AIDS-Associated Opportunistic Infections			
Chemoprophylaxis to Prevent First Episode	**Preferred Therapy**	**Alternative Therapy**	**Other Comments**
Not applicable	Cryptococcal Meningitis *Induction Therapy (2 weeks, followed by consolidation therapy)* • Liposomal amphotericin B 3–4 mg/kg IV daily plus flucytosine 25 mg/kg PO four times a day **(AI)** (Note: Flucytosine dose should be adjusted in patients with renal dysfunction.) • Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily plus flucytosine 25 mg/kg PO four times a day **(AI)** (if cost is an issue and the risk of renal dysfunction is low), or • If not improved clinically or remain clinically unstable, continue induction therapy until the CSF culture is confirmed to be negative **(BIII).** *Consolidation Therapy (for at least 8 weeks (AI), followed by maintenance therapy)* • Fluconazole 800 mg PO (or IV) daily **(AI)** • For clinically stable patients with negative CSF cultures, dose can be reduced to 400 mg PO once daily **(AII)** • If CSF remains positive (but clinically stable) after 2 weeks of induction therapy, increase	Cryptococcal Meningitis *Induction Therapy (for at least 2 weeks, followed by consolidation therapy)* • Amphotericin B lipid complex 5 mg/kg IV daily plus, flucytosine 25 mg/kg PO four times a day **(BII)**, or • Liposomal amphotericin B 3–4 mg/kg IV daily plus fluconazole 800–1,200 mg PO or IV daily **(BIII),** or • Fluconazole 1,200 mg PO or IV daily plus flucytosine 25 mg/kg PO four times a day **(BII),** or • Fluconazole 800 mg PO or IV daily plus flucytosine 25 mg/kg PO four times a day **(BIII)**, or • Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily plus fluconazole 800–1,200 mg PO or IV daily **(BI)**, or • Liposomal amphotericin B 3–4 mg/kg IV daily **(BI)**, or	Addition of flucytosine to amphotericin B has been associated with more rapid sterilization of CSF and decreased risk for subsequent relapse. Patients receiving flucytosine should have either blood levels monitored (peak level 2 hours after dose should be 25–100 mcg/mL) or at least twice weekly monitoring of complete blood counts for cytopenia. Dosage should be adjusted in patients with renal insufficiency **(BII).** In resource limited settings, induction of 1 week of amphotericin B deoxycholate with flucytosine followed by high dose fluconazole is preferred **(BIII).** Opening pressure should always be measured when an LP is performed. Repeated LPs or CSF shunting are essential to

Treatment of AIDS-Associated Opportunistic Infections			
Chemoprophylaxis to Prevent First Episode	**Preferred Therapy**	**Alternative Therapy**	**Other Comments**
	fluconazole dose to 1,200 mg and perform LP 2 weeks later **(BIII);** duration of consolidation therapy should be 8 weeks from the time of negative CSF culture **(AI).** *Maintenance Therapy* • Fluconazole 200 mg PO daily for ≥1 year from initiation of antifungal therapy (AI) **For Non-CNS, Extrapulmonary Cryptococcosis and Diffuse Pulmonary Disease or Patients with Isolated Asymptomatic Antigenemia Without Meningitis and Serum CrAg. ≥1:640 by LFA** • Treatment same as for cryptococcal meningitis (BIII) **Non-CNS Cryptococcosis with Mild to-Moderate Symptoms and Focal Pulmonary Infiltrates, or Patients with Isolated Asymptomatic Antigenemia Without Meningitis and Serum CrAg ≤1:320 by LFA)** • Fluconazole, 400 to 800 mg PO daily for 10 weeks, followed by 200 mg daily for a total of 6 months (BIII)	• Amphotericin B deoxycholate 0.7–1.0 mg/kg IV once daily alone **(BI),** or • Liposomal amphotericin B 3–4 mg/kg IV once daily plus, flucytosine 25 mg/kg PO four times a day for 1 week followed by fluconazole 1,200 mg PO once daily **(BIII),** or • Fluconazole 1,200 mg PO or IV daily **(CI)** *Consolidation Therapy (for at least 8 weeks (AI), followed by maintenance therapy)* • If patient's CSF culture remains positive at the end of 2 weeks, but the patient is not ill enough to be hospitalized, continue flucytosine for an additional 2 weeks with fluconazole 1,200 mg daily, before starting a single-drug consolidation regimen. • Itraconazole 200 mg PO twice a day for 8 weeks-less effective than fluconazole **(CI)** *Maintenance Therapy* • No alternative therapy recommendation	effectively manage increased intracranial pressure. Corticosteroids and mannitol are ineffective in reducing ICP and are not recommended **(AIII).** Some specialists recommend a brief course of tapering dose of corticosteroid for management of severe IRIS symptoms **(BIII).**

Cytomegalovirus (CMV) Disease

Table 6.1e Treatment of HIV-Associated Opportunistic Infections

Treatment of AIDS-Associated Opportunistic Infections			
Chemoprophylaxis to Prevent First Episode	**Preferred Therapy**	**Alternative Therapy**	**Other Comments**
Not applicable	**CMV Retinitis** **Induction Therapy (followed by Chronic Maintenance Therapy)** ***For Immediate Sight Threatening Lesions (within 1,500 microns of the fovea)*** • Ganciclovir 5 mg/kg every 12 hours IV or valganciclovir 900 mg PO twice a day or for 14–21 days (AI) (some prefer IV ganciclovir initially and transition to PO valganciclovir when there is evidence of clinical response) with or without • Intravitreal injections of ganciclovir (2 mg) or foscarnet (2.4 mg) to rapidly achieve high intraocular concentration, continue weekly until lesion inactivity is achieved (AIII); plus ***For Peripheral Lesions*** • Valganciclovir 900 mg PO twice a day for 14–21 days, then 900 mg once daily (AI) ***Maintenance Therapy*** • Valganciclovir 900 mg PO daily (AI) for 3–6 months until ART induced immune recovery. **CMV Esophagitis or Colitis** • Ganciclovir 5 mg/kg IV every 12 hours; may switch to valganciclovir 900 mg PO every 12 hours once the patient can tolerate oral therapy (BI)	**CMV Retinitis** For Immediate Sight-Threatening Lesions (within 1,500 microns of the fovea): Intravitreal therapy as listed in the Preferred section, plus one of the following: **Alternative Systemic Induction Therapy (followed by Chronic Maintenance Therapy)** • Foscarnet 90 mg/kg IV every 12 hours or 60 mg/kg every 8 hours for 14–21 days (BI), or • Cidofovir 5 mg/kg/week IV for 2 weeks; saline hydration before and after therapy and probenecid, 2 g PO 3 hours before dose, followed by 1 g PO 2 hours and 8 hours after the dose (total of 4 g) (CI) (Note: This regimen should be avoided in patients with sulfa allergy because of cross hypersensitivity with	The choice of therapy for CMV retinitis should be individualized, based on tolerance of systemic medications, prior exposure to anti-CMV drugs, and location of the lesion (AIII). Given the evident benefits of systemic therapy in preventing contralateral eye involvement, reduce CMV visceral disease and improve survival. Whenever feasible, treatment should include systemic therapy. The ganciclovir ocular implant, which is effective for treatment of CMV retinitis, is no longer available. Routine (i.e., every 3 months) ophthalmologic follow-up is recommended after stopping chronic maintenance therapy for early detection of relapse or IRU, and then periodically after sustained immune reconstitution (AIII).

Treatment of AIDS-Associated Opportunistic Infections			
Chemoprophylaxis to Prevent First Episode	**Preferred Therapy**	**Alternative Therapy**	**Other Comments**
	• Valganciclovir 900 mg PO every 12 hours may be considered as initial therapy in mild diseases (CIII) • Duration: 21–42 days or until symptoms have resolved (CII) • Maintenance therapy is usually not necessary, but should be considered after relapses (BII). **Well-Documented, Histologically Confirmed CMV Pneumonia** • Experience for treating CMV pneumonitis in HIV patients is limited. Use of IV ganciclovir or IV foscarnet is reasonable (doses same as for CMV retinitis) (CIII). • The optimal duration of therapy and the role of oral valganciclovir have not been established. **CMV Neurological Disease** Note: Treatment should be initiated promptly. • Ganciclovir 5 mg/kg IV every 12 hours plus (foscarnet 90 mg/kg IV every 12 hours or 60 mg/kg IV every 8 hours) to stabilize disease and maximize response, continue until symptomatic improvement and resolution of neurologic symptoms (CIII) • The optimal duration of therapy and the role of oral valganciclovir have not been established.	probenecid.) ***Chronic Maintenance (for 3–6 months until ART induced immune recovery)*** • Foscarnet 90–120 mg/kg IV once daily (AI), or • Cidofovir 5 mg/kg IV every other week with saline hydration and probenecid as above (BI) **CMV Esophagitis or Colitis** • Foscarnet 90 mg/kg IV every 12 hours or 60 mg/kg every 8 hours (BI) for patients with treatment limiting toxicities to ganciclovir or with ganciclovir resistance, or • Valganciclovir 900 mg PO every 12 hours in milder disease and if able to tolerate PO therapy (BII), or • Duration: 21–42 days or until symptoms have resolved (CII) • For mild disease, if ART can be initiated without delay, consider withholding CMV therapy (CIII).	IRU may develop in the setting of immune reconstitution. Treatment of IRU Periocular, intravitreal, or short courses of systemic steroid (BIII) Initial therapy in patients with CMV retinitis, esophagitis, colitis, and pneumonitis should include initiation or optimization of ART (BIII).

Herpes Simplex Virus (HSV) Disease

Table 6.1f Treatment of HIV-Associated Opportunistic Infections

Treatment of AIDS-Associated Opportunistic Infections			
Chemoprophylaxis to Prevent First Episode	**Preferred Therapy**	**Alternative Therapy**	**Other Comments**
Not applicable	Orolabial Lesions (for 5–10 Days) • Valacyclovir 1 g PO twice a day **(AIII),** or • Famciclovir 500 mg PO twice a day **(AIII),** or • Acyclovir 400 mg PO three times a day **(AIII)** Initial or Recurrent Genital HSV (for 5–14 days) • Valacyclovir 1 g PO twice a day **(AI),** or • Famciclovir 500 mg PO twice a day **(AI),** or • Acyclovir 400 mg PO three times a day **(AI)** Severe Mucocutaneous HSV • Initial therapy acyclovir 5 mg/kg IV every 8 hours **(AIII)** • After lesions begin to regress, change to PO therapy as above. Continue until lesions are completely healed. *Chronic Suppressive Therapy For Patients with Severe Recurrences of Genital Herpes* (AI) *or Patients Who Want to Minimize Frequency of Recurrences* (AI) • Valacyclovir 500 mg PO twice a day **(AI),** or • Famciclovir 500 mg PO twice a day **(AI),** or • Acyclovir 400 mg PO twice a day **(AI)** • Continue indefinitely, regardless of CD4 count.	For Acyclovir-Resistant HSV *Preferred Therapy* • Foscarnet 80–120 mg/kg/day IV in two to three divided doses until clinical response **(AI)** Alternative Therapy (CIII) • IV cidofovir (dosage as in CMV retinitis), or • Topical trifluridine 1% three times a day, or • Topical cidofovir 1% once daily, or • Topical imiquimod 5% three times weekly, or • Topical foscarnet 1% five times daily Duration of Therapy • 21–28 days or longer	Patients with HSV infection can be treated with episodic therapy when symptomatic lesions occur, or with daily suppressive therapy to prevent recurrences. Extemporaneous compounding of topical products can be prepared using trifluridine ophthalmic solution and the IV formulation of cidofovir and foscarnet. An expanded access program of oral pritelivir is now available for immunocompromised patients with acyclovir-resistant HSV infection.

Malaria

Table 6.1g Treatment of HIV-Associated Opportunistic Infections

Treatment of AIDS-Associated Opportunistic Infections			
Chemoprophylaxis to Prevent First Episode	**Preferred Therapy**	**Alternative Therapy**	**Other Comments**
INDECATION: Travel to disease-endemic area Recommendations are the same for HIV infected and HIV-uninfected patients. Recommendations are based on the region of travel, malaria risks, and drug susceptibility in the region	Because Plasmodium falciparum malaria can progress within hours from mild symptoms or low-grade fever to severe disease or death, all HIV-infected patients with confirmed or suspected P. falciparum infection should be hospitalized for evaluation, initiation of treatment, and observation **(AIII).** Treatment recommendations for HIV infected patients are the same as for HIV uninfected patients **(AIII)**. Choice of therapy is guided by the degree of parasitemia, the species of Plasmodium, the patient's clinical status, region of infection, and the likely drug susceptibility of the infected	When suspicion for malaria is low, antimalarial treatment should not be initiated until the diagnosis is confirmed.	

Mycobacterium avium Complex (MAC) Disease

Table 6.1h Treatment of HIV-Associated Opportunistic Infections

Treatment of AIDS-Associated Opportunistic Infections			
Chemoprophylaxis to Prevent First Episode	**Preferred Therapy**	**Alternative Therapy**	**Other Comments**
CD4 count <50 cells/mm^3 Not recommended for those who immediately initiate ART **(AII)**. Recommended for those who are not on fully suppressive ART, after ruling out active disseminated MAC disease **(AI)**. Azithromycin 1,200 mg PO once weekly (AI), or Clarithromycin 500 mg PO BID **(AI)**, or Azithromycin 600 mg PO twice weekly **(BIII)**	At Least 2 Drugs as Initial Therapy to Prevent or Delay Emergence of Resistance • Clarithromycin 500 mg PO two times daily (AI) plus ethambutol 15 mg/kg PO daily **(AI),** or • If drug interaction or intolerance precludes the use of clarithromycin, (azithromycin 500–600 mg plus ethambutol 15 mg/kg) PO daily **(AII)** Duration • At least 12 months of therapy, can discontinue if no signs and symptoms of MAC disease and sustained (>6 months) CD4 count >100 cells/mm3 in response to ART	Some experts recommend addition of a third or fourth drug for patients with high mycobacterial loads (>2 log CFU/mL of blood), or in the absence of effective ART **(CIII)**. Third or Fourth Drug Options May Include • Rifabutin 300 mg PO daily (dose adjustment may be necessary based on drug interactions) **(CI),** or • A fluoroquinolone, such as moxifloxacin 400 mg PO daily (CIII) or levofloxacin 500 mg PO daily **(CIII),** or • An injectable aminoglycoside such as amikacin 10–15 mg/kg IV daily **(CIII)** or streptomycin 1 g IV or IM daily **(CIII)**	Testing of susceptibility to clarithromycin and azithromycin is recommended **(BIII)**. NSAIDs can be used for moderate to severe symptoms attributed to IRIS **(CIII).** If IRIS symptoms persist, short course (i.e., 4 weeks–8 weeks) systemic corticosteroid (equivalent to 20–40 mg prednisone) can be used **(CII).**

Pneumocystis Pneumonia (PCP)

Table 6.1i Treatment of HIV-Associated Opportunistic Infections

Treatment of AIDS-Associated Opportunistic Infections			
Chemoprophylaxis to Prevent First Episode	**Preferred Therapy**	**Alternative Therapy**	**Other Comments**
CD4 count <200cells/mm^3 **(AI),** or CD4 <14% **(BII),** or If ART initiation must be delayed, CD4 count≥200 cells/mm^3 but<250 cells/mm^3 and if monitoring of CD4 cell count every 3 months is not possible **(BII)** Note: Patients who are receiving pyrimethamine/sulfadiazine for treatment or suppression of toxoplasmosis do not require additional PCP prophylaxis **(AII)** **PREFERRED** TMP-SMXc 1 DS tablet PO daily **(AI),** or TMP-SMXc 1 SS tablet daily **(AI)** **ALTERNATIVE** • TMP-SMXc 1 DS PO three times weekly **(BI**), or •Dapsoned 100 mg PO daily or 50 mg PO BID **(BI),** or •Dapsoned 50 mg PO daily with (pyrimethaminee 50 mg plus leucovorin 25 mg) PO weekly **(BI),** or	Patients who develop PCP despite TMP-SMX prophylaxis can usually be treated with standard doses of TMPSMX **(BIII).** Duration of PCP treatment: 21 days **(AII)** **For Moderate-to-Severe PCP** • TMP-SMX: (TMP 15–20 mg and SMX 75–100mg)/kg/day IV given every 6 hours or every 8 hours **(AI);** may switch to PO formulations after clinical improvement **(AI).** **For Mild-to-Moderate PCP** • TMP-SMX: (TMP 15–20 mg and SMX 75–100 mg)/kg/day, given PO in 3 divided doses (AI), or • TMP-SMX: (160 mg/800 mg or DS) two tablets PO three times daily **(AI)** Secondary Prophylaxis, After Completion of PCP Treatment • TMP-SMX DS: 1 tablet PO daily **(AI),** or • TMP-SMX (80 mg/400 mg or SS): 1 tablet PO daily **(AI)**	**For Moderate-to-Severe PCP** • Pentamidine 4 mg/kg IV daily infused over ≥60 minutes **(AI);** can reduce dose to 3 mg/kg IV daily in the event of toxicities **(BI),** or • Primaquine 30 mg (base) PO daily plus (clindamycin 600 mg IV every 6 hours or 900 mg IV every 8 hours) or (clindamycin 450 mg PO every 6 hours or 600 mg PO every 8 hours) **(AI) For Mild-to-Moderate PCP** • Dapsone 100 mg PO daily plus TMP 5 mg/kg PO three times a day **(BI),** or • Primaquine 30 mg (base) PO daily plus (clindamycin 450 mg PO every 6 hours or 600 mg PO every 8 hours) **(BI),** or Atovaquone 750 mg PO twice daily with food **(BI)** Secondary Prophylaxis, After	**Indications for Adjunctive Corticosteroids (AI)** • PaO2 35 mmHg Prednisone Doses (Beginning as Early as Possible and Within 72 Hours of PCP Therapy) **(AI)** • Days 1–5: 40 mg PO twice daily • Days 6–10: 40 mg PO daily • Days 11–21: 20 mg PO daily IV methylprednisolone can be administered as 75% of prednisone dose. Benefit of corticosteroid if started after 72 hours of treatment is unknown, but some clinicians will use it for moderate-to-severe PCP **(BIII).** Whenever possible, patients should be tested for G6PD before use of dapsone or primaquine. Alternative therapy should be used in patients found to have G6PD deficiency. Patients who are receiving pyrimethaminea/sulfadiazine for treatment or suppression of toxoplasmosis do not require additional PCP prophylaxis **(AII).** If TMP-SMX is discontinued because of a mild adverse reaction, re-institution should be considered after the reaction resolves **(AII).** The dose can be increased

