HUMAN IMMUNODEFICIENCY VIRUS (HIV)

CHI Formulary Development Project

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Council of Health Insurance

INDICATION UPDATE

ADDENDUM- August 2023

To the CHI Original HIV Clinical Guidance- Issued September 2020

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Related Documents

Related SOPs

- IDF-FR-P-02-01-IndicationsReview&IDFUpdates
- IDF-FR-P-05-01-UpdatedIndicationReview&IDFUpdates

Related WI:

- IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

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Abbreviations

3TC	Lamivudine
ABC	Abacavir
AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Therapy
ARV	Antiretroviral
ATV	Atazanavir
BIC	Bictegravir
CAB	Cabotegravir
CAB-LA	Long-Acting Cabotegravir
CADTH	Canadian Agency for Drugs and Technologies in Health
CD4	Cluster of Differentiation 4
CHI	Council of Health Insurance
CMV	Cytomegalovirus
COBI or /c	Cobicistat
CVD	Cardiovascular Disease
DHHS	United States Department of Health and Human Services
DOR	Doravirine
DRV	Darunavir
DTG	Dolutegravir
EFV	Efavirenz
EVG	Elvitegravir
FPV	Fosamprenavir
FTC	Emtricitabine
FTR	Fostemsavir
GRF	Growth Hormone Releasing Factor
HAART	Highly Active Retroviral Therapy
HAS	Haute Autorité de Santé
HBsAb	Hepatitis B Surface Antibody
HbsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDV	Hepatitis D Virus
HIV	Human Immunodeficiency Virus
HTA	Health Technology Assessment
IBA	Ibalizumab

IM	Intramuscular
INSTI	Integrase Strand Transfer Inhibitor
IQWIG	Institute for Quality and Efficiency in Health Care
LEN	Lenacapavir
LTBI	Latent Tuberculosis Infection
MMR	Measles, Mumps and Rubella
MVC	Maraviroc
NICE	National Institute for Health and Care Excellence
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside/Nucleotide Reverse Transcriptase Inhibitor
PBAC	Pharmaceutical Benefits Advisory Committee
PEP	Post-Exposure Prophylaxis
PI	Protease Inhibitor
PJP	Pneumocystis Jirovecii Pneumonia
PR	Protease
PrEP	Pre-Exposure Prophylaxis
RAL	Raltegravir
RPV	Rilpivirine
RT	Reverse Transcriptase
RTV or /r	Ritonavir
SQ	Subcutaneous
T-20	Enfuvirtide
TAF	Tenofovir Alafenamide
TB	Tuberculosis
TDF	Tenofovir Disoproxil Fumarate
TFV	Tenofovir
TFV-DP	Tenofovir Diphosphate
TMP-SMX	Trimethoprim-Sulfamethoxazole
VariZIG	Varicella Zoster Immune Globulin
VZV	Varicella Zoster Virus
ZDV	Zidovudine

Executive Summary

The Human Immunodeficiency Virus (HIV) is an enveloped retrovirus containing two copies of single-stranded RNA genome. HIV can be classified into HIV-1 and HIV-2. HIV-1 is more globally expanded and virulent and originated in Central Africa, while HIV-2 is much less virulent and comes from West Africa. Both viruses are related antigenically to immunodeficiency viruses found primarily in primates. HIV could trigger acquired immunodeficiency syndrome (AIDS), which represents the final phase of HIV infection. Roughly two to four weeks following the virus's entry into the body, the individual might exhibit signs of primary infection. Subsequently, chronic HIV infection takes place and could potentially last for decades. The figure below is adapted from the 2010 American Academy of Family Physicians guideline for the management of acute HIV infection[1] and depicts the course of the disease.

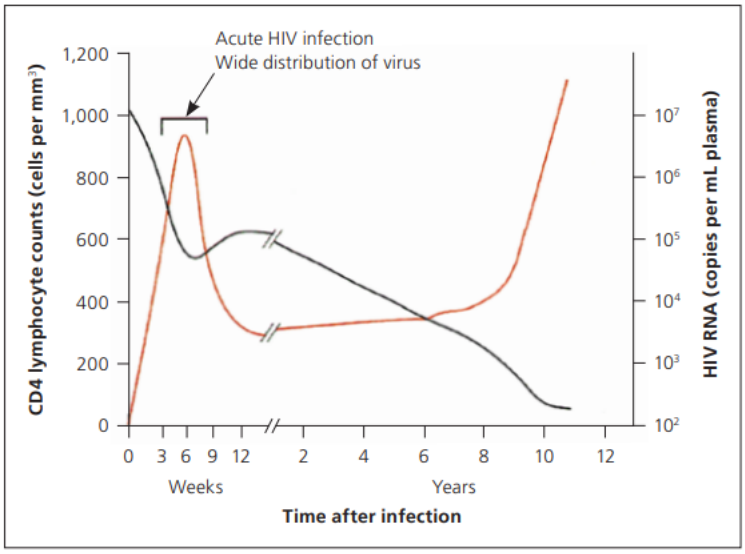

Figure 1. *Human Immunodeficiency Virus (HIV) Viremia and CD4 Lymphocyte Counts During Acute Infection*

The chief features of AIDS encompass opportunistic infections and tumors, typically leading to fatality in the absence of medical intervention[2]. Opportunistic infections are defined as infections caused by bacteria, fungi, viruses, or other organisms that typically reside in the human body and might not necessarily cause a disease in healthy people but become pathogenic with a weakened immune system[3].

As per the World Health Organization, 0.7% of adults aged 15-49 years worldwide are living with HIV in 2022. An average of 1.3 million people acquired HIV in 2022. Since 2010, the number of people acquiring HIV has been reduced by 38%, from an average of 2.1 million people[4]. As of 2022 in Saudi Arabia, the HIV incidence in individuals aged 15 to 49 was 0.06 per 1000 population. Furthermore, an average of

11,000 adults and children are currently living with HIV, 1300 people were attained by new HIV infection and less than 200 were subject to AIDS-related death[5]. The lifetime costs for managing HIV differ according to country income level. Currently, the lifetime treatment cost of an HIV infection is estimated at $379,668, therefore a prevention intervention is deemed cost-saving[6].

In terms of clinical manifestations, some patients may develop a flu-like illness within a month or two after exposure to the HIV virus. The symptoms usually disappear within a week to a month and are often mistaken for those of another viral infection. These may include fever, headache, malaise and enlarged lymph nodes. As the immune system deteriorates, complications begin to surface. The most common complications include lack of energy, weight loss, short-term memory loss, and one or more opportunistic infections[7].

Drug therapy is an integral component for the management of HIV. Many therapeutic agents are available or still under investigation for treatment of HIV, even though none of which proves to be curative. Antiretrovirals are the mainstay treatment for HIV infections/AIDS, and they are used in various combinations, commonly referred to as highly active retroviral therapy (HAART). These agents include nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), NRTI fixed-dose combinations, integrase inhibitors, non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors, and CCR5 inhibitors. All patients with HIV, regardless of their CD4 level, should be started on HAART, which should be continued for life. This therapy has been shown to reduce morbidity and mortality and lower the risk of transmitting the infection to others, as long as they have a low or undetectable viral load[2].

A patient diagnosed with HIV and presenting with a CD4 count exceeding 500 (considered normal) can expect a life span similar to that of an individual without HIV. In the case of an untreated AIDS patient, life expectancy is typically around 1 to 2 years following the initial occurrence of an opportunistic infection. The utilization of antiretroviral therapy has the potential to elevate CD4 counts and transform the patient's condition from AIDS to that of an individual with HIV[2].

CHI issued HIV clinical guidance after thorough review of renowned international and national clinical guidelines in September 2020. Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations.

This report functions as an addendum to the prior CHI HIV clinical guidance and seeks to offer guidance for the effective management of HIV. It provides an **update on the HIV Guidelines** for CHI Formulary with the ultimate objective of updating the IDF (CHI Drug Formulary) while addressing **the most updated best available clinical and economic evidence related to drug therapies.**

Main triggers for the update are summarized, being **the issuance of updated versions of previously reviewed guidelines** as the 2023 DHHS Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV, 2022 the European AIDS Clinical Society (EACS) Guidelines and the 2022 Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults Recommendations of the International Antiviral Society–USA Panel. **New guidelines are added to the report** such as the 2021 WHO Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service Delivery and Monitoring, the 2020 Primary Care Guidance for Persons with Human Immunodeficiency Virus: Update by the HIV Medicine Association of the Infectious Diseases Society of America and the 2019 CDC Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. Other triggers include **newly approved SFDA registered combination therapies** as Lamivudine/Zidovudine and Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate, **newly approved non-SFDA registered drugs** as Cabotegravir XR Injectable Suspension, Cabotegravir and Rilpivirine injectable formulation, Cabotegravir tablet formulation, Emtricitabine/Rilpivirine/Tenofovir Disoproxil Fumarate, Tesamorelin for injection, Dolutegravir/Rilpivirine, Emtricitabine/Rilpivirine/Tenofovir Alafenamide, Crofelemer, Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate, Lenacapavir, Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide and Abacavir Sulfate/Lamivudine/Zidovudine AZT and **updated drug safety recommendations.**

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) in all tables reflecting specific drug classes' role in the HIV therapeutic management.

Below is a table summarizing the major changes based on the different HIV guidelines used to issue this report:

Table 1. General Recommendations for the Management of HIV

Management of HIV		
General Recommendations	**Level of Evidence/Grade of Recommendation**	**Reference**
All people with HIV are to be started on ART regardless of WHO clinical staging and CD4 cell count.	Strong Recommendation for adults, pregnant and breastfeeding women, and infants diagnosed	WHO Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service Delivery and Monitoring [2021][8]

	in the first year of life. Conditional recommendation for adolescents and children living with HIV one year old to less than 10 years old.	
In order to increase ART uptake, enhance engagement in care, accelerate the time to viral suppression, and to reduce the time during which people with newly diagnosed HIV can transmit HIV, many clinics have adopted a rapid start policy to initiate ART on the day of HIV diagnosis.	Strong recommendation	Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV [2023][9]
Measurement of plasma viral load should take place before initiation of ART, within 4 to 8 weeks after treatment initiation, before ART change and within 4 to 8 weeks after changing therapy/treatment modification; the purpose of the measurements is to confirm an adequate virologic response to ART, indicating patient adherence to therapy and appropriate regimen selection.	Level AIII	Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV [2023][9]
Individuals at significant risk of contracting HIV should be presented with the option of oral pre-exposure prophylaxis (PrEP) containing TDF.	Strong Recommendation	WHO Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service Delivery and Monitoring [2021][8]
Long-acting injectable cabotegravir (CAB-LA) was approved by the FDA for HIV pre-exposure prophylaxis (PrEP).	Level AII	Guidelines for the Use of Antiretroviral Agents in Adults

		and Adolescents with HIV [2023][9]
For HIV patients who do not have a history of using long-acting cabotegravir (CAB-LA) as pre-exposure prophylaxis (PrEP), the following regimens are recommended: • Bictegravir/tenofovir alafenamide (TAF)/emtricitabine (FTC) • DTG/abacavir/3TC (Only for individuals who are HLA-B*5701 negative and without chronic hepatitis B virus (HBV) coinfection) • DTG plus (TAF or tenofovir disoproxil fumarate [TDF]) plus (FTC or 3TC) • DTG/3TC (With the exception of individuals with HIV RNA >500,000 copies/mL, HBV coinfection, or when ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available)	Level AI	Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV [2023][9]
For HIV patients with a history of using CAB-LA as PrEP, INSTI genotypic resistance testing should be done before the start of ART. If treatment is initiated prior to results of genotypic testing, the following regimen is recommended: A boosted PI regimen of darunavir/ritonavir (DRV/r) or darunavir/cobicistat (DRV/c) plus (TAF or TDF) plus (FTC or 3TC).	Level AIII	Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV [2023][9]
During Pregnancy: TAF/XTC plus dolutegravir or TDF/XTC plus dolutegravir (If tenofovir alafenamide is not available) can be used in pregnant patients.	Level AIa	Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults Recommendations of the

		International Antiviral Society–USA Panel [2022][10]
In pregnancy, if Dolutegravir is not available, the following drugs serve as alternative options: Raltegravir (400 mg twice daily) Atazanavir plus ritonavir Darunavir plus ritonavir Rilpivirine	Raltegravir – Level AIIa Atazanavir plus ritonavir –Level BIIa Darunavir plus ritonavir – Level BIIa Rilpivirine – Level BIIa	Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults Recommendations of the International Antiviral Society–USA Panel [2022][10]
Mothers living with HIV should breastfeed for at least 12 months up to 24 months or longer while being fully supported for ART adherence.	Strong Recommendation	WHO Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service Delivery and Monitoring [2021][8]
For HIV patients who are initiating ART, DTG in combination with an NRTI backbone is recommended as first line therapy.	Strong Recommendation for adults and adolescents. Conditional Recommendation for infants and children with approved DTG dosing.	WHO Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service Delivery and Monitoring [2021][8]
Alternative first line therapy that is recommended for adults and adolescents with HIV: EFV at low dose (400 mg) in combination with an NRTI backbone.	Strong Recommendation	WHO Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service Delivery and Monitoring [2021][8]
First line therapy for neonates: An RAL-based regimen.	Conditional Recommendation	WHO Consolidated Guidelines on HIV Prevention,

		Testing, Treatment, Service Delivery and Monitoring [2021][8]
For HIV patients who are non-responsive to non-DTG-based regimens: DTG in combination with an optimized nucleoside reverse-transcriptase inhibitor backbone may be recommended as second line therapy.	Conditional Recommendation	WHO Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service Delivery and Monitoring [2021][8]
For HIV patients who are non-responsive to DTG-based regimens: Boosted protease inhibitors in combination with an optimized nucleoside reverse-transcriptase inhibitor backbone are recommended as second line therapy.	Strong Recommendation	WHO Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service Delivery and Monitoring [2021] [8]
Third line therapy should include new drugs with minimal risk of cross-resistance to previously used regimens, such as INSTIs and second-generation NNRTIs and PIs.	Conditional Recommendation	WHO Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service Delivery and Monitoring [2021] [8]
Lamivudine/Zidovudine, a combination of two nucleoside analogue reverse transcriptase inhibitors, is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. It is usually given as one tablet (lamivudine 150 mg/zidovudine 300 mg) twice daily.	No Grade of Recommendation	CenterWatch[11], SFDA Drug List[12], Lexicomp[13]
Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate is a three-drug combination of doravirine (a nonnucleoside reverse transcriptase inhibitor [NNRTI]), lamivudine, and tenofovir disoproxil fumarate (both nucleoside analogue reverse	No Grade of Recommendation	CenterWatch[11], SFDA Drug List[12], Lexicomp[13]

transcriptase inhibitors) and is indicated as a complete regimen for the treatment of HIV-1 infection in adult patients with no antiretroviral treatment history. The recommended dosage is one tablet (doravirine 100 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg) taken orally once daily with or without food in adult patients.		

Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

This section is divided into two parts; the first includes recommendations from **updated versions of guidelines** mentioned in the previous CHI HIV report, and the second includes **newly added guidelines** that have helped generate this report.

1.1 Revised Guidelines

The following segment contains the updated versions of the guidelines mentioned in the September 2020 CHI HIV Report and the corresponding recommendations:

Table 2. Guidelines Requiring Revision

Guidelines Requiring Revision	
Old Versions	**Updated versions**
1.1 Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV Developed by the **DHHS** Panel [**2019**]	1.1.1 Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV [**2023**]
1.2 The European AIDS Clinical Society (**EACS**) Guidelines [**2019**]	1.1.2 The European AIDS Clinical Society (**EACS**) Guidelines [**2022**]
1.4 Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults Recommendations of the International Antiviral Society–USA Panel [**2020**]	1.1.3 Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults Recommendations of the International Antiviral Society–USA Panel [**2022**]

1.1.1 Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV [2023]

*Please refer to **Section 1.1** of the CHI HIV Report Version 3.*

The United States Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents – a Working Group of the NIH Office of AIDS Research Advisory Council (OARAC) – published in 2023 its updated guidelines for the use of antiretroviral agents in adults and adolescents with HIV. They introduced a set of recommendations accompanied by a grading scheme, outlined as follows[9]:

Table 3. DHHS Grading/Level of Evidence

Strength of Recommendation	
A	Strong recommendation for the statement
B	Moderate recommendation for the statement
C	Weak recommendation for the statement
Quality of Evidence	
I	One or more randomized trials with clinical outcomes and/or validated laboratory endpoints
II	One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes
III	Expert opinion

Baseline Testing:

- In order to increase ART uptake, enhance engagement in care, accelerate the time to viral suppression, and to reduce the time during which people with newly diagnosed HIV can transmit HIV, many clinics have adopted a **rapid start policy** to initiate ART on the day of HIV diagnosis.
- Prior to ART initiation:
    - HIV infection should be confirmed; whereby HIV RNA and CD4 count (Determining the need for prophylaxis for certain opportunistic infections) should be obtained, but results should not necessarily be available before starting ART therapy regimens.
    - Genotypic resistance testing for RT and PR (and INSTI resistance testing if patient has a history of CAB PrEP use or if INSTI transmission is suspected) should be obtained.

- Screening for viral hepatitis should be done. If ART initiation occurs before results are available, a regimen that has activity against hepatitis B virus should be selected.
- A complete immunization history (including for SARS-CoV-2) should also be obtained.

- It is important to inform HIV patients that maintaining a plasma HIV RNA of <200 copies/mL, including any measurable value below this threshold, with ART prevents sexual transmission of HIV to their partners.

Plasma HIV-1 RNA (Viral Load) and CD4 Count Monitoring:

- Viral suppression can be achieved 8 to 12 weeks after ART initiation or after modification (Attributed to virologic failure) in individuals who are adherent to their ARV regimens and are not subject to resistance mutations to the component drugs.
- Measurement of plasma viral load should take place before initiation of ART, within 4 to 8 weeks after treatment initiation, before ART change and within 4 to 8 weeks after changing therapy/treatment modification; the purpose of the measurements is to confirm an adequate virologic response to ART, indicating patient adherence to therapy and appropriate regimen selection.

Frequency of CD4 Count Monitoring:

- For patients being started on ART:

  If CD4 count <300 cells/mm3: CD4 count monitoring should be repeated every 3 months for the first 2 years of suppressive ART.

  If CD4 count is ≥300 cells/mm3: CD4 count monitoring is to be repeated every 6 months.
- After 2 years of suppressive ART, CD4 count monitoring can be reduced to every 6 months for patients whose CD4 counts remain at <300 cells/mm3 and every year for patients with CD4 counts between 300 cells/mm3 and 500 cells/mm3 and is optional for those with CD4 counts >500 cells/mm3.

What to Start: Initial Combination Antiretroviral Regimens for People with HIV:

- For HIV patients who do not have a history of using long-acting cabotegravir (CAB-LA) as pre-exposure prophylaxis (PrEP), the following regimens are recommended:
  - Bictegravir/tenofovir alafenamide (TAF)/emtricitabine (FTC)

- DTG/abacavir/3TC (Only for individuals who are HLA-B*5701 negative and without chronic hepatitis B virus (HBV) coinfection.)
- DTG plus (TAF or tenofovir disoproxil fumarate [TDF]) plus (FTC or 3TC)
- DTG/3TC (With the exception of individuals with HIV RNA >500,000 copies/mL, HBV coinfection, or when ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available.)

- For HIV patients with a history of using CAB-LA as PrEP, INSTI genotypic resistance testing should be done before the start of ART.

  If treatment is initiated prior to results of genotypic testing, the following regimen is recommended:

  - A boosted PI regimen of darunavir/ritonavir (DRV/r) or darunavir/cobicistat (DRV/c) plus (TAF or TDF) plus (FTC or 3TC).
- Long-acting injectable cabotegravir (CAB-LA) was approved by the FDA for HIV pre-exposure prophylaxis (PrEP). Drug levels may be present in some individuals for up to 4 years which is associated with the long half-life of CAB-LA.
- The presence of cabotegravir (CAB)-resistant mutations may have cross-resistance to other INSTIs, as Bictegravir (BIC) and Dolutegravir (DTG). Therefore, it is recommended that INSTI genotypic resistance test results be available prior to initiating an INSTI-based regimen.
- When ART is initiated prior to an INSTI genotype result is available, a non-INSTI regimen containing boosted darunavir (DRV) **plus** (tenofovir alafenamide [TAF] or tenofovir disoproxil fumarate [TDF]) **plus** (emtricitabine [FTC] or lamivudine [3TC]) should be initiated, pending genotype results.
- If an INSTI-based regimen is initiated and viral suppression is not achieved, genotypic resistance testing (including for INSTIs) should be repeated.

Safety Information:

- Bictegravir lacks sufficient data and should therefore not be initiated in pregnant people.
- TAF is now recommended as an alternative drug in pregnancy.
- Both DRV and COBI are to be avoided in pregnancy if possible.

  DRV and COBI exposures are reduced markedly during second and third trimesters of pregnancy.

Monitoring viral load frequently is recommended if pregnant women with viral suppression while on DRV/c choose to stay on the drug.

- Other drugs that are not recommended for use in pregnancy include Oral CAB and the long-acting injectable regimen of CAB and RPV; insufficient data exist for people who are trying to conceive or who become pregnant while on this regimen.
- In a subset of patients, LEN SQ Injections have shown headache, swelling, erythema, pain, nodules, inflammation, and induration.

Updates to Pharmacological Treatment:

- For heavily treatment-experienced adults with multidrug-resistant HIV-1 infection: Lenacapavir, a first-in-class HIV capsid inhibitor, was recently approved to be used in combination with other antiretroviral (ARV) drugs. Lenacapavir can be given by one of two initiation schemes (oral plus subcutaneous dosing), followed by SQ injections every 6 months.
- To replace oral ART in patients with virologic suppression and no history of resistance to RPV or INSTIs: RPV has recently been approved as an extended-release injectable suspension as part of a long-acting injectable complete ARV regimen when used with cabotegravir (CAB).
- Patients who are keen on using injectable CAB plus RPV early in their treatment history should first attain viral suppression on a recommended regimen, then transition to a month of oral CAB and RPV with maintenance of suppression before transitioning to injectable CAB plus RPV.
- Ibalizumab (IBA) is a long-acting CD4 post-attachment inhibitor that is given intravenously every 2 weeks. Patients with drug-resistant HIV may receive IBA as part of a salvage regimen; initiated with a 2,000-mg loading dose given as an intravenous (IV) infusion, then followed by 800 mg given as IV infusion every 14 days as maintenance therapy.
- Fostemsavir (FTR) is a gp120 attachment inhibitor that is given in combination with other antiretroviral(s) and is indicated for heavily treatment-experienced HIV patients with multidrug-resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations. It is given orally twice daily at a dose of 600mg.
- Three newly available agents for HIV pre-exposure prophylaxis include oral emtricitabine (FTC) with either tenofovir alafenamide (TAF) or tenofovir disoproxil fumarate (TDF), and intramuscular long-acting cabotegravir (CAB-LA).

- Tuberculosis/HIV Coinfection: Tuberculosis-preventive treatment for HIV patients and latent tuberculosis infection (LTBI) should be based on the individual's antiretroviral (ARV) regimen.
    - With once-weekly isoniazid plus rifapentine for 3 months: Dolutegravir (DTG) 50 mg once daily may be used for those in whom once-daily DTG is appropriate.
    - With once-daily isoniazid and rifapentine for 1 month: EFV 600 mg once daily (in combination with either ABC/3TC or TDF/FTC) can be used.

Optimizing Antiretroviral Therapy in the Setting of Viral Suppression:

- In the setting of existing nucleoside reverse transcriptase inhibitor (NRTI) resistance, two NRTIs—tenofovir alafenamide or tenofovir disoproxil fumarate **plus** emtricitabine (FTC) or lamivudine (3TC) should be included in the regimen with a fully active, high resistance barrier drug, such as dolutegravir, boosted-darunavir, or bictegravir.

Discontinuation or Interruption of Antiretroviral Therapy:

- Unplanned interruptions by accident or by necessity are unfavorable. Minimizing the duration of the interruption would also be appropriate if it were to incur.

Interruption of Long-Acting Antiretroviral Drugs:

- When stopping a long-acting injectable ART, the transition to a suppressive oral ARV regimen should occur within 4 weeks of the last planned IM doses.
- Patients who miss doses or discontinue therapy without bridging with an oral ARV regimen are at increased risk of virologic failure with development of drug resistance.

1.1.2 The European AIDS Clinical Society (EACS) Guidelines [2022]

*Please refer to **Section 1.2** of the CHI HIV Report Version 3.*

The 2022 EACS guidelines introduced a set of recommendations stated below[14]:

Characteristics of Antiretroviral Therapy:

- In case of a positive HLA-B*57:01 status, ABC is contraindicated and is not to be used for a same day start regimen.

  Even in case of a negative HLA-B*57:01 status, counselling on the risk for hypersensitivity reactions is still mandatory.

- Drugs to be used with caution in HIV patients with a high CVD risk:

  ABC, DRV/r.

- DOR is not active against HIV-2. Results of genotypic resistance test are necessary before starting DOR.
- Efavirenz is usually given at a dose of 400 or 600mg daily.

  If HIV patients have a history of suicide attempts or mental illness, EFV is not to be given.

  If the patient is on a rifampicin-based regimen for tuberculosis, 600 mg EFV dosing must be used.

  EFV is not active against HIV-2 and HIV-1 group O strains.

ART and TB Co-infection:

- ATV/r and LPV/r have been removed from combinations to use with rifabutin.

Viral Hepatitis Co-infection:

- **Hepatitis D Virus:**

  In HDV-RNA positive HIV patients with compensated liver disease, Bulevirtide (2mg/d SQ) in combination with TDF/TAF is recommended where available. The optimal duration for treatment, however, remains unclear.

1.1.3 Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults: Recommendations of the International Antiviral Society – USA Panel [2022]

*Please refer to **Section 1.4** of the CHI HIV Report Version 3.*

The International Antiviral Society introduced a set of recommendations accompanied by a grading scheme, outlined as follows[10]:

Table 4. International Antiviral Society Grading/Level of Evidence

Category, Rating	Definition
Strength of Recommendation	
A	Strong panel support for the recommendation
B	Moderate panel support for the recommendation
C	Limited or weak panel support for the recommendation

Quality of Evidence	
Ia	Evidence from 1 or more randomized clinical trials published in the peer-reviewed literature
Ib	Evidence from 1 or more randomized clinical trials presented in abstract form at peer-reviewed scientific meetings
IIa	Evidence from nonrandomized clinical trials or cohort or case-control studies published in the peer-reviewed literature
IIb	Evidence from nonrandomized clinical trials or cohort or case-control studies presented in abstract form at peer-reviewed scientific meetings
III	Recommendation based on the panel's analysis of the accumulated available evidence

The following recommendations were stated:

When to Start Antiretroviral Therapy (ART):

- Initiation of ART is recommended as soon as possible after diagnosis, **ideally within 7 days**, including on the same day as diagnosis or at the first clinic visit if the patient is ready and there is no suspicion for a concurrent opportunistic infection.
- Initiation of ART is recommended **within 2 weeks** of initiation of treatment for most opportunistic infections.
- ART should be initiated within 2 weeks after starting tuberculosis treatment for HIV patients with active tuberculosis without evidence of tuberculous meningitis.
- For a patient subject to tuberculous meningitis, high-dose steroids should be initiated along with tuberculosis treatment and ART should be initiated within 2 weeks after starting tuberculosis treatment and steroids.
- For individuals with cryptococcal meningitis, ART should be initiated 2 to 4 weeks after starting antifungal therapy.
    - ART-naïve individuals who have asymptomatic cryptococcal antigenemia and a negative lumbar puncture result with no evidence of cryptococcal meningitis should start ART immediately.
- In case a new cancer is diagnosed, initiation of ART is recommended immediately with attention to drug-drug interactions.

