© Copyright 2021 Oregon State University. All Rights Reserved

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Drug Class Update: Human Immunodeficiency Virus

Date of Review: August 2021

Date of Last Review: July 2015
Dates of Literature Search: 01/01/2020 - 05/24/2021

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
The purpose of this review is to evaluate new comparative literature published since the previous review and define place in therapy for a new long-acting injectable agent cabotegravir/rilpivirine (CABENUVA), recently approved by the Food and Drug Administration (FDA) for the treatment of Human Immunodeficiency Virus (HIV) type-1 infection in adults who are virologically suppressed on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine (see accompanying New Drug Evaluation).

Research Questions:
1. What are the current antiretroviral drug regimens recommended in the United States (US) for treatment and prevention of HIV transmission?
2. What is the comparative effectiveness of antiretroviral agents for treatment and prevention of HIV?
3. Are certain sub-populations (based on age, gender, ethnicity, comorbidities, disease duration, or severity) in which certain agents may be beneficial or cause more harm?

Conclusions:
- This update includes a review of 2 Drug Effectiveness Review Project (DERP) reports[1,2] related to the treatment and prevention of HIV-1. These reports summarize available literature and compare and contrast various guideline recommendations in this clinical area. A review of guidelines for clinical context include recommendations applicable to pregnant individuals and children.
- There is variation amongst guidelines related to the recommended initial treatment regimens and alternative regimens in adults. Guideline methodology and quality varies significantly.[1,2] **(Table 4, Table 5)**
- Initial therapy for most patients should consist of:[1]
    - A two-drug nucleoside reverse transcriptase inhibitor backbone combined with:
    - An add-on therapy of a non-nucleoside reverse transcriptase inhibitor, integrase strand transfer inhibitor (INSTI), or boosted protease inhibitor
- Treatment with antiretroviral therapy should begin immediately, or as soon as possible after diagnosis of HIV.[1-5]
- Majority of direct comparative evidence available is in the form of non-inferiority studies **(Table 2, Table 3)**.[1]

- Pre-exposure prophylaxis (PrEP) using continuous daily emtricitabine 200mg/tenofovir disoproxil fumarate 300 mg is recommended by reviewed guidelines for high-risk individuals. Recommended alternative drug regimens of on-demand emtricitabine 200mg/tenofovir disoproxil fumarate 300 mg vs continuous daily tenofovir disoproxil fumarate 300 mg vary between guidelines for some subpopulations.[2] **(Table 6)**
- PrEP prophylaxis using continuous emtricitabine 200 mg/tenofovir alafenamide is FDA-approved for use in at-risk adults and adolescents weighing at least 35 kg to reduce the risk of HIV-1 infection from sexual acquisition, but the indication does not include individuals at risk from receptive vaginal sex.[6]
    - Emtricitabine/tenofovir alafenamide was non-inferior to emtricitabine/tenofovir disoproxil fumarate in reducing HIV acquisition in high-risk men who have sex with men and transgender women at high-risk of HIV acquisition (incident rate ratio 0.47 [95% confidence interval 0.19-1.15]-met prespecified 50% non-inferiority margin).[7]
- Dolutegravir use in individuals at risk of conception should involve informed patient decision making. Dolutegravir is considered a preferred option in combination with a nucleoside reverse transcriptase inhibitor backbone in this sub-population.[3,5]
- Recommended medication regimens for children are highly dependent on age and weight of child. Some recommendations in infants and younger children are extrapolated from studies in adults and adolescents.[4]
- Patients with hepatitis B coinfection should receive regimens with contain at least 2 agents active against hepatitis B.[1]
- Antiretroviral use may result in weight gain, particularly when initiating and changing regimens. Women, and specifically Black women, generally experience more weight gain than men. (Grade AI) This may be higher with dolutegravir or bictegravir based regimens. The quantity of weight gained varied by study; including ≥ 10% weight gain (17.4% female vs 12.2% male; 19.7% Black females vs. 12.4% non-Black females) and 4.2 kg gain in women switching to or adding an INSTI vs. 0.2 kg for women remaining on non-INSTI regimens after 2 years.[3]
- There are limitations relating to lack of generalizability of the study populations. Most participants were white males. Few studies included participants of other genders, races, and ethnicities. This may lead to underrepresentation of severe adverse effects such as HIV-associated nephropathy (HIVAN), which disproportionately affects Black individuals. Few studies reported the percentage of participants with specific HIV risk factors, including men who have sex with men (MSM), transgender individuals, and people who inject drugs. No studies focused on findings in Medicaid populations.[1]

Recommendations:
- Evidence does not support changes to Preferred Drug List (PDL) or current policy.
- No PDL changes recommended after review of costs in executive session.

Summary of Prior Reviews and Current Policy:
- Antiretroviral class was first reviewed in 2015. At that time a preferred drug list (PDL) was created for all antiretroviral drugs and drug combinations, and all antiretroviral agents were designated as preferred.
- In the 4th quarter of 2020, there were just under 200 patients in the Oregon Health Plan (OHP) Fee for Service (FFS) population with paid claims for ARVs.