Treatment of AIDS-Associated Opportunistic Infections			
Chemoprophylaxis to Prevent First Episode	**Preferred Therapy**	**Alternative Therapy**	**Other Comments**
• (Dapsoned 200 mg plus pyrimethaminee 75 mg plus leucovorin 25 mg) PO weekly **(BI);** or •Aerosolized pentamidine 300 mg via Respigard II™ nebulizer every month **(BI),** or •Atovaquone 1,500 mg PO daily **(BI),** or •(Atovaquone 1,500 mg plus pyrimethaminee 25 mg plus leucovorin 10 mg) PO daily **(CIII)**		Completion of PCP Treatment • TMP-SMX DS: 1 tablet PO three times weekly **(BI),** or • Dapsone 100 mg PO daily **(BI),** or • Dapsone 50 mg PO daily with (pyrimethaminea 50 mg plus leucovorin 25 mg) PO weekly **(BI),** or • (Dapsone 200 mg plus pyrimethaminea 75 mg plus leucovorin 25 mg) PO weekly **(BI),** or • Aerosolized pentamidine 300 mg monthly via Respirgard II™ nebulizer **(BI),** or • Atovaquone 1,500 mg PO daily **(BI),** or • (Atovaquone 1,500 mg plus pyrimethaminea 25 mg plus leucovorin 10 mg) PO daily **(CIII)**	gradually (desensitization) **(BI),** reduced, or the frequency modified **(CIII).** TMP-SMX should be permanently discontinued in patients with possible or definite StevensJohnson Syndrome or toxic epidermal necrosis **(AII).**

Syphilis (Treponema pallidum Infection)

Table 6.1j Treatment of HIV-Associated Opportunistic Infections

Treatment of AIDS-Associated Opportunistic Infections			
Chemoprophylaxis to Prevent First Episode	**Preferred Therapy**	**Alternative Therapy**	**Other Comments**
Indication -For individuals exposed to a sex partner with a diagnosis of primary, secondary, or early latent syphilis within the past 90 days **(AII),** or -For individuals exposed to a sex partner >90 days before syphilis diagnosis in the partner, if serologic test results are not available immediately and the opportunity for follow-up is uncertain **(AIII)** **Preferred** Benzathine penicillin G 2.4 million units IM for 1 dose **(AII)** **Alternative** For penicillin-allergic patients: •Doxycycline 100 mg PO BID for 14 days **(BII),** or •Ceftriaxone 1 g IM or IV daily for 8–10 days **(BII),** or	**Early-Stage (Primary, Secondary, and Early-Latent Syphilis)** • Benzathine penicillin G 2.4 million units IM for 1 dose (AII) Late-Latent Disease (>1 year or of Unknown Duration, and No Signs of Neurosyphilis) Benzathine penicillin G 2.4 million units IM weekly for 3 doses **(AII)** **Late-Stage (Tertiary–Cardiovascular or Gummatous Disease)** • Benzathine penicillin G 2.4 million units IM weekly for 3 doses (AII) (Note: Rule out neurosyphilis before initiation of benzathine penicillin, and obtain infectious diseases consultation to guide management.) Neurosyphilis (Including Optic or Ocular Disease) • Aqueous crystalline penicillin G 18–24 million units per day (administered as 3–4 million units IV q4h or by continuous IV infusion) for 10–14 days (AII) +/- benzathine penicillin G 2.4 million units IM weekly for 3 doses after completion of IV therapy (CIII)	**Early-Stage (Primary, Secondary, and Early-Latent Syphilis) For penicillin-allergic patients** • Doxycycline 100 mg PO twice a day for 14 days **(BII),** or • Ceftriaxone 1 g IM or IV daily for 10–14 days **(BII),** or • Azithromycin 2 g PO for 1 dose (BII) (Note: Azithromycin is not recommended for men who have sex with men or pregnant women **[AII]**.) **Late-Latent Disease (>1 year or of Unknown Duration, and No Signs of Neurosyphilis) For penicillin-allergic patients** • Doxycycline 100 mg PO twice a day for 28 days (BIII) Neurosyphilis • Procaine penicillin 2.4 million units IM daily plus probenecid 500 mg PO four times a day for 10–14 days (BII) +/- benzathine penicillin G 2.4 million units IM weekly for 3 doses after	The efficacy of non-penicillin alternatives has not been evaluated in HIV-infected patients and they should be used only with close clinical and serologic monitoring. Combination of procaine penicillin and probenecid is not recommended for patients who are allergic to sulfa-containing medications **(AIII)**. The Jarisch-Herxheimer reaction is an acute febrile reaction accompanied by headache and myalgia that can occur within the first 24 hours after therapy for syphilis. This reaction occurs most frequently in patients with early syphilis, high nontreponemal titers, and prior penicillin treatment.

Treatment of AIDS-Associated Opportunistic Infections			
Chemoprophylaxis to Prevent First Episode	**Preferred Therapy**	**Alternative Therapy**	**Other Comments**
•Azithromycin 2 g PO for 1 dose **(BII)**—not recommended for men who have sex with men or pregnant people **(AII)**		completion of above **(CIII),** or • For penicillin-allergic patients: Desensitization to penicillin is the preferred approach **(BIII);** if not feasible, ceftriaxone, 2 g IV daily for 10–14 days **(BII)**	

Toxoplasma gondii Encephalitis

Table 6.1k Treatment of HIV-Associated Opportunistic Infections

Treatment of AIDS-Associated Opportunistic Infections			
Chemoprophylaxis to Prevent First Episode	**Preferred Therapy**	**Alternative Therapy**	**Other Comments**
Indication Toxoplasma IgG-positive patients with CD4 count<100 cells/μL **(AII)** Note: All regimens recommended for primary prophylaxis against toxoplasmosis also are effective as PCP prophylaxis. **Preferred** TMP-SMXa 1 DS PO daily **(AII).** **Alternative** TMP-SMXc 1 DS PO three times weekly **(BIII),** or • TMP-SMXc 1 SS PO daily **(BIII),** or •Dapsoned 50 mg PO daily plus (pyrimethaminee 50 mg plus leucovorin 25 mg) PO weekly **(BI)**, or • (Dapsoned 200 mg plus pyrimethaminee 75 mg plus leucovorin 25 mg) PO weekly **(BI),** or	**Treatment of Acute Infection (AI)** • Pyrimethamine a 200 mg PO one time, followed by weight-based therapy: Treatment of Acute Infection **(AI)** • Pyrimethamine a 200 mg PO one time, followed by weight-based therapy: o If <60 kg: pyrimethaminea 50 mg PO once daily plus sulfadiazine 1,000 mg PO every 6 hours plus leucovorin 10–25 mg PO once daily o If ≥60 kg: pyrimethamine a 75 mg PO once daily plus sulfadiazine 1,500 mg PO every 6 hours plus leucovorin 10–25 mg PO once daily • Leucovorin dose can be increased to 50 mg daily or twice a day. *Duration for Acute Therapy* • At least 6 weeks (BII); longer duration if clinical or radiologic disease is extensive or response is incomplete at 6 weeks • After completion of acute therapy, all patients should be initiated on chronic maintenance therapy.	**Treatment of Acute Infection** • Pyrimethaminea (leucovorin)* plus clindamycin 600 mg IV or PO every 6 hours **(AI),** or • TMP-SMX (TMP 5 mg/kg and SMX 25 mg/kg) IV or PO twice a day **(BI),** or • Atovaquone 1,500 mg PO twice a day with food plus pyrimethaminea (leucovorin)*(**BII),** or • Atovaquone 1,500 mg PO twice a day with food plus sulfadiazine 1,000–1,500 mg PO every 6 hours (weight-based dosing, as in preferred therapy) **(BII),** or • Atovaquone 1,500 mg PO twice a day with food **(BII),** Or Chronic Maintenance Therapy • Clindamycin 600 mg PO every 8 hours' plus (pyrimethaminea 25–50 mg plus leucovorin 10–25 mg) PO daily **(BI)**, or TMP-SMX DS 1 tablet twice a day **(BII),** or	If pyrimethamine is unavailable or there is a delay in obtaining it, TMP-SMX should be utilized in place of pyrimethamine sulfadiazine (BI). For patients with a history of sulfa allergy, sulfa desensitization should be attempted using one of several published strategies (BI). Atovaquone should be administered until therapeutic doses of TMP-SMX are achieved **(CIII).** Adjunctive corticosteroids (e.g., dexamethasone) should only be administered when clinically indicated to treat mass effect associated with focal lesions or associated edema **(BIII);** discontinue as soon as clinically feasible. Anticonvulsants should be administered to patients with a history of seizures **(AIII)** and continued through acute treatment, but should not be used as seizure prophylaxis **(AIII).** If clindamycin is used in place of sulfadiazine, additional therapy must be

Treatment of AIDS-Associated Opportunistic Infections			
Chemoprophylaxis to Prevent First Episode	**Preferred Therapy**	**Alternative Therapy**	**Other Comments**
• Atovaquone 1500 mg PO daily **(CIII),** or • (Atovaquone 1500 mg plus pyrimetaminee 25 mg plus leucovorin 10 mg) PO daily **(CIII)**	**Chronic Maintenance Therapy** • Pyrimethaminea 25–50 mg PO daily plus sulfadiazine 2,000–4,000 mg PO daily (in 2–4 divided doses) plus leucovorin 10–25 mg PO daily **(AI)**	• TMP-SMX DS 1 tablet once daily **(BII);** or • Atovaquone 750–1,500 mg PO twice a day plus (pyrimethaminea 25 mg plus leucovorin 10 mg) PO daily **(BII),** or • Atovaquone 750–1,500 mg PO twice a day plus sulfadiazine 2,000–4,000 mg PO daily (in 2–4 divided doses **(BII),** or • Atovaquone 750–1,500 mg PO twice a day with food **(BII)** * Pyrimethaminea and leucovorin doses are the same as for preferred therapy	added to prevent PCP **(AII).**

Varicella Zoster Virus (VZV) Disease

Table 6.1l Treatment of HIV-Associated Opportunistic Infections

Treatment of AIDS-Associated Opportunistic Infections			
Chemoprophylaxis to Prevent First Episode	**Preferred Therapy**	**Alternative Therapy**	**Other Comments**
	Primary Varicella Infection (Chickenpox) Uncomplicated Cases • Initiate as soon as possible after symptom onset and continue for 5–7 days: o Valacyclovir 1 g PO three times a day **(AII),** or o Famciclovir 500 mg PO three times a day **(AII)** **Severe or Complicated Cases** • Acyclovir 10 mg/kg IV every 8 hours for 7–10 days **(AIII)** • May switch to oral valacyclovir, famciclovir, or acyclovir after defervescence if no evidence of visceral involvement **(BIII).** Herpes Zoster (Shingles) **Acute Localized Dermatomal** • For 7–10 days; consider longer duration if lesions are slow to resolve Valacyclovir 1 g PO three times a day **(AII),** or • Famciclovir 500 mg three times a day **(AII)** **Extensive Cutaneous Lesion or Visceral Involvement** • Acyclovir 10 mg/kg IV every 8 hours until clinical improvement is evident **(AII)** • May switch to PO therapy (valacyclovir, famciclovir, or	Primary Varicella Infection (Chickenpox) Uncomplicated Cases (for 5–7 Days) • Acyclovir 800 mg PO five times a day **(BII)** Herpes Zoster (Shingles) Acute Localized Dermatomal • For 7–10 days; consider longer duration if lesions are slow to resolve • Acyclovir 800 mg PO five times a day **(BII)**	In managing VZV of the eyes, consultation with an ophthalmologist experienced in management of VZV retinitis is strongly recommended **(AIII).** Duration of therapy for VZV retinitis is not well defined, and should be determined based on clinical, virologic, and immunologic responses and ophthalmologic responses. Optimization of ART is recommended for serious and difficult-to-treat VZV infections (e.g., retinitis, encephalitis) **(AIII)**. In patients with herpes zoster ophthalmicus who have stromal keratitis and anterior uveitis, topical corticosteroids to reduce inflammation may be necessary. The role of ART has not been established in these cases.

Treatment of AIDS-Associated Opportunistic Infections			
Chemoprophylaxis to Prevent First Episode	**Preferred Therapy**	**Alternative Therapy**	**Other Comments**
	acyclovir) after clinical improvement (i.e., when no new vesicle formation or improvement of signs and symptoms of visceral VZV), to complete a 10- to 14-day course **(BIII).** ARN • Acyclovir 10 mg/kg IV every 8 hours for 10–14 days, followed by valacyclovir 1g PO three times a day for >14 weeks **(AIII),** plus • Intravitreal ganciclovir 2 mg/0.05 mL twice weekly for 1–2 doses **(BIII)** PORN • Acyclovir 10 mg/kg IV every 8 hours or ganciclovir 5 mg/kg IV every 12 hours **(AIII),** plus • ≥1 intravitreal antiviral injection: ganciclovir 2 mg/0.05 mL or foscarnet 1.2 mg/0.05 mL twice weekly **(AIII)** • Initiate or optimize ART **(AIII)**		

Mpox

Table 6.1m Treatment of HIV-Associated Opportunistic Infections

Treatment of AIDS-Associated Opportunistic Infections			
Chemoprophylaxis to Prevent First Episode	**Preferred Therapy**	**Alternative Therapy**	**Other Comments**
	• **For Severe Disease or at Risk for Severe Disease** Tecovirimat 600 mg PO Q 12 hours (<120 kg) or Q 8 hours (≥120 kg) for 14 days **(BIII)** within 30 minutes of a fattymeal; *or* • Tecovirimat 200 mg IV Q 12 hours for 14 days (<120 kg) or 300 mg IV Q 12 hours (≥ 120 kg), if concern exists regarding altered GI absorption capacity, inability to take PO, or extent of organ systems affected by mpox **(BIII).** *Adjunctive Therapy for Severe Disease or at Risk for Severe Disease* • Cidofovir 5 mg/kg/week IV for 2 doses with saline hydration before and after therapy and probenecid 2 g PO 3 hours before the dose followed by 1 g PO 2 hours after the dose, and 1 g PO 8 hours after the dose (total of 4 g) **(BIII),** *or*		ART should be initiated treatment as soon as possible **(AIII).** For severe disease, consider early intervention with adding one of the adjunctive therapies at the time of first medical encounter, in consultation with CDC or an expert in mpox treatment **(CIII)**. Patients with severe immunocompromise might benefit from extended treatment (i.e., >14 days) of preferred and/or adjunctive therapies if new confirmed mpox lesions occur or existing lesions worsen despite treatment. Vaccination with any live virus vaccines should be delayed until 3 months after VIGIV administration **(CIII).** People who received VIGIV shortly after a live virus vaccination should be revaccinated 3 months after administration of the immune globulin **(CIII).**

Treatment of AIDS-Associated Opportunistic Infections			
Chemoprophylaxis to Prevent First Episode	**Preferred Therapy**	**Alternative Therapy**	**Other Comments**
	• Brincidofovir 200 mg PO once weekly for 2 doses **(BIII),** *or* • VIGIV 6,000–9,000 units/kg IV single dose **(BIII)** ***Preferred Therapy for Ocular Mpox*** • Tecovirimat 600 mg PO Q 12 hours (<120 kg) or Q 8 hours (≥120 kg) for 14days **(CIII)** within 30 minutes of a fatty meal, *and* • Trifluridine (Viroptic) 1 drop into affected eye(s) Q 2 hours when awake (max: 9 drops/day) until re epithelialization, then Q 4 hours (min: 5 drops/day) for 7 days or until all periocular lesions have healed **(CIII)** • Prolonged use of trifluridine beyond 21 days might cause corneal epithelial toxicity and should be avoided **(AII).**		**Definition for Severe Disease or at Risk for Severe Disease:** People with HIV who are not virologically suppressed or who have CD4 counts <350 cells/mm^3 are considered at high risk for severe mpox. Severe mpox might manifest as hemorrhagic disease; large number of lesions such that they are confluent; sepsis; encephalitis; ocular or periorbital infections; or other conditions requiring hospitalization.

