

CONFIDENTIAL, PROPRIETARY AND TRADE SECRET INFORMATION OF OPTUM RX**Introduction**

- Human immunodeficiency virus (HIV) infects cells expressing cluster of differentiation 4 (CD4) receptors, such as T-helper lymphocytes, monocytes, macrophages, dendritic cells, and brain microglia. HIV is characterized by a progressive decline in CD4 cell count, leading to the development of severe immunosuppression which increases the risk for infectious diseases caused by opportunistic pathogens (*Anderson et al 2023, Wood et al 2023*).
- At the end of 2021, there were approximately 1.2 million persons aged ≥ 13 years with HIV-1 infection in the United States (US), including an estimated 158,500 people whose infections had not been diagnosed. Pre-exposure prophylaxis (PrEP) is highly effective at preventing individuals from acquiring HIV, when taken as prescribed (*Centers for Disease Control and Prevention [CDC] 2023*).
- There are regional differences in the incidence of HIV. In 2019, the rate of HIV incidence by region was 7.9 per 100,000 people in the Midwest, 9.8 per 100,000 people in the Northeast, 10.9 per 100,000 people in the West, and the highest in the Southern region at 17.6 per 100,000 people (*CDC 2022[a]*).
- PrEP reduces the risk of acquiring HIV from sex by about 99% and from injection drug use by at least 74%. PrEP is less effective when not taken as prescribed. Since PrEP only protects against HIV, condom use is still important for the protection against other sexually transmitted diseases (STDs) (*CDC 2022[b]*).
 - The key to HIV prevention is education, condom use and clean syringe access, reducing stigma, and adherence. Reducing barriers are essential to HIV prevention. Should individuals acquire HIV, detection is important to promote appropriate access to antiretroviral (ARV) treatment and to minimize resistance.
- Should an individual acquire HIV, the goal of antiretroviral therapy (ART) is multifaceted. Treatment should be continued to maximally suppress plasma HIV, restore and preserve immunologic function, prevent transmission, reduce HIV-associated morbidity and mortality, and prolong the duration or quality of survival (*Anderson et al 2023, Department of Health and Human Services [DHHS] 2023[a]*).
 - Virologic failure is defined as the inability to achieve or maintain suppression of viral replication to HIV-1 RNA levels ≤ 200 copies/mL (*DHHS 2023[a]*).
- Currently, ART is considered lifelong. As persons living with HIV live longer due to the advent of ART, clinicians are now challenged with treating individuals with co-morbidities. A wide spectrum of complications associated with older age has become common, some of which overlap with adverse events (AEs) from ART. Management of these complications is constantly evolving (*Anderson et al 2023*).
- The recommendations for initial treatment of HIV usually include a minimum of 3 ARV agents: 1 “anchor” drug and 2 “backbone” drugs. The backbone is usually 2 nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs). The anchor can be a non-nucleoside reverse transcriptase inhibitor (NNRTI), a boosted protease inhibitor (PI), or an integrase strand transfer inhibitor (INSTI). In adults, some 2 drug regimens have also demonstrated efficacy. There is an increased risk for HIV to select for ARV-resistant variants. Therefore, individuals should be tested for susceptibility via genotypic (preferred) or phenotypic resistance testing at treatment entry and when virologic failure occurs. (*Anderson et al 2023, DHHS 2023[a-c]*).
- More than 30 medications in 6 classes are Food and Drug Administration (FDA)-approved for treatment of HIV infection. Drug classes that are active against the HIV virus include the NRTIs, NNRTIs, PIs, INSTIs, and the entry inhibitors (including a fusion inhibitor, CC chemokine receptor 5 [CCR5] inhibitor, post-attachment or CD4 inhibitor, and a gp120 attachment inhibitor). In addition, 2 drugs, ritonavir (RTV or r) and cobicistat (COBI or c), are used solely as pharmacokinetic (PK) enhancers to improve the PK profiles of some ARV drugs (*DHHS 2023[a]*).
- The focus of this overview will be the NRTIs, for the treatment of HIV-1.
 - The NRTIs are comprised of 2 chemical derivatives, purine- and pyrimidine-based nucleosides and nucleotides.
 - The 6 single entity NRTIs currently FDA-approved for HIV include: Emtriva (emtricitabine [FTC]), Epivir (lamivudine [3TC]), Retrovir (zidovudine [ZDV], also known as azidothymidine [AZT]), Viread (tenofovir disoproxil fumarate [TDF]), and Ziagen (abacavir [ABC]). Tenofovir alafenamide (TAF) is an additional NRTI that is only available as a combination product with other ARVs.
 - The 7 FDA approved combination drugs included in this review are: Cimduo (3TC/TDF), Combivir (3TC/ZDV), Descovy (FTC/TAF), Epzicom (ABC/3TC), Trizivir (ABC/3TC/ZDV), and Truvada (FTC/TDF).

- Tenofovir is available in 2 different formulations. TDF is an ester pro-drug that releases tenofovir upon first pass metabolism, resulting in relatively high concentrations of tenofovir and some renal risk of the proximal tubulopathy and bone demineralization. TAF, however, is more of an intact prodrug that results in higher intracellular concentrations, but lower systemic tenofovir concentrations and less opportunity to modify markers of proximal tubulopathy and bone demineralization. Safety, cost, and access are among the factors to consider when choosing between these drugs (*Anderson et al 2023, DHHS 2023[a]*). Of note, Vemlidy (TAF) 25 mg tablet is not covered in this review since this agent is only approved for the treatment of hepatitis B virus (HBV) infection.
- Medispan Class: Antiretrovirals – Reverse Transcriptase Inhibitors, Nucleoside/Nucleotide Analogues

Table 1. Medications Included Within Class Review

Drug	Abbreviation	Generic Availability *
Single drug formulations		
Emtriva (emtricitabine)	FTC	✓ §
Epivir (lamivudine)	3TC	✓
Retrovir (zidovudine)	ZDV	✓ ‡
Viread (tenofovir disoproxil fumarate)	TDF	✓ †
Ziagen (abacavir)	ABC	✓
Multiple drug formulations		
Cimduo (lamivudine/tenofovir disoproxil fumarate)	3TC/TDF	-
Combivir (lamivudine/zidovudine)	3TC/ZDV	✓
Descovy (emtricitabine/tenofovir alafenamide)	FTC/TAF	-
Epzicom (abacavir/lamivudine)	ABC/3TC	✓
Trizivir (abacavir/lamivudine/zidovudine)	ABC/3TC/ZDV	✓
Truvada (emtricitabine/tenofovir disoproxil fumarate)	FTC/TDF	✓

*For example, authorized generic, branded generic (unless not considered therapeutically equivalent by the Orange Book), generic, unbranded biologic, or interchangeable biologic.

§ Oral solution only available as a brand product.

‡ Injection for intravenous use only available as a brand product.

† Oral powder only available as a brand product.

(*Drugs@FDA 2023, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2023*)

Indications

Table 2. Food and Drug Administration Approved Indications

Brand name (generic)	In combination with other ARV agents for the treatment of HIV-1 infection	In combination with other ARV-treatment other than PIs that require a cytochrome p450 (CYP) 3A inhibitor, in HIV-1	Maternal-fetal HIV-1 transmission	In combination with safer sex practices for PrEP to reduce the risk of sexually acquired HIV-1 in at-risk patients
Single Drug Formulations				
Emtriva (emtricitabine)	✓*			
Epivir (lamivudine)	✓†,‡			
Retrovir (zidovudine)	✓§		✓	

Brand name (generic)	In combination with other ARV agents for the treatment of HIV-1 infection	In combination with other ARV-treatment other than PIs that require a cytochrome p450 (CYP) 3A inhibitor, in HIV-1	Maternal-fetal HIV-1 transmission	In combination with safer sex practices for PrEP to reduce the risk of sexually acquired HIV-1 in at-risk patients
Viread (tenofovir disoproxil fumarate)	✓ ^Δ			
Ziagen (abacavir)	✓ [‡]			
Multiple Drug Formulations				
Cimduo (lamivudine/tenofovir disoproxil fumarate)	✓ ^{**}			
Combivir (lamivudine/zidovudine)	✓ ^{††}			
Descovy (emtricitabine/tenofovir alafenamide)	✓ ^{**}	✓ ^{‡‡}		✓ ^{###}
Epzicom (abacavir/lamivudine)	✓ ^{§§}			
Trizivir (abacavir/lamivudine/zidovudine)	✓			
Truvada (emtricitabine/tenofovir disoproxil fumarate)	✓ ^{¶¶}			✓ ^{###}

*Indicated in individuals from birth and older.

† Limitation of use: the dosage of this product is for HIV-1 and not for hepatitis B virus (HBV).

‡ Recommended dosing starts for oral tablets in children who weigh at least 14 kg and for oral solution in children aged ≥ 3 months.

§ Recommended dosing starts for individuals aged ≥ 4 weeks and weight of ≥ 4 kg.

|| Recommended dosing start for pregnant women > 14 weeks of pregnancy and their neonates. Neonatal dosing begins within 12 hours after birth and continues through 6 weeks of age (consider intravenous formulations in those neonates unable to receive oral dosing).

¶ Recommended dosing starts for individuals aged ≥ 2 weeks; pharmacokinetics are too variable in children aged < 2 weeks.

Recommended dosing starts for oral tablets in individuals weighing ≥ 20 kg.

Δ Indicated for individuals aged ≥ 2 years and weighing ≥ 10 kg.

** Indicated in individuals weighing ≥ 35 kg.

†† Recommended dosing starts for individuals weighing ≥ 30 kg. Due to the lack of dose adjustments, use is not recommended for: (1) children weighing < 30 kg, or (2) patients with creatinine clearance (CrCL) < 50 mL/min, or (3) patients with hepatic impairment, or (4) patients with dose-limiting AEs.

‡‡ Indicated in children weighing at least 14 to < 35 kg.

§§ Recommended dosing starts for individuals weighing ≥ 25 kg. Due to the lack of dose adjustment, use is not recommended for: (1) CrCL < 30 mL/min, or (2) mild hepatic impairment, and is contraindicated in individuals with moderate to severe hepatic impairment.

|| Limitation of use: limited data exist on the use of Trizivir alone in individuals with higher baseline viral load levels (> 100,000 copies/mL). Due to the lack of dose adjustment, use is not recommended for: (1) children weighing < 40 kg, or (2) patients with CrCL < 50 mL/min, or (3) patients with mild hepatic impairment (contraindicated in individuals with moderate to severe hepatic impairment).

¶¶ Indicated in individuals weighing ≥ 17 kg.

Indicated in individuals weighing ≥ 35 kg. The indication does not include use in individuals at risk of HIV-1 from receptive vaginal sex because effectiveness in this population has not been evaluated (Descovy). Individuals must have a negative HIV-1 test immediately prior to initiating Truvada or Descovy for PrEP. If clinical symptoms consistent with acute viral infection are present and recent (< 1 month) exposures are suspected, delay starting PrEP for at least 1 month and reconfirm HIV-1 status or use a test cleared by the FDA as an aid in the diagnosis of HIV-1 infection, including acute or primary HIV-1 infection.

(Prescribing information: Cimduo 2021, Combivir 2023, Descovy 2022, Emtriva 2021, Epivir 2020, Epzicom 2022, Retrovir 2023, Trizivir 2021, Truvada 2021, Viread 2021, Ziagen 2023).