Background:

Human immunodeficiency virus is transmitted through contact with bodily fluids such as blood, semen, vaginal secretions, and breast milk. Once infected, the virus works to destroy immune system cells. Two to 4 weeks after contracting this infection, patients often have a high viral load and are very infectious, which then progresses to a chronic phase which can last for years. While still able to infect others, the viral load is generally lower than during the acute phase.

Without antiretroviral treatment, the viral load again increases and the patient will develop Acquired Immunodeficiency Syndrome (AIDS), and become susceptible to a wide range of opportunistic infections which increase morbidity and mortality.[8]

There are an estimated 1.2 million people with HIV in the United States (US), and this includes roughly 14% who do not know they are infected. HIV type-1 is far more common in the US than HIV type-2, which is less transmittable and less virulent.[9] New diagnoses fell by 7% from 2014 to 2018.[9] Men who have sex with men (MSM) is the most common mode of transmission for new cases (66.0%), followed by heterosexual contact (23.8%), people who inject drugs (PWID) (6.6%), and combination of MSM plus PWID (3.6%).[9] Vertical transmission from mother to baby is uncommon in the US. People who are Black/African American (42.2%) and Hispanic/Latino (27.0%) make up the majority of these new cases by ethnicity, with the subgroup of Black/African American gay and bisexual men being the most affected subpopulation.[9] In 2018, Oregon had 229 (6.4/100,000) newly diagnosed and 7,050 (197.9/100,000) total cases.[9] Most patients in Oregon were male (88%).[10] Prevalence among transgender patients is difficult to quantify as health care providers have only recently begun asking about gender identity. Over half (66%) of patients in Oregon with HIV have been diagnosed for more than 10 years.[10] In 2018 there were 66 pediatric patients living with HIV who had been diagnosed at or after birth.[10] Of all patients who have been diagnosed in Oregon, roughly 88% are both in care and on treatment and 77% are virally suppressed.[10]

Since the advent of antiretroviral drugs (ARVs) in the 1980's, the prognosis for those infected with HIV has changed, and HIV is now managed as a long-term, chronic condition. Due to the propensity to develop resistance, treatment with ARVs usually includes a combination of 3 drugs from at least 2 different drug classes. Select 2-drug regimens are also approved. ARV therapies consist of 7 classes: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), integrase strand transfer inhibitors (INSTIs), protease inhibitors (PIs), a fusion inhibitor, a CCR5 antagonist, a CD4 Post-attachment inhibitor, and a gp120 attachment inhibitor.[3] The latter 4 are primarily used in situations of multidrug resistance or salvage therapy. A pharmacokinetic (PK) enhancer or "booster" is often given with PIs or elvitegravir, and does not count as 1 of the total 2 or 3 drugs drugs in combination.[3] Many of these agents are co-formulated to reduce pill burden and improve adherence. A full list of available agents can be seen in **Table 1**.[3] **Appendix 5** includes a reference list of 3 letter drug abbreviations used for HIV medications.

Table 1. FDA-approved antiretroviral agents[3]

Generic Name (Abbreviation) **BRAND NAME**	**Formulation**	**Fixed-Dose Combination (FDC)**	**Single Tablet Regimen (STR)**
Nucleoside Reverse Transcriptase Inhibitors			
Emtricitabine (FTC) EMTRIVA	EMTRIVA: 200-mg hard gelatin capsule 10-mg/mL oral solution	DESCOVY (TAF/FTC) TRUVADA (TDF/FTC)	ATRIPLA (EFV/TDF/FTC) BIKTARVY (BIC/TAF/FTC) COMPLERA (RPV/TDF/FTC) GENVOYA (EVG/c/TAF/FTC) ODEFSEY (RPV/TAF/FTC) STRIBILD (EVG/c/TDF/FTC) SYMTUZA (DRV/c/TAF/FTC)
Lamivudine (3TC) EPIVIR	EPIVIR: 150-mg and 300-mg tablets 10-mg/mL oral solution	CIMDUO (TDF/3TC) EPZICOM (ABC/3TC) TEMIXYS (TDF/3TC	DELSTRIGO (DOR/TDF/3TC) DOVATO (DTG/3TC) SYMFI (EFV 600 mg/TDF/3TC) SYMFI LO (EFV 400 mg/TDF/3TC)