Leishmaniasis

Table 6.1n Treatment of HIV-Associated Opportunistic Infections

Treatment of AIDS-Associated Opportunistic Infections			
Chemoprophylaxis to Prevent First Episode	**Preferred Therapy**	**Alternative Therapy**	**Other Comments**
	Visceral		
	For Initial Infection • Liposomal amphotericin B 2–4 mg/kg IV daily **(AII)**, *or* • Liposomal amphotericin B interrupted schedule (e.g., 4 mg/kg on days 1–5, 10, 17, 24, 31, 38) **(AII)** • To achieve total dose of 20–60 mg/kg **(AII)** **Chronic Maintenance Therapy (Secondary Prophylaxis); Especially in Patients with CD4 Count <200 cells/mm³** • Liposomal amphotericin B 4 mg/kg every 2–4 weeks (AII), or • Amphotericin B lipid complex (AII) 3 mg/kg every 21 days (AII)	**For Initial Infection** • Other lipid formulation of amphotericin B, dose and schedule as in Preferred Therapy, *or* • Amphotericin B deoxycholate 0.5–1.0 mg/kg IV daily for total dose of 1.5–2.0 g **(BII)**, *or* • Sodium stibogluconate (pentavalent antimony) **(BII)** 20 mg/kg IV or IM daily for 28 days. • Miltefosine—if 30–44 kg: 50 mg two times daily; if ≥45 kg, 50 mg three times a day—for 28 days **(CIII)** **Chronic Maintenance Therapy (Secondary Prophylaxis)** • Sodium stibogluconate 20 mg/kg IV or IM every 4 weeks **(BII)**	ART should be initiated or optimized **(AIII).**

Treatment of AIDS-Associated Opportunistic Infections			
Chemoprophylaxis to Prevent First Episode	**Preferred Therapy**	**Alternative Therapy**	**Other Comments**
	Cutaneous		
	Liposomal amphotericin B 2–4 mg/kg IV daily for 10 days **(BIII),** *or* Liposomal amphotericin B interrupted schedule (e.g., 4 mg/kg on days 1–5, 10, 17, 24, 31, 38) to achieve total dose of 20–60 mg/kg **(BIII),** *or* Sodium stibogluconate 20 mg/kg IV or IM daily for 3–4 weeks **(BIII)** **Chronic Maintenance Therapy** May be indicated in immunocompromised patients with multiple relapses **(CIII)**	**Possible Options** Oral miltefosine (can be obtained via a treatment IND), *or* Topical paromomycin, *or* Intralesional sodium stibogluconate, *or* Local heat therapy No data exist for any of these agents in HIV-infected patients; choice and efficacy dependent on species of *Leishmania.*	None

References

1. Kaplan JE, Masur H, Holmes KK, et al. USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus: an overview. USPHS/IDSA Prevention of Opportunistic Infections Working Group. Clin Infect Dis. 1995;21 Suppl 1:S12-31. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8547500.
2. Bacchetti P, Moss AR. Incubation period of AIDS in San Francisco. Nature. 1989;338(6212):251-253. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2922052.
3. Alcabes P, Munoz A, Vlahov D, Friedland GH. Incubation period of human immunodeficiency virus. Epidemiol Rev. 1993;15(2):303-318. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8174659.
4. Bacchetti P, Osmond D, Chaisson RE, et al. Survival patterns of the first 500 patients with AIDS in San Francisco. J Infect Dis. 1988;157(5):1044-1047. Available at: https://www.ncbi.nlm.nih.gov/pubmed/3258900.
5. Palella FJ, Jr., Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med. 1998;338(13):853-860. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9516219.
6. Detels R, Munoz A, McFarlane G, et al. Effectiveness of potent antiretroviral therapy on time to AIDS and death in men with known HIV infection duration. Multicenter AIDS Cohort Study Investigators. JAMA. 1998;280(17):1497-1503. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9809730.

7. Mocroft A, Vella S, Benfield TL, et al. Changing patterns of mortality across Europe in patients infected with HIV-1. EuroSIDA Study Group. Lancet. 1998;352(9142):1725-1730. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9848347.
8. McNaghten AD, Hanson DL, Jones JL, Dworkin MS, Ward JW. Effects of antiretroviral therapy and opportunistic illness primary chemoprophylaxis on survival after AIDS diagnosis. Adult/Adolescent Spectrum of Disease Group. AIDS. 1999;13(13):1687-1695. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10509570.
9. Miller V, Mocroft A, Reiss P, et al. Relations among CD4 lymphocyte count nadir, antiretroviral therapy, and HIV-1 disease progression: results from the EuroSIDA study. Ann Intern Med. 1999;130(7):570-577. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10189326.
10. Mocroft A, Ledergerber B, Katlama C, et al. Decline in the AIDS and death rates in the EuroSIDA study: an observational study. Lancet. 2003;362(9377):22-29. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12853195.
11. Buchacz K, Lau B, Jing Y, et al. Incidence of AIDS-defining opportunistic infections in a multicohort analysis of HIV-infected persons in the United States and Canada, 2000-2010. J Infect Dis. 2016;214(6):862-872. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27559122.
12. Gardner EM, McLees MP, Steiner JF, Del Rio C, Burman WJ. The spectrum of engagement in HIV care and its relevance to test-and-treat strategies for prevention of HIV infection. Clin Infect Dis. 2011;52(6):793-800. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21367734.
13. Ives NJ, Gazzard BG, Easterbrook PJ. The changing pattern of AIDS-defining illnesses with the introduction of highly active antiretroviral therapy (HAART) in a London clinic. J Infect. 2001;42(2):134-139. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11531320.
14. Coelho L, Veloso VG, Grinsztejn B, Luz PM. Trends in overall opportunistic illnesses, Pneumocystis carinii pneumonia, cerebral toxoplasmosis and Mycobacterium avium complex incidence rates over the 30 years of the HIV epidemic: a systematic review. Braz J Infect Dis. 2014;18(2):196-210. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24275372.
15. Rubaihayo J, Tumwesigye NM, Konde-Lule J. Trends in prevalence of selected opportunistic infections associated with HIV/AIDS in Uganda. BMC Infect Dis. 2015;15:187. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25879621.
16. Centers for Disease Control and Prevention. HIV surveillance report: diagnoses of HIV infection in the United States and dependent areas, 2019. 2021.Available at: http://www.cdc.gov/hiv/library/reports/hiv-surveillance.html. Accessed: April 1, 2022.
17. Centers for Disease Control and Prevention. Monitoring selected national HIV prevention and care objectives by using HIV surveillance data—United States and 6 dependent areas, 2019. 2021.Available at: https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-report-vol-26-no-2.pdf. Accessed: April 1, 2022.
18. Panel on Antiretroviral Guidelines for Adults and Adolescents. Limitations to treatment safety and efficacy. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. 2022. Available at: https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/whats-new-guidelines.
19. Kelly C, Gaskell KM, Richardson M, Klein N, Garner P, MacPherson P. Discordant immune response with antiretroviral therapy in HIV-1: a systematic review of clinical outcomes. PLoS One. 2016;11(6):e0156099. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27284683.
20. Sonnenberg P, Glynn JR, Fielding K, Murray J, Godfrey-Faussett P, Shearer S. How soon after infection with HIV does the risk of tuberculosis start to increase? A retrospective cohort study in South African gold miners. J Infect Dis. 2005;191(2):150-158. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15609223.
21. Wood R, Maartens G, Lombard CJ. Risk factors for developing tuberculosis in HIV-1-infected adults from communities with a low or very high incidence of tuberculosis. J Acquir Immune Defic Syndr. 2000;23(1):75-80. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10708059.
22. Wallace JM, Hansen NI, Lavange L, et al. Respiratory disease trends in the Pulmonary Complications of HIV Infection Study cohort. Pulmonary Complications of HIV Infection Study Group. Am J Respir Crit Care Med. 1997;155(1):72-80. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9001292.

23. Hirschtick RE, Glassroth J, Jordan MC, et al. Bacterial pneumonia in persons infected with the human immunodeficiency virus. Pulmonary Complications of HIV Infection Study Group. N Engl J Med. 1995;333(13):845-851. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7651475.

24. Engels EA, Rosenberg PS, Biggar RJ. Zoster incidence in human immunodeficiency virus-infected hemophiliacs and homosexual men, 1984-1997. District of Columbia Gay Cohort Study. Multicenter Hemophilia Cohort Study. J Infect Dis. 1999;180(6):1784-1789. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10558932.

25. Gebo KA, Kalyani R, Moore RD, Polydefkis MJ. The incidence of, risk factors for, and sequelae of herpes zoster among HIV patients in the highly active antiretroviral therapy era. J Acquir Immune Defic Syndr. 2005;40(2):169-174. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16186734.

26. Vanhems P, Voisin L, Gayet-Ageron A, et al. The incidence of herpes zoster is less likely than other opportunistic infections to be reduced by highly active antiretroviral therapy. J Acquir Immune Defic Syndr. 2005;38(1):111-113. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15608535.

27. Toossi Z, Mayanja-Kizza H, Hirsch CS, et al. Impact of tuberculosis (TB) on HIV-1 activity in dually infected patients. Clin Exp Immunol. 2001;123(2):233-238. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11207653.

28. Sadiq ST, McSorley J, Copas AJ, et al. The effects of early syphilis on CD4 counts and HIV-1 RNA viral loads in blood and semen. Sex Transm Infect. 2005;81(5):380-385. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16199736.

29. Bentwich Z. Concurrent infections that rise the HIV viral load. J HIV Ther. 2003;8(3):72-75. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12951545.

30. Kublin JG, Patnaik P, Jere CS, et al. Effect of Plasmodium falciparum malaria on concentration of HIV-1-RNA in the blood of adults in rural Malawi: a prospective cohort study. Lancet. 2005;365(9455):233-240. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15652606.

31. Abu-Raddad LJ, Patnaik P, Kublin JG. Dual infection with HIV and malaria fuels the spread of both diseases in sub-Saharan Africa. Science. 2006;314(5805):1603-1606. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17158329.

32. Centers for Disease Control and Prevention. Guidelines for prophylaxis against Pneumocystis carinii pneumonia for persons infected with human immunodeficiency virus. MMWR Suppl. 1989;38(5):1-9. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2524643.

33. Masur H. Recommendations on prophylaxis and therapy for disseminated Mycobacterium avium complex disease in patients infected with the human immunodeficiency virus. Public Health Service Task Force on Prophylaxis and Therapy for Mycobacterium avium Complex. N Engl J Med. 1993;329(12):898-904. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8395019.

34. USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus: a summary. MMWR Recomm Rep. 1995;44(RR-8):1-34. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7565547.

35. USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus: disease-specific recommendations. USPHS/IDSA Prevention of Opportunistic Infections Working Group. Clin Infect Dis. 1995;21 Suppl 1:S32-43. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8547510.

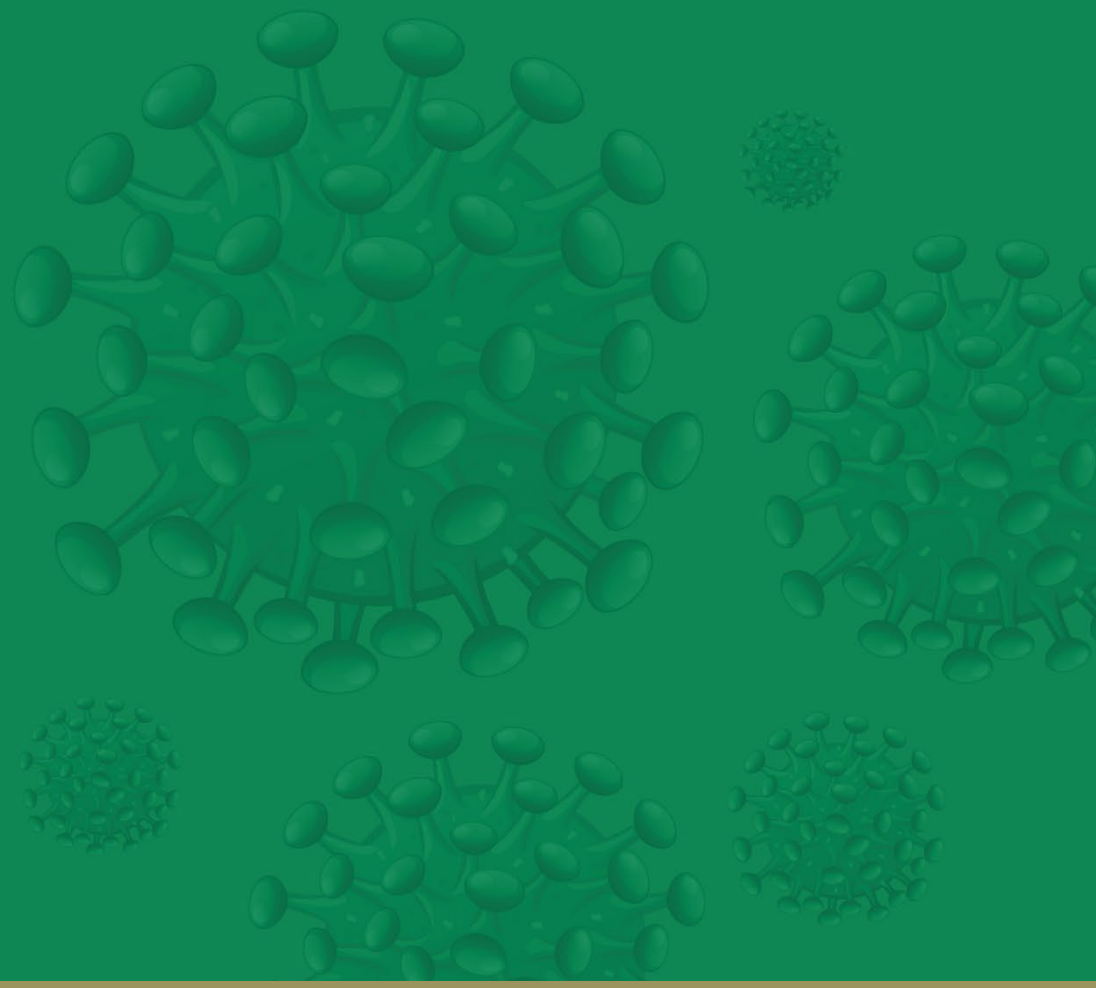
36. 1997 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with HIV: Part I. Prevention of exposure. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention. Am Fam Physician. 1997;56(3):823-834. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9301575.

37. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: Recommendations for a Public health approach. July 2021.

38. WHO guidelines for diagnosing, preventing and managing cryptococcal disease among adults, adolescents and children living with HIV. https://www.who.int/publications/i/item/9789240052178

CHAPTER 07

GUIDELINES FOR PREVENTION OF MOTHER TO CHILD TRANSMISSION (PMTCT) OF HIV



Guidelines for Prevention of Mother to Child Transmission (PMTCT) of HIV

Introduction

Globally, an estimated 1.3 million women and girls living with HIV become pregnant each year. In the absence of intervention, the rate of transmission of HIV from a mother living with HIV to her child during pregnancy, labor, delivery, or breastfeeding ranges from 15% to 45%. Identification of HIV infection should be immediately followed by an offer of linkage to lifelong treatment and care. This includes support to remain in care and virally suppressed, and an offer of partner services.

The elimination of MTCT of HIV is strongly supported by global commitments and the promotion of integration of prevention of MTCT intervention into maternal, child, and adolescent health services, as well as strengthened health systems.

Antenatal Care

A. Recommendations for Pregnant Women with Negative/Unknown HIV Status

- All pregnant women should be screened for HIV infection at the time of antenatal care entry (AII).
- Repeating the HIV test at the third trimester is recommended in high-risk women, e.g., injection drug users; HIV-positive partners with unsuppressed virus; signs or symptoms of acute HIV infection; presenting with other sexually transmitted infections (STIs) (AII), if the first screen was negative.
- An HIV test at the time of delivery is recommended if the patient's HIV status is unknown (AII).
- Pregnant women with a negative HIV test but still at high risk of acquiring the infection should be counseled about pre-exposure prophylaxis (PrEP) (AII). Early safety studies of PrEP among pregnant women without HIV infection are reassuring, and ongoing studies will contribute extensive new data to bolster the safety profile of PrEP use in pregnancy.
- For discordant couples, i.e., an HIV-positive male partner virally suppressed on antiretroviral therapy (ART) and an HIV-negative pregnant woman, condomless sex is allowed with no risk of HIV transmission (BI). This recommendation is based on prospective studies that demonstrated safer conception strategies to empower couples to safely conceive, and the PARTNER study, which showed no genetically

linked HIV transmissions between heterosexual couples while the partner with HIV was virally suppressed.