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

Clinical Efficacy Summary

• PrEP

- Truvada (TDF/FTC) and Descovy (TAF/FTC) are 2 oral regimens FDA-approved for the treatment of PrEP. A wide range of clinical evidence, including randomized controlled trials (RCTs), observational studies and open-label (OL) studies have demonstrated the safety and efficacy of these combination products to reduce the risk of acquiring HIV in several at-risk populations.

Data as of December 26, 2023 HJ-U/KS-U/RLP

Page 3 of 22

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- The iPrEx trial, a phase 3, double blind (DB), multinational RCT found Truvada to be efficacious in men who have sex with men (MSM) and transgender women (TGW), with a 44% risk reduction of acquiring HIV (95% confidence interval [CI], 15 to 63). The study also noted a greater risk reduction (50%; 95% CI, 18 to 70) in individuals with ≥ 50% adherence (*Grant et al 2010*).
- The Partners PrEP trial, a phase 3, DB, RCT (N = 4758), evaluated the effectiveness of TDF/FTC or TDF monotherapy for preventing the acquisition of HIV in the uninfected partner of discordant heterosexual couples. The study found a 75% risk reduction with TDF/FTC (95% CI, 55 to 87) and 67% (95% CI, 44 to 81) with TDF alone, among individuals of both sexes combined. High medication adherence was also noted in this study (*Baeten 2012*).
- The approval of Descovy was based on data from the DISCOVER trial, which evaluated the safety and efficacy of FTC/TAF vs FTC/TDF in MSM and TGW at a high risk of sexually acquired HIV. Results showed that FTC/TAF was non-inferior to FTC/TDF with an annualized incidence rate of infection of 0.16 vs 0.34 per 100 individuals, respectively (HIV incidence rate ratio, 0.47; 95% CI, 0.19 to 1.15 [prespecified non-inferiority margin = 1.62]). The authors also noted significant bone and renal advantages with TAF. However, FTC/TAF was not approved in cis-gender women due to inadequate efficacy data in this population (*Descovy prescribing information 2022, Mayer et al 2020*).
 - In a follow-up report from the DISCOVER trial including all subjects that had completed 96 weeks of follow-up, HIV infections occurred in 8 participants who received FTC/TAF (0.16 infections/100 person-years; 95% CI, 0.07 to 0.31) and 15 participants given FTC/TDF (0.30 infections/100 person-years; 95% CI, 0.17 to 0.49). FTC/TAF maintained its non-inferiority to FTC/TDF for HIV prevention and FTC/TAF continued to show superiority in the majority of bone and renal biomarkers (*Ogbuagu et al 2021*).
- Three DB, RCTs (TDF2, FEM-PrEP, VOICE) were conducted in heterosexual men (HSM) and/or heterosexual women (HSW) evaluating the efficacy of TDF/FTC compared to TDF or placebo. Overall, 1 study found a 62% reduction in HIV transmission, while noting high adherence among enrolled individuals. Two studies found no difference between groups in terms of HIV transmission rates, which could be due to low medication adherence; although adherence and operational issues prevented reliable conclusions on efficacy in the 2 trials, all 3 trials have found PrEP to be safe in these populations (*Marrazzo et al 2015, Thigpen et al 2012, Van Damme et al 2012*).
- The US MSM Safety trial was a phase 2 RCT that evaluated the safety and behavioral effects of PrEP (TDF monotherapy vs placebo) for HIV prevention. The evidence showed that PrEP with TDF is safe and was not associated with an increase in risk-taking behaviors. The most frequent AE reported was back pain in the TDF treated patients, with an overall small decrease in bone mineral density (BMD) (1% femoral neck; 0.8% total hip), with no reported fractures. No significant renal concerns were noted (*Grohskopf et al 2013*).
- The ATN 113 study was a phase 2, OL safety study (N = 78) that evaluated the use of TDF/FTC in HIV negative adolescent MSM aged 15 to 17. The study considered PrEP acceptability, patterns of use, behavior, and adherence in this age group. The majority of patients achieved protective drug levels by 12 weeks, however as visits decreased, so did adherence as noted by declining TDF levels (54% at week 4 vs 22% at week 48). The authors noted 23 STDs, and an annualized HIV rate of 6.4 per 100 individuals. The key takeaway from this trial is that adolescent MSM need access to PrEP in youth-friendly settings with tailored adherence support; FTC/TDF is FDA-approved in this population (*Hosek et al 2017*).
- The Bangkok Tenofovir Study (BTS) was a phase 3, DB, RCT that showed efficacy of TDF/FTC in reducing the risk of acquiring HIV in people who inject drugs (PWID), specifically in individuals with high adherence. The trial evaluated 2411 PWIDs who were randomized to FTC/TDF vs placebo. A total of 17 infections among 1204 individuals were observed in the FTC/TDF arm compared to 33 infections among 1207 individuals in the placebo arm (incidence, 0.35 vs 0.68 cases per 100 person-years). FTC/TDF reduced the risk of acquiring HIV by 49% (hazard ratio [HR], 0.51; 95% CI, 0.96 to 1.15). FTC/TDF is the only PrEP regimen with evidence in PWIDs to date (*Choopanya et al 2013*).
- Several meta-analyses (MAs) support the use of PrEP.
 - One MA of 12 RCTs concluded that treatment with TDF/FTC reduced the risk of acquiring HIV (relative risk [RR] 0.49; 95% CI, 0.28 to 0.85) compared to TDF alone (RR 0.33; 95% CI, 0.20 to 0.55); specifically in MSM, serodiscordant couples, and other high risk men and women (*Okwundu et al 2012*).
 - Another recent systematic review/MA of 13 RCTs evaluated the risk of AEs in TDF/FTC and TDF alone regimens. Analysis found no significant difference in the risk of grade 3 or 4 AEs between either group. Additionally, they noted no major differences in the risk of renal or bone AEs (*Pilkington et al 2018*).

- A systematic review of 29 studies completed for the US Preventative Services Task Force (USPSTF) concluded that PrEP was associated with a decreased risk of HIV infection vs placebo or no PrEP after 4 months to 4 years (RR 0.46; 95% CI, 0.33 to 0.66) (*Chou et al 2019*). Significant statistical heterogeneity was noted in all 3 studies.
 - Oral TAF/FTC and long-acting injectable cabotegravir (CAB) for PrEP were FDA-approved since this review; thus, the USPSTF commissioned an updated systematic review to inform an updated recommendation on the use of PrEP. A total of 32 studies were included. One new trial found oral TAF/FTC to be noninferior to TDF/FTC in MSM (RR, 0.53; 95% CI, 0.23 to 1.26). Two new trials found CAB to be associated with a decreased risk of HIV infection vs oral TDF/FTC in cisgender MSM and transgender women (RR, 0.33; 95% CI, 0.18 to 0.62), and in cisgender women (RR, 0.11; 95% CI, 0.04 to 0.31). Investigators concluded that, in adults at increased risk of HIV infection, oral PrEP was associated with decreased risk of HIV infection compared with placebo or no PrEP (*Chou et al 2023*).
- **TAF/FTC vs TDF/FTC**
 - Several studies have compared the clinical safety and efficacy of dual NRTI backbones TAF/FTC vs TDF/FTC in combination with anchor drugs as complete ART in people living with HIV. Overall, clinical evidence supports similar virologic suppression rates between the 2 tenofovir formulations while higher rates of renal and bone related AEs were observed with TDF.
 - Two large, randomized, DB phase 3 non-inferiority trials (N = 1733) comparing TAF to TDF each co-formulated with elvitegravir/cobicistat/FTC were found to be non-inferior at weeks 48 and 96. At week 144, TAF was found to be superior to TDF in virologic efficacy, with 84.2% (TAF) vs 80% (TDF) having HIV-1 RNA < 50 copies/mL (difference 4.2%; CI, 0.6 to 7.8). Through week 144, TAF continued to have less impact on BMD and renal markers than TAF; this led to 6 discontinuations in the TDF group vs none in the TAF group, which may have contributed to the lower rate of virologic success seen with TDF. The study also observed a greater increase in lipids levels with TAF vs TDF (*Arribas et al 2017, Sax et al 2015, Wohl et al 2016*).
 - The AMBER Study, a phase 3, randomized, DB, active controlled, non-inferiority study evaluated TAF/FTC vs TDF/FTC in a PI boosted regimen. At week 48, TAF was non-inferior (p < 0.0001) to TDF in achieving viral suppression of HIV-1 RNA < 50 copies/mL (91.4% vs 88.4%, difference 2.7%; 95% CI, 1.6 to 7.1). TAF demonstrated renal and bone advantages in the PI boosted regimen (*Eron et al 2018*).
 - The ADVANCE trial compared dolutegravir (DTG)/FTC/(TAF or TDF) vs efavirenz (EFV)/FTC/TDF as initial treatment for HIV-1 infection. At 96 weeks, viral suppression (< 50 copies/mL) was achieved in 79% of patients given DTG/FTC/TAF, in 79% given DTG/FTC/TDF, and in 74% given EFV/FTC/TDF. The difference in response was 5.1% (98.3% CI, -2.5 to 12.8) between DTG/FTC/TAF and EFV/FTC/TDF, 4.8% (98.3% CI, -2.8 to 12.5) for DTG/FTC/TDF and EFV/FTC/TDF, and 0.3% (98.3% CI, -7.1 to 7.7) between DTG/FTC/TAF and DTG/FTC/TDF (*Venter et al 2020*).
 - The efficacy and safety of DTG/FTC/(TAF or TDF) and EFV/FTC/TDF started in pregnancy (at 14 to 28 weeks gestation) were assessed in the IMPAACT 2010/VESTED trial. At delivery, DTG-based regimens resulted in viral suppression (<200 copies/mL) in 98% of patients and in 91% of patients in the EFV/FTC/TDF regimen (estimated difference, 6.5%; 95% CI, 2.0 to 10.7). A composite adverse pregnancy outcome (spontaneous abortion, stillbirth, preterm delivery, or small for gestation age) occurred in 24% of patients given DTG/FTC/TAF, in 33% of the DTG/FTC/TDF group (estimated difference vs DTG/FTC/TAF, -8.8%; 95% CI, -17.3 to -0.3), and in 33% given EFV/FTC/TDF (estimated difference vs DTG/FTC/TAF, -8.6%; 95% CI, -17.1 to -0.1; estimated difference vs DTG/FTC/TDF, 0.2%; 95% CI, -8.8 to 9.1) (*Lockman et al 2021*).
 - Comparative effectiveness reviews have demonstrated comparable rates of virologic suppression between TAF and TDF, as well as bone and renal benefits with TAF, and lipid benefits with TDF (*Tao et al 2020, Thompson et al 2019, Wang et al 2016*). A MA of 11 clinical trials compared the safety and efficacy of PK boosted vs unboosted TDF vs TAF. Overall, the analysis concluded no difference in HIV RNA suppression rates < 50 copies/mL between boosted and unboosted TAF vs TDF. Boosted TDF was associated with more prominent renal and bone AEs, which may be due to increased plasma concentrations of TDF (25 to 37%) (*Hill et al 2018*).
 - Another MA of 14 trials found that boosted TAF regimens were associated with a significantly higher rate of virologic suppression (HIV RNA < 50 copies/mL) vs boosted TDF regimens (94% vs 92%; p = 0.0004); there was no statistically significant difference in the rates of virologic suppression between TAF and TDF in patients receiving unboosted regimens (89% vs 90%, respectively; p = not significant). There were no differences in rates of AEs between TAF and TDF in boosted and unboosted regimens; however, boosted TAF regimens had an increased risk of discontinuation due to renal AEs vs boosted TDF regimens (3 patients vs 0 patients; p = 0.03) (*Pilkington et al 2020*).