			TRIUMEQ (DTG/ABC/3TC)
Tenofovir Alafenamide (TAF) VEMLIDY Note: VEMLIDY is available as a 25-mg tablet for the treatment of hepatitis B.	N/A	DESCOVY (TAF/FTC)	BIKTARVY (BIC/TAF/FTC) GENVOYA (EVG/c/TAF/FTC) ODEFSEY (RPV/TAF/FTC) SYMTUZA (DRV/c/TAF/FTC)
Tenofovir Disoproxil Fumarate (TDF) VIREAD	VIREAD: 150-mg, 200-mg, 250-mg, and 300-mg tablets 40 mg/g oral powder	CIMDUO (TDF/3TC) TEMIXYS (TDF/3TC) TRUVADA (TDF/FTC)	ATRIPLA (EFV/TDF/FTC) COMPLERA (RPV/TDF/FTC) DELSTRIGO (DOR/TDF/3TC) STRIBILD (EVG/c/TDF/FTC) SYMFI (EFV 600 mg/TDF/3TC) SYMFI LO (EFV 400 mg/TDF/3TC)
Non-Nucleoside Reverse Transcriptase Inhibitors			
Doravirine (DOR) PIFELTRO	PIFELTRO: 100-mg tablet		DELSTRIGO (DOR/TDF/3TC)
Efavirenz (EFV) SUSTIVA	SUSTIVA: 50-mg and 200-mg capsules 600-mg tablet		ATRIPLA (EFV/TDF/FTC) SYMFI (EFV 600 mg/TDF/3TC) SYMFI LO (EFV 400 mg/TDF/3TC)
Etravirine (ETR) INTELENCE	INTELENCE: 25-mg, 100-mg, and 200-mg tablets		
Nevirapine (NVP) VIRAMUNE or VIRAMUNE XR	VIRAMUNE: 200-mg tablet 50-mg/5-mL oral suspension VIRAMUNE XR: 400-mg tablet		
Rilpivirine (RPV) EDURANT	EDURANT: 25 mg tablet		COMPLERA (RPV/TDF/FTC) JULUCA (DTG/RPV) ODEFSEY (RPV/TAF/FTC) <u>CABENUVA (CAB plus RPV)-Intramuscular Injection rather than tablet</u>
Protease Inhibitors			
Atazanavir (ATV) REYATAZ EVOTAZ (ATV/c)	REYATAZ: 150-mg, 200-mg, and 300-mg cap-sules 50-mg oral powder/packet	EVOTAZ: ATV 300-mg/COBI 150-mg tablet	

Darunavir (DRV) PREZISTA PREZCOBIX (DRV/c)	PREZISTA: 75-mg, 150-mg, 600-mg, and 800-mg tablets 100-mg/mL oral suspension PREZCOBIX: DRV 800-mg/COBI 150-mg tablet		SYMTUZA (DRV/c/TAF/FTC)
Lopinavir/Ritonavir (LPV/r) KALETRA Note: LPV is only available as a component of an FDC tablet that also contains RTV.	KALETRA: LPV/r 200-mg/50-mg tablets LPV/r 100-mg/25-mg tablets LPV/r 400-mg/100-mg per 5 mL of oral solution. Oral solution contains 42% alcohol.		
Ritonavir (RTV) NORVIR Note: RTV is currently used at lower doses as a PK enhancer to increase the concentrations of other PIs and not as a stand-alone PI.	NORVIR: 100-mg tablet 100-mg soft gel capsule 80-mg/mL oral solution. Oral solution contains 43% alcohol. 100 mg single packet oral powder	KALETRA (LPV/r)	
Integrase Strand Transfer Inhibitors			
Bictegravir (BIC)	50 mg in combination product only		BIKTARVY (BIC/TAF/FTC)
Cabotegravir (CAB)	VOCABRIA (CAB PO): 30-mg tablet Obtain from manufacturer for oral lead-in and oral bridging during administration of CABENUVA (CAB IM/RPV IM)		CABENUVA (CAB IM and RPV IM): 400-mg/2-mL vial 600-mg/3-mL vial
Dolutegravir (DTG) TIVICAY	TIVICAY: 10 mg, 25 mg, and 50 mg tablets 5 mg soluble tablet		DOVATO (DTG/3TC) JULUCA (DTG/RPV) TRIUMEQ (DTG/ABC/3TC)
Elvitegravir (EVG)	150 mg in combination products only		GENVOYA (EVG/c/TAF/FTC) STRIBILD (EVG/c/TDF/FTC)
Raltegravir (RAL)	ISENTRESS:		

ISENTRESS ISENTRESS HD	400-mg tablet 25-mg and 10-mg chewable tablets 100-mg single-use packet for oral suspension ISENTRESS HD: 600-mg tablet		
Other Antiretroviral Classes			
Fusion Inhibitor Enfuvirtide (T-20) FUZEON	FUZEON: Injectable; supplied as lyophilized powder. Each vial contains 108 mg of T-20; reconstitute with 1.1 mL of sterile water for injection for delivery of approximately 90 mg/1 mL.		
CCR5 Antagonist Maraviroc (MVC) SELZENTRY	SELZENTRY: 150-mg and 300-mg tablets		
CD4 Post-Attachment Inhibitor Ibalizumab (IBA) TROGARZO	TROGARZO: Single-dose 2-mL vial containing 200 mg/1.33 mL (150 mg/mL) of ibalizumab		
gp120 Attachment Inhibitor Fostemsavir (FTR) RUKOBIA	600-mg extended-release tablets		
Pharmacokinetic booster (cytochrome p-450 inhibitor) Cobicistat (COBI, c) TYBOST	TYBOST: 150-mg tablets	EVOTAZ: ATV 300-mg/COBI 150-mg tablet PREZCOBIX: DRV 800-mg/COBI 150-mg tablet	SYMTUZA (DRV/c/TAF/FTC) GENVOYA (EVG/c/TAF/FTC) STRIBILD (EVG/c/TDF/FTC)
Abbreviations: Drug abbreviations in Appendix 5; FDC = fixed dose combination; IM = intramuscular; PI = protease inhibitor; STR = single tablet regimen.			