Recommended for Most People with HIV:

- If an individual acquires HIV while receiving pre-exposure prophylaxis with tenofovir alafenamide or tenofovir disoproxil fumarate with emtricitabine, a blood sample for genotyping should be drawn before therapy initiation.
    - A 3-drug regimen, preferably dolutegravir or bictegravir plus TXF/XTC, should be initiated if ART is to be started before genotype results are available.
- If an individual acquires HIV while receiving pre-exposure prophylaxis with cabotegravir, a blood sample for INSTI genotyping should be drawn prior to therapy initiation with an INSTI-based regimen.
    - If therapy is desired before genotype results are available or if INSTI-resistance is present, a boosted PI regimen containing darunavir and TXF/XTC is recommended.

Recommended During Pregnancy:

- TAF/XTC **plus** dolutegravir **or** TDF/XTC **plus** dolutegravir (If tenofovir alafenamide is not available) can be used in pregnant patients.
- If Dolutegravir is not available, the following drugs serve as alternative options:
    - Raltegravir (400 mg twice daily)
    - Atazanavir plus ritonavir
    - Darunavir plus ritonavir
    - Rilpivirine
- Therapy regimens that are **not recommended** to be opted in pregnancy:
    - Bictegravir
    - Doravirine
    - Cabotegravir
    - DTG/3TC
    - DTG/RPV
    - Cobicistat-containing regimens; associated with inadequate drug levels.

Switching for Virological Failure:

- If INSTI resistance is relatively limited and a new ART regimen is to include an INSTI, dolutegravir should be administered twice daily along with at least 1 and favorably 2 other fully active drugs, preferably from drug classes not

previously used. These might include fostemsavir, lenacapavir, maraviroc, ibalizumab, or enfuvirtide.

- A multidrug regimen with at least 2 fully active agents from novel drug classes should be used, along with recycled NRTIs taking into consideration their ongoing partial antiviral activity in case of high-level INSTI resistance and decreased PI susceptibility.

Weight Gain and Metabolic Complications While Receiving Antiretroviral Therapy:

- For HIV patients initiating or switching regimens, it is recommended to document weight and BMI at baseline and subsequently every 6 months to identify those with excessive weight gain.
- It is important that patients be counselled on the possibility of weight gain and potential cardiometabolic complications.
- It is also recommended to conduct an annual diabetes screening and an assessment of the cardiovascular risk score for patients receiving INSTI-based ART regimen.
- For HIV patients who gain greater than 5% body weight, lifestyle changes (exercise and diet) are recommended.

Recommendations for Persons at Risk for and With HIV Who Use Substances and Who Have Substance Use Disorders:

- HIV prevention and treatment services should incorporate substance use treatment.
- Persons with substance use disorders and HIV infection or risk for HIV should receive integrated addiction treatment with:
    - Pharmacotherapy for opioid and alcohol use disorders.
    - Contingency management for stimulant use disorders.

1.2 Additional Guidelines

This section includes the added guidelines to the previous CHI HIV report, along with their recommendations.

Table 5. List of Additional Guidelines

Additional Guidelines
WHO Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service Delivery and Monitoring [**2021**]
Primary Care Guidance for Persons with Human Immunodeficiency Virus: Update by the HIV Medicine Association of the **Infectious Diseases Society of America** [**2020**]
CDC Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV [**2019**]
Guidelines for the Prevention and Treatment of Opportunistic Infections in Children with and Exposed to HIV [**2023**]
Recommendations for the Use of Antiretroviral Drugs During Pregnancy and Interventions to Reduce Perinatal HIV Transmission in the United States [**2023**]

1.2.1 WHO Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service Delivery and Monitoring [2021]

The World Health Organization (WHO) introduced a set of recommendations accompanied by a grading scheme, outlined as follows[8]:

Table 6. WHO Quality of Evidence Grades

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

The WHO has issued the recommendations below:

Pre-Exposure Prophylaxis for Preventing the Acquisition of HIV:

- Individuals at significant risk of contracting HIV should be presented with the option of oral pre-exposure prophylaxis (PrEP) containing TDF.

This should be considered as an extra preventive measure within comprehensive strategies for preventing HIV transmission.

Post-Exposure Prophylaxis:

- A regimen with two ARV drugs is effective, but three drugs are preferred for post-exposure prophylaxis.
- The preferred HIV PEP regimen would consist of TDF + 3TC (or FTC).
- Alternative third drug options for PEP include: DTG (Preferred), ATV/r, DRV/r, LPV/r and RAL when available.
- PEP must be taken exactly as instructed and for a total of 28 days.

Co-Trimoxazole Prophylaxis:

- Recommended for adults with severe or advanced HIV disease (WHO stage 3 or 4) and/or with CD4 cell count ≤350 cells/mm3.
- Co-trimoxazole prophylaxis should be initiated regardless of CD4 cell count or WHO classification and staging in settings where malaria and/or severe bacterial infections are highly prevalent.

ART for People Living with HIV:

- All people with HIV are to be started on ART regardless of WHO clinical staging and CD4 cell count.
- After having confirmed the HIV diagnosis and after having conducted the appropriate clinical assessment, Rapid ART initiation should be offered to all HIV patients.

Pharmacological Therapy:

1. **First Line Therapy:**

- For HIV patients who are initiating ART, DTG in combination with an NRTI backbone is recommended as first line therapy.
- Alternative first line therapy that is recommended for adults and adolescents with HIV: EFV at low dose (400 mg) in combination with an NRTI backbone.
- First line therapy for neonates: An RAL-based regimen.

2. **Second Line Therapy:**

- For HIV patients who are non-responsive to non-DTG-based regimens:

  DTG in combination with an optimized nucleoside reverse-transcriptase inhibitor backbone may be recommended as second line therapy.

- For HIV patients who are non-responsive to DTG-based regimens:

  Boosted protease inhibitors in combination with an optimized nucleoside reverse-transcriptase inhibitor backbone are recommended as second line therapy.

3. **Third Line Therapy:**

- Third line therapy should include new drugs with minimal risk of cross-resistance to previously used regimens, such as INSTIs and second-generation NNRTIs and PIs.

Monitoring the Response to ART:

- In situations where viral load measurement is unavailable, treatment efficacy can be determined through CD4 count and clinical observation to identify and diagnose treatment failure.

Advanced HIV Disease:

- **Treatment of Cryptococcal Meningitis:**
  - **Induction:** A short-course (one-week) induction regimen with amphotericin B deoxycholate (1.0 mg/kg per day) and flucytosine (100 mg/kg per day, divided into four doses per day) is recommended.

    Alternative options include:

    Two weeks of fluconazole (1200 mg daily, 12 mg/kg per day for children and adolescents) **plus** flucytosine (100 mg/kg per day, divided into four doses per day)

    Two weeks of amphotericin B deoxycholate (1.0 mg/kg per day) **plus** fluconazole (1200 mg daily, 12 mg/kg per day for children and adolescents up to a maximum of 800 mg daily)
  - **Consolidation:** Fluconazole (400–800 mg daily for adults or 6–12 mg/kg per day for children and adolescents up to a maximum of 800 mg daily) is recommended.
  - For **Maintenance (Secondary Prophylaxis)**: Fluconazole (200 mg daily for adults or 6 mg/kg per day for adolescents and children) is recommended.
- **Histoplasmosis:**
  - **Induction:**

    For mild to moderate Histoplasmosis: Itraconazole 200 mg three times daily for three days and then 200 mg twice daily is recommended.

For severe or moderately severe Histoplasmosis: Liposomal amphotericin B, 3.0 mg/kg, for two weeks is recommended.

In settings in which liposomal amphotericin B is unavailable, deoxycholate amphotericin B, 0.7–1.0 mg/kg, is recommended for two weeks.

- **Maintenance Therapy:** Itraconazole 200 mg twice daily for 12 months is recommended.

- **Leishmaniasis:**
  - For HIV patients who are co-infected with visceral leishmaniasis in eastern Africa:

    A Liposomal amphotericin B (up to a total of 30 mg/kg at 5 mg/kg on days 1, 3, 5, 7, 9 and 11) + miltefosine (100 mg/day for 28 days) regimen is recommended.
  - For HIV patients who are coinfected with visceral leishmaniasis in South-East Asia:

    A Liposomal amphotericin B (up to a total of 30 mg/kg at 5 mg/kg on days 1, 3, 5, 7, 9 and 11) + miltefosine (100 mg/day for 14 days) regimen is recommended.

Lifestyle Modifications:

- HIV patients are to engage in vigorous-intensity aerobic activities, as well as those that strengthen muscle and bone at least three days a week.
- All adults should undertake regular physical activity.
- Adults should do at least 150–300 minutes of moderate-intensity aerobic physical activity; or at least 75–150 minutes of vigorous intensity aerobic physical activity; or an equivalent combination of moderate- and vigorous-intensity activity throughout the week, for substantial health benefits.

Breastfeeding Considerations:

- Mothers living with HIV should breastfeed for at least 12 months up to 24 months or longer while being fully supported for ART adherence.

1.2.2 Primary Care Guidance for Persons with Human Immunodeficiency Virus: Update by the HIV Medicine Association of the Infectious Diseases Society of America [2020]

The Infectious Diseases Society of America (IDSA) has opted for the following Grading Scheme/Level of Evidence[15]:

Table 7. IDSA Grading/Level of Evidence

Category, Grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use
Quality of Evidence	
I	Evidence from ≥1 properly randomized, controlled trial
II	Evidence from ≥1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time series; or from dramatic results from uncontrolled experiments.
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

The IDSA has issued the recommendations below:

Initial Care and Screening:

- A comprehensive present and past medical history that includes HIV-related information, medication/social/family history, review of systems, and physical examination should be obtained for all patients.
- Baseline laboratory assessments should also be conducted; the following should be obtained upon initiation of care:
    - A CD4 cell count with percentage
    - A quantitative HIV RNA (viral load) level

    - A lipid panel, complete blood count with differential white blood cell count, chemistry panel with calculated creatinine clearance and glucose level, and urinalysis
- All HIV patients of childbearing potential should have a pregnancy test done upon initiation of or reengagement in care.
- A regular cervical cancer screening, initiated at the age of 25 among women living with HIV, should be conducted at an interval of every 3–5 years when using HPV DNA detection as the primary screening test.
- Semiannual oral health examinations are to be conducted for all HIV patients.
- Screening for substance use should be conducted at all healthcare encounters.
- Screening for depression should be conducted at least annually and as needed.
- HIV patients should be screened for gonorrhea and chlamydia infection at initial presentation.
- All patients who have receptive vaginal sex should be screened for trichomoniasis at initial presentation.
- Screening for syphilis should be conducted at entry to care.
- HIV patients without a history of tuberculosis or a prior positive tuberculosis screening test should be screened for Mycobacterium tuberculosis infection.
    - Those with positive test results should be treated for latent M. tuberculosis infection after active tuberculosis has been excluded.
    - HIV patients who are in close contact with people with infectious tuberculosis should be treated for latent M. tuberculosis infection; active tuberculosis should be excluded first.
- Screening for HBV and HCV infections should be conducted upon initiation of care.
- HIV patients should be screened for evidence of immunity to hepatitis A virus (HAV); those who are not immune to HAV and HBV should be immunized.
- Testing for immunity to measles, mumps, and rubella (MMR) should be conducted for all HIV patients born in 1957 or later.
- Screening for varicella zoster virus (VZV) may be considered for HIV patients who have not had chicken pox or shingles and who have not been previously vaccinated.

Resistance Testing:

- Upon entry to care, HIV patients should be assessed for transmitted drug resistance with a genotype assay for protease inhibitor (PI), nonnucleoside reverse transcriptase inhibitor (NNRTI), and nucleoside reverse transcriptase inhibitor (NRTI) mutations.
- HIV patients who are subject to virological failure are candidates for resistance testing, including for integrase strand transfer inhibitor (INSTIs), to guide modification of ART. Testing should be performed while the patient is on the failing ART regimen or within 4 weeks of discontinuing the ART regimen.
- If transmitted INSTI resistance is suspected, genotypic testing for INSTI resistance should be obtained.

HLA B*5701:

- HLA B*5701 testing should be performed before initiation of abacavir therapy.
- Patients who are positive for the HLA B*5701 haplotype are at high risk for abacavir hypersensitivity reaction and are not candidates for treatment with abacavir.

HIV-specific Monitoring Following the Initial Assessment:

- HIV RNA measurement should take place after 2 to 4 weeks but no later than 8 weeks and then every 4 to 8 weeks until suppression is achieved. (Viral load becomes undetectable)
    - Viral load should then be monitored every 3 to 4 months to confirm maintenance of suppression.
    - This interval may be prolonged to every 6 months for adherent patients whose viral load has been suppressed for more than 2 years and whose clinical and immunologic status is stable.
- CD4 cell count should be monitored to determine the need for prophylaxis against opportunistic infections; measurements are conducted every 3 to 6 months for the first 2 years or if the virus is not suppressed.
    - For patients on suppressive ART regimens with CD4 cell counts 300–500/μL, CD4 cell count can be monitored every 12 months unless there are changes in the patient's clinical or virologic status.
    - If the CD4 cell count rises above 500 cells/μL, CD4 monitoring is optional.