- Several single arm studies have evaluated the safety and efficacy of FTC/TAF in children. FTC/TAF when combined with EVG/c has demonstrated safe and effective use in treatment-naïve children aged 6 to 18 years (weighing ≥ 25 kg) in 48 week studies. FTC/TAF has been studied in combination with bicittegravir (BIC) in children ≥ 2 years (weighing ≥ 14 kg) in a 24 week study. Guidelines do recommend TAF over TDF in children, because TAF has a lower risk of renal and bone AEs than TDF (*Descovy prescribing information 2022, DHHS 2023[b]*).
- **ABC/3TC vs TDF/FTC**
 - Clinical evidence has shown ABC/3TC to have comparable virologic suppression efficacy to TDF/FTC backbone containing regimens with lopinavir/r, dolutegravir (DTG) or darunavir (DRV)/r (*Smith et al 2009, Molina et al 2014*).
 - However, in the ACTG 5202 study that compared ABC/3TC to TDF/FTC with either efavirenz (EFV) or atazanavir (ATV)/r, virologic suppression rates were found to be significantly lower in the ABC/3TC group, particularly among patients with viral loads ≥ 100,000 copies/mL; the study also noted that time to virologic failure was significantly shorter in individuals taking ABC/3TC vs TDF/FTC (*Daar et al, 2011, Sax et al 2009*).
 - The Single Trial, a Phase 3, randomized, non-inferiority study evaluating the efficacy of DTG plus ABC/3TC vs EFV plus TDF/FTC found DTG/ABC/3TC to be superior to EFV/TDF/FTC for virologic suppression to levels < 50 copies/mL (88% vs 81%, $p = 0.003$) as well as having a shorter median time to suppression (28 days vs 84 days; $p = 0.0001$). Two MAs support the conclusions of key clinical trials, finding similar virological efficacy and time to virologic failure, regardless of baseline viral load (*Cruciani et al 2014, Hemkens et al 2015*).
 - The GS-US-380-1489 and GS-US-380-1490 were 2 large RCTs that evaluated the efficacy of BIC/FTC/TAF and also directly compared it to DTG plus 2 NRTI regimens: DTG/ABC/3TC or DTG/FTC/TAF, respectively (*Gallant et al 2017, Sax et al 2017*). At 48 weeks, BIC/FTC/TAF showed non-inferiority to the 2 DTG-regimens for viral suppression (< 50 copies/mL). At 96 weeks, non-inferiority for viral suppression was maintained for BIC/FTC/TAF vs DTG/FTC/TAF (84 vs 86%; respectively; difference, -2.3%; 95% CI, -7.9 to 3.2) and vs DTG/ABC/3TC (88 vs 90%; respectively; difference, -1.9%; 95% CI, -6.9 to 3.1) (*Stellbrink et al 2019, Wohl et al 2019*). No emergence of resistance occurred in either trial. At 144 weeks viral suppression was seen in 82% (difference from DTG/ABC/3TC regimen, -2.6%; 95% CI, -8.5 to 3.4) and 81% (difference from DTG/FTC/TAF regimen, -1.9%; 95% CI, -7.8 to 3.9) of patients given BIC/FTC/TAF vs 84% in DTG-containing regimens, with non-inferiority of the BIC regimen maintained (*Orkin et al 2020*).
 - In terms of safety profiles, TDF/FTC was associated with greater bone and renal AEs (ie, decreased BMD, tubular dysfunction) while ABC/3TC was associated with higher lipid levels and drug related hypersensitivity (*Moyle et al 2013, Sax et al 2009, Stellbrink et al 2010*).
 - A comparative efficacy review of 12 RCTs directly comparing 3TC vs FTC, found the overall pooled RR for treatment success was non-significant (RR 1; 95% CI, 0.97 to 10.2) with no heterogeneity observed ($I^2 = 0$). Similarly, there was no difference in the pooled RR for treatment failure (RR = 1.08; 95% CI, 0.94 to 1.22), with low heterogeneity observed ($I^2 = 3.4\%$) (*Ford et al 2013*).
- **TDF/3TC**
 - TDF/3TC is another preferred dual-NRTI backbone that is DHHS guideline recommended in certain clinical situations. It is FDA-approved as a complete fixed dose regimen with doravirine (DOR). The DRIVE-AHEAD trial demonstrated non-inferiority to Atripla (EFV/FTC/TDF) with viral suppression rates of 84% with Delstrigo (DOR/3TC/TDF) and 81% with EFV/FTC/TDF (difference 3.5%; 95% CI, -2% to 9%). In terms of safety, Delstrigo demonstrated better lipid profiles and lower rates of neuropsychiatric AEs (eg, dizziness, sleep disorders and disturbances, altered sensorium). Discontinuation rates were also noted to be lower with DOR/3TC/TDF (3%) vs EFV/FTC/TDF (6%) (*Orkin et al 2019*).
 - At 96 weeks, 77.5% of patients receiving DOR/3TC/TDF and 73.6% of patients receiving EFV/FTC/TDF achieved virologic suppression (difference 3.8%, 95% CI, -2.4% to 10%). Neuropsychiatric AEs, rash, and lipid changes continued to be reported less frequently with DOR/3TC/TDF vs EFV/FTC/TDF (*Orkin et al 2021*).
 - A multicenter, DB, randomized trial evaluated the efficacy, safety, and CNS effects when switching from EFV/FTC/TDF to DOR/3TC/TDF in virologically suppressed adults with HIV and CNS complaints; the switch took place either immediately or was deferred for 12 weeks. At week 12, the occurrence of Grade 2 or higher CNS toxicity was not significantly improved in those who switched immediately vs those who deferred switching (42% vs 37%, respectively; treatment difference, 4.7%, 95% CI, -16 to 25; $p = 0.33$). At 24 weeks, HIV-1 RNA < 50 copies/ml was maintained in 95.3% of all patients in the study along with improved lipid profiles (*Nelson et al 2021*).
- **ZDV to reduce risk of mother to child transmission (MTCT)**

- ACTG 076 was a landmark RCT trial which established that ZDV significantly reduced MTCT of HIV by 65% (95% CI, 40.7 to 82.1). Treatment consistent of ZDV for the mother after week 14 of pregnancy, intrapartum intravenous (IV) ZDV, and oral ZDV for the infant post-delivery for 6 weeks (*Connor et al 1994*). A systematic review of 25 trials concluded that triple therapy with a dual-NRTI backbone is most effective for preventing MTCT. Additionally, the authors concluded that HIV infection rates were not significantly different at birth when longer or shorter courses of therapy were administered (*Siegfried et al 2011*).
- A MA of 11 trials found that ZDV was associated with a significant risk reduction of MTCT after 1 or 2 doses. In terms of safety, a MA of 20 studies in the same review found that ZDV administered with 3TC/indinavir was associated with a higher risk of preterm birth, while ZDV/nevirapine increased the risk of still births (*Veroniki et al 2018*).
- **Trizivir (ABC/3TC/ZDV)**
 - Several trials comparing triple NRTI therapy (ABC/3TC/ZDV) to NNRTI or PI based regimens have resulted in inferior virologic efficacy and shorter time to virologic failure of ABC/3TC/ZDV, particularly with viral loads > 100,000 copies/mL in some studies, though data are limited. As a part of a 4-drug regimen for initial therapy, ABC/3TC/ZDV did not provide more benefit than a standard 3 drug regimen (*Gulick et al 2004, Kumar et al 2009, Staszewski et al 2001*). One MA of 4 RCTs concluded no significant difference in virological suppression between ABC/3TC/ZDV and NNRTI or PI based therapy (risk ratio 0.73; 95% CI, 0.39 to 1.36). However, the study noted significant heterogeneity ($I^2 = 62\%$) due to differences in the control therapy used (*Shey et al 2013*).

Clinical Guidelines

- **DHHS Guidelines for the Use of ARV Agents in Adults and Adolescents with HIV (2023)** (*DHHS 2023[a]*)
 - This guideline recommends ART for all individuals with HIV to reduce morbidity and mortality (**AI**) and to prevent the transmission of HIV to others (**AI**); Treatment should be initiated as soon as possible after HIV diagnosis (**AII**) (see Appendix for ratings of recommendations and evidence). The goals of treatment in early HIV infection (acute or recent) are to suppress plasma HIV RNA to undetectable levels (**AI**) and prevent transmission to others (**AI**).
 - Initial therapy for a person with HIV generally consists of 2 NRTIs administered in combination with a third active ARV drug from 1 of 3 drug classes: an INSTI, a NNRTI, or a PI with a PK enhancer (also known as a booster). Data also support the use of the 2-drug combination regimen dolutegravir (DTG)/lamivudine (3TC).
 - Selection of a regimen should be guided by factors such as virologic efficacy, toxicity, pill burden, dosing frequency, drug–drug interaction potential, resistance-test results, comorbid conditions, and access.
 - Recommended initial regimens for most people with HIV (for individuals who do not have a history of long-acting CAB use as PrEP):
 - INSTI plus 2 NRTIs
 - BIC/TAF/FTC (**AI**)
 - DTG/ABC/3TC (**AI**)—if HLA-B*5701 negative
 - DTG plus (TAF or TDF) plus (FTC or 3TC) (**AI**)
 - INSTI plus 1 NRTI
 - DTG/3TC (**AI**), except for individuals with HIV-1 RNA > 500,000 copies/mL, HBV coinfection or in individuals in whom ART is to be started before results of resistance testing or HBV testing are available.
 - For individuals with HIV and a history of long-acting CAB use as PrEP, INSTI genotypic resistance testing should be performed prior to start of ART.
 - If treatment is started prior to results of genotype testing, the following regimen is recommended:
 - DRV/c or DRV/r with (TAF or TDF) plus (FTC or 3TC) pending the results of the genotype test (**AIII**)
 - Note: TAF and TDF are 2 forms of tenofovir approved by FDA. TAF has fewer bone and kidney toxicities than TDF, while TDF is associated with lower lipid levels.
 - FTC and 3TC are generally used interchangeably in combination with other ARV drugs.
 - Regimens to consider when ABC, TAF, and TDF cannot be used or are not optimal: DTG/3TC (**AI**), except for individuals with HIV-1 RNA > 500,000 copies/mL, HBV coinfection, or in individuals in whom ART is to be started before results of resistance testing or HBV testing are available.
 - For patients with a baseline HIV RNA level > 100,000 copies/mL, ABC/3TC NRTI backbone should be avoided if used with EFV or ATV/r.
 - ABC should not be used in patients who test positive for HLA-B*5701 because of the risk of developing a hypersensitivity reaction.
 - Special considerations specific to individuals with HBV coinfection include:

- Before initiation of ART, all patients who test positive for hepatitis B surface antigen (HBsAg) should be tested for HBV deoxyribonucleic acid (DNA) using a quantitative assay to determine the level of HBV replication (**AIII**).
- NRTIs including FTC, 3TC, TDF, and TAF have activity against both HIV and HBV. Therefore, an ART regimen for individuals with HIV/HBV coinfection should include (TAF or TDF) plus (3TC or FTC) as the NRTI backbone of a fully suppressive regimen (**AI**).
- Using 3TC or FTC as the only drug in a regimen with HBV activity is not recommended (**AII**).
- Special considerations specific to individuals with hepatitis C virus (HCV) coinfection include:
 - All people with HIV should be screened for HCV infection (**AIII**).
 - Initial ART regimens that are recommended for most patients with HCV/HIV coinfection are the same as those recommended for individuals without HCV infection. However, when treatment for both HIV and HCV is indicated, the ART and HCV treatment regimens should be selected with special consideration for potential drug-drug interactions and overlapping toxicities (**AIII**).
 - In terms of NRTIs, 3TC, ABC, FTC, TDF, and TAF may all be co-administered with all other HCV direct-acting antivirals (DAAs). However, TDF requires monitoring for potential TDF-toxicity when co-administered with ledipasvir/sofosbuvir, sofosbuvir/velpatasvir, or sofosbuvir/velpatasvir/voxilaprevir.
- In persons with HCV/HBV coinfection, HBV reactivation has been observed during HCV treatment with DAAs. Therefore, persons with HCV/HIV coinfection and active HBV infection (HBsAg positive) should receive ART that includes at least 2 agents with anti-HBV activity (such as [TDF or TAF] + [FTC or 3TC]) prior to initiating HCV therapy (**AIII**).
- **DHHS Guidelines for the Use of ARV Agents in Pediatric HIV Infection (2023) (DHHS 2023[b])**
 - In treatment-naïve children living with HIV, ART should be initiated in all infants and children with HIV infection (**AI** for children aged < 3 months, **AI*** for older children) immediately or within days of diagnosis, otherwise known as rapid ART initiation (except for children with cryptococcal meningitis, disseminated Mycobacterium avium Complex Disease, or Mycobacterium tuberculosis due to risk of immune reconstitution inflammatory syndrome; treatment may be deferred relative to treatment of infection). Treatment initiation in young infants with HIV during the early stages of HIV infection may control viral replication before HIV can evolve into diverse and potentially more pathogenic quasi-species. Early therapy also preserves immune function, preventing clinical disease progression.
 - For treatment-naïve children, the guideline recommends initiating ART with 3 drugs: a dual-NRTI backbone plus an INSTI, a NNRTI, or a boosted PI (**AI***).
 - ABC plus (3TC or FTC) is recommended as the preferred dual-NRTI combination for children aged ≥ 3 months (**AI**) and for full-term infants from birth (**BIII**).
 - FTC/TAF is recommended as a preferred dual-NRTI combination in children and adolescents weighing ≥ 14 kg who have estimated CrCL ≥ 30 mL/min when this combination is used with an INSTI or NNRTI; this combination is considered a preferred dual-NRTI combination when used with a PI in children and adolescents weighing ≥ 35 kg who have estimated CrCL ≥ 30 mL/min (**AI***). This combination is also recommended as a preferred drug combination when used in the regimen BIC/FTC/TAF for children and adolescents weighing ≥ 14 kg (**AI***). Elvitegravir (EVG)/c/FTC/TAF is recommended as an alternative drug regimen for children and adolescents weighing ≥ 25 kg (**AI***).
 - TDF plus 3TC or FTC is recommended as an alternative dual-NRTI combination for children aged ≥ 2 years to 12 years (**AI***).
 - ZDV plus ABC is recommended as an alternative dual-NRTI combination for children aged ≥ 1 month (**BII**).
 - ZDV plus 3TC or FTC is recommended as a preferred dual-NRTI combination for infants and children from birth to age ≤ 1 month, and as an alternative combination in children aged ≥ 1 month and adolescents (**AI***). In children aged ≥ 6 years and adolescents who are not sexually mature (ie, those with sexual maturity ratings [SMRs] of 1 to 3), ZDV plus 3TC or FTC is recommended as an alternative dual-NRTI combination (**BII**).
 - Newborn ARV regimens to reduce the risk of perinatal transmission of HIV are outlined in the DHHS perinatal HIV guideline summarized below. The use of ARV drugs other than ZDV, 3TC, and NVP cannot be recommended for any indication in premature newborns (< 37 weeks gestational age) because of the lack of dosing and safety data (**BII**).
 - Preferred initial regimens based on age and weight at the time of treatment initiation:
 - Newborns, birth to age < 14 days
 - Weight ≥ 2 kg: 2 NRTIs plus RAL
 - No weight restriction: 2 NRTIs plus NVP
 - Neonates ≥ 14 days to age < 4 weeks

- Weight $\geq$ 2 kg: 2 NRTIs plus RAL
- No weight restriction: 2 NRTIs plus lopinavir (LPV)/r
- Infants and children aged $\geq$ 4 weeks
 - Weight $\geq$ 3 kg: 2 NRTIs plus DTG
- Children aged $\geq$ 2 years
 - Weight $\geq$ 14 kg: 2 NRTIs plus BIC
- Adolescents aged $\geq$ 12 years with SMR of 4 to 5
 - Refer to adult and adolescent ARV guidelines (previously summarized above)
- TAF has a lower risk of renal and bone AEs than TDF.
- Coadministration of TAF with boosted ATV, DRV, or LPV increases TAF exposure to concentrations that are higher than those seen with use of EVG/c/FTC/TAF. Because no data exist on the use of this combination in children weighing $<$ 35 kg, the safety of FTC/TAF combined with boosted PIs in children weighing $<$ 35 kg cannot be assured and is not recommended.
- The advantages/disadvantages of NRTIs include:
 - ABC + (3TC or FTC)
 - Advantages: Palatable liquid formulations; can take with food; a 1 tablet combination.
 - Disadvantages: Risk of ABC hypersensitivity reaction; perform HLA-B*5701 screening before initiation of ABC.
 - FTC/TAF for children aged $\geq$ 6 years
 - Advantages: Once daily dosing; small tablet size; lower risk of renal and bone toxicity with TAF vs TDF in adults; a 1 tablet combination.
 - Disadvantages: Limited data for this combination in children; increased lipid levels.
 - TDF + (3TC or FTC) for adolescents with SMRs of 4 or 5
 - Advantages: Once daily dosing; resistance is slow to develop; lower risk of mitochondrial toxicity than other NRTIs; can take with food; available as reduced-strength tablets and oral powder for use in younger children; a 1 tablet combination.
 - Disadvantages: Limited pediatric experience; potential bone and renal toxicity; numerous drug-drug interactions with other ARV agents (ie, LPV/r, ATV, and TPV).
 - ZDV + (3TC or FTC)
 - Advantages: Extensive pediatric experience; co-formulations of ZDV and 3TC are available for children weighing $\geq$ 30 kg; palatable liquid formulations; can take with food; FTC is available as a palatable liquid formulation that can be administered once daily.
 - Disadvantages: Bone marrow suppression and lipoatrophy with ZDV; ZDV requires twice-daily dosing
 - ZDV + ABC
 - Advantages: Palatable liquid formulations; can take with food
 - Disadvantages: Risk of ABC hypersensitivity reactions; perform HLA-B*5701 screening before initiation of ABC; bone marrow suppression and lipoatrophy with ZDV; ZDV requires twice-daily dosing.
- **DHHS Recommendations for the Use of ARV Drugs During Pregnancy with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States (2023) (DHHS 2023[c])**
 - This guideline recommends that all pregnant people with HIV should initiate ART as early in pregnancy as possible, regardless of their HIV RNA level or CD4 cell count, to maximize their health and prevent perinatal HIV transmission and secondary sexual transmission (**AI**). Persons with HIV should maintain an HIV viral load that is below the limit of detection prior to conception, during pregnancy, postpartum, and throughout their lives (**AII**). Neonates born to persons with HIV should receive appropriate ARV drugs (**AI**).
 - The same regimens that are recommended for the treatment of non-pregnant adults should be used in pregnant people when sufficient data suggest that appropriate drug exposure is achieved during pregnancy (**AII**).
 - For pregnant people who have never received ART, ART should be initiated as soon as possible, even before results of drug-resistance testing are available (**AI**).
 - Preferred ARV regimens in ARV-naïve pregnant people include a dual-NRTI combination and either DRV/r or DTG (**AIII**).
 - Preferred dual-NRTI backbones in pregnancy include ABC/3TC, TDF or TAF plus (FTC or 3TC)
 - ZDV/3TC is an alternative NRTI backbone (this combination has significant experience for use in pregnancy; however, it requires twice daily dosing and is associated with higher rates of AEs).

- Newborn ARV management according to risk of HIV infection in the newborn:
 - Low risk of perinatal HIV transmission:
 - ZDV for 2 weeks
 - For infant ≥ 37 weeks gestation and born to a person who meets *all* of these criteria: a) is currently receiving and has received ≥ 10 consecutive weeks of ART during pregnancy, b) has achieved and maintained *or* maintained viral suppression for the duration of pregnancy, c) has a viral load <50 copies/mL at or after 36 weeks, d) did not have acute HIV infection during pregnancy, and e) has reported good ART adherence, and adherence concerns have not been identified
 - ZDV for 4 to 6 weeks
 - For infants born to persons who do not meet the criteria above but who have a HIV RNA < 50 copies/mL at or after 36 weeks gestation
 - ZDV for 4 to 6 weeks
 - For premature infants (< 37 weeks gestation) who are not at high risk of perinatal acquisition of HIV
 - High risk of perinatal HIV transmission: Presumptive HIV therapy using either ZDV, 3TC, and NVP (treatment dose) *or* ZDV, 3TC, and RAL administered together from birth for 2 to 6 weeks; if the duration of the 3-drug regimen is < 6 weeks, ZDV should be continued alone to complete a total of 6 weeks of prophylaxis
 - For newborns born to people with HIV who:
 - Have not received antepartum ARV agents, *or*
 - Have received only intrapartum ARV agents, *or*
 - Have received antepartum ARV agents but who did not achieve viral suppression within 4 weeks of delivery, *or*
 - Have primary or acute HIV infection during pregnancy
 - Presumed HIV exposure: ARV management as described for newborns with high risk
 - With HIV infection: Three drug ARV regimen using treatment doses
 - Infants who are breastfed by individuals with HIV infection should be managed as infants considered high-risk for perinatal transmission
 - The use of ARV drugs other than ZDV, 3TC, and NVP cannot be recommended for any indication in premature newborns (< 37 weeks gestational age) because of the lack of dosing and safety data (**BII**).
- One of the following ARV regimens is recommended for individuals diagnosed with early HIV infection during the postpartum period: BIC/TAF/FTC; DTG with (TAF or TDF) plus (FTC or 3TC); DRV/r with (TAF or TDF) plus (FTC or 3TC) (**AIII**). People who receive a diagnosis of HIV infection when they are breastfeeding should be counseled to discontinue breastfeeding immediately to reduce the risk of postnatal HIV transmission to the infant (**AII**).
- **International Antiretroviral Society (IAS)-USA Panel (2022)** (*Gandhi et al 2023*)
 - Treatment for HIV should be initiated as soon as possible after diagnosis. Recommendations for therapy selection are generally consistent with the DHHS guidelines.
 - The following regimens are recommended for initial ART in most people with HIV:
 - BIC/TAF/FTC (**AIIa**)
 - DTG plus TFX (ie, TAF or TDF)/XTC (ie, FTC or 3TC) (**AIIa**)
 - DTG/3TC (only if HIV RNA < 500,000 copies/mL and HBV coinfection not present); do not use this regimen for rapid initiation when genotype, HIV RNA, and HBV serology results are not yet available (**AIIa**)
 - Persons who acquired HIV while receiving PrEP with TAF or TDF with FTC should have a blood sample for genotyping drawn prior to initiating therapy and a 3-drug regimen, preferably DTG or BIC plus TFX/XTC, should be initiated if ART is to be started before genotype results are available (**AIII**)
 - Initial ART regimens recommended during tuberculosis treatment:
 - TFX/XTC with 1 of the following: DTG (**BIIa**), EFV (**AIIa**), or RAL (**BIIa**)
 - PI regimen (r-boosted) with TFX/XTC may be used only if it is not possible to use any of the above regimens; use with rifabutin (**BIII**)
 - DTG/3TC is not recommended with rifampin (**BIII**)
 - During pregnancy, TAF/XTC plus DTG (AIIa) is recommended, with TDF/XTC plus DTG as a suitable alternative if TAF is not available (**AIIa**)
- For PrEP:
 - Oral PrEP: TDF/FTC daily remains a recommended PrEP regimen for all populations at risk (**AIIa**)