Antiretrovirals can be used to treat and prevent HIV. The goal of treatment is to achieve virologic suppression, which is defined as an HIV RNA (viral load) of less than 50 copies/mL for at least 6 months.[11] The ability to achieve and maintain a suppressed HIV RNA are important endpoints in clinical trials. A virologic blip occurs in patients who achieve suppression and subsequently have an isolated viral load of >200 copies/mL, followed by a return to suppression. Incomplete

virologic response is defined as 2 consecutive viral load measurements of ≥ 200 copies/mL after 24 weeks of ARV treatment when a patient has never had documented virologic suppression on the current regimen. The inability to achieve or maintain suppression with an HIV RNA level of < 200 copies/mL is virologic failure. A virologic blip is not usually associated with later virologic failure. Some data suggest that low level viremia of 50-199 copies/mL can be predictive of later virologic failure and development of drug resistance. Sustained viremia of ≥ 200 copies/mL is associated with virologic failure and the accumulation of viral mutations, and this association is even stronger with persistent viremia of > 500 copies/mL. Virologic failure can be related to many aspects, these include patient adherence related factors (e.g., comorbidities, adverse drug effects, etc), HIV related factors (e.g., presence of transmitted or acquired drug resistance, etc), and ARV regimen factors (e.g., drug-drug interactions, etc).[12] Management of virologic failure should be individualized. Interpretation of resistance test results and management of patients with archived drug-resistance mutations is complicated and generally requires specialist oversight.

Guidance recommends initiation of ART immediately, or as soon as possible after diagnosis.[3-5,11] This has multiple benefits, including improved linkage to care, increased uptake of ART, reduced risk of transmission, and an improved rate of virologic suppression.[3] Initial treatment is dependent on many variables, including comorbidities, virologic efficacy, toxicity, pill burden, resistance test results, drug-drug interactions, and cost. Prevention using ARVs falls into the following main categories: 1) use in infected individuals to maintain HIV RNA below specific thresholds and prevent transmission, and 2) use by uninfected individuals to prevent viral acquisition via pre-exposure prophylaxis (PrEP), occupational and non-occupational post-exposure prophylaxis (PEP), or prophylaxis of newborns with potential perinatal exposure.[3-5]

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was also conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

Three DERP reports were used to inform recommendations for this drug class: the August 2020 DERP drug class report on Initial Antiretroviral therapies for Treatment-Naïve Individuals with HIV-1: Update (rapid review)[1], the January 2019 DERP report on Prevention and Treatment of HIV-1 Infection: Guidelines[2], and the August 2017 DERP report on Antiretroviral Therapy for HIV-1[13]. The 2017 report findings were updated by the later reports and it will not be described in detail in this document. The original DERP reports are available to Oregon Pharmacy and Therapeutics Committee members upon request. The purpose of the DERP reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. DERP reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. OHSU does not recommend or endorse any guideline or recommendation developed by users of these reports.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

Drug Effectiveness Review Project report on Initial Antiretroviral therapies for Treatment-Naïve Individuals with HIV-1: Update (rapid review)[1]-August 2020

Drug Effectiveness Review Project updated a report on effectiveness and harms of initial first-line HIV-1 therapy. Multiple guidelines were reviewed, including the International Antiviral Society-USA panel (IAS-USA), Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and adolescents (DHHS), European AIDS Clinical Society (EACS), and interim guidelines from the World Health Organization (WHO). Additionally, a total of 21 studies (in 37 publications) were evaluated, and all trials were rated as moderate or high risk of bias.

This report focused on the following key questions in treatment-naïve adults and adolescents infected with HIV-1:

1. What is the comparative effectiveness and harms of recommended antiretroviral backbone medications? Are there differences in effectiveness that would suggest one backbone medication be used over another initially?
2. What is the comparative effectiveness and harms of recommended antiretroviral add-on medications? Are there differences in effectiveness that would suggest one add-on be used over another initially?
3. Are there differences in benefits and harms of antiretroviral therapy regimens across subgroups of HIV-infected patients coinfected with HBV, HCV, or tuberculosis?

Findings related to data on backbone therapies, add-on therapies, and preferred first line therapies are included in **Table 2, Table 3, and Table 4**.