Vaccinations:

- Vaccinations for pneumococcal infection, influenza, tetanus-diphtheria-whooping cough, and meningococcus should be offered to HIV patients.
- **Hepatitis A and B:**
    - Those who are susceptible to infection should be vaccinated against HBV.
    - HIV patients whose HBsAb levels are negative or <100 mIU/mL after a primary vaccine series require a second series using elevated doses or an additional dose.
    - Ideally, revaccination should be attempted after suppression of HIV viral load and improvement in CD4 cell count.
    - For nonimmune sexual partners of patients with a positive HbsAg, vaccination is also recommended.
    - All nonimmune individuals also require HAV vaccination.
      HAV IgG antibody testing should be repeated 1–2 months or at the next scheduled visit after the second vaccine to assess for immunogenicity.
    - In patients who remain seronegative, repeat vaccination is required.
- **Human Papillomavirus:**
    - Individuals ranging from 9 to 26 years of age should receive the HPV vaccine, and those between 27 and 45 years old who have HIV and were not vaccinated or did not receive adequate vaccination should be provided the vaccination regimen if appropriate.
- **Varicella Zoster Virus:**
    - Following the exposure to individuals with varicella or shingles, HIV patients who are susceptible to VZV should receive postexposure prophylaxis with varicella zoster immune globulin (VariZIG) as soon as possible – but within 10 days.
    - Varicella primary vaccination may be considered in VZV seronegative persons aged >8 years with CD4 cell counts >200 cells/μL and in children with HIV aged 1–8 years with CD4 cell percentages >15%.
    - Recombinant zoster vaccine (2-dose series) should be given to those aged >50 years on ART with CD4 cell count >200 cells/μL to prevent herpes zoster.

Contraception and Preconception Care:

- All pregnant HIV patients should be treated with ART, regardless of their immunologic or virologic status to prevent perinatal transmission, therapy should be initiated as early as possible, favorably before conception.

Special Considerations for Children:

- Resistance testing is to be conducted in HIV infants prior to ART initiation.
- All children with HIV should initiate ART as early as possible regardless of CD4 cell count, HIV RNA level, or clinical status due to rapid clinical progression.
- CD4 cell counts and HIV RNA should be monitored no less than every 3–4 months in infants and children.
- Childhood vaccinations should be administered to HIV children and infants as appropriate.

1.2.3 CDC Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV [2019]

The CDC has opted for the following Grading Scheme/Level of Evidence[16]:

Table 8. CDC Grading/Level of Evidence

Strength of Recommendation	
A	Strong recommendation for the statement
B	Moderate recommendation for the statement
C	Weak recommendation for the statement
Quality of Evidence	
I	One or more randomized trials with clinical outcomes and/or validated laboratory endpoints
II	One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes
III	Expert opinion

The CDC has issued the recommendations below:

- **Other Opportunistic Infections to Consider:**

1. **Cryptosporidiosis:**

Prevention: Chronic cryptosporidiosis occurs primarily in patients with advanced immunodeficiency. Therefore, starting the patient on ART before severe immunosuppression should prevent the disease.

Treatment: Aggressive oral and/or IV rehydration **and** replacement of electrolyte loss **and** Symptomatic treatment of diarrhea with anti-motility agent (Tincture of opium may be more effective than Loperamide), **and** initiation or optimization of ART for immune restoration to CD4 count >100 cells/mm3.

Consider: Nitazoxanide 500 mg to 1,000 mg PO twice daily with food for 14 days plus optimized ART, symptomatic treatment, and rehydration and electrolyte replacement **OR** Paromomycin 500 mg PO four times a day for 14 days–21 days plus optimized ART, symptomatic treatment, and rehydration and electrolyte replacement.

2. **Cytomegalovirus:**

Prevention: Starting the patient on ART to maintain a CD4 count >100 cells/mm3 helps prevent CMV end-organ disease.

Treatment:

a. **<u>CMV Retinitis:</u>**

Initial Therapy Followed by Chronic Maintenance Therapy for Immediate Sight Threatening Lesions (within 1500 microns of the fovea): Intravitreal injections of ganciclovir (2 mg/injection) or foscarnet (2.4 mg/injection) for 1–4 doses over a period of 7–10 days to provide higher intraocular levels of drug and faster control of the infection until steady state intraocular ganciclovir concentrations are achieved **plus** Valganciclovir 900 mg PO BID for 14–21 days, then 900 mg once daily.

Alternative Therapy: Intravitreal injections as listed above; plus one of the following systemic therapy: Ganciclovir 5 mg/kg IV q12h for 14–21 days, then 5 mg/kg IV daily, **or** Ganciclovir 5 mg/kg IV q12h for 14–21 days, then valganciclovir 900 mg PO daily **or** Foscarnet 60 mg/kg IV q8h or 90 mg/kg IV q12h for 14–21 days, then 90–120 mg/kg IV q24h **or** Cidofovir 5 mg/kg/week IV for 2 weeks, then 5 mg/kg every other week with saline hydration before and after therapy and probenecid 2 g PO 3 hours before the dose followed by 1 g PO 2 hours after the dose, and 1 g PO 8 hours after the dose (total of 4 g).

For Peripheral Lesions: Administer one of the systemic antiviral therapies listed above for the first 3–6 months until ART induced immune recovery is attained.

Treatment of Immune Recovery Uveitis (IRU): Periocular corticosteroid or a short course of a systemic steroid.

b. CMV Esophagitis or Colitis:

Preferred Therapy: Ganciclovir 5 mg/kg IV q12h, may switch to valganciclovir 900 mg PO q12h once the patient can absorb and tolerate PO therapy.

Alternative Therapy: For patients with treatment limiting toxicities to ganciclovir or with ganciclovir resistance: Foscarnet 60 mg/kg IV q8h or 90 mg/kg IV q12h is recommended.

Oral valganciclovir may be used if symptoms are not severe enough to interfere with oral absorption.

For mild cases: If ART can be initiated or optimized without delay, withholding CMV therapy may be considered.

Duration of Anti-CMV Therapy: 21–42 days or until signs and symptoms have resolved.

c. CMV Pneumonitis:

IV ganciclovir or IV foscarnet are reasonable regimens.

d. CMV Neurological Disease:

To stabilize the disease and allow for a maximum response, a combination of ganciclovir IV plus foscarnet IV is considered.

3. Mycobacterium Avium Complex:

Treatment: Clarithromycin 500 mg PO twice daily plus ethambutol 15 mg/kg PO daily, **or** Azithromycin 500–600 mg plus ethambutol 15 mg/kg PO daily when clarithromycin cannot be used. (In case of drug interactions or intolerance)

Alternative Therapy: For HIV patients with high mycobacterial loads, (>2 log CFU/mL of blood) it is recommended to add a third or fourth drug such as Rifabutin 300 mg PO daily, **or** A fluoroquinolone (e.g., levofloxacin 500 mg PO daily or moxifloxacin 400 mg PO daily), **or** An injectable aminoglycoside (e.g., amikacin 10–15 mg/kg IV daily or streptomycin 1 gm IV or IM daily).

1.2.4 Guidelines for the Prevention and Treatment of Opportunistic Infections in Children with and Exposed to HIV [2023]

These guidelines were developed by the CDC, the HIV Medicine Association of the Infectious Diseases Society of America (IDSA), the Pediatric Infectious Diseases Society, and the HHS Panel on Opportunistic Infections in Children with and Exposed to HIV—A Working Group of the Office of AIDS Research Advisory Council

(OARAC). They have introduced a set of recommendations for the management of opportunistic infections in children with and exposed to HIV accompanied by a grading scheme, outlined as follows[17]:

Table 9. DHHS Opportunistic Infections in Children with HIV Grade of Evidence/Level of Recommendation

Strength of Recommendation	
A	Strong recommendation for the statement
B	Moderate recommendation for the statement
C	Optional recommendation for the statement
Quality of Evidence for Recommendation	
I	One or more randomized trials in children with clinical outcomes and/or validated laboratory endpoints
I*	One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes
II	One or more well-designed, non-randomized trials or observational cohort studies in children with long-term clinical outcomes
II*	One or more well-designed, non-randomized trials or observational cohort studies in adults with long-term clinical outcomes with accompanying data in children from one or more smaller nonrandomized trials or cohort studies with clinical outcome data
III	Expert Opinion

The recommendations are detailed below:

1. **Cryptosporidiosis:**

- For prevention of severe enteric cryptosporidiosis, it is recommended that children with HIV be started on combination antiretroviral therapy (ART) to prevent or reverse severe immunodeficiency.
- The primary initial treatment consists of effective ART. A regimen containing a PI has shown to be effective; associated with the direct activity of the PI on the parasite.
- Nitazoxanide can be considered as an adjunct agent to ART.
- The provision of optimal nutrition is recommended.

- Dehydration and electrolyte abnormalities are also recommended to be corrected.

2. Cytomegalovirus:

- CMV end-organ disease is best prevented by antiretroviral therapy (ART) to maintain the CD4 count >100 cells/mm3 in children aged ≥6 years, or CD4 percentage >10% in children aged <6 years.
- **Primary Prophylaxis:** Valganciclovir is recommended for CMV-seropositive children who are severely immunosuppressed.

  Primary prophylaxis may be halted when the CD4 count is sustained at >100 cells/mm3 for children ≥6 years of age, or CD4 percentage >10% in children <6 years.
- **Initial treatment** for acquired CMV disease consists of Intravenous (IV) ganciclovir. Transition from IV ganciclovir to oral valganciclovir can be considered for patients who improve on IV therapy.
- Foscarnet may be used as an alternative agent or in case patients are subject to ganciclovir-resistant CMV infections.
- Combination therapy with ganciclovir and foscarnet may delay progression of retinitis in patients who failed monotherapy. The combination can also be used as initial therapy in children with sight-threatening disease and as initial therapy to stabilize CMV neurologic disease.
- In HIV children with symptomatic congenital CMV infection, treatment with valganciclovir (or IV ganciclovir) for 6 months is recommended provided it can be started during the first month of life.
- **Secondary Prophylaxis:** Secondary prophylaxis is recommended for most forms of CMV disease (except for CMV gastrointestinal disease of CMV pneumonitis) until immune reconstitution or, in the absence of immune reconstitution, for the remainder of a patient's life.

  Secondary prophylaxis regimens include IV ganciclovir, oral valganciclovir, IV foscarnet, combined IV ganciclovir and foscarnet, and IV cidofovir.

3. Mycobacterium Avium Complex

- **Prophylaxis:** For children with HIV who are subject to advanced immunosuppression, MAC prophylaxis is recommended with either Clarithromycin, Azithromycin or Rifabutin.
    - Children aged <1 year: <750 cells/mm3
    - Children aged 1 to <2 years: <500 cells/mm3

    - Children aged 2 to <6 years: <75 cells/mm3
    - Children aged ≥6 years: <50 cells/mm3
- Rifabutin is suggested for patients who are not able to tolerate clarithromycin or azithromycin; however its use is limited due to potential drug interactions and due to a lack of efficacy data.
- **Treatment:** Monotherapy is associated with the emergence of high-level drug resistance. Combination therapy with a minimum of 2 drugs (e.g., clarithromycin or azithromycin plus ethambutol) is recommended to prevent or delay the emergence of resistance.
- **In case of treatment failure** (Defined as the absence of clinical response and the persistence of mycobacteremia after 8 to 12 weeks of treatment) repeat susceptibility testing of MAC isolates is recommended.

  A new multidrug regimen of two or more drugs not previously used, and to which the isolate is susceptible, should be administered; drugs that should be considered for this scenario include rifabutin, amikacin, and a quinolone.
- **Secondary Prophylaxis:** Lifelong prophylaxis to prevent recurrence is opted for in children with a history of disseminated MAC and continued immunosuppression.

  Secondary prophylaxis typically consists of continued multidrug therapy used in treatment of disease.

1.2.5 Recommendations for the Use of Antiretroviral Drugs During Pregnancy and Interventions to Reduce Perinatal HIV Transmission in the United States [2023]

These guidelines were developed by the HHS Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission— A Working Group of the NIH Office of AIDS Research Advisory Council (OARAC). They have introduced a set of recommendations for the management of HIV in Pregnancy accompanied by a grading scheme, outlined as follows[18]:

Table 10. DHHS Grading/Level of Evidence

Strength of Recommendation	
A	Strong recommendation for the statement
B	Moderate recommendation for the statement
C	Weak recommendation for the statement
Quality of Evidence	

I	One or more randomized trials with clinical outcomes and/or validated laboratory endpoints
II	One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes
III	Expert opinion

The recommendations are detailed below:

Pre-Exposure Prophylaxis (PrEP) to Prevent HIV During Periconception, Antepartum, and Postpartum Periods:

- The only FDA approved PrEP option for HIV prevention with known safety and efficacy data in people with receptive vaginal exposure and with demonstrated safety in pregnancy is Tenofovir disoproxil fumarate/emtricitabine (TDF/FTC).
- Long-acting injectable cabotegravir (CAB-LA) is also FDA approved for people with vaginal exposure to HIV; however, its dosing, efficacy and safety remain unknown for people with PrEP indications in pregnancy.
- Additional HIV prevention strategies as condoms are recommended for the first 20 days after initiating TDF/FTC PrEP and for 28 days after last potential vaginal exposure.
- Routine PrEP follow-up should be offered by HCPs, including testing for HIV every 3 months and counseling on signs and symptoms of acute retroviral syndrome. If clinically indicated, more frequent testing may be appropriate.

Reproductive Options When One or Both Partners Have HIV:

- HIV patients should achieve sustained viral suppression – two recorded measurements of plasma viral loads that are below the limits of detection at least 3 months apart – before attempting conception to maximize their health, prevent HIV sexual transmission, and to minimize the risk of HIV transmission from pregnant people to their infants.
- Both individuals who are attempting to conceive are recommended to be screened and treated for genital tract infections prior to conception.
- Administration of antiretroviral pre-exposure prophylaxis (PrEP) to the partner without HIV reduces the risk of sexual acquisition of HIV.