- Injectable PrEP: Long-acting intramuscular CAB every 8 weeks is recommended for prevention of sexual transmission of HIV across populations **(AIIa)**
- For post exposure prophylaxis (PEP):
 - A 3-drug fully suppressive ART regimen for 28 days is recommended to be administered as rapidly as possible but within 72 hours of exposure
 - The recommended regimen is TXF/XTC plus DTG or BIC **(AIII)**
 - Initiate PEP even if awaiting results of HIV testing on the source person **(BIII)**
- **CDC: US Public Health Service Guidelines PrEP prophylaxis for the prevention of HIV infection in the US – 2021 update (CDC 2021)**
 - Acute and chronic HIV infection must be excluded before PrEP is prescribed **(IA)**.
 - Daily oral PrEP with FTC in combination with 1) TDF for all men and women or 2) TAF, for men and TGW, has been shown to be safe and effective in reducing the risk of sexual HIV acquisition; therefore:
 - All sexually active adult and adolescent patients should receive information about PrEP **(IIIB)**.
 - PrEP is recommended in the following populations:
 - FTC/TDF: For all adults and adolescents weighing ≥ 35 kg (regardless of gender) who report sexual behaviors that place them at substantial ongoing risk of HIV exposure and acquisition **(IA)** and in PWIDs **(IA)**.
 - FTC/TAF: For MSM **(IA)** and TGW **(IIB)**; persons assigned male sex at birth whose gender identity is female) who have sex with men, are adults or adolescents weighing ≥ 35 kg, who report sexual behaviors that place them at substantial ongoing risk of HIV exposure and acquisition.
 - FTC/TAF has not yet been studied in cisgender women (persons assigned female sex at birth whose gender identity is female) and so FTC/TAF is not recommended for HIV prevention for cisgender women or other persons at risk through receptive vaginal sex **(IA)**.
 - The efficacy and safety of other daily oral ARVs medications for PrEP, either in place of, or in addition to, FTC/TDF or FTC/TAF, have not been studied extensively and are not recommended **(IIIA)**.
 - Renal function should be assessed by CrCL at baseline for PrEP patients taking daily oral FTC/TDF or FTC/TAF, and monitored periodically so that persons in whom clinically significant renal dysfunction is developing do not continue to take these medications.
 - CrCL should be assessed every 6 months for patients over age 50 or those who have a CrCL < 90 mL/min at initiation **(IIA)**. For all other daily oral PrEP patients, CrCL should be assessed at least every 12 months **(IIA)**.
 - The 2-drug regimens of FTC/TDF or FTC/TAF are inadequate therapy for established HIV infection, and their use in persons with early HIV infection may engender resistance to one or more of the PrEP medications **(IA)**.
- **USPSTF: Preexposure Prophylaxis to Prevent Acquisition of HIV (2023) (USPSTF 2023)**
 - The USPSTF performed an assessment of the magnitude of the net benefit of PrEP, and concluded with high certainty that there is a substantial net benefit from the use of effective ART to reduce the risk of HIV acquisition in individuals at increased risk of acquiring HIV.
 - For adults and adolescents weighing ≥ 35 kg who are at increased risk of HIV, the USPSTF recommends that clinicians prescribe PrEP with effective ART in order to decrease the risk of acquiring HIV **(Grade A recommendation)**.
 - This recommendation is consistent with the previous 2019 USPSTF recommendation on PrEP.
 - For the current recommendation, the USPSTF reviewed additional evidence on FTC/TAF and CAB, which were not FDA-approved at the time of the 2019 review.
 - The USPSTF recommends that the following persons be considered for PrEP since they are at increased risk of acquiring HIV:
 - Sexually active adults and adolescents weighing ≥ 35 kg who have engaged in anal or vaginal sex in the past 6 months and have any of the following:
 - A sexual partner with HIV (especially if the partner has an unknown or detectable viral load)
 - A bacterial STD in the past 6 months
 - A history of inconsistent or no condom use with sex partner(s) whose HIV status is unknown
 - Individuals who inject drugs and share injection equipment or have a drug-injecting partner with HIV
 - Agents available for PrEP:

- Oral TDF/FTC and injectable CAB: FDA-approved for use in at-risk adults and adolescents weighing ≥ 35 kg to reduce the risk of sexually acquired HIV
 - Oral TAF/FTC: FDA-approved for use in at-risk adults and adolescents weighing ≥ 35 kg to reduce the risk of sexually acquired HIV, excluding those at risk from receptive vaginal sex
 - Per the CDC, individuals who inject drugs are likely to benefit with any FDA-approved PrEP medication.
- **American Academy of Pediatrics (AAP). Adolescents and young adults: the pediatrician's role in HIV testing and pre- and postexposure HIV prophylaxis (2022)** (*Hsu et al 2022*)
 - All youth at risk for HIV acquisition should be offered HIV PrEP as part of a comprehensive prevention strategy that includes other prevention measures, including adherence to daily administration, and safer sex practices, including barrier protection, to reduce the risk of STDs.
 - The following are indicators of substantial risk of acquiring HIV, and warrant PrEP use:
 - Sexually active youth: HIV-positive sexual partner, high HIV prevalence area, high HIV prevalence sexual network, high number of sexual partners, recent bacterial STD, recurrent PEP use, inconsistent or no barrier protection use, and/or exchanging sex for drugs or money.
 - Youth who inject drugs: HIV-positive injecting partner and/or sharing injection equipment
 - Pediatricians should be familiar with state laws regarding partner notification and should use reasonable means to persuade and support HIV-infected youth to encourage and/or refer partner(s) to be tested when applicable.
- **CDC: US Public Health Service Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Postexposure Prophylaxis (2018)** (*CDC 2018[a]*)
 - Start PEP medication regimens as soon as possible after occupational exposure to HIV and continue them for a 4-week duration
 - PEP regimens should contain 3 (or more) ARV drugs
 - Preferred PEP regimen: TDF/FTC plus RAL
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 - **CDC: US Public Health Service Guidelines for ARV Postexposure Prophylaxis After Sexual, Injection Drug Use, or Other Non-Occupational Exposure to HIV (2018)** (*CDC 2018[b]*)
 - A 28-day course of non-occupational post exposure prophylaxis (nPEP) is recommended for HIV-uninfected persons who seek care ≤ 72 hours after a non-occupational exposure to blood, genital secretions, or other potentially infected body fluids of persons known to be HIV infected or of unknown HIV status when that exposure represents a substantial risk for HIV acquisition
 - PEP regimens should contain 3 (or more) ARV drugs
 - Preferred ARV nPEP regimens:
 - Adults and adolescents aged ≥ 13 years, including pregnant women, with normal renal function: TDF/FTC plus RAL or DTG
 - Adults and adolescents aged ≥ 13 years with renal dysfunction ($\text{CrCL} < 59$ mL/min): ZDV/3TC (renally dose adjusted) plus RAL or DTG
 - Children aged 2 to 12 years: TDF/3TC plus RAL
 - Children aged 4 weeks to < 2 years: ZDV/3TC (oral solutions) plus RAL or LPV/r (oral solutions)

Safety Summary

- **Contraindications**
 - Most agents (FTC, 3TC, ZDV, ABC, 3TC/TDF, 3TC/ZDV, ABC/3TC): hypersensitivity to any component of the product.
 - Abacavir, Epzicom, Trizivir: positive for HLA-B*5701 allele; moderate to severe hepatic impairment.
 - Truvada, Descovy: Individuals with unknown or positive HIV-1 status.
 - Epzicom, Trizivir: Patients with moderate to severe hepatic impairment.
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- **Boxed Warnings and Key Warnings/Precautions**
 - There are multiple warnings and precautions with each agent. Key safety concerns associated with the NRTI class are due to hallmark mitochondrial toxicity that may manifest as lactic acidosis, severe hepatomegaly with steatosis,

peripheral neuropathy, myopathy, lipodystrophy, and immune reconstitution syndrome. The incidence of these AEs are much lower with the newer NRTIs (ie, 3TC, FTC, ABC, TDF, and TAF) (*DHHS 2023[a]*).

- Triple nucleoside-only regimens: Early virologic failure has been reported in HIV patients.
- Single drug formulations
 - Abacavir
 - **Boxed Warning:** hypersensitivity reactions (especially in patients who carry HLA-B*5701 allele)
 - Warnings/precautions: May increase the risk of myocardial infarction (association unclear)
 - Emtricitabine
 - **Boxed Warning:** Severe acute exacerbations of HBV have been reported in patients who are coinfecting with HIV-1 and HBV and have discontinued FTC. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are coinfecting with HIV-1 and HBV and discontinue FTC.
 - Warnings/precautions: Dose adjustment in renal impairment.
 - Lamivudine:
 - **Boxed Warning:** Severe acute exacerbations of HBV have been reported in patients who are co-infected with HBV and HIV-1 and have discontinued lamivudine. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue 3TC and are co-infected with HIV-1 and HBV. Epivir tablets and oral solution (used to treat HIV-1 infection) contain a higher dose of the active ingredient (lamivudine) than Epivir-HBV tablets and oral solution (used to treat chronic HBV infection). Patients with HIV-1 infection should receive only dosage forms appropriate for treatment of HIV-1.
 - Warnings/precautions: Pancreatitis; lower virologic suppression rates and increased risk of viral resistance with oral solution
 - Zidovudine
 - **Boxed Warning:** Risk of hematological toxicity, myopathy, lactic acidosis, and severe hepatomegaly with steatosis.
 - Warnings/precautions: Vial stoppers contain natural rubber latex that may cause allergic reactions in sensitive individuals.
 - Tenofovir
 - **Boxed Warning:** Severe acute exacerbations of HBV have been reported in patients who are co-infected with HBV and HIV-1 and have discontinued tenofovir. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue tenofovir and are co-infected with HIV-1 and HBV.
 - Warnings/precautions: Decreases in BMD, new onset or worsening renal impairment, AEs due to drug-drug interactions.
- Multiple drug formulations
 - 3TC/TDF (Cimduo)
 - **Boxed Warning:** Post treatment acute exacerbations of HBV.
 - Warnings/precautions: Pancreatitis, decreases in BMD, new onset or worsening renal impairment, redistribution/accumulation of body fat, early virologic failure.
 - 3TC/ZDV (Combivir)
 - **Boxed Warning:** Hematologic toxicity, myopathy, lactic acidosis, severe hepatomegaly with steatosis, exacerbation of HBV.
 - Warnings/precautions: Pancreatitis
 - FTC/TAF (Descovy)
 - **Boxed Warning:** Post treatment acute exacerbations of HBV, risk of drug resistance with use for HIV-1 PrEP in undiagnosed early HIV infected individuals.
 - Warnings/precautions: Comprehensive management/prevention strategies to reduce the risk of STDs, including HIV-1 infection, and/or drug resistance, new onset or worsening renal impairment
 - ABC/3TC (Epzicom)
 - **Boxed Warning:** Post treatment acute exacerbations of HBV, hypersensitivity reactions (especially in patients who carry HLA-B*5701 allele)
 - Warnings/precautions: Myocardial infarction
 - ABC/3TC/ZDV (Trizivir)