Table 2. Key Findings for Backbone therapies[1]

2-drug vs. 3-drug regimens	**Effectiveness**	**Harms**	**Quality of Evidence**
Lamivudine (3TC) vs. tenofovir disoproxil fumarate/emtricitabine (TDF/FTC)	At 48 weeks, more participants in the 3-drug regimen group (TDF/FTC) achieved viral suppression (HIV-1 RNA < 50 copies/mL) compared to the 2-drug group (3TC); however, the difference was not statistically significant. The 2-drug regimen (3TC) was considered noninferior to the 3-drug regimen.	No participants in either treatment group developed resistance mutations over the course of the study, and there were no numerical differences between groups in serious adverse events (SAEs). At 48 weeks, the 2-drug regimen (3TC) led to smaller increases in serum creatinine compared to the 3-drug regimen (TDF/FTC), indicating less severe kidney effects.	very low to low
3-drug vs. 3-drug regimens	**Effectiveness**	**Harms**	**Quality of Evidence**
Tenofovir alafenamide/emtricitabine (TAF/FTC) vs. TDF/FTC	TAF/FTC was noninferior to TDF/FTC in terms of viral suppression, and the difference between groups was not statistically significant. Few participants developed resistance to study drugs, and there were largely no differences between treatment groups. Adherence was high in both	There were no numerical differences between groups in SAEs; however, TDF/FTC led to significantly greater increases in serum creatinine clearance than TAF/FTC.	very low

	groups, but no significant differences were observed between them.		
TAF/FTC vs. abacavir/lamivudine (ABC/3TC)	TAF/FTC was noninferior to ABC/3TC in terms of viral suppression, and the difference between groups was not statistically significant.	There were no differences between groups in terms of drug resistance, SAEs, or increased serum creatinine level which is indicative of kidney injury.	very low to low
ABC/3TC vs. TDF/FTC	ABC/3TC was noninferior to TDF/FTC and led to a significantly greater percentage of participants achieving viral suppression at 48, 96, and 144 weeks (week 48 adjusted treatment difference DTG+ABC/3TC vs EFV/TDF/FTC 7%; 95% CI 2% to 12%).	There were no resistance mutations in the ABC/3TC group and few resistance mutations in the TDF/FTC group at both 48 and 144 weeks. There was no difference in SAEs between groups. Mean serum creatinine level remained stable through week 144 for patients in the DTG + ABC/3TC group but was not reported for the TDF/FTC group.	very low to moderate
Tenofovir disoproxil fumarate/lamivudine (TDF/3TC) vs. TDF/FTC	TDF/3TC was noninferior to TDF/FTC in terms of viral suppression, and the difference between groups was not statistically significant.	There were fewer resistance mutations in the TDF/3TC group than in the TDF/FTC group. There were no differences in SAEs or increased serum creatinine level indicative of kidney injury between groups.	very low to low

Table 3. Key Findings for Add-on Therapies[1]

3-drug vs. 3-drug regimens	**Effectiveness**	**Harms**	**Quality of Evidence**
Bictegravir (BIC) vs. Dolutegravir (DTG)	BIC was noninferior to DTG in terms of viral suppression, and the treatment difference between groups was not statistically significant.	There were largely no differences between groups in terms of drug resistance, adherence, or increased serum creatinine level indicative of kidney injury. However, there was a greater number of participants with SAEs in the BIC group than in the DTG group, but this was only seen at 96 weeks.	very low to low
Dolutegravir (DTG) vs. Raltegravir (RAL)	DTG was noninferior to RAL in terms of viral suppression, and the difference between treatment groups was not statistically significant.	Few participants in in the RAL group developed resistance to study drugs through week 48. There was no difference between treatment groups in terms of SAEs. There was a greater increase in serum creatinine in the DTG group compared to the RAL group at 48 and 96 weeks.	low to moderate
Darunavir/ritonavir (DRV/r) vs. Doravirine (DOR)	DOR was noninferior to DRV/r in terms of viral suppression, and the difference between groups was not statistically significant.	More DRV/r participants developed resistance to study drugs compared to DOR participants. There was no numerical difference in SAEs between groups and no statistically significant differences in measures of kidney injury or hepatotoxicity between groups at week 96.	low to moderate
DRV/r vs. RAL	Statistically significantly fewer participants achieved viral suppression in the DRV/r group	Statistically significantly fewer participants experienced drug resistance in the DRV/r group compared to the RAL group	very low to low

	compared to the RAL group (week 96 89.4% vs 93.9%, 95% CI not provided).	(4/601 [0.67%] vs 18/603 [3.0%]). Numerically, more participants in the DRV/r group experienced withdrawals due to adverse events and hepatic toxicity than participants in the RAL group (no statistical test reported).	
DTG vs. Efavirenz (EFV)	DTG was noninferior to EFV in terms of viral suppression, and the difference between groups was not statistically significant.	There were few participants with virologic failure and resistance mutations overall, and there were largely no differences between treatment groups. There were no differences between groups in terms of adherence to study drugs and SAEs. The effects of DTG and EFV on serum creatinine level were mixed across studies.	low to low
RAL vs. EFV	RAL was noninferior to EFV in terms of viral suppression at 24, 48, 96, and 156 weeks, and there were no statistically significant differences between groups.	There were no differences between treatment groups in terms of drug resistance, adherence to study medications, SAEs, and serum creatinine level indicative of kidney injury.	very low to low
Rilpivirine (RPV) vs. EFV	RPV was noninferior to EFV in terms of viral suppression, and the difference between groups was not statistically significant.	A greater percentage of RPV patients experienced virologic failure and resistance to study drugs than EFV patients. There were no differences between groups in terms of adherence to study medications and SAEs. Participants in the RPV group experienced a small increase in serum creatinine level over the course of the study, but the EFV group experienced no change.	very low to low
Abbreviations: See Appendix 5			

Majority of direct comparative evidence available is in the form of non-inferiority studies. The assessment of subgroups focused on a pooled analysis of the ECHO and THRIVE trials, in which participants received either RPV or EFV in conjunction with a nucleoside reverse transcriptase inhibitor (NRTI)/NRTI backbone. In this analysis, a numerically higher percentage of participants achieved viral suppression in the subgroup without hepatitis B virus (HBV) or hepatitis C virus (HCV) coinfection than in the subgroup with coinfection. Occurrence of hepatic adverse events was low in both treatment groups in the overall population and was higher in patients with HBV or HCV than in those without coinfection.