Initial Evaluation and Continued Monitoring of HIV-Related Assessments During Pregnancy:

- Monitoring the plasma HIV RNA levels in pregnant HIV patients is recommended to take place at the initial antenatal visit with a review of prior HIV RNA levels, 2 to 4 weeks after initiating (or changing) antiretroviral therapy (ART), monthly until RNA levels are undetectable, and then at least every 3 months during pregnancy.
- HIV RNA levels also should be assessed at approximately 36 weeks gestation, or within 4 weeks of delivery, to inform decisions about mode of delivery and appropriate management of the newborn.
- CD4 T lymphocyte (CD4) cell count should be measured at the initial antenatal visit with review of prior CD4 counts.
- Patients who have been on ART for ≥2 years and who have had consistent viral suppression and CD4 counts that are consistently >300 cells/mm3 do not need to have their CD4 counts monitored after the initial antenatal visit during this pregnancy.
- Patients who have been on ART for < 2 years, patients with CD4 counts < 300 cells/mm3, and patients with inconsistent adherence and/or detectable viral loads should have CD4 counts monitored every 3 months during pregnancy.
- HIV drug-resistance testing is recommended to be performed during pregnancy in those whose HIV RNA levels are above the threshold for resistance testing (usually >500 copies/mL to 1,000 copies/mL but may be possible for HIV RNA >200 to ≤500 copies in some laboratories).
- Testing should be conducted:
    - Before initiating ART in ARV-naive pregnant patients who have not been previously tested for ARV drug resistance.
    - Before initiating ART in ARV-experienced pregnant patients including those who have received pre-exposure prophylaxis
    - When modifying ARV regimens for HIV patients who become pregnant while receiving ARV drugs or patients who have suboptimal virologic response to ARV drugs that were started during pregnancy
- Prior to receiving ARV-resistance test results, ART is recommended to be initiated in pregnant patients and modified based on the results if need be.
- All pregnant people with HIV should initiate antiretroviral therapy (ART) as early in pregnancy as possible, regardless of their HIV RNA level or CD4 T lymphocyte count, to maximize their health and prevent perinatal HIV transmission and secondary sexual transmission.

Use of Antiretroviral Drugs:

- Neonates should receive antiretroviral prophylaxis or presumptive HIV therapy appropriate to their risk of perinatal HIV acquisition.
- All pregnant people with HIV should initiate antiretroviral therapy (ART) as early in pregnancy as possible. Pregnant HIV patients should not delay initiating ART due to concerns about teratogenicity with first trimester exposure.
- Preferred ART regimens to be initiated in pregnant HIV patients include the regimens below:

Table 11. Preferred ART Regimens for Pregnant HIV Patients

Preferred Dual-NRTI Backbones	Advantages	Disadvantages
ABC/3TC	• Once-daily dosing • Available as an FDC • Well-tolerated during pregnancy • Reassuring PK data during pregnancy	• Requires HLA-B*5701 testing before use. ABC **should not be used** in patients who test positive for HLA-B*5701 because of the risk of developing a hypersensitivity reaction. Requires education about hypersensitivity reactions. • Not able to be used for Hepatitis B Virus/HIV Coinfection • ABC/3TC administered with ATV/r or EFV is not recommended if pretreatment HIV RNA is >100,000 copies/mL. • ABC is not recommended as part of regimens for initial treatment of early (acute or recent) HIV infection since it requires HLA-B*5701 testing before use. When results of HLA-B*5701 testing are not available, use of TDF or TAF

		rather than ABC will avoid delays in initiating ART.
TAF/FTC *or* TAF plus 3TC	• Once-daily dosing • Available as an FDC • Reassuring PK data and extensive use during pregnancy; no dose adjustment required in pregnancy • Activity against HBV • Minimal toxicity compared to ZDV/3TC • When combined with DTG, the efficacy and toxicity of TAF/FTC and TDF/FTC for treatment of pregnant patients are similar, but TAF/FTC is associated with fewer adverse birth outcomes and less risk of insufficient weight gain in pregnancy.	• When combined with DTG, TAF/FTC is associated with more treatment-emergent obesity in nonpregnant adult women compared to TDF/FTC. (Notably, the impact on weight gain in pregnancy may be beneficial, as noted in the Advantages column.)
TDF/FTC *or* TDF/3TC	• Once-daily dosing • Available as an FDC • Reassuring PK data during pregnancy; no dose adjustment required in pregnancy • Activity against HBV • When combined with DTG, the efficacy and toxicity of TAF/FTC and TDF/FTC for treatment of pregnant patients are similar.	• Potential concerns about fetal bone and early-life growth abnormalities with TDF, although clinical findings are reassuring to date • TDF has potential renal toxicity; thus, TDF-based, dual-NRTI combinations should be used with caution in patients with renal insufficiency.
***Preferred* INSTI Regimens**	**Advantages**	**Disadvantages**
DTG/ABC/3TC (FDC) *or*	• Once-daily dosing • DTG/ABC/3TC is available as an FDC.	• Potential concerns about excess weight gain with DTG

DTG plus a *Preferred* Dual-NRTI Backbone	• Sufficient data about PK, efficacy, and safety of DTG in pregnancy • High rates of viral suppression • Dose adjustments during pregnancy are not needed. • May be particularly useful when drug interactions or the potential for preterm delivery with a PI-based regimen are a concern. • DTG has been shown to rapidly decrease viral load in ARV-naive pregnant women who present to care later in pregnancy. In nonpregnant adults, DTG is associated with lower rates of INSTI resistance than RAL, and DTG allows for once-daily dosing; for these reasons, DTG is particularly useful for pregnant people presenting late in pregnancy. • DTG with a NRTI backbone of TAF or TDF with 3TC or FTC is the *Preferred* regimen for initial treatment in people with early (acute or recent) HIV infection in people without a history of CAB exposure for PrEP, see Early (Acute or Recent) HIV Infection.	• DTC/ABC/3TC requires HLA-B*5701 testing before use (see ABC/3TC above). • Specific timing and/or fasting recommendations apply if DTG is taken with calcium or iron (e.g., in prenatal vitamins; see Table 14. Antiretroviral Drug Use in Pregnant People With HIV: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy). • DTG is not *Preferred* for initial treatment in people with early (acute or recent) HIV infection and a history of CAB exposure for PrEP due to concerns about INSTI resistance mutations; DRV/r is *Preferred* in this situation.
***Preferred* PI Regimens**	**Advantages**	**Disadvantages**

DRV/r plus a *Preferred* Dual-NRTI Backbone	• When a PI-based regimen is indicated, ATV or DRV is recommended over LPV/r. • DRV/r with a NRTI backbone of TAF or TDF with 3TC or FTC is the *Preferred* regimen for initial treatment in people with early (acute or recent) HIV infection and a history of CAB exposure for PrEP, see Early (Acute or Recent) HIV Infection.	• Not available as an FDC • Requires twice-daily dosing during pregnancy • Requires administration with food • PIs may increase the risk of preterm birth.

Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection:

- Postpartum ARV regimens are to be initiated in all newborns who were exposed perinatally to HIV to reduce the risk of HIV perinatal transmission within 6 hours of delivery.
- For newborns at low-risk of perinatal HIV acquisition, a 2-week zidovudine (ZDV) ARV regimen is recommended for ARV prophylaxis **if** the newborn is ≥37 weeks gestation and is born to a person with HIV who:
    - Currently is undergoing and has undergone a minimum of 10 uninterrupted weeks of antiretroviral therapy (ART) while pregnant
    - Has successfully reached and sustained viral suppression, which is defined as having at least two consecutive HIV RNA tests with results below 50 copies/ml, with the tests being at least 4 weeks apart
    - Has a viral load below 50 copies/ml either at or after 36 weeks of gestation
    - Had no occurrence of acute HIV infection during the pregnancy
    - Has reported consistent adherence to ART, and there have been no concerns or issues identified regarding their adherence to the treatment.
- Infants born to individuals who do not meet the criteria above but who have a viral load <50 copies/mL at or after 36 weeks gestation should receive ZDV for 4 to 6 weeks.
- Newborns at high risk of perinatal acquisition of HIV (Those born to people with HIV who have not received antepartum ARV drugs, or have received only

intrapartum ARV drugs, or have received antepartum ARV drugs but did not achieve viral suppression within 4 weeks of delivery, or those who have primary or acute HIV infection during pregnancy) should receive presumptive HIV therapy with 3-drug regimens administered from birth for 2 to 6 weeks; if the duration of the 3-drug regimen is shorter than 6 weeks, ZDV should be continued alone, to complete total of 6 weeks of prophylaxis.

- All premature infants <37 weeks gestation who are not at high risk of perinatal acquisition of HIV should receive ZDV for 4 to 6 weeks.
- To prevent Pneumocystis Jirovecii Pneumonia (PJP), all infants born to HIV patients should begin PJP prophylaxis at age 4 to 6 weeks.

Section 2.0 Drug Therapy

This section comprises four subsections: the first contains the newly recommended drugs, the second covers drug modifications, the third one outlines the drugs that have been withdrawn from the market, and the fourth details FDA/EMA approved drugs that are not SFDA registered.

2.1 Additions

The following drugs have been newly approved for HIV; some of which are SFDA registered, and others are not. The first section below tackles the SFDA registered new molecules along with their HTA analysis and the second section includes non-SFDA registered new molecules.

2.1.1 Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

2.1.1.1 Lamivudine/Zidovudine

The following table describes the characteristics of the combination agent Lamivudine/Zidovudine[12,13]:

Table 12. Drug Therapy with Lamivudine/Zidovudine

SCIENTIFIC NAME LAMIVUDINE/ZIDOVUDINE	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	B20
Drug Class	Antiretroviral Agent
Drug Sub-class	Nucleoside Reverse Transcriptase Inhibitor
ATC Code	J05AR01
Pharmacological Class (ASHP)	Nucleoside Reverse Transcriptase Inhibitor
DRUG INFORMATION	
Dosage Form	Tablet
Route of Administration	Oral Use

Dose (Adult) [DDD]*	One tablet (lamivudine 150 mg/zidovudine 300 mg) twice daily
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	Children and Adolescents weighing ≥30 kg: Lamivudine 150 mg and zidovudine 300 mg per tablet: One tablet twice daily.
Maximum Daily Dose Pediatrics*	N/A
Adjustment	Altered Kidney Function: For CrCl <50 mL/minute, use is not recommended. Hepatic Impairment: Use is not recommended.
Prescribing edits*	PA, AGE, CU, MD
AGE (Age Edit)	The pharmacokinetics of lamivudine and zidovudine have not been studied in subjects over 65 years of age.
CU (Concurrent Use Edit)	Lamivudine/Zidovudine is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. For Pediatrics: Use in combination with other antiretroviral (ARV) agents; evaluate gene mutation and ARV resistance patterns.
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	Therapy should be initiated by a physician experienced in the management of HIV infection.
PA (Prior Authorization)	Lamivudine/Zidovudine, a combination of two nucleoside analogue reverse transcriptase inhibitors, is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. It is usually given as one tablet (lamivudine 150 mg/zidovudine 300 mg) twice daily. Patients require a positive HIV test in order to initiate therapy. Because Lamivudine/Zidovudine is a fixed-dose tablet and cannot be dose adjusted, it is not recommended in

	patients requiring dosage adjustment or with hepatic impairment or experiencing dose-limiting adverse reactions + Check other PEs (AGE, CU, MD)
QL (Quantity Limit)	N/A
ST (Step Therapy)	N/A
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common:** Headache, nausea, malaise and fatigue, nasal signs and symptoms, diarrhea, and cough. **Most serious:** Lactic acidosis, myopathy, severe anemia, neutropenia.
Drug Interactions*	**Category X:** BCG (Intravesical) Betibeglogene Autotemcel Cladribine Dipyrone Elivaldogene Autotemcel Fexinidazole Pacritinib Stavudine
Special Population	N/A
Pregnancy	Lamivudine in combination with zidovudine is considered as an alternative NRTI backbone for pregnant patients with HIV infection who are antiretroviral-naive, who have had antiretroviral therapy (ART) in the past but are restarting, or who require a new ART regimen (due to poor tolerance or poor virologic response of current regimen). Patients who become pregnant while taking this combination may continue if viral suppression is effective and the regimen is well tolerated. Although use of this combination has the most experience

	for use in pregnancy, it has an increased potential for hematologic toxicity and requires twice-daily dosing.
Lactation	Breastfeeding is not recommended.
Contraindications	Lamivudine/Zidovudine is contraindicated in patients with a previous hypersensitivity reaction to lamivudine or zidovudine.
Monitoring Requirements	Monitoring parameters include amylase, bilirubin, signs and symptoms of pancreatitis. Monitor CBC with differential and platelet count at least every 2 weeks, liver function tests (including signs/symptoms of hepatomegaly), MCV, serum creatinine kinase, viral load, and CD4 count; observe for appearance of opportunistic infections; signs of muscle weakness or pain; blood lactate levels and signs of acidosis.
Precautions	Lamivudine/Zidovudine should not be administered with other lamivudine- or zidovudine-containing products or emtricitabine-containing products. Hepatic decompensation, some fatal, has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy and interferon alfa with/without ribavirin. Discontinue Lamivudine/Zidovudine as medically appropriate and consider dose reduction or discontinuation of interferon alfa, ribavirin, or both. Exacerbation of anemia has been reported in HIV-1/HCV co-infected patients receiving ribavirin and zidovudine. Coadministration of ribavirin and zidovudine is not advised.