- Pregnant women have a higher risk of HIV acquisition, more so in late pregnancy (third trimester of pregnancy), during delivery, and the postpartum periods, than non-pregnant women. For this reason, if acute HIV infection is suspected, like in a high-risk group, a negative HIV Ag/Ab test should be followed by HIV plasma RNA (AIII).

B. Recommendations for Pregnant Women with Positive HIV Status

The clinical care for HIV-infected pregnant women is not different from the standard care for non-pregnant women. However, special considerations should be applied during pregnancy.

1. Pregnant Women Not on ART

- Pregnant women should be linked and engaged in clinical care early or rapidly after HIV diagnosis or once conceived if known to have HIV infection (AI).
- All pregnant women with HIV infection should be started on ART as soon as possible regardless of their CD4 cell counts, HIV RNA level, or availability of HIV genotype assay, to prevent MTCT of the virus (AI).
- Selection of ART regimen should be based on drug-drug interactions, drug pharmacokinetics during pregnancy, and the need to modify ART dose, as well as the available safety and efficacy clinical data from ART use in pregnant patients (AII).
- The potential benefits, adverse events, and fetal outcomes should be discussed with the patient before starting ART (AIII).

Recommended ART During Pregnancy

- Nucleoside reverse transcriptase inhibitor (NRTI) containing combination regimens; (abacavir [ABC] + lamivudine [3TC]), (tenofovir disoproxil fumarate [TDF] + either emtricitabine [FTC] or 3TC), or (tenofovir alafenamide [TAF] + either FTC or 3TC).
- Integrase strand transfer inhibitor (INI) based regimens with dolutegravir (DTG) once daily dose or raltegravir (RAL) twice daily dose.
- Ritonavir-boosted protease inhibitor (PI) based regimens with atazanavir/ritonavir (ATZ/r) once daily dose or darunavir/ritonavir (DRV/r) twice daily dose.
- Efavirenz-based regimen can be used as an alternative option during pregnancy but it is inferior to INI-based regimens which have a rapid virological response and are more likely to suppress the virus at the time of delivery.

ART NOT Recommended During Pregnancy:

- NNRTI: Oral rilpivirine (RPV) is recommended to be avoided due to low plasma level during the second and third trimesters with possible viral breakthroughs; needs regular follow up with every 1 – 2 months HIV RNA level. No sufficient data available for etravirine (ETR), injectable RPV, or doravirine (DOR) use in pregnancy.
- INI: Elvitegravir/cobicistat (EVG/c) have been linked to low plasma level and viral breakthroughs in the second and third trimesters. For this reason, EVG/c is not recommended for HIV-naïve pregnant women. No sufficient data to support the use of bictegravir (BIC) or cabotegravir (CAB) in pregnancy.
- PI: Lopinavir/ritonavir (LPV/r) is not recommended because it is associated with gastrointestinal side effects and needs twice daily dose. DRV/cobi has lower plasma levels and may give rise to virological failure!
- No sufficient data available for maraviroc (MVC), enfuvirtide (T-20), or ibalizumab (IBA) use in pregnancy.
- Cobicistat combined regimens are not recommended due to its low plasma level during pregnancy.
- Dual therapies, DTG/3TC or DTG/RPV, have no sufficient data to support their use in pregnancy yet.

2. Pregnant Women Taking ART

- Pregnant women who are taking ART and have suppressed HIV RNA can continue on their regimens unless those have no sufficient data supporting their use in pregnancy. The treating physician should counsel the patient about the benefit and risk of current versus alternative ART options.
- If the decision has been made to switch, the timing of the switch must take into account the half-life of the former ART.
- EVG/c, LPV/r, and RPV-based regimens can be continued if the patients have been already suppressed with close monitoring every 1 – 2 months with HIV RNA level.
- Pregnant women who are taking ART but have unsuppressed HIV RNA should be assessed for adherence, food requirements, and drug interactions. Resistance testing should be done and consider an alternative ART regimen if needed.

3. Laboratory Monitoring for Pregnant Women Living with HIV (PWLHIV)

- All PWLHIV should have a baseline HIV RNA level at the time of antenatal care entry (AI).
- After starting ART, the RNA level should be repeated in 2 to 4 weeks, then monthly, until achieving an undetectable level, then every 3 months (BI).
- The HIV RNA level should be repeated at 34 to 36 weeks' gestation (AII).

Intrapartum Care

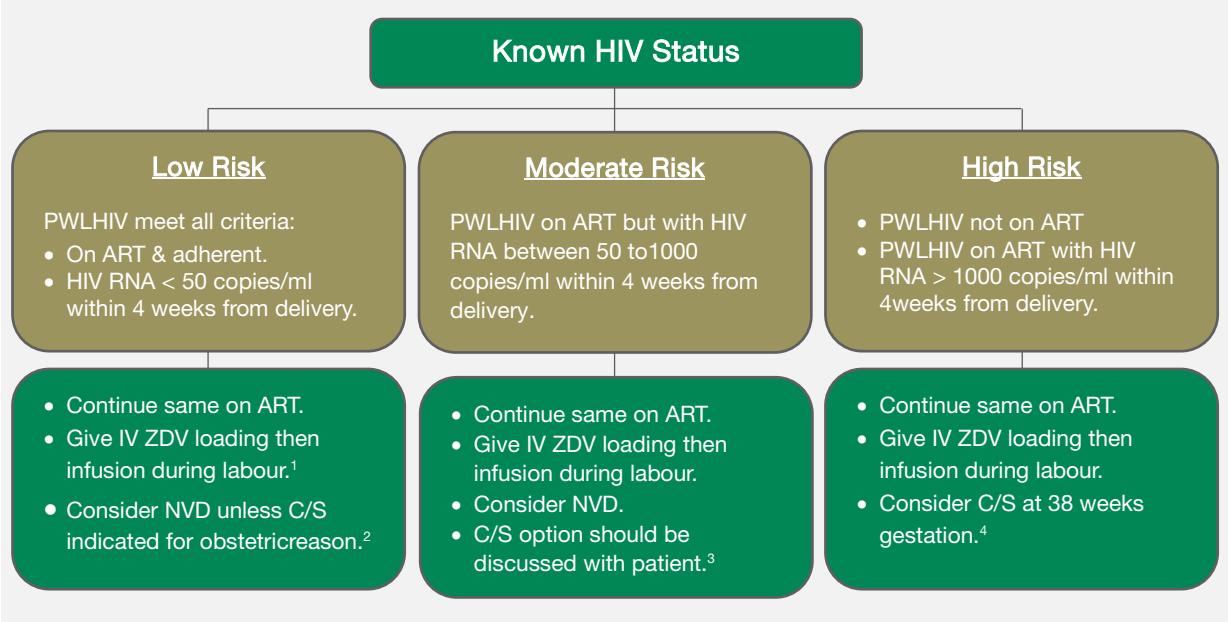
The management of a pregnant woman who comes in labor with known HIV status depends on her antenatal care background, including the received ART regimen and HIV RNA level at 36 weeks' gestation or within 4 weeks apart from the delivery.

A pregnant woman who comes in labor with unknown HIV status should be managed depending on her HIV infection risk, e.g., injection drug user; positive partner with unsuppressed virus; signs or symptoms of acute HIV infection; presenting with other sexually transmitted infections (STIs). Consult an HIV expert for case-by-case management.

In the case of premature or prolonged rupture of the membrane, the duration of membrane rupture of 4 or more hours is not a risk factor for perinatal transmission of HIV in women with a viral load < 1000 copies/mL receiving ART. Only a viral load > 10,000 copies/mL was found as an independent risk factor for perinatal transmission.

The MTCT risk of HIV with the use of intrapartum mother or fetal instruments or procedures is unclear. Most of the procedures, including forceps/vacuum use, artificial rupture of the membrane, amniocentesis, and delayed cord clamp, are considered low risk for perinatal transmission of HIV in women with suppressed virus on ART. Fetal invasive monitoring like fetal scalp electrodes may increase the risk of HIV transmission to the fetus if the mother was not on ART.

Fig. 7.1 Intrapartum Management of Pregnant Woman with Known HIV Status



1. Use of Intrapartum IV Zidovudine (ZDV) for Pregnant Women Living with HIV (PWLHIV): The current available data support the use of intrapartum IV Zidovudine (ZDV) for PWLHIV on ART who have an HIV RNA level greater than 1000 copies/ml within 4 weeks of labor. On the other hand, there is not enough evidence to support the use of IV ZDV if the viral load is less than 1000 copies/ml. However, a rebound in HIV viral load near delivery in previously suppressed pregnant women on ART can occur. IV ZDV should be given at a 2 mg/kg loading dose followed by continuous infusion at 1 mg/kg/hour until delivery.
2. Risk of Transmission for PWLHIV on ART: PWLHIV on ART with a suppressed virus have a low risk of transmitting the virus to their infant intrapartum.
3. Cesarean Section (C/S) Delivery: Cesarean section (C/S) delivery is associated with a high risk of complications compared to normal vaginal delivery (NVD). The mother should be counseled about the benefits and risks of the procedure in case of detectable HIV RNA but less than 1000 copies/ml, which is considered a low risk for HIV transmission compared to greater than 1000 copies/ml.
4. PWLHIV Not Receiving ART or with High HIV RNA: PWLHIV who are not receiving ART or have an HIV RNA level greater than 1000 copies/ml at the time of delivery have a high risk for MTCT of the virus. For this reason, a scheduled C/S is recommended at 38 weeks of gestation. The benefits and risks should be discussed with the mother. IV ZDV should be started at least 3 hours before the time of the section, with a 1-hour loading dose followed by a continuous infusion for 2 hours.

Postpartum Care

After delivery, Antiretroviral Therapy (ART) should be continued for the better health of the woman. ART regimens can be modified and simplified depending on the patient's preference, future pregnancy plans, and use of oral contraceptives. It is crucial to ensure patient adherence and engagement in care after delivery.

The safety of breastfeeding and the risk of HIV transmission if the mother is already on ART and has a suppressed virus is unclear. However, available data from the early ART era, when not all women were on ART and not all infants received prophylaxis, reported a risk of HIV transmission of 16.2% (95% CI, 6.5%-25.9%) from breastfeeding over a 2-year period. Therefore, breastfeeding is not recommended when there is an alternative feeding formula available.

The newborn infant of a PWLHIV should be assessed by a pediatric HIV expert and started on prophylaxis therapy soon after delivery.

References

1. Global heath strategy for women's ,children's and adolescents health, WHO (2016-2030)
2. Ministry of Health. Premarital Screening. https://www.moh.gov.sa/en/HealthAwareness/Beforemarriage/Pages/default.aspx
3. Bureau Of Experts At The Council Of Ministers. The System for the Prevention of Acquired Immunodeficiency syndrome (AIDS) and The Right and Duties of Those Infected. 2018. https://laws.boe.gov.sa/BoeLaws/Laws/LawDetails/9d240ae2-a709-48ee-ac82-a9ed0119f62d/1
4. Mofenson LM, Baggaley RC, Mameletzis I. Tenofovir disoproxil fumarate safety for women and their infants during pregnancy and breastfeeding. AIDS. 2017; 31(2): 213-32.
5. Joseph Davey DL, Pintye J, Baeten JM, et al; PrEP in Pregnancy Working Group. Emerging evidence from a systematic review of safety of pre-exposure prophylaxis for pregnant and postpartum women: where are we now and where are we heading? J Int AIDS Soc. 2020; 23(1): e25426.
6. Schwartz SR, Bassett J, Mutunga L, et al. HIV incidence, pregnancy, and implementation outcomes from the Sakh'umndeni safer conception project in South Africa: a prospective cohort study. Lancet HIV. 2019; 6(7): e438-e446.
7. Baza MB, Jerónimo A, Río I, et al. Natural Conception is Safe for HIV-Serodiscordant Couples with Persistent Suppressive Antiretroviral Therapy for the Infected Partner. J Womens Health (Larchmt). 2019; 28(11): 1555-62.
8. Rodger AJ, Cambiano V, Bruun T, et al. Sexual activity without condoms and risk of HIV transmission in serodifferent couples when the HIV-positive partner is using suppressive antiretroviral therapy. JAMA. 2016; 316(2): 171-81.
9. Thomson KA, Hughes J, Baeten JM, et al; Partners in Prevention HSV/HIV Transmission Study and Partners PrEP Study Teams. Increased Risk of HIV Acquisition Among Women Throughout Pregnancy and During the Postpartum Period: A Prospective Per-Coital-Act Analysis Among Women With HIV-Infected Partners. J Infect Dis. 2018; 218(1): 16-25.
10. Shapiro RL, Hughes MD, Ogwu A, et al. Antiretroviral regimens in pregnancy and breast-feeding in Botswana. NEJM. 2010; 362(24): 2282-94.
11. Veroniki AA, Antony J, Straus SE, et al. Comparative safety and effectiveness of perinatal antiretroviral therapies for HIV-infected women and their children: Systematic review and network meta-analysis including different study designs. PLoS One. 2018; 13(6) :e0198447.
12. Brooks KM, Momper JD, Pinilla M, et al; IMPAACT P1026s Protocol Team. Pharmacokinetics of tenofovir alafenamide with and without cobicistat in pregnant and postpartum women living with HIV. AIDS. 2021; 35(3): 407-17.
13. Pinnetti C, Baroncelli S, Villani P, et al. Rapid HIV-RNA decline following addition of raltegravir and tenofovir to ongoing highly active antiretroviral therapy in a woman presenting with high-level HIV viraemia at week 38 of pregnancy. J Antimicrob Chemother. 2010; 65(9): 2050-52.
14. McKeown DA, Rosenvinge M, Donaghy S, et al. High neonatal concentrations of raltegravir following transplacental transfer in HIV-1 positive pregnant women. AIDS. 2010; 24(15): 2416-18.
15. Waitt C, Orrell C, Walimbwa S, et al. Safety and pharmacokinetics of dolutegravir in pregnant mothers with HIV infection and their neonates: A randomised trial (DolPHIN-1 study). PLoS Med. 2019; 16(9): e1002895.
16. Caniglia EC, Patel K, Huo Y, et al; Pediatric HIVAIDS Cohort Study. Atazanavir exposure in utero and neurodevelopment in infants: a comparative safety study. AIDS. 2016; 30(8): 1267-78.
17. Floridia M, Ravizza M, Masuelli G, et al; Italian Group on Surveillance on Antiretroviral Treatment in Pregnancy. Atazanavir and lopinavir profile in pregnant women with HIV: tolerability, activity and pregnancy outcomes in an observational national study. J Antimicrob Chemother. 2014; 69(5): 1377-84.
18. Schalkwijk S, Ter Heine R, Colbers A, et al. Evaluating darunavir/ritonavir dosing regimens for HIV-positive pregnant women using semi-mechanistic pharmacokinetic modelling. J Antimicrob Chemother. 2019; 74(5): 1348-56.

19. João EC, Morrison RL, Shapiro DE, et al. Raltegravir versus efavirenz in antiretroviral-naive pregnant women living with HIV (NICHD P1081): an open-label, randomised, controlled, phase 4 trial. Lancet HIV. 2020; 7(5): e322-e331.

20. Kintu K, Malaba TR, Nakibuka J, et al; DolPHIN-2 Study Group. Dolutegravir versus efavirenz in women starting HIV therapy in late pregnancy (DolPHIN-2): an open-label, randomised controlled trial. Lancet HIV. 2020; 7(5): e332-e339.

21. Frange P, Tubiana R, Sibiude J, et al. Rilpivirine in HIV-1-positive women initiating pregnancy: to switch or not to switch? J Antimicrob Chemother. 2020; 75(5): 1324-31.

22. Bukkems V, Necsoi C, Tenorio CH, et al. Clinically significant lower elvitegravir exposure during third trimester of pregnant patients living with HIV: data from the PANNA study. Clin Infect Dis. 2020; ciaa488.

23. Momper J, Best BM, Wang J, et al. Elvitegravir/cobicistat pharmacokinetics in pregnant and postpartum women with HIV. AIDS. 2018; 32(17): 2507-16

24. Crauwels HM, Osiyemi O, Zorrilla C, Bicer C, Brown K. Reduced exposure to darunavir and cobicistat in HIV-1-infected pregnant women receiving a darunavir/cobicistat-based regimen. HIV Med. 2019; 20(5): 337-43.

25. Badell ML, Sheth AN, Momplaisir F, et al. A multicenter analysis of elvitegravir use during pregnancy on HIV viral suppression and perinatal outcomes. Open Forum Infect Dis. 2019; 6(4): ofz129.

26. Cotter AM, Brookfield KF, Duthely LM, Gonzalez Quintero VH, Potter JE, O'Sullivan MJ. Duration of membrane rupture and risk of perinatal transmission of HIV-1 in the era of combination antiretroviral therapy. Am J Obstet Gynecol. 2012; 207(6): 482 e481-485.

27. Peters H, Byrne L, De Ruiter A, et al. Duration of ruptured membranes and mother-to-child HIV transmission: a prospective population-based surveillance study. BJOG. 2015.

28. Mofenson LM, Lambert JS, Stiehm ER, et al. Risk factors for perinatal transmission of human immunodeficiency virus type 1 in women treated with zidovudine. Pediatric AIDS Clinical Trials Group Study 185 Team. NEJM. 1999; 341(6): 385-93.