This report noted limitations relating to lack of generalizability of the study populations. Most participants were white males. Few studies included participants of other genders, races, and ethnicities. This may lead to underrepresentation of severe adverse effects such as HIV-associated nephropathy (HIVAN), which disproportionately affects Black individuals. Few studies reported the percentage of participants with specific HIV risk factors, including MSM, transgender individuals, and PWID. No studies focused on findings in Medicaid populations.

Table 4 below lists guideline recommended first line therapy for most individuals with HIV. Updates for the DHHS guidelines are included later in this document. See **Table 5** for details of methodology and quality for guidelines included in 2019 and 2020 DERP reviews on the treatment and prevention of HIV-1.

Table 4. Guideline Recommended Initial ART Regimens (First-Line Therapy) for Most People with HIV[1]

Regimen	U.S. Trade Name	Guideline Organizations			
		IAS-USA (2018)[14]	DHHS (2019)[15]	EACS (2019)[16]	WHO (2019)[17]
3-drug Regimens: INSTI + 2 NRTIs					
BIC + TAF/FTC	BIKTARVY	x	x	x	
DTG + ABC/3TC	TRIUMEQ	x	x	x	
DTG + TAF/FTC	TIVICAY + DESCOVY	x	x	x	
DTG + TDF/FTC	TIVICAY + TRUVADA		x	x	x
DTG + TDF/3TC	TIVICAY + CIMDUO or TEMIXYS		x	x	x
DTG + TAF/3TC	TIVICAY + VEMLIDY + EPIVIR		x		
RAL + TDF/FTC	ISENTRESS + TRUVADA		x	x	
RAL + TAF/FTC	ISENTRESS + DESCOVY		x	x	
RAL + TDF/3TC	ISENTRESS + CIMDUO or TEMIXYS		x	x	
RAL + TAF/3TC	ISENTRESS + VEMLIDY + EPIVIR		x		
3-drug Regimens: NNRTI + 2 NRTIs					
DOR + TDF/3TC	DELSTRIGO			x	
DOR + TAF/FTC	PIFELTRO + DESCOVY			x	
DOR + TDF/FTC	PIFELTRO + TRUVADA			x	
EFV + TDF/3TC	SYMFI or SYMFI LO				x
EFV + TDF/FTC	ATRIPLA				x
RPV + TAF/FTC	ODEFSEY			x	
RPV + TDF/FTC	COMPLERA			x	
RPV + TDF/3TC	EDURANT + CIMDUO or TEMIXYS			x	
3-drug Regimens: PI/r or PI/c + 2 NRTIs					
DRV/c + TAF/FTC	SYMTUZA			x	
DRV/c + TDF/FTC	PREZCOBIX + TRUVADA			x	
DRV/c + TDF/3TC	PREZCOBIX + CIMDUO or TEMIXYS			x	
DRV/r + TAF/FTC	PREZISTA + NORVIR + DESCOVY			x	
DRV/r + TDF/FTC	PREZISTA + NORVIR + TRUVADA			x	
DRV/r + TDF/3TC	PREZISTA + NORVIR + CIMDUO or TEMIXYS			x	
2-drug Regimen: INSTI + NRTI					
DTG + 3TC	DOVATO		x	x	

Abbreviations: 3TC=lamivudine; ABC=abacavir; BIC=bictegravir; c=cobicistat; DHHS=Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents; DOR=doravirine; DRV=darunavir; DTG=dolutegravir; EACS=European AIDS Clinical Society; EFV=efavirenz; FTC=emtricitabine; IAS-USA=International Antiviral Society-USA Panel; INSTI=integrase

strand transfer inhibitor; NRTI=nucleoside reverse transcriptase inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; PI/c=cobicistat-boosted protease inhibitor; PI/r=ritonavir-boosted protease inhibitor; r=ritonavir; RAL=raltegravir; RPV=rilpivirine; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate; WHO=World Health Organization

Prevention and Treatment of HIV-1 Infection: Guidelines[2]- January 2019

A DERP summary evaluated current guideline recommendations for the treatment and prevention of HIV-1 in adults and adolescents. Eight guidelines were reviewed; 7 included recommendations for pre-exposure prophylaxis (PrEP) and 3 provided recommendations for initial ART regimens for treatment-naïve patients. Guidelines methodologic quality was described as poor, fair, or good **(Table 5)**. See full report for complete descriptions of rating systems used by these guidelines.