- Boxed Warning: hypersensitivity reactions, hematologic toxicity, myopathy, lactic acidosis, severe hepatomegaly with steatosis and exacerbations of HBV
- Warnings/precautions: Myocardial infarction, therapy-experienced patients had limited response to abacavir
- FTC/TDF (Truvada)
 - Boxed Warning: Post treatment exacerbation of HBV, risk of drug resistance with use for HIV-1 PrEP in undiagnosed early HIV infected individuals.
 - Warnings/precautions: Comprehensive management/prevention strategies to reduce the risk of STDs, including HIV-1 infection, and/or drug resistance, decreases in BMD, new onset or worsening renal impairment.
- **Adverse events**
 - Single drug formulations:
 - Abacavir (≥ 10%): Nausea, vomiting, headache, malaise, fatigue, dreams/sleep disorders
 - Fever, chills, nausea, vomiting, skin rashes, and ear/nose/throat infections were most common (≥ 5%) in pediatric patients
 - Emtricitabine (≥ 10%): Headache, diarrhea, nausea, fatigue, dizziness, depression insomnia, abnormal dreams, rash, abdominal pain, asthenia, increased cough, rhinitis
 - Skin hyperpigmentation was very common (≥ 10%) in pediatric patients
 - Lamivudine (≥ 15%): Headache, nausea, malaise/fatigue, nasal signs and symptoms, diarrhea, cough
 - Pediatrics (≥ 15%): fever, cough
 - Tenofovir disoproxil fumarate (≥ 10%): Rash diarrhea, nausea, headache, pain, depression, asthenia
 - Zidovudine (≥ 15%): Headache, malaise, nausea, anorexia, vomiting
 - Pediatrics (≥ 15%): Fever, cough
 - Neonates (≥ 15%): Anemia, neutropenia
 - Multiple drug formulations:
 - 3TC/TDF (> 10%): Headache, pain, depression, diarrhea, and rash
 - 3TC/ZDV (> 15%): Headache, nausea, malaise and fatigue, nasal signs and symptoms, diarrhea, cough
 - FTC/TAF
 - HIV-1 infected patients (≥ 10%): Nausea
 - HIV-1 uninfected patients in PrEP trials (≥ 5%): diarrhea
 - ABC/3TC (> 5%): Hypersensitivity, insomnia, depression/depressed mood, headache/migraine, fatigue/malaise, dizziness/vertigo, nausea, diarrhea
 - ABC/3TC/ZDV (≥ 10%): Nausea, headache, malaise, fatigue, vomiting
 - FTC/TDF (Truvada, Descovy)
 - HIV-1 infected patients (> 10%): Diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, and rash
 - HIV-1 uninfected patients in PrEP trials (> 2%): Headache, abdominal pain, and weight decrease
- **Drug-Drug Interactions**
 - Drug–drug interactions between ARVs and concomitant medications are common and may lead to increased or decreased drug exposure (*DHHS 2023[a]*). Consider the potential for drug interactions prior to and throughout ART and refer to package labeling and the DHHS HIV guidelines for steps to prevent or manage possible and known significant drug interactions, including dosing recommendations.
 - Co-administration with ribavirin and/or interferon alfa (HCV co-infection): hepatic decompensation
 - Retrovir, Cymduo, Combivir, Epzicom
 - Co-administration with ribavirin (HCV co-infection): Exacerbation of anemia
 - Combivir, Retrovir, Trizivir,
 - Methadone: dose adjustments may be required for some individuals
 - Ziagen, Trizivir, Epzicom, Trizivir
 - Coadministration with sorbitol may decrease 3TC concentrations
 - Epivir, Cymduo, Combivir, Epzicom, Trizivir
 - Coadministration with bone marrow suppressive or cytotoxic agents may increase hematologic toxicity

- Retrovir, Combivir, Trizivir
- Coadministration decreases ATV concentrations; use boosted ATV
 - Viread, Cymduo, Truvada
- Coadministration with certain HIV-1 PIs or certain drugs to treat HCV increases tenofovir concentrations
 - Viread, Cymduo, Truvada
- Coadministration may require dose adjustments for rilociguat
 - Ziagen, Epzicom, Trizivir

Dosing and Administration

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Single drug formulation				
Emtriva (emtricitabine)	Capsule, solution	Oral	Once daily	Prior to initiation test for the presence of HBV, as severe acute HBV exacerbation may occur upon discontinuation. Dose adjustments in renal impairment. In cases of dialysis, dose should be given after dialysis if dosing on day of dialysis. May use in severe renal impairment, including hemodialysis.
Epivir (lamivudine)	Solution, Tablet	Oral	1 to 2 times daily depending on strength.	Epivir-HBV (3TC 100 mg tablet and 5 mg/mL oral solution) for HBV contains a lower dose of 3TC than Epivir (3TC 150 mg) for HIV infection. If Epivir-HBV is administered with unrecognized/untreated HIV, rapid emergence of HIV resistance is likely because of sub therapeutic doses and inappropriate monotherapy. May use in severe renal impairment, including hemodialysis. No hepatic dose adjustment necessary.
Retrovir (zidovudine)	Capsule, oral syrup, tablet, solution for injection	Oral, IV	2 to 6 times daily	Consider interruption of therapy in cases of anemia (Hgb < 7.5 g/dL or decline > 25% from baseline) or neutropenia (granulocyte < 750 cells/mm³ or decline > 50% from baseline).

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				May use in severe renal impairment, including hemodialysis.
Viread (tenofovir disoproxil fumarate)	Tablet, powder for reconstitution	Oral	Once daily	Testing prior to initiation: HBV and renal status on a clinically appropriate schedule Dosing scoop for powder: 1 scoop = 40 mg tenofovir. Take oral powder with food. May use in severe renal impairment in adults, including hemodialysis; however, no data are available in patients with CrCL < 10 mL/min not on hemodialysis No hepatic dose adjustment necessary.
Ziagen (abacavir)	Oral solution, tablet	Oral	1 to 2 times daily	Perform HLA-B*5701 testing prior to initiation or re-initiation. Use is contraindicated in cases of HLA-B*5701 allele positive. Dose reduction may be warranted for mild hepatic impairment Child-Pugh Class A. Use is contraindicated in moderate to severe hepatic impairment (Child-Pugh Class B or C). No dose adjustment for renal impairment.
Multiple drug formulation				
Cimduo (lamivudine/tenofovir disoproxil fumarate)	Tablet	Oral	Once daily	Testing prior to initiation: HBV and renal status on a clinically appropriate schedule Use is not recommended in CrCL < 50 mL/min or ESRD requiring hemodialysis.
Combivir (lamivudine/zidovudine)	Tablet	Oral	Twice daily	Use is not recommended in CrCL < 50 mL/min.
Descovy (emtricitabine/tenofovir alafenamide)	Tablet	Oral	Once daily	Testing prior to initiation: HBV and renal status on a clinically appropriate schedule

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Prior to initiating for PrEP, confirm that individual is negative for HIV-1. Use is not recommended in CrCL < 30 mL/min or ESRD and not receiving hemodialysis. No hepatic dose adjustment for Child-Pugh Class A or B.
Epzicom (abacavir/lamivudine)	Tablet Tablet for suspension	Oral	Once daily	Perform HLA-B*5701 testing prior to initiation or re-initiation. Use is contraindicated in cases of HLA-B*5701 allele positive. Use is not recommended in hepatic impairment, CrCL < 30 mL/min, or weight < 25 kg. Do not use in impaired hepatic function.
Trizivir (abacavir/lamivudine/zidovudine)	Tablet	Oral	Twice daily	Perform HLA-B*5701 testing prior to initiation or re-initiation. Use is contraindicated in cases of HLA-B*5701 allele positive. Use is not recommended in hepatic impairment, CrCL < 50 mL/min, or weight < 40 kg.
Truvada (emtricitabine/tenofovir disoproxil fumarate)	Tablet	Oral	Once daily	Testing prior to initiation: HBV and renal status on a clinically appropriate schedule Prior to initiating for PrEP, confirm that individual is negative for HIV-1. Use is not recommended for HIV-1 in CrCL < 30 mL/min, or for PrEP in CrCL < 60 mL/min.

Abbreviations: 3TC = lamivudine; BSA = body surface area; CrCL = creatinine clearance; ESRD = end stage renal disease; HBV = hepatitis B virus; Hgb = hemoglobin; PrEP = pre-exposure prophylaxis. See the current prescribing information for full details.

(Lexicomp 2023, Micromedex 2023)

Additional Information

- **Pediatrics** (and weight-based dosing)
 - Liquid formulations of NRTIs include Emtriva (FTC), Epivir (3TC), Retrovir (ZDV), Viread (TDF), and Ziagen (ABC) which may be prescribed in individuals unable to swallow.
- **Abacavir and Zidovudine containing single and multiple drug formulations**

- The National Institute for Occupational Safety and Health (NIOSH) recommends single gloving for administration of intact tablets or capsules. NIOSH recommends double gloving, a protective gown, and (if there is a potential for vomit or spit up) eye/face protection for administration of an oral liquid (NIOSH 2016).

Conclusion

- PrEP reduces the risk of acquiring HIV from sex by about 99% and from injection drug use by at least 74%. PrEP is less effective when not taken as prescribed and is most effective when combined with additional strategies to minimize HIV transmission. In areas of high HIV transmission, rates of new HIV diagnoses are also higher; therefore, an importance should be placed on access to PrEP and reducing barriers for prevention.
- PrEP is recommended for adults and adolescents weighing ≥ 35 kg who are at risk of acquiring HIV. Three PrEP medications have been approved by the FDA: oral FTC/TDF (Truvada or generic equivalent), oral FTC/TAF (Descovy), and long-acting injectable CAB (Apretude).
 - Truvada and Descovy are each available with a different formulation of tenofovir.
 - Truvada is for all people at risk for HIV through sex or injection drug use.
 - Descovy is for sexually active men and TGW at risk of acquiring HIV; it is not approved for people assigned female at birth who are at risk for HIV through receptive vaginal sex.
 - Apretude has demonstrated efficacy in cisgender MSM, TGW, and cisgender women at risk for acquiring HIV through sexual (both anal and vaginal) transmission.
- For the treatment of HIV, dual-NRTI regimens have demonstrated virologic potency and durability when paired with an INSTI, NNRTI, or a boosted PI. There are currently 7 FDA-approved NRTIs: 3TC (Epivir [3TC], Cimduo [3TC/TDF], Combivir [3TC/ZDV], Trizivir [3TC/ABC/ZDV]); ABC (Ziagen [ABC], Epzicom [ABC/3TC], Trizivir [ABC/3TC/ZDV]); FTC (Emtriva [FTC], Descovy [FTC/TAF], Truvada [FTC/TDF]); TAF (Descovy); TDF (Viread [TDF], Cimduo [TDF/3TC], Truvada [TDF/FTC]); and ZDV (Retrovir [ZDV], Combivir [ZDV/3TC], Trizivir [ZDV/3TC/ABC]).
 - Vemlidy (TAF) is available, but is not FDA-approved for the treatment of HIV-1 infection. In cases of HBV co-infection, Vemlidy alone is not recommended for the treatment of HIV-1 infection as HIV-1 resistance may develop in these patients.
- For background therapy, when paired with an anchor drug, the following should be followed:
 - 3TC and FTC should not be used together as they are similar with similar resistance mutations (ie, M184V).
 - ABC and tenofovir should not be used together as they do not provide any additional synergistic effect and may increase the risk of resistance.
- The 2023 DHHS guidelines for adults and adolescents recommend the following 2 NRTI combinations as background therapy for most individuals living with HIV: ABC/3TC (Epzicom), TAF/FTC (Descovy), TDF/FTC (Truvada), and TDF/3TC (Cimduo). Additionally, the guidelines recommend ZDV as the preferred NRTI to reduce MTCT as well as newborns with perinatal HIV exposure.
 - Head-to-head studies have not demonstrated superiority of 1 preferred NRTI backbone regimen over another. However, selection should be individualized based on factors such as: viral load/virologic efficacy, AEs, childbearing potential, potential drug-drug interactions, co-morbid conditions, resistance test results, cost, and access.
- In people living with HIV, TAF has fewer bone and kidney toxicities than TDF, while TDF is associated with lower lipid levels. Tenofovir-based regimens vary in metabolism. TAF has higher intracellular concentrations, thus lower systemic circulating tenofovir and subsequently is less likely to cause renal or bone toxicities vs TDF. Descovy is the only TAF-containing therapy in the class and is a preferred dual NRTI in children when prescribed with certain anchors. Guidelines state TAF is preferred over TDF in children because TAF has a lower risk of renal and bone AEs. TAF is also the preferred tenofovir agent in individuals with diseases associated with bone loss or renal impairment.
- For renal dysfunction, ABC is an option as no dose adjustment is required and may be prescribed instead of TDF for those who are at high risk for adverse renal effects. In individuals who carry the HLA-B*5701 allele, there is a higher risk for hypersensitivity reactions. Use of ABC is contraindicated in individuals with a prior hypersensitivity reactions to ABC and in HLA-B*5701-positive individuals.
- Several trials comparing triple NRTI therapy (ABC/3TC/ZDV) to NNRTI- or PI- based regimens have resulted in inferior virologic efficacy and shorter time to virologic failure. As part of a 4-drug regimen for initial therapy, Trizivir does not provide more benefit than a standard 3-drug regimen. Within the United States, Trizivir does not have a role in clinical practice.
- Overall, some of the most frequent AEs of the NRTIs include nausea, vomiting, headache, malaise, rash, neuropathy, asthenia, and abdominal pain. The NRTIs carry a class wide warning of mitochondrial toxicity that may manifest as lactic