	Pancreatitis: Use with caution in patients with a history of pancreatitis or other significant risk factors for pancreatitis. Discontinue treatment as clinically appropriate. Immune reconstitution syndrome and redistribution/accumulation of body fat have been reported in patients treated with combination antiretroviral therapy.
Black Box Warning	**Hematologic Toxicity:** Zidovudine, a component of lamivudine/zidovudine tablets, has been associated with hematologic toxicity, including neutropenia and severe anemia, particularly in patients with advanced HIV-1 disease. **Myopathy:** Prolonged use of zidovudine has been associated with symptomatic myopathy. **Exacerbations of Hepatitis B:** Severe, acute exacerbations of hepatitis B have been reported in patients who are coinfected with hepatitis B virus (HBV) and HIV-1 and have discontinued lamivudine, a component of lamivudine/zidovudine. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue lamivudine/zidovudine and are coinfected with HIV-1 and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted. **Lactic acidosis and severe hepatomegaly with steatosis:** Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with use of nucleoside

	analogues, including lamivudine and zidovudine. Discontinue lamivudine/zidovudine if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur.
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of HIV treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Lamivudine/Zidovudine.**

Table 13. Lamivudine/Zidovudine HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Lamivudine/Zidovudine	NICE	N/A
	CADTH	N/A
	HAS[19]	June 29, 2017 – Positive Recommendation: The actual benefit of Lamivudine/Zidovudine remains substantial in the Marketing Authorization indication.
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT- Lamivudine/Zidovudine

Lamivudine/Zidovudine, a combination of two nucleoside analogue reverse transcriptase inhibitors, is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. It is usually given as one tablet (lamivudine 150 mg/zidovudine 300 mg) twice daily. The use of Lamivudine/Zidovudine is backed by HAS as an HTA body. Its use is limited by the risk of lactic acidosis, myopathy, severe anemia, and neutropenia.

2.1.2 Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)/Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

2.1.2.1 Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate

The following table describes the characteristics of the combination agent Doravirine, Lamivudine, and Tenofovir Disoproxil Fumarate[12,13]:

Table 14. Drug Therapy with Doravirine, Lamivudine, and Tenofovir Disoproxil Fumarate

SCIENTIFIC NAME DORAVIRINE/LAMIVUDINE/TENOFOVIR DISOPROXIL FUMARATE	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	B20
Drug Class	Antiretroviral Agent
Drug Sub-class	Non-Nucleoside Reverse Transcriptase Inhibitor/Nucleoside Reverse Transcriptase Inhibitor
ATC Code	J05AR24
Pharmacological Class (ASHP)	Antiretroviral, Reverse Transcriptase Inhibitor, Non-nucleoside (Anti-HIV); Antiretroviral, Reverse Transcriptase Inhibitor, Nucleoside (Anti-HIV); Antiretroviral, Reverse Transcriptase Inhibitor, Nucleotide (Anti-HIV)
DRUG INFORMATION	
Dosage Form	Tablet
Route of Administration	Oral route
Dose (Adult) [DDD]*	1 tablet (doravirine 100 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg) once daily.
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	Children and Adolescents weighing ≥35 kg: Oral: 1 tablet (doravirine 100 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg) once daily.

Maximum Daily Dose Pediatrics*	N/A
Adjustment	Altered Kidney Function: CrCl <50 mL/minute: Use is not recommended. Hepatic Impairment: No dosage adjustment necessary.
Prescribing edits*	PA, AGE, MD
AGE (Age Edit)	Safety and efficacy of Doravirine/ Lamivudine/Tenofovir Disoproxil Fumarate have not been established in pediatric patients less than 18 years of age. Clinical trials of doravirine, lamivudine, or TDF did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects.
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	Delstrigo can only be obtained with a prescription and treatment should be started by a doctor experienced in managing HIV infection.
PA (Prior Authorization)	The three-drug combination of doravirine, lamivudine, and tenofovir disoproxil fumarate is indicated as a complete regimen for the treatment of HIV-1 infection in adult patients with no antiretroviral treatment history. It is usually given as 1 tablet (doravirine 100 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg) once daily. Testing for HBV infection prior to or when initiating therapy. Assessment of serum creatinine, estimated creatinine clearance, urine glucose and urine protein is also deemed necessary. The combination agent is not recommended in patients with estimated creatinine clearance below

	50 mL per minute. + Check other PEs (AGE, MD)
QL (Quantity Limit)	N/A
ST (Step Therapy)	N/A
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** Dizziness, nausea, and abnormal dreams. **Most serious:** Acute exacerbation of Hepatitis B, worsening kidney function, decreased bone mineral density, immune reconstitution syndrome.
Drug Interactions*	**Category X:** Adefovir Apalutamide Betibeglogene Autotemcel CarBAMazepine Cladribine Delavirdine Efavirenz Elivaldogene Autotemcel Enzalutamide Ergonovine Etravirine Fosphenytoin Leniolisib Lumacaftor and Ivacaftor Mitotane Nevirapine OXcarbazepine Pacritinib PHENobarbital Phenytoin Primidone RifAMPin Rifapentine Rilpivirine Sparsentan St John's Wort

	Taurursodiol
Special Population	N/A
Pregnancy	Insufficient data is available to make recommendations for use in pregnant patients with HIV who are antiretroviral-naive, who have had antiretroviral therapy (ART) in the past but are restarting, or who require a new ART regimen (due to poor tolerance or poor virologic response of current regimen). Patients who become pregnant while taking this combination may continue with frequent monitoring if viral suppression is effective and the regimen is well tolerated or consider changing to a preferred or alternate regimen due to insufficient data for doravirine. If continued in patients who are virologically suppressed, frequent viral load monitoring (every 1 to 2 months) is recommended.
Lactation	Breastfeeding is not recommended due to the potential for HIV-1 transmission.
Contraindications	Hypersensitivity to lamivudine or any component of the formulation; concurrent administration of strong CYP3A inducers, including, but not limited to carbamazepine, oxcarbazepine, phenobarbital, phenytoin, enzalutamide, rifampin, rifapentine, mitotane, St John's wort.
Monitoring Requirements	Monitor CD4 count, viral load; liver function tests, serum creatinine, urine glucose, urine protein (prior to initiation and as clinically indicated during therapy); serum phosphorous (in patients with chronic kidney disease); bone density (patients with a history of bone fracture or have risk factors for bone loss); testing for HBV is

	recommended prior to the initiation of antiretroviral therapy. Patients with HIV and HBV coinfection should hepatic function monitored for several months following therapy discontinuation.
Precautions	**New onset or worsening renal impairment:** Prior to or when initiating Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate, and during treatment with Doravirine/ Lamivudine/Tenofovir Disoproxil Fumarate, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. Avoid administering Doravirine/ Lamivudine/Tenofovir Disoproxil Fumarate with concurrent or recent use of nephrotoxic drugs. **Bone loss and mineralization defects:** Consider monitoring BMD in patients with a history of pathologic fracture or other risk factors of osteoporosis or bone loss. Monitor for **Immune Reconstitution Syndrome.**
Black Box Warning	**Posttreatment acute exacerbation of hepatitis B:** Severe acute exacerbations of hepatitis B (HBV) have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued lamivudine or tenofovir disoproxil fumarate (TDF). Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are coinfected with HIV-1 and HBV and discontinue

	doravirine/lamivudine/tenofovir disoproxil fumarate. If appropriate, initiation of anti-hepatitis B therapy may be warranted.
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of HIV treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate.**

Table 15. Doravirine/ Lamivudine/Tenofovir Disoproxil Fumarate HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Doravirine/ Lamivudine/Tenofovir Disoproxil Fumarate	NICE	N/A
	CADTH[20]	Positive Recommendation – May 16, 2019: The CADTH Canadian Drug Expert Committee (CDEC) recommends that DOR/3TC/tenofovir disoproxil fumarate (TDF) be reimbursed as a complete regimen for the treatment of HIV-1 infection in adults without past or present evidence of viral resistance to DOR, 3TC, or tenofovir only if the following condition is met. **Condition for Reimbursement:** **Pricing Condition:** The total cost of treatment with DOR/3TC/TDF should not exceed the total drug plan cost of treatment with the least costly alternative regimen for the treatment of HIV-1.
	HAS[21]	Positive Recommendation – September 2, 2022: Opinion in favor of reimbursement in the care of **adolescents aged 12 to under 18,**

		and weighing at least 35 kg , infected with HIV-1 without previous or current evidence of resistance to the class of non-nucleoside inhibitors of reverse transcriptase (NNRTI), in an **indication restricted** to patients with a low viral load ≤ 100,000 copies/mL, when an NNRTI is indicated and the use of rilpivirine is not appropriate.
	IQWIG[22]	Negative Recommendation – July 28, 2022: In its dossier, the company does not present suitable data to assess the added benefit of DOR/3TC/TDF compared with the ACT in adolescents aged 12 years and older and with a body weight of ≥ 35 kg who are infected with HIV 1, whereby the HIV viruses must not have mutations that are known to be associated with resistances to the substance class of NNRTIs, 3TCs or tenofovir, and who have experienced toxicities that preclude the use of other treatment regimens without TDF. This resulted in no hint of an added benefit of DOR/3TC/TDF in comparison with the ACT; an added benefit is therefore not proven. The negative recommendation is attributed to insufficient data.
	PBAC	N/A

CONCLUSION STATEMENT- Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate

Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate is a three-drug combination of doravirine (a nonnucleoside reverse transcriptase inhibitor [NNRTI]), lamivudine, and tenofovir disoproxil fumarate (both nucleoside analogue reverse transcriptase inhibitors) and is indicated as a complete regimen for the treatment of HIV-1 infection in adult patients with no antiretroviral treatment history. The recommended dosage is one tablet (doravirine 100 mg/lamivudine 300 mg/tenofovir

disoproxil fumarate 300 mg) taken orally once daily with or without food in adult patients. Its use is backed by several HTA bodies as CADTH and HAS. Limitations to the use of the combination regimen include the heightened risk of acute exacerbation of Hepatitis B, worsening kidney function, decreased bone mineral density, and immune reconstitution syndrome.

2.2 Drug Modifications

The following modifications and adjustments have been implemented since the 2020 report:

- An MD Prescribing Edit (PE) was added to every ART agent; “Therapy should be prescribed by a physician experienced in the management of HIV infection.”
- An AGE restriction was added to the Abacavir PEs: “The pharmacokinetics of Abacavir have not been studied in patients over 65 years of age.”
- An AGE restriction was added to the Lamivudine PEs: “The pharmacokinetics of Lamivudine have not been studied in patients over 65 years of age.”
- An AGE restriction was added to the Tenofovir Alafenamide PEs: “Safety and effectiveness of Tenofovir Alafenamide in pediatric patients less than 18 years of age have not been established. Limited data exists for patients aged 65 years and older.”
- An AGE restriction was added to the Zidovudine PEs: “The pharmacokinetics of Zidovudine have not been studied in patients over 65 years of age.”
- An AGE restriction was added to Dolutegravir PEs: “Safety and efficacy of Dolutegravir have not been established in pediatric patients younger than 12 years or weighing less than 40 kg, or in pediatric patients who are INSTI-experienced with documented or clinically suspected resistance to other INSTIs. (Raltegravir, Elvitegravir)”
- An AGE restriction was added to the Raltegravir PEs: “The safety and efficacy of Raltegravir have not been established in children less than 2 years of age.”
- The AGE PE was modified for Maraviroc. Instead of the restriction for use in patients under the age of 2, the restriction is applied to patients less than 16 years of age.
- An AGE restriction was added to the Dolutegravir, Abacavir, Lamivudine PEs: “The pharmacokinetics of abacavir or lamivudine have not been studied in subjects older than 65 years.”

- Prior Authorization (PA) was removed for Trimethoprim/Sulfamethoxazole. An AGE restriction was added “There are limited data on the safety of repeated use of BACTRIM in pediatric patients under two years of age.”
- PA was removed for Amphotericin B, Fluconazole, and Itraconazole.
- An AGE restriction was added to the Ketoconazole PEs: “Limited data is available for children less than 2 years of age.”
- An AGE restriction was added to Aciclovir PEs: “Safety and effectiveness of oral formulations of acyclovir in pediatric patients younger than 2 years of age have not been established.”
- An AGE restriction and a quantity limit were added to the Betamethasone Valerate: “Betamethasone valerate is contraindicated in children under one year of age. Quantity limit: A maximum of 50g weekly.”
- An AGE restriction was added to the Betamethasone Dipropionate PEs: “Use of Betamethasone Dipropionate in pediatric patients younger than 13 years of age is not recommended due to the potential for HPA axis suppression.”
- An AGE restriction was added to Mometasone Furoate PEs: “Mometasone Furoate should not be used in children under 2 years of age.”
- An AGE restriction was added to Fluticasone Propionate PEs: “The safety and effectiveness of Fluticasone Propionate in children younger than 1 year of age have not been established.”
- An AGE restriction was added to Clobetasol Propionate PEs: “The safety and effectiveness of Clobetasol Propionate in children younger than 1 year of age have not been established.”
- A Quantity Limit (QL) was added to Clobetasol Propionate PEs: “The maximum weekly dose should not exceed 50 gms/week.”
- An AGE restriction was added to Bilastine PEs: “Bilastine is not to be given to children less than 12 years of age.”
- An AGE restriction was added to Cetirizine Hydrochloride: “The safety and effectiveness of cetirizine in pediatric patients under the age of 6 months have not been established.”
- An AGE restriction was added to Chlorpheniramine Maleate: “Limited data is available for children under the age of 6 years old and is considered a high-risk and potentially inappropriate medication to be avoided in patients 65 years and older.”