Table 5. Clinical Practice Guidelines on Prevention and Treatment of HIV-1[2]

Guideline	Date	Focus	Methodological Quality	Rating System
Australasian Society for HIV, Viral Hepatitis, and Sexual Health Medicine (ASHM)[18]	2018	PrEP	Poor	No grading of evidence or recommendations
British HIV Association/British Association for Sexual Health and HIV (BHIVA/BASHH)[19]	2018	PrEP	Good	GRADE methodology
Canadian Medical Association (CMA)[20]	2018	PrEP	Fair	GRADE methodology
Centers for Disease Control and Prevention (CDC)[21]	2017	PrEP	Good	Strength of recommendations ranges from A to C; quality of evidence for recommendations ranges from I to III
DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents (DHHS)[12]	2018	Treatment	Poor	Strength of recommendations ranges from A to C; quality of evidence for recommendations ranges from I to III
European AIDS Clinical Society (EACS)[16]	2018	PrEP and Treatment	Poor	No grading of evidence or recommendations
International Antiviral Society-USA Panel (IAS-USA)[14]	2018	PrEP and Treatment	Fair	Adapted from Canadian Task Force on Periodic Health Examination
US Preventive Services Task Force (USPSTF) Draft Recommendation*[22]	2018	PrEP	Good	USPSTF rating system

Abbreviations: GRADE=Grading of Recommendations Assessment, Development and Evaluation; PrEP=pre-exposure prophylaxis.
*Finalized June 11, 2019

This report focused on the following key questions:

1. What recommendations do clinical practice guidelines make for preventing and treating HIV-1 infection among adults and adolescents?
2. Do these recommendations differ by patient characteristics (e.g., MSM, PWID)?

Recommendations for PrEP are separated into regimen used and population of use (MSM, heterosexual men and women, PWID, and transgender and gender-diverse people). All guidelines did not include all of these subpopulations, and ratings systems varied **(Table 5)**. Continuous use of daily, oral FTC/TDF 200 mg/300 mg is consistently recommended in all populations by the guidelines. The alternative regimen of on-demand ("2-1-1" or event-driven) dosing of FTC/TDF

200 mg/300 mg was endorsed by most guidelines for MSM and one guideline for transgender and gender-diverse people specifically for use in transgender women. Use of on-demand PrEP was not endorsed by any guideline in heterosexual men and women or PWID, and specifically not recommended by one guideline in heterosexual men and women given the absence of data. The alternative regimen of TDF alone is not recommended by 2 guidelines in the MSM population due to lack of evidence, and not endorsed by any guideline for transgender and gender-diverse people. The use of TDF alone is recommended as an alternative by several guidelines for heterosexual men and women and PWID **(Table 6)**.

Those beginning PrEP should meeting the following criteria: documented negative HIV test, no signs or symptoms of acute HIV infection, normal renal function, no use of contraindicated medication, and documented vaccination or negative HBV test. Individuals beginning therapy should receive a maximum initial supply of 90-days, with follow-up clinical services and monitoring to support PrEP treatment. These services should include HCV screening, pregnancy testing, access to clean needles/syringes, and substance use treatment services.

Emtricitabine and tenofovir alafenamide (DESCOVY) is absent from this table. It received the FDA indication for use as PrEP in at-risk adults and adolescents weighing at least 35 kg to reduce the risk of HIV-1 infection from sexual acquisition, excluding individuals at risk from receptive vaginal sex on December 3rd, 2019[6], which was after publication of the guidelines included in this summary. Guidelines have not been updated since this approval.

Table 6. Recommendations for PrEP by Patient Population[2]

Regimen	MSM	Heterosexual Men and Women	PWID	Transgender and Gender-Diverse People
Primary Recommended Regimen				
Daily, continuous, oral FTC/TDF 200 mg/300 mg	ASHM • Not rated BHIVA/BASHH • Rating 1A CDC • Rating IA CMA • Strong recommendation; high-quality evidence EACS •Not rated	ASHM • Not rated BHIVA/BASHH • Rating 1A to 2B CDC •Rating IA to IIB CMA • High risk: strong recommendation; high quality of evidence • Low risk: weak recommendation; moderate quality of evidence EACS • Not rated	ASHM • Not rated CDC • Rating IA CMA • Weak recommendation; moderate quality of evidence	ASHM •Not rated BHIVA/BASHH • Rating 1A CMA •Transgender women: strong recommendation; moderate quality of evidence EACS •Not rated

	IAS-USA •Rating AIa USPSTF Rating A	IAS-USA • Rating AIa USPSTF • Rating A	IAS-USA • Rating BIa USPSTF • Rating A	IAS-USA •Rating AIIa USPSTF •Rating A
Alternative Regimens				
On-demand ("2-1-1" or event-driven) dosing of FTC/TDF 200 mg/300 mg	ASHM •Not rated BHIVA/BASHH • Rating 1A CMA • Weak recommendation; high quality of evidence EACS • Not rated IAS-USA • Rating AIa Use NOT recommended if active HBV	BHIVA/BASHH • NR	Not endorsed by any guideline	ASHM •Transgender women: not rated
TDF alone	BHIVA/BASHH •NR CDC •NR	ASHM • Not rated BHIVA/BASHH •Rating A1 CDC •Rating IC USPSTF •Rating A	ASHM • Not rated CDC • Rating IC USPSTF • Rating A	Not endorsed by any guideline