acidosis, severe hepatomegaly with steatosis, peripheral neuropathy, myopathy, lipodystrophy and immune reconstitution syndrome. However, the incidence of these are much lower with the newer NRTIs (3TC, FTC, ABC, TDF, and TAF).

- Severe acute exacerbations of HBV have been reported in patients who are co-infected with HBV and HIV-1 and have discontinued certain NRTIs (FTC, TAF, or TDF). Prior to initiation or re-initiation of abacavir, testing for HLA-B*5701 allele should be performed; use is contraindicated in patients who are HLA-B*5701 allele positive.
- Treatment of individuals living with HIV requires an individualized approach. Management of these complications is constantly evolving. An importance is placed on access in order to manage complications and prevent resistance.

Appendix

- **Rating scheme for DHHS 2023 Guidelines for the for the Use of ARV Agents in Adults and Adolescents with HIV (DHHS 2023[a])**
 - Rating of Recommendations: A = Strong; B = Moderate; C = Weak
 - Rating 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
- **Rating scheme for DHHS 2023 Guidelines for the use of ARV Agents in Pediatric HIV Infection (DHHS 2023[b])**
 - Rating of Recommendations: A = Strong; B = Moderate; C = Optional
 - Rating of Evidence: 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, plus accompanying data in children from ≥ 1 well-designed, non-randomized trials or observational cohort studies with clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children with clinical outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes, plus accompanying data in children from ≥ 1 smaller nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion
- **Rating scheme for DHHS 2023 Recommendations for the Use of ARV Drugs During Pregnancy with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States (DHHS 2023[c])**
 - Rating of Recommendations: A = Strong; B = Moderate; C = Optional
 - Rating 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
- **Rating scheme for IAS-USA Panel 2022 Guidelines for the Use of ARVs in Treatment and Prevention of HIV in Adults (Gandhi et al 2023)**
 - Rating of Recommendations: A = Strong; B = Moderate; C = Limited or weak
 - Quality of Evidence: Ia = Evidence from ≥ 1 RCTs in peer-reviewed literature; Ib = Evidence from ≥ 1 RCTs presented in abstract form at peer-reviewed scientific meeting; IIa = Evidence from nonrandomized clinical trials or cohort or case-controlled studies published in peer-reviewed literature; IIb = Evidence from nonrandomized clinical trials or cohort or case-controlled studies presented in abstract form at peer-reviewed scientific meeting; III = Based on panel's analysis of accumulated available evidence
- **Rating scheme for CDC/USPHS 2021 recommendations for PrEP (CDC 2021)**
 - Rating of Recommendations: A = Strong; B = Moderate; C = Optional
 - Rating of Evidence: I = One of more well-executed RCTs with clinical outcomes, validated laboratory endpoints, or both; II = One of more well-executed, non-randomized trials or observational cohort studies with clinical outcomes; III = Expert opinion

References

- Anderson PL, Brooks KM, Fletcher CV. Chapter 148: Human immunodeficiency virus infection. In: DiPiro JT, Yee GC, Haines ST, Nolin TD, Ellingrod VL, Posey M, editors. *Dipiro's Pharmacotherapy: A Pathophysiologic Approach*, 12th edition. McGraw-Hill, 2023.
- Arribas JR, Thompson M, Sax P, et al. Brief Report: Randomized, Double-Blind Comparison of Tenofovir Alafenamide (TAF) vs Tenofovir Disoproxil Fumarate (TDF), Each Coformulated With Elvitegravir, Cobicistat, and Emtricitabine (E/C/F) for Initial HIV-1 Treatment: Week 144 Results. *J Acquir Immune Defic Syndr*. 2017;75(2):211-218.
- Baeten JM, Donnell D, Ndase P, et al. Antiretroviral Prophylaxis for HIV Prevention in Heterosexual Men and Women. *N Engl J Med*. 2012; 367:399-410.
- Centers for Disease Control and Prevention (CDC). Basic statistics. May 22, 2023. [Basic Statistics | HIV Basics | HIV/AIDS | CDC](#). Accessed December 26, 2023

- CDC. Pre-Exposure Prophylaxis (PrEP). Updated July 5, 2022[b]. <https://www.cdc.gov/hiv/risk/prep/index.html>. Accessed November 7, 2023.
- CDC. US Public Health Service Preexposure Prophylaxis for The Prevention Of HIV Infection in the United States – 2021 Update. 2021. <https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2021.pdf>. Accessed November 7, 2023.
- CDC. US Public Health Service. Updated U.S. Public Health Service guidelines for the management of occupational exposures to HIV and recommendations for postexposure prophylaxis. Updated May 23, 2018[a]. Website. <https://stacks.cdc.gov/view/cdc/20711>. Accessed November 7, 2023.
- CDC. US Public Health Service. Updated guidelines for antiretroviral postexposure prophylaxis after sexual, injection drug use, or other nonoccupational exposure to HIV. Updated May 23, 2018[b]. Website. <https://stacks.cdc.gov/view/cdc/38856>. Accessed November 7, 2023.
- Choopanya K, Martin M, Suntharasamai P, et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2013;381(9883):2083-2090.
- Chou R, Evans C, Hoverman A, et al. Preexposure prophylaxis for the prevention of HIV infection: evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2019;321(22):2214-2230.
- Chou R, Spencer H, Bougatsos C, Blazina I, Ahmed A, Selph S. Preexposure prophylaxis for the prevention of HIV: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2023;330(8):746-763.
- Cimduo [package insert], Morgantown, WV: Mylan Specialty L.P. February 2021.
- Combivir [package insert], Research Triangle Park, NC: ViiV Healthcare, Inc.; August 2023.
- Connor EM, Sperling RS, Gelber R, et al. Reduction of Maternal-Infant Transmission of Human Immunodeficiency Virus Type 1 with Zidovudine Treatment. *N Engl J Med* 1994; 331:1173-1180.
- Cruciani M, Mengoli C, Malena M, et al. Virological efficacy of abacavir: systematic review and meta- analysis. *J Antimicrob Chemother*. 2014;69(12):3169-3180.
- Daar ES, Tierney C, Fischl MA, et al. Atazanavir plus ritonavir or efavirenz as part of a 3-drug regimen for initial treatment of HIV-1. *Ann Intern Med*. 2011;154:445-456.
- Descovy [package insert], Foster City, CA: Gilead Sciences, Inc.; January 2022.
- DHHS panel on antiretroviral guidelines for adults and adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. Updated December 6, 2023[a]. <https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf>. Accessed December 26, 2023.
- DHHS panel on antiretroviral therapy and medical management of children living with HIV. Guidelines for the use of antiretroviral agents in pediatric HIV infection. Updated April 11, 2023[b]. <https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/pediatric-arv/guidelines-pediatric-arv.pdf>. Accessed November 7, 2023.
- DHHS panel on treatment of HIV during pregnancy and prevention of perinatal transmission. Recommendations for the use of antiretroviral drugs during pregnancy and interventions to reduce perinatal HIV transmission in the United States. Updated January 31, 2023[c]. <https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/perinatal-hiv/guidelines-perinatal.pdf>. Accessed November 7, 2023.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. <https://www.accessdata.fda.gov/scripts/cder/daf/>. Accessed November 7, 2023.
- Emtriva [package insert], Foster City, CA: Gilead Sciences, Inc.; June 2021.
- Epivir [package insert], Research Triangle Park, NC: ViiV Healthcare, Inc.; September 2020.
- Epzicom [package insert], Durham, NC: ViiV Healthcare, Inc.; December 2022.
- Eron JJ, Orkin C, Gallant J, et al. A week-48 randomized phase-3 trial of darunavir/cobicistat/emtricitabine/tenofovir alafenamide in treatment-naïve HIV-1 patients. *AIDS*. 2018;32(11):1431-1442.
- Ford N, Shubber Z, Hill A, et al. Comparative efficacy of lamivudine and emtricitabine: a systematic review and meta-analysis of randomized trials. *PLoS one*. 2013;8(11):e79981.
- Gallant J, Lazzarin A, Mills A, et al. Bictegravir, emtricitabine, and tenofovir alafenamide vs dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial. *Lancet* 2017;390(10107):2063-2071.
- Gandhi RT, Bedimo R, Hoy JF, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2022 recommendations of the International Antiviral Society-USA Panel. *JAMA*. 2023;329(1):63-84.
- Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med*. 2010; 363:2587-2599.
- Grohskopf LA, Chillag KL, Gvetadze R, et al. Randomized trial of clinical safety of daily oral tenofovir disoproxil fumarate among HIV-uninfected men who have sex with men in the United States. *J Acquir Immune Defic Syndr*. 2013;64(1):79-86.
- Gulick RM, Ribaudo HJ, Shikuma CM, et al. Triple-nucleoside regimens vs efavirenz-containing regimens for the initial treatment of HIV-1 infection. *N Engl J Med*. 2004;350:1850-1861.
- Hemkens LG, Ewald H, Santini-Oliveira M, et al. Comparative effectiveness of tenofovir in treatment-naïve HIV-infected patients: systematic review and meta-analysis. *HIV Clin Trials*. 2015;16(5):178-189.
- Hill A, Hughes SL, Gotham D, et al. Tenofovir alafenamide vs tenofovir disoproxil fumarate: is there a true difference in efficacy and safety? *J Virus Erad*. 2018;4(2):72-79.
- Hosek SG, Rudy B, Landovitz R, et al. An HIV Pre-Exposure Prophylaxis (PrEP) Demonstration Project and Safety Study for Young MSM. *J Acquir Immune Defic Syndr*. 2017; 74(1): 21–29.
- Hsu KK, Rakhmanina NY; for the Committee on Pediatric AIDS for the American Academy of Pediatrics (AAP). Adolescents and young adults: the pediatrician's role in HIV testing and pre- and postexposure HIV prophylaxis. *Pediatrics*. 2022;149(1):e2021055207.
- Kumar PN, Salvato P, Lamarca A, et al. A randomized, controlled trial of initial anti-retroviral therapy with abacavir/lamivudine/zidovudine twice-daily compared to atazanavir once-daily with lamivudine/zidovudine twice-daily in HIV-infected patients over 48 weeks (ESS100327, the ACTION Study). *AIDS Res Ther*. 2009;6:3.
- Lexicomp [database on the Internet]. Wolters Kluwer; 2023. [Online.lexi.com](https://online.lexi.com). Accessed November 7, 2023.