- An AGE restriction was added to Cyproheptadine Hydrochloride PEs: “Safety and effectiveness in children below the age of two years have not been established.”
- An AGE restriction was added to Desloratadine PEs: “Efficacy of Desloratadine has not been investigated in pediatric trials in children less than 12 years of age.”
- An AGE restriction was added to Dimenhydrinate PEs: “Dimenhydrinate is not to be used in children less than 2 years of age. It is also identified in the Beers Criteria as a potentially inappropriate and high-risk medication to be avoided in patients 65 years and older.”
- An AGE restriction was added to Dimetindene Maleate PEs: “Dimethindene may be a potentially inappropriate medication to be avoided in patients 65 years and older.”
- An AGE restriction was added to Fexofenadine Hydrochloride PEs: “The FDA does not recommend OTC uses for these products in pediatric patients <2 years of age and recommends using with caution in pediatric patients ≥2 years of age.”
- An AGE restriction was added to Levocetirizine Hydrochloride PEs: “Safety and efficacy for the use of cough and cold products in pediatric patients <4 years of age is limited.”
- An AGE restriction was added to Loratadine PEs: “The FDA does not recommend OTC uses for these products in pediatric patients <2 years of age and recommends using with caution in pediatric patients ≥2 years of age.”
- An AGE restriction was added to Promethazine PEs: “Promethazine should not be used in pediatric patients younger than 2 years because of the potential for fatal respiratory depression. It is also identified in the Beers Criteria as a potentially inappropriate and high-risk medication to be avoided in patients 65 years and older.”

2.3 Delisting

The medications below are no longer SFDA registered, therefore, it is recommended to delist the following drugs from CHI formulary[12]:

- Nevirapine
- Efavirenz
- Enfuvirtide
- Atazanavir

- Flucytosine
- Griseofulvin

2.4 Other Drugs

The following drugs discussed are newly approved drugs which are FDA approved; however, they are not yet SFDA registered.

Cabotegravir XR Injectable Suspension (Apretude®)[23]

Cabotegravir XR Injectable Suspension was approved by the FDA on December 21st of 2021. It was granted a marketing authorization by the EMA on July 20th of 2023. Apretude is an HIV-1 integrase strand transfer inhibitor (INSTI) indicated in at-risk adults and adolescents weighing at least 35 kg for PrEP to reduce the risk of sexually acquired HIV-1 infection. Individuals must have a negative HIV-1 test prior to initiating Apretude (with or without an oral lead-in with oral cabotegravir) for HIV-1 PrEP. Apretude is to be initiated as a single 600-mg (3-mL) injection given 1 month apart for 2 consecutive months on the last day of an oral lead-in if used or within 3 days and continue with the injections every 2 months thereafter.

Cabotegravir, Tablet Formulation (Vocabria®)[24]

Vocabria was approved by the FDA in January of 2021 and by the EMA in December of 2020. Vocabria is an HIV-1 integrase strand transfer inhibitor (INSTI) indicated in combination with Rilpivirine for short-term treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA less than 50 copies/mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine, for use as oral lead-in to assess the tolerability of cabotegravir prior to administration of Cabenuva (cabotegravir; rilpivirine) extended-release injectable suspensions or as oral therapy for patients who will miss planned injection dosing with Cabenuva. Vocabria 30mg is taken orally once daily for approximately 1 month in combination with one tablet of rilpivirine 25 mg taken orally once daily with a meal.

Cabotegravir and Rilpivirine, Injectable Formulation (Cabenuva®)[25]

Cabenuva was approved by the FDA in January of 2021 and by the EMA in December 2020. CABENUVA, a 2-drug co-packaged product of cabotegravir, an integrase strand transfer inhibitor (INSTI), and rilpivirine, a non-nucleoside reverse transcriptase inhibitor (NNRTI), is indicated as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or

suspected resistance to either cabotegravir or rilpivirine. Prior to initiating treatment with CABENUVA, oral lead-in dosing should be used for approximately 1 month to assess the tolerability of cabotegravir and rilpivirine. Cabenuva injections (600 mg of cabotegravir and 900 mg of rilpivirine) are initiated on the last day of oral lead-in and continued at a dose of 400 mg of cabotegravir and 600 mg of rilpivirine every month thereafter.

Tipranavir (Aptivus®)[26]

Tipranavir was approved by the FDA on June 22nd of 2005. The European Commission granted a marketing authorization valid throughout the European Union for Aptivus on 25 October 2005. APTIVUS, a protease inhibitor, co-administered with ritonavir, is indicated for combination antiretroviral treatment of HIV-1 infected patients who are treatment-experienced and infected with HIV-1 strains resistant to more than one protease inhibitor. Aptivus/Ritonavir is not to be used in treatment-naïve patients. 500 mg Aptivus should be co-administered with 200 mg ritonavir, twice daily.

Emtricitabine/Rilpivirine/Tenofovir Disoproxil Fumarate (Complera®)[27]

Complera was approved by the FDA in August of 2011 and was granted a marketing authorisation valid throughout the European Union on 28 November 2011. Complera, a combination of two nucleoside analog HIV-1 reverse transcriptase inhibitors (emtricitabine and tenofovir disoproxil fumarate) and one non-nucleoside reverse transcriptase inhibitor (rilpivirine), is indicated for use as a complete regimen for the treatment of HIV-1 infection in patients weighing at least 35 kg as initial therapy in those with no antiretroviral treatment history and with HIV-1 RNA less than or equal to 100,000 copies/mL at the start of therapy, or to replace a stable antiretroviral regiment in those who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen for at least 6 months with no treatment failure and no known substitutions associated with resistance to the individual components of Complera.

Tesamorelin for Injection (Egrifta SV®)[28]

Egrifta SV was approved by the FDA in November of 2010. Ferrer Internacional, S.A. proceeded to withdraw its application for a centralised marketing authorisation for the medicine Egrifta (tesamorelin), 2 mg, powder for solution for injection across the European Union. Egrifta is a growth hormone releasing factor (GRF) analog indicated for the reduction of excess abdominal fat in HIV-infected patients with lipodystrophy. Egrifta is to be given as a 2mg injection subcutaneously once daily.

Dolutegravir and Rilpivirine (Juluca®)[29]

Juluca was approved by the FDA in 2017 and by the EMA in 2018. Juluca, a two-drug combination of dolutegravir, an integrase strand transfer inhibitor (INSTI), and rilpivirine, a non-nucleoside reverse transcriptase inhibitor (NNRTI), is indicated as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Juluca. It is given as one tablet (50 mg of dolutegravir (equivalent to 52.6 mg dolutegravir sodium) and 25 mg of rilpivirine (equivalent to 27.5 mg rilpivirine hydrochloride)) taken orally once daily with a meal.

Emtricitabine, Rilpivirine, and Tenofovir Alafenamide (Odefsey®)[30]

Odefsey was approved by the FDA in March of 2016 and by the EMA in June of 2016. Odefsey is a three-drug combination of emtricitabine (FTC) and tenofovir alafenamide (TAF), both nucleoside analog reverse transcriptase inhibitors (NRTIs), and rilpivirine (RPV), a non-nucleoside reverse transcriptase inhibitor (NNRTI), and is indicated as a complete regimen for the treatment of HIV-1 infection in patients weighing at least 35kg as initial therapy in those with no antiretroviral treatment history with HIV-1 RNA less than or equal to 100,000 copies per mL; or to replace a stable antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Odefsey. It is given as one tablet (200 mg of FTC, 25 mg of RPV and 25 mg of TAF) orally once daily with a meal.

Crofelemer (Mytesi®)[31]

Crofelemer was approved by the FDA in December of 2012. It was designated as an orphan medicine for the treatment of short bowel syndrome in the European Union on 10 December 2021. Mytesi is an anti-diarrheal indicated for the symptomatic relief of non-infectious diarrhea in adult patients with HIV/AIDS on antiretroviral therapy. The recommended adult dosage is 125 mg taken orally twice a day, with or without food.

Elvitegravir, Cobicistat, Emtricitabine, Tenofovir Disoproxil Fumarate (Stribild®)[32]

Stribild was approved by the FDA in August of 2012 and by the EMA in May of 2013. Stribild is a four-drug combination of elvitegravir, an integrase strand transfer inhibitor (INSTI), cobicistat, a CYP3A inhibitor, and emtricitabine and tenofovir DF, both nucleoside analog reverse transcriptase inhibitors (NRTI) and is indicated as a complete regimen for the treatment of HIV-1 infection in adults and pediatric

patients 12 years of age and older weighing at least 35 kg who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies/mL) on a stable antiretroviral regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Stribild. It is given as one tablet (150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 300 mg of tenofovir disoproxil fumarate) taken once daily.

Lenacapavir (Sunlenca®)[33]

Sunlenca was approved by the FDA in December of 2022 and by the EMA in August of 2022. Sunlenca, a human immunodeficiency virus type 1 (HIV-1) capsid inhibitor, in combination with other antiretroviral(s), is indicated for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations. The following dosing regimen is opted:

Table 16. Lenacapavir Treatment Regimen for Initiation and Maintenance

Treatment time	Lenacapavir dosage	
Initiation dosing	**2-day initiation**	**15-day initiation**
Day 1	**Oral:** 600 mg once **and** **SUBQ:** 927 mg once	**Oral:** 600 mg once
Day 2	**Oral:** 600 mg once	**Oral:** 600 mg once
Day 8		**Oral:** 300 mg once
Day 15		**SUBQ:** 927 mg once
Maintenance dosing	**SUBQ:** 927 mg every 6 months (26 weeks) from the date of last injection ±2 weeks	

Darunavir, Cobicistat, Emtricitabine, and Tenofovir Alafenamide (Symtuza®)[34]

Symtuza was FDA approved in July of 2018 and was EMA approved in September of 2017. Symtuza is a four-drug combination of darunavir (DRV), a human immunodeficiency virus (HIV-1) protease inhibitor, cobicistat (COBI), a CYP3A inhibitor, and emtricitabine (FTC) and tenofovir alafenamide (TAF), both HIV-1 nucleoside analog reverse transcriptase inhibitors, and is indicated as a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 40 kg who have no prior antiretroviral treatment history or who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 6 months and have no known substitutions associated with resistance to darunavir or tenofovir. It is given as one tablet (800 mg of darunavir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir

alafenamide (equivalent to 11.2 mg of tenofovir alafenamide fumarate)) taken once daily.

Abacavir Sulfate; Lamivudine; Zidovudine AZT (Trizivir®)[35]

Trizivir was FDA approved in November of 2000 and EMA approved in December of 2000. Trizivir, a combination of abacavir, lamivudine, and zidovudine, each nucleoside analogue HIV-1 reverse transcriptase inhibitors, is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. It is given as 1 tablet (300 mg abacavir, 150 mg lamivudine, and 300 mg zidovudine) twice daily.

Section 3.0 Key Recommendations Synthesis

- All people with HIV are to be started on ART regardless of WHO clinical staging and CD4 cell count. **(Strong Recommendation for adults, pregnant and breastfeeding women, and infants diagnosed in the first year of life. Conditional recommendation for adolescents and children living with HIV one year old to less than 10 years old.)**
- In order to increase ART uptake, enhance engagement in care, accelerate the time to viral suppression, and to reduce the time during which people with newly diagnosed HIV can transmit HIV, many clinics have adopted a rapid start policy to initiate ART on the day of HIV diagnosis. **(Strong recommendation)**
- Measurement of plasma viral load should take place before initiation of ART, within 4 to 8 weeks after treatment initiation, before ART change and within 4 to 8 weeks after changing therapy/treatment modification; the purpose of the measurements is to confirm an adequate virologic response to ART, indicating patient adherence to therapy and appropriate regimen selection. **(Level AIII)**
- Individuals at significant risk of contracting HIV should be presented with the option of oral pre-exposure prophylaxis (PrEP) containing TDF.

  This should be considered as an extra preventive measure within comprehensive strategies for preventing HIV transmission. **(Strong Recommendation)**
- Long-acting injectable cabotegravir (CAB-LA) was approved by the FDA for HIV pre-exposure prophylaxis (PrEP). **(Level AII)**
- For HIV patients who do not have a history of using long-acting cabotegravir (CAB-LA) as pre-exposure prophylaxis (PrEP), the following regimens are recommended:

- Bictegravir/tenofovir alafenamide (TAF)/emtricitabine (FTC)
- DTG/abacavir/3TC (Only for individuals who are HLA-B*5701 negative and without chronic hepatitis B virus (HBV) coinfection.)
- DTG plus (TAF or tenofovir disoproxil fumarate [TDF]) plus (FTC or 3TC)
- DTG/3TC (With the exception of individuals with HIV RNA >500,000 copies/mL, HBV coinfection, or when ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available.) **(Level AI)**

- For HIV patients with a history of using CAB-LA as PrEP, INSTI genotypic resistance testing should be done before the start of ART.