29. Mandelbrot L, Mayaux MJ, Bongain A, et al. Obstetric factors and mother-to-child transmission of human immunodeficiency virus type 1: the French perinatal cohorts. SEROGEST French Pediatric HIV Infection Study Group. Am J Obstet Gynecol. 1996; 175(3 Pt 1): 661-67.

30. Myer L, Phillips TK, McIntyre JA, et al. HIV viraemia and mother-to-child transmission risk after antiretroviral therapy initiation in pregnancy in Cape Town, South Africa. HIV Med. 2017; 18(2): 80-88.

31. Briand N, Warszawski J, Mandelbrot L, et al. Is intrapartum intravenous zidovudine for prevention of mother-to-child HIV-1 transmission still useful in the combination antiretroviral therapy era? Clin Infect Dis. 2013; 57(6): 903-14.

32. Boucoiran I, Albert AYK, Tulloch K, et al. Human immunodeficiency virus viral load rebound near delivery in previously suppressed, combination antiretroviral therapy-treated pregnant women. Obstet Gynecol. 2017; 130(3): 497-501

33. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. NEJM. 1994; 331(18): 1173-80.

34. Garcia PM, Kalish LA, Pitt J, et al. Maternal levels of plasma human immunodeficiency virus type 1 RNA and the risk of perinatal transmission. Women and infants transmission study group. NEJM. 1999; 341(6): 394-402.

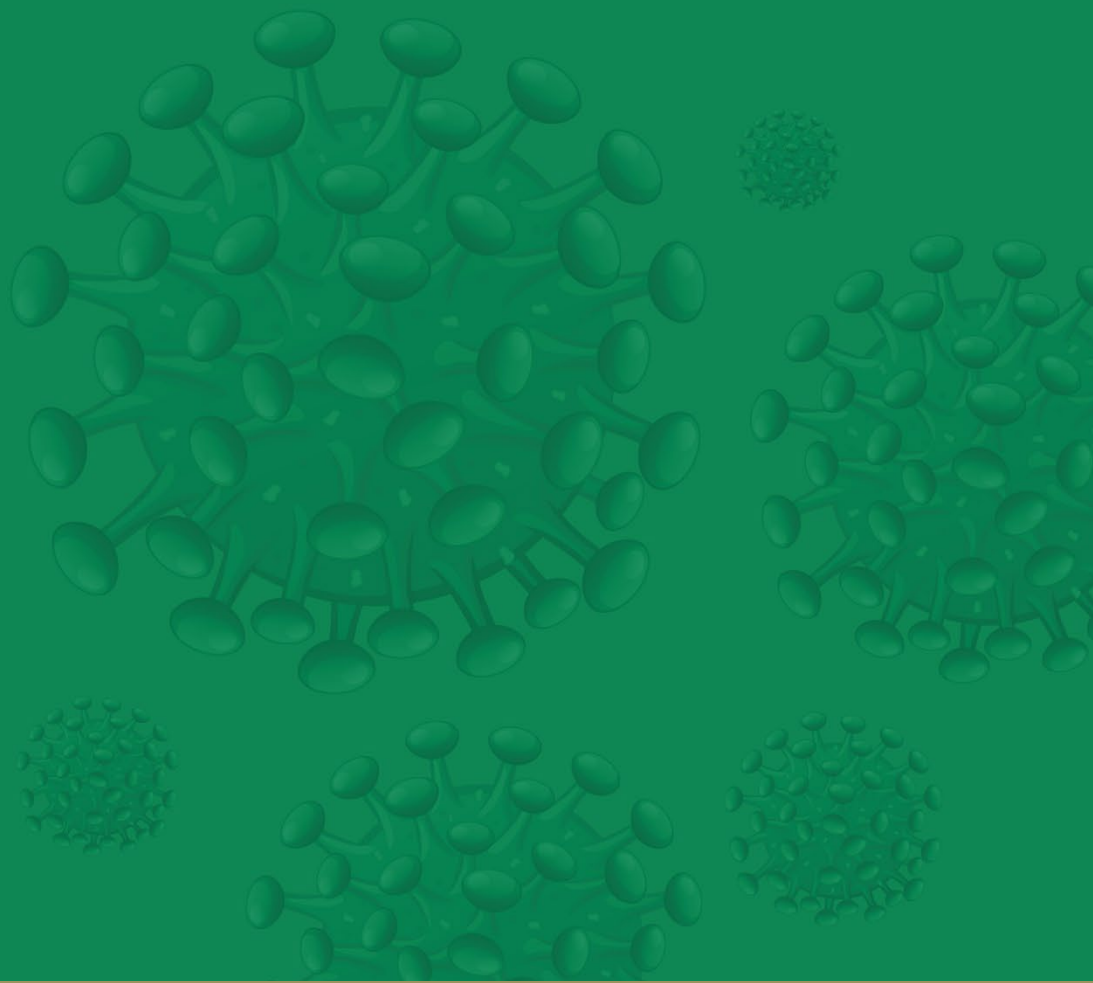
35. Briand N, Jasseron C, Sibiude J, et al. Cesarean section for HIV-infected women in the combination antiretroviral therapies era, 2000–2010. Am J Obstet Gynecol. 2013; 209(4): 335 e331-335 e312.

36. Aho I, Kaijomaa M, Kivela P, et al. Most women living with HIV can deliver vaginally: national data from Finland 1993-2013. PLoS One. 2018; 13(3): e0194370.

37. Nduati R, John G, Mbori-Ngacha D, et al. Effect of breastfeeding and formula feeding on transmission of HIV-1: a randomized clinical trial. JAMA. 2000;283(9): 1167-74.

CHAPTER 08

GENERAL CONSIDERATIONS FOR ANTIRETROVIRAL MANAGEMENT OF NEWBORNS EXPOSED TO HIV OR BORN WITH HIV



General Considerations for Antiretroviral Management of Newborns Exposed to HIV or Born with HIV

Introduction

All newborns who were exposed perinatally to HIV should receive postpartum antiretroviral (ARV) drugs to reduce the risk of transmission of HIV. The selection of the appropriate type of ARV regimens is determined based on maternal and infant factors that influence the risk of perinatal transmission of HIV. These regimens should be administered at doses that are appropriate for the infant's gestational age as close to the time of birth as possible, preferably within 6 hours of delivery.

Table 8.1 Neonatal Antiretroviral Management According to Risk of HIV Infection in the Newborn

Category	Description	Neonatal ARV Management
Low Risk of Perinatal HIV Transmission	Mothers who received ART during pregnancy with viral suppression (defined as a confirmed HIV RNA level <50 copies/mL) within 4 weeks prior to delivery and no concerns related to adherence	ZDV for 4 weeks[a]
Higher Risk of Perinatal HIV Transmission	Mothers who did not receive antepartum ARV drugs, mothers who received only intrapartum ARV drugs, mothers who received antepartum ARV drugs but did not have viral suppression (defined as a confirmed HIV RNA level <50 copies/mL) within 4 weeks prior to delivery, mothers with acute or primary HIV infection during pregnancy or breastfeeding (in which case, the mother should immediately discontinue breastfeeding)[b]	Presumptive HIV therapy using either ZDV, 3TC, and NVP (treatment dose) or ZDV, 3TC, and RAL administered from birth up to 6 weeks[c]
Presumed Newborn HIV Exposure	Mothers with unconfirmed HIV status who have at least one positive HIV test at delivery or postpartum, or mothers whose newborns have a positive HIV antibody test	ARV management as described above for newborns with a high risk of perinatal HIV transmission. Infant ARV drugs should be discontinued immediately if supplemental testing confirms that the mother does not have HIV.

Category	Description	Neonatal ARV Management
Newborn with HIV[d]	Positive newborn HIV virologic test/NAT	Three-drug ARV regimen using treatment doses.

Key: 3TC = lamivudine; ART = antiretroviral therapy; ARV = antiretroviral; NAT = nucleic acid test; NVP = nevirapine; Panel = Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission; RAL = raltegravir; ZDV = zidovudine.

[a]: ZDV prophylaxis regimen is recommended for infants born to mothers with HIV-2 mono-infection. Because HIV-2 is not susceptible to NVP, RAL should be considered for infants at high risk of perinatal HIV-2 transmission. [b]: Most Panel members would opt to administer presumptive HIV therapy to infants whose mothers had acute HIV during pregnancy because of the higher risk for in utero transmission. If acute HIV is diagnosed during breastfeeding, the mother should immediately discontinue breastfeeding. [c]: The optimal duration of presumptive HIV therapy in newborns who are at a high risk for perinatal HIV transmission is unknown. If possible, newborns who are at a high risk for HIV acquisition should receive ZDV for 6 weeks. Additional medications—such as 3TC, RAL, or NVP—may need to be administered for 2 to 6 weeks; the recommended duration for these drugs varies depending on infant HIV NAT results, maternal viral load at the time of delivery, and additional risk factors for HIV transmission. Consultation with an expert in pediatric HIV is recommended when selecting a therapy duration because this decision should be based on case-specific risk factors and interim infant HIV NAT results. [d]: Infant ART should be initiated without waiting for the results of confirmatory HIV NAT testing, given the low likelihood of a false-positive HIV NAT. However, the specimen for confirmatory HIV testing should be obtained prior to ART initiation.

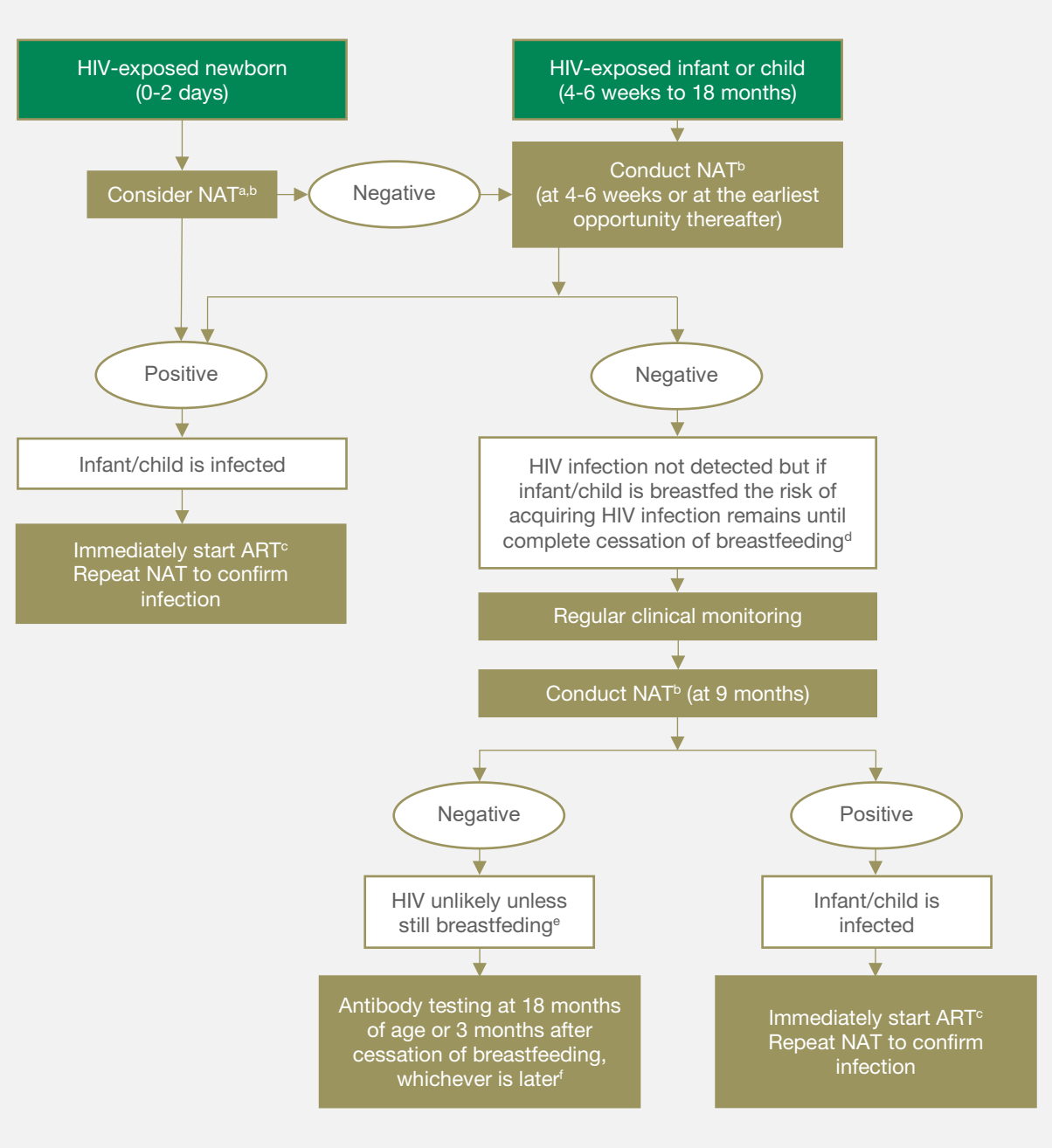
Guidelines for Management of HIV Infection in Infants & Children

Diagnosis of HIV Infection in Infants and Children

- Virologic assays (i.e., HIV RNA or HIV DNA nucleic acid tests [NATs]) that directly detect HIV must be used to diagnose HIV in infants and children aged less than 18 months with perinatal and postnatal HIV exposure; HIV antibody and HIV antigen/antibody tests should not be used.
- Plasma HIV RNA or cell-associated HIV DNA NATs are generally equally recommended (AII). However, the results of plasma HIV RNA NAT or plasma HIV RNA/DNA NAT can be affected by antiretroviral therapy (ART), or by antiretroviral (ARV) drugs administered to the infant as prophylaxis or presumptive HIV therapy.
- Virologic diagnostic testing is recommended for all infants with perinatal HIV exposure at the following ages:
    - 14 to 21 days
    - 1 to 2 months
    - 4 to 6 months
- For infants who are at high risk of perinatal HIV infection, virologic diagnostic testing is recommended at birth (AII) and at 2 to 6 weeks after ARV drugs are discontinued.

- A positive virologic test should be confirmed as soon as possible by a repeat virologic test.
- Definitive exclusion of HIV infection in non-breastfed infants is based on two or more negative virologic tests with one negative test obtained at age greater than or equal to 1 month and one at age greater than or equal to 4 months, or two negative HIV antibody tests from separate specimens that were obtained at age greater than or equal to 6 months.
- Infants with potential HIV exposure after birth (e.g., from breastfeeding, premasticated feeding, sexual abuse, contaminated blood products, percutaneous exposure) who are aged less than 18 months require additional testing using HIV RNA/DNA NAT assays to establish their HIV status. Infants aged greater than or equal to 18 months who have these potential exposures require HIV antibody testing.
- Age-appropriate HIV testing also is recommended for infants and children with signs and/or symptoms of HIV, even in the absence of documented or suspected HIV exposure.
- HIV antibody (or HIV antigen/antibody) tests are recommended for diagnostic testing in children with non-perinatal exposure only or in children with perinatal exposure aged greater than 24 months.

Fig. 8.1 Simplified Early infant diagnosis (EID) algorithm



Notes:

a. Based on 2016 WHO Consolidated ARV Guidelines10, addition of NAT at birth to the existing testing algorithm can be considered.

b. POC NAT can be used to diagnose HIV infection as well as to confirm positive results.

c. Start ART without delay. At the same time, retest to confirm infection. As maternal treatment is scaled up and MTCT transmission rates decrease, false-positive results are expected to increase: retesting after a first positive NAT is hence important to avoid unnecessary treatment, particularly in settings with lower transmission rates. If the second test is negative, a third NAT should be performed before interrupting ART.

d. For children who were never breastfed, additional testing following a negative NAT at 4–6 weeks is included in this algorithm to account for potential false-negative NAT results.

e. The risk of HIV transmission remains as long as breastfeeding continues. If the 9-month test is conducted earlier than 3 months after cessation of breastfeeding, infection acquired in the last days of breastfeeding may be missed. Retesting at 18 months or 3 months after cessation of breastfeeding (whichever is later) should be carried out for final assessment of HIV status.

f. If breastfeeding extends beyond 18 months, the final diagnosis of HIV status can only be assessed at the end of breastfeeding. If breastfeeding ends before 18 months, the final diagnosis of HIV status with antibody testing can only be assessed at 18 months. Antibody testing should be undertaken at least 3 months after cessation of breastfeeding (to allow for development of HIV antibodies). For infants younger than 18 months of age NAT should be performed to confirm infection. If the infant is older than 18 months, negative antibody testing confirms that the infant is uninfected; positive antibody testing confirms infant is infected.