- Lockman S, Brummel SS, Ziemia L, et al. Efficacy and safety of dolutegravir with emtricitabine and tenofovir alafenamide fumarate or tenofovir disoproxil fumarate, and efavirenz, emtricitabine, and tenofovir disoproxil fumarate HIV antiretroviral therapy regimens started in pregnancy (IMPAACT 2010/VESTED): a multicentre, open-label, randomised, controlled, phase 3 trial. *Lancet*. 2021;397(10281):1276-1292.
- Marrazzo, JM, Ramjee G, Richardson BA, et al. Tenofovir-Based Preexposure Prophylaxis for HIV Infection among African Women. *N Engl J Med*. 2015; 372:509-518
- Mayer KH, Molina JM, Thompson MA, et al. Emtricitabine and tenofovir alafenamide vs emtricitabine and tenofovir disoproxil fumarate for HIV pre-exposure prophylaxis (DISCOVER): primary results from a randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial. *Lancet*. 2020;396(10246):239-254.
- Micromedex Solutions [database on the Internet]. Merative US L.P; 2023. <http://www.micromedexsolutions.com/home/dispatch>. Accessed November 7, 2023.
- Molina JM, Clotet B, van Lunzen J, et al. Once-daily dolutegravir is superior to once-daily darunavir/ritonavir in treatment-naïve HIV-1-positive individuals: 96 week results from FLAMINGO. *J Int AIDS Soc*. 2014;17:19490.
- Moyle GJ, Stellbrink HJ, Compston J, et al. 96-Week results of abacavir/lamivudine vs tenofovir/emtricitabine, plus efavirenz, in antiretroviral-naïve, HIV-1-infected adults: ASSERT study. *Antivir Ther*. 2013;18:905-913.
- National Institute for Occupational Safety and Health (NIOSH) Alert: Preventing occupational exposures to antineoplastic and other hazardous drugs in health care settings. CDC website. Updated 2016. [CDC.gov/niosh/docs/2004-165](https://www.cdc.gov/niosh/docs/2004-165). Accessed November 7, 2023.
- Nelson M, Winston A, Hill A, et al. Efficacy, safety and central nervous system effects after switch from efavirenz/tenofovir/emtricitabine to doravirine/tenofovir/lamivudine. *AIDS*. 2021;35(5):759-767.
- Ogbuagu O, Ruane PJ, Podzamczar D, et al, on behalf of the DISCOVER study team. Long-term safety and efficacy of emtricitabine and tenofovir alafenamide vs emtricitabine and tenofovir disoproxil fumarate for HIV-1 pre-exposure prophylaxis: week 96 results from a randomized, double-blind, placebo-controlled, phase 3 trial. *Lancet HIV*. 2021;8(7):e397-e407.
- Okwundu CI, Uthman OA, Okoromah CA. Antiretroviral pre-exposure prophylaxis (PrEP) for preventing HIV in high-risk individuals. *Cochrane Database Syst Rev*. 2012;(7):CD007189.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. <https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>. Accessed November 7, 2023.
- Orkin C, DeJesus E, Sax PE, et al. Fixed-dose combination bictegravir, emtricitabine, and tenofovir alafenamide vs dolutegravir-containing regimens for initial treatment of HIV-1 infection: week 144 results from two randomised, double-blind, multicentre, phase 3, non-inferiority trials. *Lancet HIV*. 2020; 7(6):e389-e400.
- Orkin C, Squires KE, Molina JM, et al. Doravirine/lamivudine/tenofovir disoproxil fumarate is non-inferior to efavirenz/emtricitabine/tenofovir disoproxil fumarate in treatment-naïve adults with human immunodeficiency virus-1 infection: week 48 results of the DRIVE-AHEAD trial. *Clin Infect Dis*. 2019; 68(4):535-544.
- Orkin C, Squires KE, Molina JM, et al. Doravirine/lamivudine/tenofovir disoproxil fumarate (TDF) vs efavirenz/emtricitabine/TDF in treatment-naïve adults with Human Immunodeficiency Virus Type 1 infection: Week 96 results of the randomized, double-blind, Phase 3 DRIVE-AHEAD noninferiority trial. *Clin Infect Dis*. 2021;73(1):33-42.
- Pilkington V, Hill A, Hughes S, et al. How safe is TDF/FTC as PrEP? A systematic review and meta-analysis of the risk of adverse events in 13 randomised trials of PrEP. *J Virus Erad*. 2018;4(4):215-224.
- Pilkington V, Hughes SL, Pepperrell T, et al. Tenofovir alafenamide vs tenofovir disoproxil fumarate: an updated meta-analysis of 14894 patients across 14 trials. *AIDS*. 2020;34(15):2259-2268.
- Retrovir [package insert], Durham, NC: ViiV Healthcare; July 2023.
- Sax PE, Pozniak A, Montes M, et al. Coformulated bictegravir, emtricitabine, and tenofovir alafenamide vs dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380-1490): a randomised, double-blind, multicentre, phase 3, non-inferiority trial. *Lancet*. 2017;390(101007): 2073-2082.
- Sax PE, Tierney C, Collier AC, et al. Abacavir-lamivudine versus tenofovir-emtricitabine for initial HIV-1 therapy. *N Engl J Med*. 2009;361(23):2230-2240.
- Sax PE, Wohl D, Yin MT, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. *Lancet*. 2015;385(9987):2606-2615.
- Shey MS, Kongnyuy EJ, Alobwede SM, et al. Co-formulated abacavir-lamivudine-zidovudine for initial treatment of HIV infection and AIDS. *Cochrane Database Syst Rev*. 2013 Mar 28;(3):CD005481.
- Siegfried N, van der Merwe L, Brocklehurst P, et al. Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection. *Cochrane Database Syst Rev*. 2011 Jul 6;(7):CD003510.
- Smith KY, Patel P, Fine D, et al. Randomized, double-blind, placebo-matched, multicenter trial of abacavir/lamivudine or tenofovir/emtricitabine with lopinavir/ritonavir for initial HIV treatment. *AIDS*. 2009;23:1547-56.
- Staszewski S, Keiser P, Montaner J, et al. Abacavir-lamivudine-zidovudine vs indinavir-lamivudine-zidovudine in antiretroviral-naïve HIV-infected adults: A randomized equivalence trial. *JAMA*. 2001;285:1155-1163.
- Stellbrink H, Arribas J, Stephens JL, et al. Co-formulated bictegravir, emtricitabine, and tenofovir alafenamide vs dolutegravir with emtricitabine and tenofovir alafenamide for initial treatment of HIV-1 infection: week 96 results from a randomised, double-blind, multicentre, phase 3, non-inferiority trial. *Lancet HIV*. 2019;6(6):e364-372.
- Stellbrink HJ, Orkin C, Arribas JR, et al. Comparison of changes in bone density and turnover with abacavir-lamivudine vs tenofovir-emtricitabine in HIV-infected adults: 48-week results from the ASSERT study. *Clin Infect Dis*. 2010;51:963-972.
- Tao X, Lu Y, Zhou Y, Zhang L, Chen Y. Efficacy and safety of the regimens containing tenofovir alafenamide vs tenofovir disoproxil fumarate in fixed-dose single-tablet regimens for initial treatment of HIV-1 infection: A meta-analysis of randomized controlled trials. *Int J Infect Dis*. 2020;93:108-117.
- Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral Preexposure Prophylaxis for Heterosexual HIV Transmission in Botswana. *N Engl J Med*. 2012; 367:423-434.
- Thompson M, Brar I, Brinson C, et al. Tenofovir alafenamide vs tenofovir DF in women: pooled analysis of 7 clinical trials. Conference on Retroviruses and Opportunistic Infections. March 4 to 7, 2019. Abstract number 519. <http://www.croiconference.org/sessions/tenofovir-alafenamide-vs-tenofovir-df-women-pooled-analysis-7-clinical-trials>. Accessed November 7, 2023.

- Trizivir [package insert], Research Triangle Park, NC: ViiV Healthcare, Inc.; February 2021.
- Truvada [package insert], Foster City, CA: Gilead Sciences, Inc.; September 2021.
- US Preventive Services Task Force, Barry MJ, Nicholson WK, et al. Preexposure Prophylaxis to Prevent Acquisition of HIV: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2023;330(8):736-745.
- Van Damme L, Corneli A, Ahmed K, et al. Preexposure Prophylaxis for HIV Infection among African Women. *N Engl J Med*. 2012;367:411-422.
- Venter WDF, Sokhela S, Simmons B, et al. Dolutegravir with emtricitabine and tenofovir alafenamide or tenofovir disoproxil fumarate vs efavirenz, emtricitabine, and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection (ADVANCE): week 96 results from a randomised, phase 3, non-inferiority trial. *Lancet HIV*. 2020;7(10):e666-e676.
- Veroniki AA, Antony J, Straus SE, et al. Comparative safety and effectiveness of perinatal antiretroviral therapies for HIV-infected women and their children: Systematic review and network meta-analysis including different study designs. *PLoS One*. 2018;13(6):e0198447.
- Viread [package insert], Foster City, CA: Gilead Sciences, Inc.; March 2021.
- Wang H, Lu X, Yang X, et al. The efficacy and safety of tenofovir alafenamide vs tenofovir disoproxil fumarate in antiretroviral regimens for HIV-1 therapy: Meta-analysis. *Medicine (Baltimore)*. 2016;95(41):e5146.
- Wohl D, Oka S, Clumeck N, et al. Brief Report: A randomized, double-blind comparison of tenofovir alafenamide vs tenofovir disoproxil fumarate, each coformulated with elvitegravir, cobicistat, and emtricitabine for initial HIV-1 treatment: week 96 results. *J Acquir Immune Defic Syndr*. 2016;72(1):58-64.
- Wohl DA, Yazdanpanah Y, Baumgarten A, et al. Bictegravir combined with emtricitabine and tenofovir alafenamide vs dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection: week 96 results from a randomised, double-blind, multicentre, phase 3, non-inferiority trial. *Lancet HIV*. 2019;6(6):e355-363.
- Wood BR. The natural history and clinical features of HIV infection in adults and adolescents. UpToDate. Website. Updated February 15, 2023. <https://www.uptodate.com/contents/the-natural-history-and-clinical-features-of-hiv-infection-in-adults-and-adolescents>. Accessed November 7, 2023.
- Ziagen [package insert], Durham, NC: ViiV Healthcare, Inc.; September 2023.

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