  If treatment is initiated prior to results of genotypic testing, the following regimen is recommended:

  - A boosted PI regimen of darunavir/ritonavir (DRV/r) or darunavir/cobicistat (DRV/c) plus (TAF or TDF) plus (FTC or 3TC). **(Level AIII)**
- During Pregnancy: TAF/XTC **plus** dolutegravir **(Level AIa) or** TDF/XTC **plus** dolutegravir (If tenofovir alafenamide is not available) can be used in pregnant patients. **(Level AIa)**

  If Dolutegravir is not available, the following drugs serve as alternative options:

  - Raltegravir (400 mg twice daily)**(Level AIIa)**
  - Atazanavir plus ritonavir **(Level BIIa)**
  - Darunavir plus ritonavir **(Level BIIa)**
  - Rilpivirine **(Level BIIa)**
- Mothers living with HIV should breastfeed for at least 12 months up to 24 months or longer while being fully supported for ART adherence. **(Strong Recommendation)**
- For HIV patients who are initiating ART, DTG in combination with an NRTI backbone is recommended as first line therapy. **(Strong Recommendation for adults and adolescents. Conditional Recommendation for infants and children with approved DTG dosing.)**
- Alternative first line therapy that is recommended for adults and adolescents with HIV: EFV at low dose (400 mg) in combination with an NRTI backbone. **(Strong Recommendation)**
- First line therapy for neonates: An RAL-based regimen. **(Conditional Recommendation)**
- For HIV patients who are non-responsive to non-DTG-based regimens:

DTG in combination with an optimized nucleoside reverse-transcriptase inhibitor backbone may be recommended as second line therapy. **(Conditional Recommendation)**

- For HIV patients who are non-responsive to DTG-based regimens:

  Boosted protease inhibitors in combination with an optimized nucleoside reverse-transcriptase inhibitor backbone are recommended as second line therapy. **(Strong Recommendation)**

- Third line therapy should include new drugs with minimal risk of cross-resistance to previously used regimens, such as INSTIs and second-generation NNRTIs and PIs. **(Conditional Recommendation)**

- Lamivudine/Zidovudine, a combination of two nucleoside analogue reverse transcriptase inhibitors, is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. It is usually given as one tablet (lamivudine 150 mg/zidovudine 300 mg) twice daily. **(No Grade of Recommendation)**

- Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate is a three-drug combination of doravirine (a nonnucleoside reverse transcriptase inhibitor [NNRTI]), lamivudine, and tenofovir disoproxil fumarate (both nucleoside analogue reverse transcriptase inhibitors) and is indicated as a complete regimen for the treatment of HIV-1 infection in adult patients with no antiretroviral treatment history. The recommended dosage is one tablet (doravirine 100 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg) taken orally once daily with or without food in adult patients. **(No Grade of Recommendation)**

Section 4.0 Conclusion

This report serves as **an annex to the previous CHI HIV report** and aims to provide recommendations to aid in the management of HIV. It is important to note that these recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with HIV. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

Some covered drugs may have additional requirements, rules or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses and sequence of therapy

Appendix B. Level of Evidence Description

Grade of research	
A	Strongly recommend; good evidence
B	Recommend; at least fair evidence
C	No recommendation for or against; balance of benefits and harms too close to justify a recommendation
D	Recommend against; fair evidence is ineffective, or harm outweighs the benefit
E	Evidence is insufficient to recommend for or against routinely; evidence is lacking or of poor quality; benefits and harms cannot be determined
Level of evidence	
Level I	Meta-analysis of multiple studies
Level II	Experimental studies
Level III	Well-designed, quasi-experimental studies
Level IV	Well-designed, non-experimental studies
Level V	Case reports and clinical examples

Appendix C. PubMed Search Methodology Terms

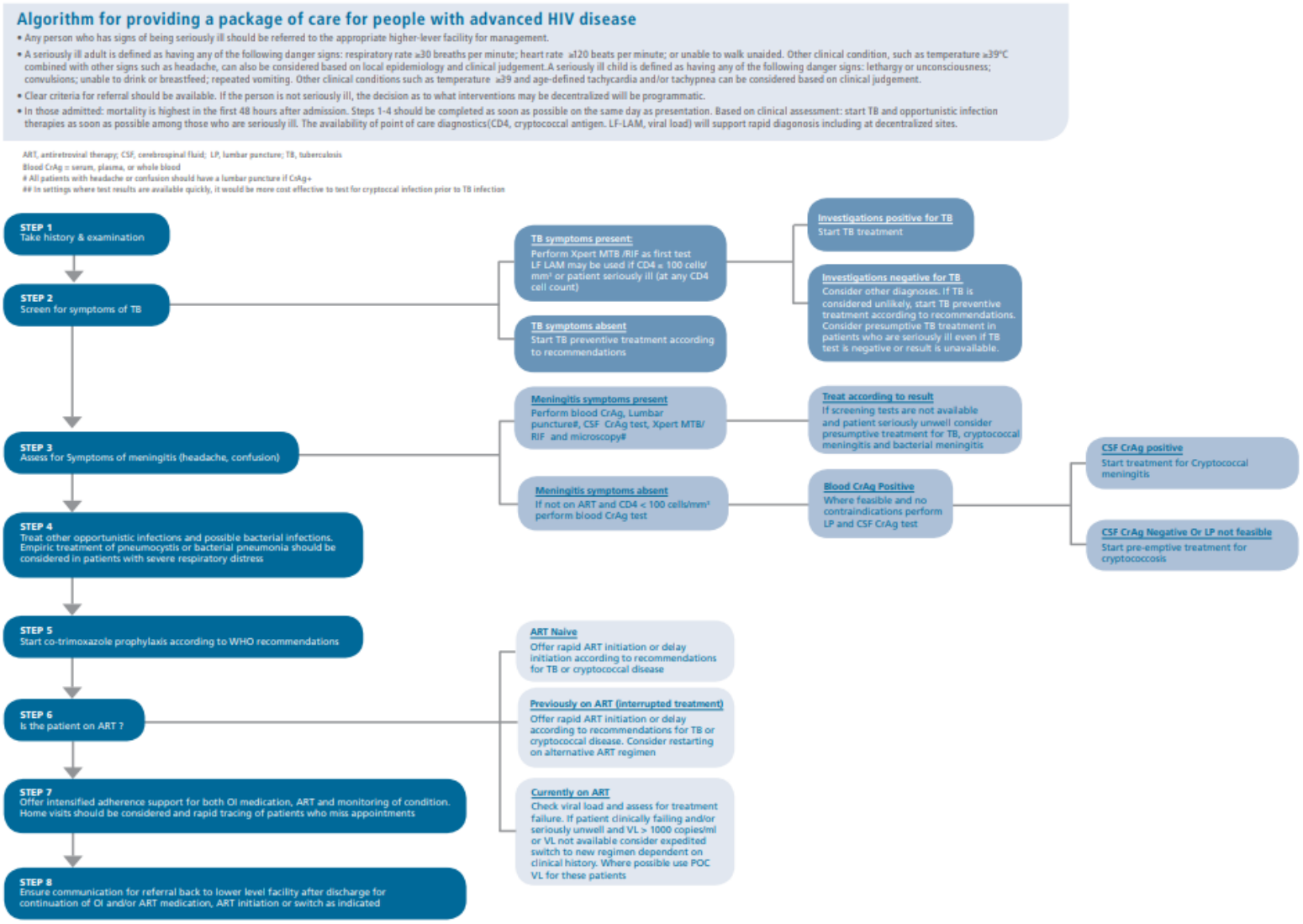
The following PubMed Search Methodology was opted:

Query	Sort By	Filters	Search Details	Results
((((((((((((((((((((((((HIV[MeSH Terms]) OR (Human Immunodeficiency Virus[Title/Abstract])) OR (Immunodeficiency Virus, Human[Title/Abstract])) OR (Immunodeficiency Viruses, Human[Title/Abstract])) OR (Virus, Human Immunodeficiency[Title/Abstract])) OR (Viruses, Human Immunodeficiency[Title/Abstract])) OR (Human Immunodeficiency Viruses[Title/Abstract])) OR (Human T Cell Lymphotropic Virus Type III[Title/Abstract])) OR (Human T-Cell Lymphotropic Virus Type III[Title/Abstract])) OR (Human T-Cell Leukemia Virus Type III[Title/Abstract])) OR (Human T Cell Leukemia Virus Type III[Title/Abstract])) OR (LAV-HTLV-III[Title/Abstract])) OR (Lymphadenopathy-Associated Virus[Title/Abstract])) OR (Lymphadenopathy Associated Virus[Title/Abstract])) OR (Lymphadenopathy-Associated Viruses[Title/Abstract])) OR (Virus, Lymphadenopathy-Associated[Title/Abstract])) OR (Viruses, Lymphadenopathy-Associated[Title/Abstract])) OR (Human T Lymphotropic Virus Type III[Title/Abstract])) OR (Human T-Lymphotropic Virus Type III[Title/Abstract])) OR (AIDS Virus[Title/Abstract])) OR (AIDS Viruses[Title/Abstract])) OR (Virus, AIDS[Title/Abstract])) OR (Viruses, AIDS[Title/Abstract])) OR (Acquired Immune Deficiency Syndrome Virus[Title/Abstract])) OR (Acquired Immunodeficiency Syndrome Virus[Title/Abstract]))		Guideline, in the last 5 years	("hiv"[MeSH Terms] OR "human immunodeficiency virus"[Title/Abstract] OR "immunodeficiency virus human"[Title/Abstract] OR "immunodeficiency viruses human"[Title/Abstract] OR "virus human immunodeficiency"[Title/Abstract] OR "viruses human immunodeficiency"[Title/Abstract] OR "human immunodeficiency viruses"[Title/Abstract] OR "human t cell lymphotropic virus type iii"[Title/Abstract] OR "human t cell lymphotropic virus type iii"[Title/Abstract] OR "human t cell leukemia virus type iii"[Title/Abstract] OR "human t cell leukemia virus type iii"[Title/Abstract] OR "LAV-HTLV-III"[Title/Abstract] OR "lymphadenopathy associated virus"[Title/Abstract] OR "lymphadenopathy associated virus"[Title/Abstract] OR ("Lymphadenopathy-Associated"[All Fields] AND "Viruses"[Title/Abstract]) OR "virus lymphadenopathy associated"[Title/Abstract] OR "viruses lymphadenopathy associated"[Title/Abstract] OR "human t lymphotropic virus type iii"[Title/Abstract] OR "human t lymphotropic virus type iii"[Title/Abstract] OR "aids virus"[Title/Abstract] OR "aids viruses"[Title/Abstract] OR "virus aids"[Title/Abstract] OR "viruses aids"[Title/Abstract] OR "acquired immune deficiency syndrome virus"[Title/Abstract] OR "acquired immunodeficiency syndrome	26

OR (HTLV-III[Title/Abstract])			virus"[Title/Abstract] OR "HTLV-III"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))	

Appendix D. Treatment Algorithm

Algorithm For Providing a Package Of Care For People With Advanced HIV Disease: The following figure was adapted from the WHO HIV Guidelines[36]:



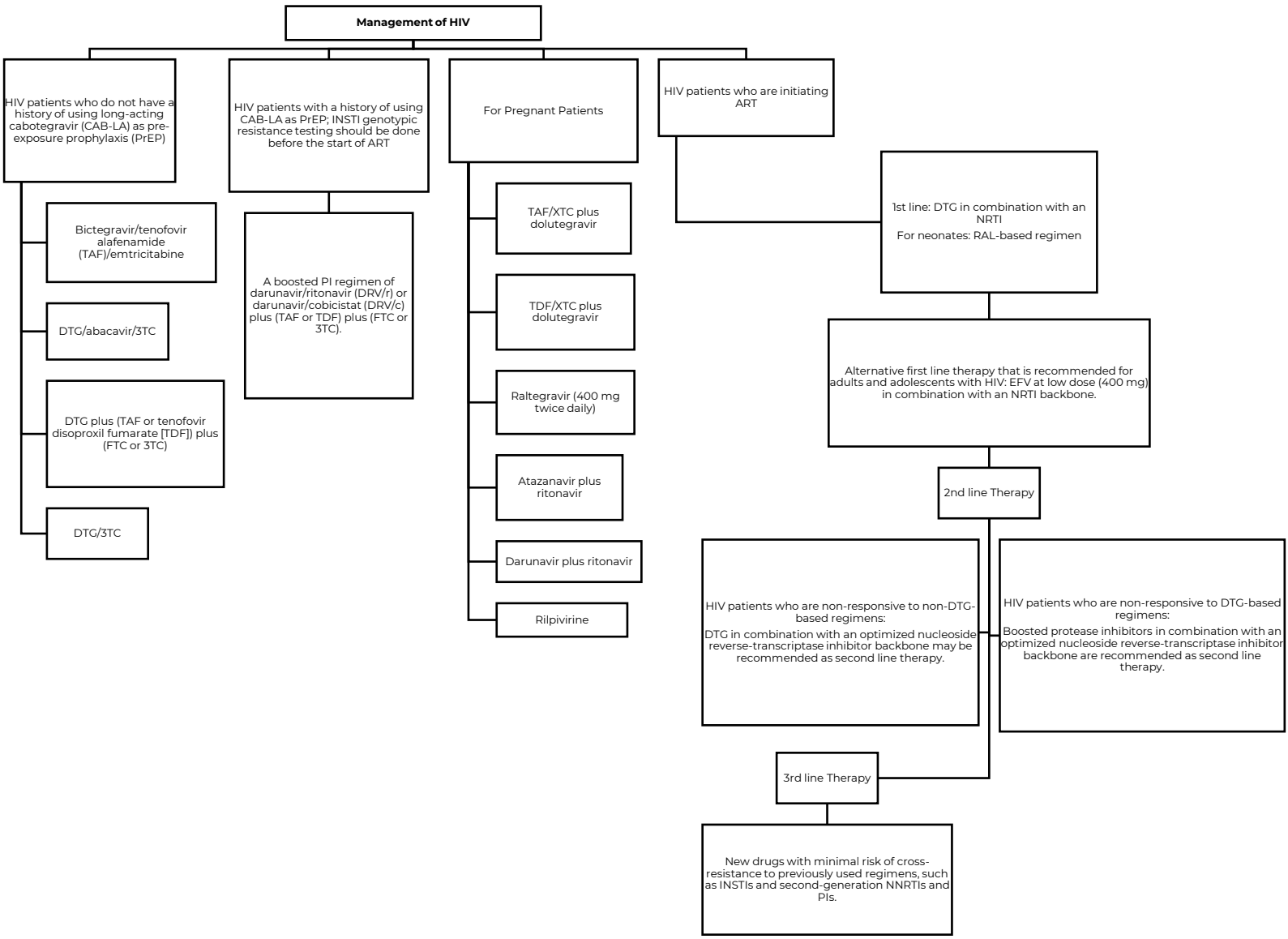


Figure 2. *Treatment Algorithm for the Management of HIV*