Clinical and Laboratory Monitoring of Pediatric HIV Infection

- An absolute CD4 T lymphocyte (CD4) cell count and plasma HIV RNA (viral load) should be measured at the time of HIV diagnosis. If a child is not started on antiretroviral therapy (ART) after diagnosis, this monitoring should be repeated at least every 3 to 4 months thereafter. An absolute CD4 count is recommended for monitoring immune status in children of all ages, with CD4 percentage as an alternative for children aged less than 5 years.
- Antiretroviral (ARV) drug-resistance testing is recommended at the time of HIV diagnosis and before initiation of therapy in all ART-naive patients. Genotypic resistance testing is preferred for this purpose.
- After initiation of ART or after a change in ARV regimen, children should be evaluated for clinical adverse effects and should receive support for treatment adherence within 1 to 2 weeks. Laboratory testing for toxicity and viral load response is recommended at 2 to 4 weeks after treatment initiation.
- Children on ART should be monitored for therapy adherence, effectiveness, and toxicities routinely (every 3 to 4 months).
- Additional CD4 count and plasma viral load monitoring should be performed to evaluate children with suspected clinical, immunologic, or virologic deterioration or to confirm an abnormal value.
- CD4 count can be monitored less frequently (every 6 to 12 months) in children and adolescents who are adherent to therapy, who have sustained virologic suppression and CD4 count values that are well above the threshold for opportunistic infection risk, and who have stable clinical status. Viral load measurement every 3 to 4 months is generally recommended to monitor ART adherence and disease progression.
- Phenotypic resistance testing should be considered (usually in addition to genotypic resistance testing) for patients with known or suspected complex drug resistance mutation patterns, which generally arise after a patient has experienced virologic failure on multiple ARV regimens.

- The absence of detectable resistance to a drug does not ensure that use of the drug will be successful, because mutations may not be detected once the drug has been discontinued. A history of all previously used ARV agents and available resistance test results must be reviewed when making decisions regarding the choice of new ARV agents.
- Viral co-receptor tropism assays are recommended whenever a CCR5-antagonist is being considered for treatment. The use of tropism assays also should be considered for patients who demonstrate virologic failure while receiving therapy that contains a CCR5 antagonist.

Table 8.2 Sample Schedule for Clinical and Laboratory Monitoring of Children Before and After Initiation of Antiretroviral Therapy

	Entry into care	ART Initiation	Weeks 1-2 on Therapy	Weeks 2-4 on Therapy	Every 3-4 months	Only required every 6-12 months	ARV switch
History and Physical	√	√	√	√	√	√	√
Adherence evaluation		√	√	√	√		√
CD4 count*	√	√			√		√
Plasma viral load	√	√		√	√		√
Resistance testing	√						√
CBC with Differential	√	√		√	√		√
Albumin level	√						
Renal profile	√	√		√	√		√
Hepatic profile	√	√		√	√		√

	Entry into care	ART Initiation	Weeks 1-2 on Therapy	Weeks 2-4 on Therapy	Every 3-4 months	Only required every 6-12 months	ARV switch
Random blood glucose	√					√	
Lipid profile (fasting)	√					√	
Thyroid function tests	√						
Hepatitis B screening	√						√
Urinalysis	√					√	
Review immunization	√	√	√	√	√	√	√

N.B. - Absolute CD4 count is recommended for monitoring immune status in children with HIV of all ages, with CD4 percentage as an alternative for children aged <5 years

- Additional CD4 count, and plasma viral load monitoring should be performed to evaluate children with suspected clinical, immunologic, or virologic deterioration or to confirm an abnormal value (AIII). CD4 count can be monitored less frequently (every 6–12 months) in children and adolescents who are adherent to therapy, who have sustained virologic suppression and CD4 count values that are well above the threshold for opportunistic infection risk, and who have stable clinical status. Viral load measurement every 3 to 4 months is generally recommended to monitor ART adherence.
- Antiretroviral (ARV) drug-resistance testing is recommended at the time of HIV diagnosis, before initiation of therapy in all ART-naive patients, and before switching regimens in patients with treatment failure. Genotypic resistance testing is preferred for this purpose (Review the history of all previously used ARVs and available resistance test results when making decisions about choice of new ARVs, because mutations may not be detected once the prior drugs have been discontinued).
- After initiation of ART or after a change in ARV regimen, children should be evaluated for clinical adverse effects and should receive support for treatment adherence within 1 week to 2 weeks; laboratory testing for toxicity and viral load response is recommended at 2 to 4 weeks after treatment initiation or change in ARV regimen.

Treatment Recommendations for Initiation of Therapy in Antiretroviral-Naive, HIV Infected Infants and Children

- Antiretroviral therapy (ART) should be initiated in all infants and children with HIV infection. Rapid ART initiation, defined as initiating ART immediately or within days of diagnosis, accompanied by a discussion of the importance of adherence, and provision of subsequent adherence support is recommended for all children with HIV.
- If a child with HIV has not initiated ART, health care providers should closely monitor the virologic, immunologic, and clinical status at least every 3 to 4 months.

Treatment Recommendations for Initiation of Therapy in Antiretroviral-Naive, HIV Infected Infants and Children

- The selection of an initial antiretroviral (ARV) regimen should be individualized based on several factors, including the characteristics of the proposed regimen, the patient's characteristics, drug efficacy, potential adverse effects, patient and family preferences, and the results of viral resistance testing.
- When developing recommendations for specific drugs or regimens, the following information should be considered:
    - Data demonstrating durable viral suppression, immunologic improvement, and clinical improvement (when available) with the drug or regimen, preferably in children, as well as adults.
    - The extent of pediatric experience with a specific drug or regimen.
    - The incidence and types of short-term and long-term drug toxicity in people who are taking the drug or regimen, focusing on toxicities that are reported in children.
    - The availability and acceptability of formulations that are appropriate for pediatric use, including palatability, ease of preparation (e.g., syrups vs. powders or dispersible tablets), pill size, and the number of pills or volume of oral solution needed for an appropriate dose.
    - Dosing frequency, and food and fluid requirements; and the potential for drug interactions with other medications.
- For treatment-naive children, initiating antiretroviral therapy with three drugs: a dual-nucleoside/nucleotide reverse transcriptase inhibitor backbone plus an integrase strand transfer inhibitor, a non-nucleoside reverse transcriptase inhibitor, or a boosted protease inhibitor.

- Recommended drugs or drug combinations fall into one of two categories:
    - **Preferred**: Drugs or drug combinations are designated as Preferred for use in treatment-naive children when clinical trial data in children or, more often, in adults have demonstrated optimal and durable efficacy with acceptable toxicity and ease of use and pediatric studies using surrogate markers have demonstrated safety and appropriate drug exposure. Additional considerations are listed above.
    - **Alternative**: Drugs or drug combinations are designated as Alternative for initial therapy when clinical trial data in children or adults show efficacy, but the drugs or drug combinations have disadvantages when compared with Preferred regimens. Drugs or drug combinations may be classified as Alternative for use in treatment-naive children if they are less effective or durable than a Preferred regimen in adults or children; if specific concerns exist about toxicity, dosing, formulation, administration, or interaction; or if experience with the use of these drugs or drug combinations in children is limited.
- **Table 8.3** provides a list of Recommended ARV regimens that are designated as Preferred or Alternative; recommendations vary by a patient's age, weight, and sexual maturity rating (SMR).

Table 8.3 Preferred Initial Regimens Based on Age and Weight at Time of Treatment Initiation

Age	Weight Restriction	Regimens	FDC Available
Newborns, Birth to Age <14 Days[a,b]	None	Two NRTIs **plus** NVP	No
	≥2 kg	Two NRTIs **plus** RAL[c]	No
Neonates ≥14 Days to Age <4 weeks	None	Two NRTIs **plus** LPV/r[b]	No
	≥2 kg	Two NRTIs **plus** RAL[c]	No
Infants and Children Aged ≥4 Weeks	³3 kg	Two NRTIs **plus** DTG[d]	No
		Two NRTIs **plus** DTG[d]	Yes (≥10 kg)
Children Aged ≥2 Years	≥14 kg	Two NRTIs **plus** BIC[e]	Yes
Adolescents Aged ≥12 Years with SMRs of 4 or 5	Refer to the Adult and Adolescent Antiretroviral Guidelines		Yes

Table 8.4 Preferred Dual-NRTI Backbone Options for Use in Combination with Other Drugs

Age	Dual-NRTI Backbone Options	FDC Available
Neonates Aged Birth to 1 Month	ABC **plus** (3TC **or** FTC)[f]	No[g]
	ZDV **plus** (3TC **or** FTC)[h]	No[g]
Infants and Children Aged >1 Month to <2 Years	ABC **plus** (3TC **or** FTC)[f]	Yes
Children and Adolescents Aged ≥2Years with SMRs of 1–3	ABC **plus** (3TC **or** FTC)[f]	Yes
	FTC/TAFi in children and adolescents weighing ≥14 kg and receiving a regimen that contains an INSTI or an NNRTI FTC/TAFi in children and adolescents weighing ≥35 kg and receiving a regimen that contains a boosted PI	Yes
Adolescents Aged ≥12 Years with SMRs of 4 or 5	Refer to the Adult and Adolescent Antiretroviral Guidelines	Yes

Table 8.5 Alternative Regimens Based on Age and Weight at Time of Treatment Initiation

Age	Weight Restriction	Regimens	FDC Available
Neonates, Infants, and Children Aged ≥14 Days to <3 Years	None	Two NRTIs **plus** NVP[j]	No
Infants and Children Aged ³4 Weeks to <3 Months	None	Two NRTIs **plus** LPV/r[b]	No
	≥2 kg	Two NRTIs **plus** RAL[c]	No
Infants and Children Aged ≥3Months to <3 Years	None	Two NRTIs **plus** ATV/[r]	No
	None	Two NRTIs **plus** LPV/r[b]	No
	None	Two NRTIs **plus** RAL[c]	No
Children Aged ≥3 Years	None	Two NRTIs **plus** ATV/[r]	No
	None	Two NRTIs **plus** DRV/rk	No
	None	Two NRTIs **plus** EFVl	No[g]
	None	Two NRTIs **plus** LPV/r[b]	No
	≥25 kg	Two NRTIs **plus** EVG/c[m]	Yes
	≥35 kg	Two NRTIs **plus** DOR[n]	Yes
Adolescents Aged ≥12 Years with SMRs of 1–3	None	Two NRTIs **plus** ATV/r	No
	None	Two NRTIs **plus** DRV/r[k]	No
	None	Two NRTIs **plus** EFV[l]	Yes
	None	Two NRTIs **plus** LPV/r[b]	No
	None	Two NRTIs **plus** RAL[c]	No
	≥25 kg	Two NRTIs **plus** EVG/c[m]	Yes
	≥35 kg	Two NRTIs **plus** ATV/c[o]	No
		Two NRTIs **plus** DOR[n]	Yes
		Two NRTIs **plus** RPV[p]	Yes
	≥40 kg	Two NRTIs **plus** DRV/c[q]	Yes
Adolescents Aged ≥12 Years with SMRs of 4 or 5	Refer to the Adult and Adolescent Antiretroviral Guidelines		Yes

Table 8.6 Alternative Dual-NRTI Backbone Options for Use in Combination with Other Drugs

Age	Dual-NRTI Backbone Options	FDC Available
Infants and Children Aged ≥1 Month to <6 Years	ZDV **plus** (3TC **or** FTC)[h]	No[g]
	ZDV **plus** ABC[f]	No
Children Aged ≥2 Years to 12 Years	TDF **plus** (3TC **or** FTC)[r]	Yes
Children and Adolescents Aged ≥6 Years and SMRs of 1–3	ZDV **plus** (3TC **or** FTC)[h]	Yes
	ZDV **plus** ABC[f]	No

a) If treatment is scheduled to begin before a patient is aged 14 days, NVP or RAL are Preferred agents because they are the only options with dosing information available for this age group. Although many pediatric experts favor initiating antiretroviral therapy as soon as possible after birth to limit the establishment of viral reservoirs, available clinical trial data do not suggest that initiating treatment within the first 14 days of life leads to better clinical outcomes than initiating treatment after 14 days of age. Clinicians should consult an expert in pediatric HIV infection before initiating treatment in infants aged <14 days. Additional considerations regarding the use of NVP or RAL in infants aged <14 days can be found in Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection. Switching from NVP to LPV/r should be considered when the infant is aged ≥14 days with a postmenstrual age of 42 weeks (the span of time between the first day of the mother's last menstrual period and birth, plus the time elapsed after birth); LPV/r has produced better clinical outcomes than NVP in studies of children aged <3 years. Data are limited on the clinical outcomes of using RAL in infants and children aged <2 years.

b) In general, LPV/r should not be administered to neonates before a postmenstrual age of 42 weeks and a postnatal age of ≥14 days (see the Lopinavir/Ritonavir section in Appendix A: Pediatric Antiretroviral Drug Information). Some experts would choose not to start with LPV/r as a Preferred initial regimen in neonates aged ≥14 days to <4 weeks but would choose to start with NVP instead.

c) RAL granules can be administered to infants and children weighing ≥2 kg from birth to age 2 years. Oral RAL granules can be used up to a dose of 100 mg in the 14 kg to <20 kg weight band. RAL pills or chewable tablets can be used in children aged ≥2 years. Chewable RAL tablets can be crushed and dispersed in liquid and administered to infants as young as 4 weeks of age who weigh at least 3 kg.

d) DTG is recommended as a Preferred agent for infants, children, and adolescents aged ≥4 weeks and weighing ≥3 kg. DTG dispersible tablets can be administered in infants and children aged ≥4 weeks and weighing ≥3 kg. DTG film-coated tablets can be used in children weighing ≥14 kg. An FDC that contains ABC/DTG/3TC is available in dispersible tablets (Triumeq PD) for children weighing ≥10 kg to <25 kg and in a single tablet to be swallowed (Triumeq) for children weighing ≥25 kg. See Dolutegravir for information about dosing and administration.

e) BIC is available only as part of an FDC tablet that contains BIC/FTC/TAF; this FDC tablet is recommended as a Preferred regimen for children weighing ≥14 kg. Two strengths of BIC/FTC/TAF are available, with dosing according to a child's weight (see Bictegravir).

f) [f] ABC is not approved by the U.S. Food and Drug Administration (FDA) for use in full-term neonates and infants aged <3 months. Recent data from the IMPAACT P1106 trial and two observational cohorts provide reassuring data on the safety of ABC in infants when initiated at the age of <3 months (see Abacavir). Before ABC administration, a negative HLA-B 5701 allele test should be available. An FDC tablet that contains ABC/3TC (Epzicom and generic) is available for use in children weighing ≥25 kg.

g) FDA-approved FDC tablets are not included in this table when they are not approved for use in the specific patient populations being discussed.

h) [h] An FDC tablet that contains 3TC/ZDV (Combivir and generic) is available for use in children weighing ≥30 kg. Some members of the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) prefer ABC over ZDV because ABC can be dosed once daily.

i) FTC plus TAF is recommended as a Preferred NRTI combination for children and adolescents weighing ≥14 kg when used with an INSTI or NNRTI; an FDC tablet that contains FTC/TAF (Descovy) is available in two strengths, with dosage determined by a child's weight (see Tenofovir Alafenamide). FTC/TAF is approved by the FDA for children weighing ≥14 kg when used in the regimen BIC/FTC/TAF, which is also available in two strengths, with dosage determined by a child's weight. EVG/c/FTC/TAF is approved for use in children weighing ≥25 kg. FTC/TAF is a Preferred NRTI combination for children and adolescents weighing ≥35 kg when used with a boosted PI; FTC/TAF is not approved or recommended for use with a boosted PI in children weighing <35 kg.

j) NVP should not be used in post-pubertal girls with T lymphocyte cell counts >250/mm3, unless the benefit clearly outweighs the risk. NVP is approved by the FDA for the treatment of infants aged ≥15 days.

k) DRV should only be used in children weighing ≥10 kg. Once-daily DRV should not be used in children aged <12 years or weighing <40 kg. Once-daily DRV should also not be used when any one of the following resistance-associated substitutions are present: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, and L89V. DRV/r is recommended as an Alternative drug combination for children aged ≥6 years to <12 years and weighing >25 kg because there are other drugs that can be administered once daily and that are better tolerated. Note that DRV/r can be administered once daily in adolescents aged ≥12 years and weighing ≥40 kg who are not sexually mature (SMR 1–3).

l) EFV is approved by the FDA for use in children aged ≥3 months and weighing ≥3.5 kg, but it is not recommended by the Panel for initial therapy in children aged ≥3 months to 3 years. FDC tablets that contain EFV/FTC/TDF (Atripla) and EFV 600 mg/3TC/TDF (Symfi) are available. See the Efavirenz section in Appendix A: Pediatric Antiretroviral Drug Information for information about use of the FDC EFV 400 mg/3TC/TDF (Symfi Lo).

m) EVG is currently recommended only as a component of FDC tablets. Tablets that contain EVG/c/FTC/TAF (Genvoya) are recommended as an Alternative regimen for children and adolescents weighing ≥25 kg due to multiple drug–drug interactions from COBI and a lower barrier to the development of resistance to EVG.

n) DOR is not FDA approved for pediatric use. Based on data from studies that evaluated the efficacy and tolerability of DOR in adults, as well as early findings from pediatric PK studies, the Panel recommends DOR as an Alternative ARV for children and adolescents weighing ≥35 kg. An FDC tablet containing DOR/3TC/TDF is available.

o) ATV/c is available as an FDC tablet containing ATV/c (Evotaz) that has been approved by the FDA for use in children and adolescents weighing ≥35 kg.

p) [p] RPV should be administered to adolescents aged ≥12 years and weighing ≥35 kg who have initial viral loads ≤100,000 copies/mL. FDC tablets that contain FTC/RPV/TAF (Odefsey) and FTC/RPV/TDF (Complera) are available.

q) DRV/c is available as part of an FDC tablet containing DRV/c/FTC/TAF (Symtuza) that has been approved by the FDA for use in children and adolescents weighing ≥40 kg.

r) [r] An FDC tablet that contains FTC/TDF (Truvada) is available.

Key: 3TC = lamivudine; ABC = abacavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDC = fixed-dose combination; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic; RAL = raltegravir; RPV = rilpivirine; SMR = sexual maturity rating; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

Management of Medication Toxicity or Intolerance

- Consultation with a Pediatric infectious disease specialist is recommended for all children who develop toxicity and intolerance.
- In children with HIV who have severe or life-threatening toxicity (e.g., a hypersensitivity reaction), all antiretroviral (ARV) drugs should be stopped immediately. Once symptoms of toxicity have resolved, ARV therapy should be resumed with substitution of a different ARV drug or drugs for the offending agent(s).
- When modifying ARV therapy because of toxicity or intolerance to a specific drug in children with virologic suppression, changing one drug in a multidrug regimen is permissible; if possible, an agent with a different toxicity and adverse effect profile should be chosen.
- The toxicity and the medication presumed responsible should be documented in the patient's medical record, and the caregiver and patient should be advised of the drug-related toxicity.
- In general, dose reduction is not a recommended option for management of ARV toxicity.

Adherence to Antiretroviral Therapy in Children with HIV

Adherence to antiretroviral therapy (ART) is a principal determinant of virologic suppression. Suboptimal adherence may include missed or late doses, treatment interruptions and discontinuations, and subtherapeutic or partial dosing. Poor adherence will result in subtherapeutic plasma antiretroviral (ARV) drug concentrations, facilitating the development of resistance to one or more drugs in a given ARV regimen and possible cross-resistance to other drugs in the same class. Multiple factors—including regimen potency, pharmacokinetics, drug interactions, viral fitness, and the genetic barrier to ARV resistance—influence the adherence–resistance relationship. In addition to compromising the efficacy of the current regimen, suboptimal adherence can limit the options for future effective ARV drug regimens in patients who develop multidrug-resistant HIV; it also can increase the risk of secondary transmission of drug-resistant virus.

Recommendations

- Strategies to maximize adherence should be discussed before and/or at initiation of antiretroviral therapy (ART) and before changing regimens.

- Adherence to therapy must be assessed and promoted at each visit, and strategies to maintain and/or improve adherence must be continually explored.
- In addition to viral load monitoring, at least one other method of measuring adherence to ART should be used.
- Once-daily antiretroviral regimens and regimens with a low pill burden should be prescribed whenever feasible.

Strategies to Improve Adherence to Antiretroviral Medications

- Establish trust and identify mutually acceptable goals for care.
- Obtain explicit agreement on the need for treatment and adherence.
- Identify depression, low self-esteem, substance abuse, or other mental health issues in the child and/or the caregiver that may affect adherence. Evaluate and initiate treatment for mental health issues before starting ARV drugs, if possible.
- Determine whether the child is aware of their HIV status. Consider talking to the child's caregivers about disclosing this information to the child in a developmentally appropriate way.
- Identify family, health team members, and others who can support adherence.
- Educate the patient and family about the critical role of adherence in therapy outcome, including the relationship between partial adherence and resistance and the potential impact on future drug regimen choices. Develop a treatment plan that the patient and family understand and to which they feel committed.
- Work with the patient and family to make specific plans for taking medications as prescribed and for supporting adherence. Assist them in arranging administration during day care, school, and in other settings, when needed. Consider home delivery of medications.
- Establish a patient's readiness to take medication by staging practice sessions or by other means.

Management of Children Receiving Antiretroviral Therapy

In Saudi Arabia, most children with HIV are receiving antiretroviral therapy (ART), making treatment-experienced children the norm. Providers may consider changes to the antiretroviral (ARV) regimen in consultation with a Pediatric infectious diseases consultant for the following reasons:

- **Treatment Simplification**: Modifying ARV regimens in children who are currently receiving effective ART in order to simplify the regimen.
- **Treatment Optimization**: Increasing the treatment potency or barrier to resistance of an effective but older or potentially fragile regimen or improving the adverse event profile.
- **Toxicity Management**: Recognizing and managing ARV drug toxicity or intolerance.
- **Treatment Failure**: Recognizing and managing treatment failure.

These considerations ensure that the treatment plan is tailored to the individual needs of each child, optimizing their health outcomes while minimizing potential side effects. It's important to regularly monitor the child's response to the treatment and make adjustments as necessary.

References

1. Jesson J, Dahourou DL, Renaud F, Penazzato M, Leroy V. Adverse events associated with abacavir use in HIV-infected children and adolescents: a systematic review and meta-analysis. Lancet HIV. 2016;3(2):e64-75. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26847228.
2. Hightow-Weidman LB, Muessig KE, Bauermeister J, Zhang C, LeGrand S. Youth, technology, and HIV: recent advances and future directions. Curr HIV/AIDS Rep. 2015;12(4):500-515. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26385582.
3. Shah AC, Badawy SM. Telemedicine in pediatrics: systematic review of randomized controlled trials. JMIR Pediatr Parent. 2021;4(1):e22696. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33556030.
4. Dandachi D, Lee C, Morgan RO, Tavakoli-Tabasi S, Giordano TP, Rodriguez-Barradas MC. Integration of telehealth services in the healthcare system: with emphasis on the experience of patients living with HIV. J Investig Med. 2019;67(5):815-820. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30826803.
5. Ohl ME, Richardson K, Rodriguez-Barradas MC, et al. Impact of availability of telehealth programs on documented HIV viral suppression: a cluster-randomized program evaluation in the Veterans Health Administration. Open Forum Infect Dis. 2019;6(6):ofz206. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31211155.
6. Health Resources and Services Administration (HRSA). Telehealth programs. 2019. Available at: http://www.hrsa.gov/rural-health/telehealth/index.html.
7. Krogstad P, Patel K, Karalius B, et al. Incomplete immune reconstitution despite virologic suppression in HIV-1 infected children and adolescents. AIDS. 2015;29(6):683-693. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25849832.
8. Arrow Trial team, Kekitiinwa A, Cook A, et al. Routine versus clinically driven laboratory monitoring and first-line antiretroviral therapy strategies in African children with HIV (ARROW): a 5-year open-label randomised factorial trial. Lancet. 2013;381(9875):1391-1403. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23473847.
9. Buscher A, Mugavero M, Westfall AO, et al. The association of clinical follow-up intervals in HIV-infected persons with viral suppression on subsequent viral suppression. AIDS Patient Care STDS. 2013;27(8):459-466. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23886048.
10. Hyle EP, Sax PE, Walensky RP. Potential savings by reduced CD4 monitoring in stable patients with HIV receiving antiretroviral therapy. JAMA Intern Med. 2013;173(18):1746-1748. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23978894.

11. Buclin T, Telenti A, Perera R, et al. Development and validation of decision rules to guide frequency of monitoring CD4 cell count in HIV-1 infection before starting antiretroviral therapy. PLoS One. 2011;6(4):e18578. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21494630.

12. Gaur AH, Flynn PM, Bitar W, Liang H. Optimizing frequency of CD4 assays in the era of highly active antiretroviral therapy. AIDS Res Hum Retroviruses. 2013;29(3):418-422. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23016543.

13. Gale HB, Gitterman SR, Hoffman HJ, et al. Is frequent CD4+ T-lymphocyte count monitoring necessary for persons with counts >=300 cells/muL and HIV-1 suppression? Clin Infect Dis. 2013;56(9):1340-1343. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23315315.

14. Davies MA, Ford N, Rabie H, et al. Reducing CD4 monitoring in children on antiretroviral therapy with virologic suppression. Pediatr Infect Dis J. 2015;34(12):1361-1364. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26379169.

15. Kosalaraksa P, Boettiger DC, Bunupuradah T, et al. Low risk of CD4 decline after immune recovery in human immunodeficiency virus-infected children with viral suppression. J Pediatric Infect Dis Soc. 2017;6(2):173-177. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27295973.

16. Agwu AL, Yao TJ, Eshleman SH, et al. Phenotypic co-receptor tropism in perinatally HIV-infected youth failing antiretroviral therapy. Pediatr Infect Dis J. 2016;35(7):777-781. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27078121.

17. HIV Paediatric Prognostic Markers Collaborative Study, Boyd K, Dunn DT, et al. Discordance between CD4 cell count and CD4 cell percentage: implications for when to start antiretroviral therapy in HIV-1 infected children. AIDS. 2010;24(8):1213-1217. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20386428.

18. Centers for Disease Control and Prevention. Revised surveillance case definition for HIV infection—United States, 2014. MMWR Recomm Rep. 2014;63(RR-03):1-10. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24717910.

19. Dunn D, HIV Paediatric Prognostic Markers Collaborative Study Group. Short-term risk of disease progression in HIV-1-infected children receiving no antiretroviral therapy or zidovudine monotherapy: a meta-analysis. Lancet. 2003;362(9396):1605-1611. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14630440.

20. Raszka WV, Jr., Meyer GA, Waecker NJ, et al. Variability of serial absolute and percent CD4+ lymphocyte counts in healthy children born to human immunodeficiency virus 1 infected parents. Military pediatric HIV consortium. Pediatr Infect Dis J. 1994;13(1):70-72. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7909598.

21. Henrard DR, Phillips JF, Muenz LR, et al. Natural history of HIV-1 cell-free viremia. JAMA. 1995;274(7):554-558. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7629984.

22. Katzenstein TL, Pedersen C, Nielsen C, Lundgren JD, Jakobsen PH, Gerstoft J. Longitudinal serum HIV RNA quantification: correlation to viral phenotype at seroconversion and clinical outcome. AIDS. 1996;10(2):167-173. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8838704.

23. Mellors JW, Kingsley LA, Rinaldo CR, Jr., et al. Quantitation of HIV-1 RNA in plasma predicts outcome after seroconversion. Ann Intern Med. 1995;122(8):573-579. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7887550.

24. Abrams EJ, Weedon J, Steketee RW, et al. Association of human immunodeficiency virus (HIV) load early in life with disease progression among HIV-infected infants. New York City Perinatal HIV Transmission Collaborative Study Group. J Infect Dis. 1998;178(1):101-108. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9652428.

25. Palumbo PE, Kwok S, Waters S, et al. Viral measurement by polymerase chain reaction-based assays in human immunodeficiency virus-infected infants. J Pediatr. 1995;126(4):592-595. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7699539.

26. Shearer WT, Quinn TC, LaRussa P, et al. Viral load and disease progression in infants infected with human immunodeficiency virus type 1. Women and Infants Transmission Study Group. N Engl J Med. 1997;336(19):1337-1342. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9134873.

27. McIntosh K, Shevitz A, Zaknun D, et al. Age- and time-related changes in extracellular viral load in children vertically infected by human immunodeficiency virus. Pediatr Infect Dis J. 1996;15(12):1087-1091. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8970217.

28. Mofenson LM, Korelitz J, Meyer WA, 3rd, et al. The relationship between serum human immunodeficiency virus type 1 (HIV-1) RNA level,

29. CD4 lymphocyte percent, and long-term mortality risk in HIV-1-infected children. National Institute of Child Health and Human Development Intravenous Immunoglobulin Clinical Trial Study Group. J Infect Dis. 1997;175(5):1029-1038. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9129063.

30. Palumbo PE, Raskino C, Fiscus S, et al. Predictive value of quantitative plasma HIV RNA and CD4+ lymphocyte count in HIV-infected infants and children. JAMA. 1998;279(10):756-761. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9508151.

31. Krogstad P, Uittenbogaart CH, Dickover R, Bryson YJ, Plaeger S, Garfinkel A. Primary HIV infection of infants: the effects of somatic growth on lymphocyte and virus dynamics. Clin Immunol. 1999;92(1):25-33. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10413650.

32. Hughes MD, Johnson VA, Hirsch MS, et al. Monitoring plasma HIV-1 RNA levels in addition to CD4+ lymphocyte count improves assessment of antiretroviral therapeutic response. ACTG 241 Protocol Virology Substudy Team. Ann Intern Med. 1997;126(12):929-938. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9182469.

33. Mellors JW, Munoz A, Giorgi JV, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. Ann Intern Med. 1997;126(12):946-954. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9182471.

34. Grennan JT, Loutfy MR, Su D, et al. Magnitude of virologic blips is associated with a higher risk for virologic rebound in HIV-infected individuals: a recurrent events analysis. J Infect Dis. 2012;205(8):1230-1238. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22438396.

35. Coovadia A, Abrams EJ, Strehlau R, et al. Efavirenz-based antiretroviral therapy among nevirapine-exposed HIV-infected children in South Africa: a randomized clinical trial. JAMA. 2015;314(17):1808-1817. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26529159.

36. Brambilla D, Leung S, Lew J, et al. Absolute copy number and relative change in determinations of human immunodeficiency virus type 1 RNA in plasma: effect of an external standard on kit comparisons. J Clin Microbiol. 1998;36(1):311-314. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9431977.

37. Raboud JM, Montaner JS, Conway B, et al. Variation in plasma RNA levels, CD4 cell counts, and p24 antigen levels in clinically stable men with human immunodeficiency virus infection. J Infect Dis. 1996;174(1):191-194. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8655993.

38. Lelie N, van Drimmelen H. Accuracy of quantitative HIV-1 RNA test methods at 1000 copies/mL and the potential impact of differences in assay calibration on therapy monitoring of patients. J Med Virol. 2020;doi:10.1002/jmv.25877(Epub ahead of print). Available at: https://www.ncbi.nlm.nih.gov/pubmed/32285945.

39. Bourlet T, Signori-Schmuck A, Roche L, et al. HIV-1 load comparison using four commercial real-time assays. J Clin Microbiol. 2011;49(1):292-297. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21068276.

40. Yan CS, Hanafi I, Kelleher AD, et al. Lack of correlation between three commercial platforms for the evaluation of human immunodeficiency virus type 1 (HIV-1) viral load at the clinically critical lower limit of quantification. J Clin Virol. 2010;49(4):249-253. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20884287.

41. Jennings C, Harty B, Granger S, et al. Cross-platform analysis of HIV-1 RNA data generated by a multicenter assay validation study with wide geographic representation. J Clin Microbiol. 2012;50(8):2737-2747. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22692747.

42. Haas J, Geiss M, Bohler T. False-negative polymerase chain reaction-based diagnosis of human immunodeficiency virus (HIV) type 1 in children infected with HIV strains of African origin. J Infect Dis. 1996;174(1):244-245. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8656008.

43. Kline NE, Schwarzwald H, Kline MW. False negative DNA polymerase chain reaction in an infant with subtype C human immunodeficiency virus 1 infection. Pediatr Infect Dis J. 2002;21(9):885-886. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12380591.

44. Zaman MM, Recco RA, Haag R. Infection with non-B subtype HIV type 1 complicates management of established infection in adult patients and diagnosis of infection in newborn infants. Clin Infect Dis. 2002;34(3):417-418. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11774090.

45. Luft LM, Gill MJ, Church DL. HIV-1 viral diversity and its implications for viral load testing: review of current platforms. Int J Infect Dis. 2011;15(10):e661-670. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21767972.

46. Sire JM, Vray M, Merzouk M, et al. Comparative RNA quantification of HIV-1 group M and non-M with the Roche Cobas AmpliPrep/Cobas TaqMan HIV-1 v2.0 and Abbott real-time HIV-1 PCR assays. J Acquir Immune Defic Syndr. 2011;56(3):239-243. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21164353.

47. Bienczak A, Cook A, Wiesner L, et al. The impact of genetic polymorphisms on the pharmacokinetics of efavirenz in African children. Br J Clin Pharmacol. 2016;82(1):185-198. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26991336.

48. Bolton Moore C, Capparelli EV, Samson P, et al. CYP2B6 genotype-directed dosing is required for optimal efavirenz exposure in children 3–36 months with HIV infection. AIDS. 2017;31(8):1129-1136. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28323755.

49. Small CB, Margolis DA, Shaefer MS, Ross LL. HLA-B*57:01 allele prevalence in HIV-infected North American subjects and the impact of allele testing on the incidence of abacavir-associated hypersensitivity reaction in HLA-B*57:01-negative subjects. BMC Infect Dis. 2017;17(1):256. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28399804.

50. Violari A, Lindsey JC, Hughes MD, et al. Nevirapine versus ritonavir-boosted lopinavir for HIV-infected children. N Engl J Med. 2012;366(25):2380-2389. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22716976.

51. Barlow-Mosha L, Angelidou K, Lindsey J, et al. Nevirapine- versus lopinavir/ritonavir-based antiretroviral therapy in HIV-infected infants and young children: long-term follow-up of the IMPAACT P1060 randomized trial. Clin Infect Dis. 2016;63(8):1113-1121. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27439527.

52. Coovadia A, Abrams EJ, Stehlau R, et al. Reuse of nevirapine in exposed HIV-infected children after protease inhibitor-based viral suppression: a randomized controlled trial. JAMA. 2010;304(10):1082-1090. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20823434.

53. Murnane PM, Strehlau R, Shiau S, et al. Switching to efavirenz versus remaining on ritonavir-boosted lopinavir in HIV-infected children exposed to nevirapine: long-term outcomes of a randomized trial. Clin Infect Dis. 2017;65(3):477-485. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28419200.

54. Babiker A, Castro nee Green H, Compagnucci A, et al. First-line antiretroviral therapy with a protease inhibitor versus non-nucleoside reverse transcriptase inhibitor and switch at higher versus low viral load in HIV-infected children: an open-label, randomised phase 2/3 trial. Lancet Infect Dis. 2011;11(4):273-283. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21288774.

55. Ruel TD, Kakuru A, Ikilezi G, et al. Virologic and immunologic outcomes of HIV-infected Ugandan children randomized to lopinavir/ritonavir or nonnucleoside reverse transcriptase inhibitor therapy. J Acquir Immune Defic Syndr. 2014;65(5):535-541. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24326597.

56. Raffi F, Jaeger H, Quiros-Roldan E, et al. Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naive adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double-blind, non-inferiority trial. Lancet Infect Dis. 2013;13(11):927-935. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24074642.

57. Molina JM, Clotet B, van Lunzen J, et al. Once-daily dolutegravir is superior to once-daily darunavir/ritonavir in treatment-naive HIV-1-positive individuals: 96 week results from FLAMINGO. J Int AIDS Soc. 2014;17(4 Suppl 3):19490. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25393999.

58. Viani RM, Alvero C, Fenton T, et al. Safety, pharmacokinetics and efficacy of dolutegravir in treatment-experienced HIV-1 infected adolescents: 48-week results from IMPAACT P1093. Pediatr Infect Dis J. 2015;34(11):1207-1213. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26244832.

59. Tsiang M, Jones GS, Goldsmith J, et al. Antiviral activity of bictegravir (GS-9883), a novel potent HIV-1 integrase strand transfer inhibitor with an improved resistance profile. Antimicrob Agents Chemother. 2016;60(12):7086-7097. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27645238.

60. Hassounah SA, Alikhani A, Oliveira M, et al. Antiviral activity of bictegravir and cabotegravir against integrase inhibitor-resistant SIVmac239 and HIV-1. Antimicrob Agents Chemother. 2017;61(12):e01695-01617. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28923862.

61. Neogi U, Singh K, Aralaguppe SG, et al. Ex-vivo antiretroviral potency of newer integrase strand transfer inhibitors cabotegravir and bictegravir in HIV type 1 non-B subtypes. AIDS. 2018;32(4):469-476. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29239896.

62. Oliveira M, Ibanescu RI, Anstett K, et al. Selective resistance profiles emerging in patient-derived clinical isolates with cabotegravir, bictegravir, dolutegravir, and elvitegravir. Retrovirology. 2018;15(1):56. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30119633.

63. Gaur AH, Cotton MF, Rodriguez CA, et al. Fixed-dose combination bictegravir, emtricitabine, and tenofovir alafenamide in adolescents and children with HIV: week 48 results of a single-arm, open-label, multicentre, phase 2/3 trial. Lancet Child Adolesc Health. 2021;5(9):642-651. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34302760.

64. Gaur A, Rodriguez C, McGrath, EJ, et al. Bictegravir/FTC/TAF single-tablet-regimen in adolescents: week 24 results. Presented at: Conference on Retroviruses and Opportunistic Infections. March 4–7; 2018. Boston, MA. Available at: https://www.croiconference.org/abstract/bictegravirftctaf-single-tablet-regimen-adolescents-week-24-results.

65. Cotton M, Liberty A, Rodriguez CA, et al. Pharmacokinetics, safety, and efficacy of bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) single-tablet regimen in HIV-1-infected children (6 to <12 years) Presented at: International AIDS Conference 2018. Amsterdam, Netherlands. Available at: http://www.natap.org/2018/IAC/IAC_39.htm.

66. Zash R, L. Holmes, M. Diseko, et al. Update on neural tube defects with antiretroviral exposure in the Tsepamo study, Botswana. Presented at: 23rd International AIDS Conference 2021; 2020. Virtual conference, July 6–10, 2020. Available at: https://www.natap.org/2020/IAC/IAC_112.htm.

67. Rodriguez C, Chokephaibulkit K, Liberty A, et al. Safety, PK, and efficacy of low dose B/F/TAF in children ≥2 years old living with HIV. Presented at: Conference of Retroviruses and Opportunistic Infections; 2020. Boston, MA. Available at: https://www.croiconference.org/abstract/safety-pk-and-efficacy-of-low-dose-b-f-taf-in-children-%e2%89%a52-years-old-living-with-hiv.

68. Ruel T, Farhad M, Alvero C, et al. Twenty-four week safety, tolerability and efficacy of dolutegravir dispersible tablets in children 4 weeks to <6 years old with HIV: results from IMPAACT P1093. Presented at: International AIDS Conference (AIDS 2020); 2020. San Francisco, California.

69. Wiznia A, Alvero C, Fenton T, et al. IMPAACT 1093: dolutegravir in 6- to 12-year-old HIV-infected children: 48-week results. Presented at: Conference on Retroviruses and Opporotunistic Infections; 2016. Boston, MA.

70. Turkova A, White E, Mujuru HA, et al. Dolutegravir as first- or second-line treatment for HIV-1 infection in children. N Engl J Med. 2021;385(27):2531-2543. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34965338.

71. Zash R, Holmes L, Diseko M, et al. Neural-tube defects and antiretroviral treatment regimens in Botswana. N Engl J Med. 2019;381(9):827-840. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31329379.

72. Zash R, Holmes L, Makhema J, et al. Surveillance for neural tube defects following antiretroviral exposure from conception. Presented at: 22nd International AIDS Conference; 2018. Amsterdam, Netherlands. Available at: http://www.natap.org/2018/IAC/IAC_52.htm.

73. Zash R, L. B. Holmes, M. Diseko, et al. Update on neural tube defects with antiretroviral exposure in the Tsepamo study, Botswana. Presented at: 24th International AIDS Conference 2021; 2021. Virtual, July 18-21, 2021.

74. Walmsley S, Baumgarten A, Berenguer J, et al. Dolutegravir plus abacavir/lamivudine for the treatment of HIV-1 infection in antiretroviral therapy-naive patients: week 96 and week 144 results from the SINGLE randomized clinical trial. J Acquir Immune Defic Syndr. 2015;70(5):515-519. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26262777.

75. Viani RM, Ruel T, Alvero C, et al. Long-term safety and efficacy of dolutegravir in treatment-experienced adolescents with human immunodeficiency virus infection: results of the IMPAACT P1093 study. J Pediatric Infect Dis Soc. 2019;9(2):159-165. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30951600.

76. Wohl DA, Cohen C, Gallant JE, et al. A randomized, double-blind comparison of single-tablet regimen elvitegravir/cobicistat/emtricitabine/tenofovir DF versus single-tablet regimen efavirenz/emtricitabine/tenofovir DF for initial treatment of HIV-1 infection: analysis of week 144 results. J Acquir Immune Defic Syndr. 2014;65(3):e118-120. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24256630.

77. Clumeck N, Molina JM, Henry K, et al. A randomized, double-blind comparison of single-tablet regimen elvitegravir/cobicistat/emtricitabine/tenofovir DF vs ritonavir-boosted atazanavir plus emtricitabine/tenofovir DF for initial treatment of HIV-1 infection: analysis of week 144 results. J Acquir Immune Defic Syndr. 2014;65(3):e121-124. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24346640.

78. Sax PE, Wohl D, Yin MT, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. Lancet. 2015;385(9987):2606-2615. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25890673.

79. Natukunda E, Gaur A, Kosalaraksa P, et al. Safety, efficacy, and pharmacokinetics of single-tablet elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide in virologically suppressed, HIV-infected children: a single-arm, open-label trial. Lancet Child Adolescent Health. 2017;1(1):27-34. Available at: http://www.sciencedirect.com/science/article/pii/S2352464217300093?via%3Dihub.

80. Gaur AH, Kizito H, Prasitsueubsai W, et al. Safety, efficacy, and pharmacokinetics of a single-tablet regimen containing elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide in treatment-naive, HIV-infected adolescents: a single-arm, open-label trial. Lancet HIV. 2016;3(12):e561-e568. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27765666.

81. Lennox JL, DeJesus E, Lazzarin A, et al. Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naive patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. Lancet. 2009;374(9692):796-806. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19647866.

82. DeJesus E, Rockstroh JK, Lennox JL, et al. Efficacy of raltegravir versus efavirenz when combined with tenofovir/emtricitabine in treatment-naive HIV-1-infected patients: week-192 overall and subgroup analyses from STARTMRK. HIV Clin Trials. 2012;13(4):228-232. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22849964.

83. Rockstroh JK, DeJesus E, Lennox JL, et al. Durable efficacy and safety of raltegravir versus efavirenz when combined with tenofovir/emtricitabine in treatment-naive HIV-1-infected patients: final 5-year results from STARTMRK. J Acquir Immune Defic Syndr. 2013;63(1):77-85. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23412015.

84. Lennox JL, Landovitz RJ, Ribaudo HJ, et al. Efficacy and tolerability of 3 nonnucleoside reverse transcriptase inhibitor-sparing antiretroviral regimens for treatment-naive volunteers infected with HIV-1: a randomized, controlled equivalence trial. Ann Intern Med. 2014;161(7):461-471. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25285539.

85. Briz V, Leon-Leal JA, Palladino C, et al. Potent and sustained antiviral response of raltegravir-based highly active antiretroviral therapy in HIV type 1-infected children and adolescents. Pediatr Infect Dis J. 2012;31(3):273-277. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22330165.

86. Nachman S, Zheng N, Acosta EP, et al. Pharmacokinetics, safety, and 48-week efficacy of oral raltegravir in HIV-1-infected children aged 2 through 18 years. Clin Infect Dis. 2014;58(3):413-422. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24145879.

87. Nachman S, Alvero C, Acosta EP, et al. Pharmacokinetics and 48-week safety and efficacy of raltegravir for oral suspension in human immunodeficiency virus type-1-infected children 4 weeks to 2 years of age. J Pediatric Infect Dis Soc. 2015;4(4):e76-83. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26582887.

88. Nachman S, Alvero C, Teppler H, et al. Safety and efficacy at 240 weeks of different raltegravir formulations in children with HIV-1: a phase 1/2 open label, non-randomised, multicentre trial. Lancet HIV. 2018;5(12):e715-e722. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30527329.

89. Clarke DF, Acosta EP, Cababasay M, et al. Raltegravir (RAL) in neonates: dosing, pharmacokinetics (PK), and safety in HIV-1-exposed neonates at risk of infection (IMPAACT P1110). J Acquir Immune Defic Syndr. 2020;84(1):70-77. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31913995.

90. Orkin C, Elion R, Thompson M, et al. Changes in weight and BMI with first-line doravirine-based therapy. AIDS. 2021;35(1):91-99. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33048879.

91. Molina JM, Squires K, Sax PE, et al. Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 48-week results of a randomised, double-blind, phase 3, non-inferiority trial. Lancet HIV. 2018;5(5):e211-e220. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29592840.

92. Orkin C, Squires KE, Molina JM, et al. Doravirine/lamivudine/tenofovir disoproxil fumarate is non-inferior to efavirenz/emtricitabine/tenofovir disoproxil fumarate in treatment-naive adults with human immunodeficiency virus-1 infection: week 48 results of the DRIVE-AHEAD trial. Clin Infect Dis. 2019;68(4):535-544. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30184165.

93. Melvin A, Best B, Muresan P, et al. IMPAACT 2014 24-week PK and safety of doravirine/3TC/TDF in adolescents witH HIV-1. Presented at: Conference on Retroviruses and Opportnistic Infections; 2021. Virtual conference. Available at: https://www.croiconference.org/abstract/impaact-2014-24-week-pk-and-safety-of-doravirine-3tc-tdf-in-adolescents-with-hiv-1.

94. Bwakura Dangarembizi M, Samson P, Capparelli EV, et al. Establishing dosing recommendations for efavirenz in HIV/TB-coinfected children younger than 3 years. J Acquir Immune Defic Syndr. 2019;81(4):473-480. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31241542.

95. Starr SE, Fletcher CV, Spector SA, et al. Combination therapy with efavirenz, nelfinavir, and nucleoside reverse-transcriptase inhibitors in children infected with human immunodeficiency virus type 1. Pediatric AIDS clinical trials group 382 team. N Engl J Med. 1999;341(25):1874-1881. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10601506.

96. Teglas JP, Quartier P, Treluyer JM, Burgard M, Gregoire V, Blanche S. Tolerance of efavirenz in children. AIDS. 2001;15(2):241-243. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11216933.

97. Nunez M, Soriano V, Martin-Carbonero L, et al. SENC (Spanish efavirenz vs. nevirapine comparison) trial: a randomized, open-label study in HIV-infected naive individuals. HIV Clin Trials. 2002;3(3):186-194. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12032877.

98. Squires K, Lazzarin A, Gatell JM, et al. Comparison of once-daily atazanavir with efavirenz, each in combination with fixed-dose zidovudine and lamivudine, as initial therapy for patients infected with HIV. J Acquir Immune Defic Syndr. 2004;36(5):1011-1019. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15247553.

99. Torti C, Maggiolo F, Patroni A, et al. Exploratory analysis for the evaluation of lopinavir/ritonavir-versus efavirenz-based HAART regimens in antiretroviral-naive HIV-positive patients: results from the Italian MASTER cohort. J Antimicrob Chemother. 2005;56(1):190-195. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15917286.

100. Riddler SA, Haubrich R, DiRienzo AG, et al. Class-sparing regimens for initial treatment of HIV-1 infection. N Engl J Med. 2008;358(20):2095-2106. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18480202.

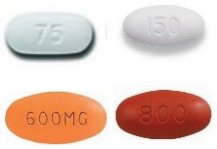
APPENDIX

Appendix I list of antiretroviral drugs

Abbreviation	Antiretroviral Drug
3TC	Lamivudine
ABC	Abacavir
ATV	Atazanavir
ATV/r	Ritonavir-boosted Atazanavir
AZT	Zidovudine
DRV	Darunavir
DRV/r	Ritonavir-boosted Darunavir
DTG	Dolutegravir
EFV	Efavirenz
ETV	Etravirine
FTC	Emtricitabine
IDV	Indinavir
LPV	Lopinavir
LPV/r	Ritonavir-boosted Lopinavir
MVC	Maraviroc
NVP	Nevirapine
RAL	Raltegravir
RPV	Rilpivirine
TDF	Tenofovir
TAF	Tenofovir Alafenamide
DOR	Doravirine
BIC	Bictegravir
CAB	Cabotegravir
RIL LA	Rilpivirine Long-Acting

Appendix II ARVrugs Catalogue

Epzicom



Darunavir

Descovy

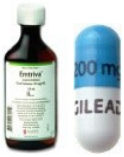
Dovato

Abaavir

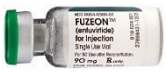
Atazanavir

Biktarvy

Cobicistat



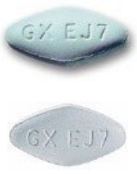
Emtriva



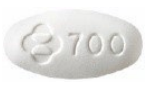
Fuzeon,T-20 SQ injection (Enfuviritide)

Genvoya

Isentress
100 mg pediatric chewable tablet, 600 mg tablets



Epivir
150 mg, 300 mg

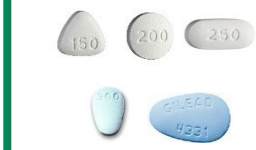


Pifeltro

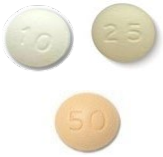
Edurant

Norvir

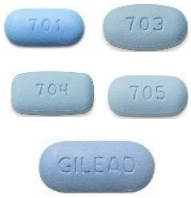
Appendix II ARVrugs Catalogue



Viread,
150 mg, 200 mg, 250 mg, 300 mg



Tivicay,
10 mg, 25 mg, 50 mg



Truvada

Retrovir,
100 mg, 300 mg

Delstrigo

Sustiva

Intelence

Evotaz

Kaletra

Atripla

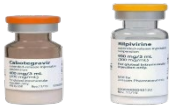
Viramune

Odefsey

Symtuza

Stribild

Symfilo



CABO.RIL LA

Saudi Guidelines for HIV Treatment

3rd edition

2024

About the Guidelines

These guidelines, developed by the Saudi AIDS National Program (NAP), aim to be a valuable tool for healthcare professionals, involved in the treatment and care of individuals living with HIV, enabling them to provide the highest standard of care for their patients with updated antiretroviral therapy (ART) strategies for both HIV treatment and prevention and contribute significantly to the ongoing global effort to end the HIV epidemic.

Major changes in this edition include an updated initial ART according to the most recent literature, in addition to updated and simplified information on their adverse effects, ART in special groups, and updated content on HIV co-infections and opportunistic infections. Every other part of this guideline has been reviewed and updated accordingly.