Abbreviations: ASHM=Australasian Society for HIV, Viral Hepatitis and Sexual Medicine; BASHH=British Association for Sexual Health and HIV; BHIV= British HIV Association; CDC=Centers for Disease Control and Prevention; CMA=Canadian Medical Association; EACS=European AIDS Clinical Society; FTC=emtricitabine; HBV=hepatitis B; IAS-USA=International Antiviral Society-USA Panel; MSM=men who have sex with men; NR=not recommended; PWID=people who inject drugs; TDF=tenofovir disoproxil fumarate; USPSTF=US Preventive Services Task Force

Treatment recommendations were included for initial therapy for HIV-1 in treatment-naïve individuals and recommendations for treatment-experienced patients. Initial treatment regimens were divided into those appropriate for most patients and for those with certain clinical conditions (e.g., HLA-B*5701 status, baseline viral load, baseline, etc), but there was limited agreement among the 3 guidelines or details of clinical niche for these regimens. The most up to date initial regimens for most patients were included in the later DERP report and are found in **Table 4.**

Recommendations for switching in treatment-experienced individuals vary among guidelines as well. These include:

- Change from current, older ARV regimens if evidence or potential for chronic toxicity, drug-drug interactions, or emergent adverse effects.[14,16]
- In virologically suppressed patients, consider switching for the following populations:[14]
    - Proactive change from TDF to TAF containing regimens to minimize renal or bone adverse effects (Grade: BIa).
    - Change from 3-drug to specific 2-drug regimens (DTG/RPV [Grade: AIa]; boosted PI with 3TC [Grade: AIIa]; DTG with 3TC [Grade: AIIa]) when there is no prior virologic failure or transmitted drug resistance (long-term follow up needed to assess durability of these strategies).
    - Coinfection with HBV to include regimen with 2 drugs that are active against HBV plus 3rd ARV (Grade: AIIa).
- In situations of virologic failure, multiple factors should be assessed (e.g., adherence, comorbidities, etc.). When switching regimens, the following should be considered:
    - Resistance testing is recommended.
    - DTG plus 2 NRTIs with at least 1 active by genotype is recommended after initial treatment failure with a non-NRTI (Grade: AIa).
    - A boosted PI plus 2 NRTIs (with at least 1 active NRTI) are recommended for initial treatment failure of an INSTI-containing regimen (Grade: AIII).
    - DTG plus at least 1 fully active other agent may be effective in patients with RAL or EVG resistance. DTG should be dosed twice daily (Grade: BIII).
    - Adding a single active agent to a failing regimen is not recommended (Grade: AIa).
    - If multi-class resistance, construct a new regimen using drugs from new classes if available (Grade: BIII).
    - In patients with extensive resistance, maximal virologic suppression might not be possible. Continue ART with regimens designed to minimize toxicity, preserve CD4 count, and delay clinical progression (Grade: AI)
    - When no viable suppressive regimen exists in multidrug-resistant HIV, consider enrollment in a clinical trial or contacting pharmaceutical companies that might have investigational agents available.

After review, 12 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses or failure to meet AMSTAR criteria), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), all trials included had high-risk of bias, outcome studied (e.g., non-clinical), wrong setting of included trials (participants all from low- or middle- income countries), or because study inclusion dates fell within literature search completed by DERP and had already been evaluated (this included 2 high-quality Cochrane reviews).

New Guidelines:
No High-quality guidelines were found since publication of DERP guideline summary.[1,2]

Guidelines for Clinical Context: DHHS guidelines[3-5]
There are multiple iterations of DHHS guidelines related to treatment and prevention of HIV as well as care of HIV infected persons in other situations, including treatment of opportunistic infections. The guidelines received a poor rating of methodological quality due to unclear reporting of methods and potential for numerous biases.[2] They are commonly used in clinical practice and included here for clinical context. The rating system used for recommendations is detailed in **Table 7**.

Table 7. Rating system for DHHS Guideline Recommendations[2-5]

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

Abbreviation: DHHS=U.S. Department of Health and Human Services.

Use of Antiretroviral Agents in Adults and Adolescents with HIV-Update June 3, 2021[3]

General recommendations and details from a past version of this guideline are included in the DERP reports above. The summary below will focus on updates since those publications.

Recommendations for use of DTG/3TC as an initial regimen in most people with HIV (Grade AI), except for individuals

- With pre-treatment HIV RNA >500,000 copies/mL;
- With active hepatitis B virus (HBV) coinfection; or
- Who will begin ART before results of HIV genotype testing for reverse transcriptase or HBV testing are available.

Information regarding the use of certain agents, including DTG based regimens, and cabotegravir with rilpivirine in individuals of childbearing potential have been updated. New data show that the risk of neural tube defects (NTDs) with DTG use near time of conception may be is much lower than 0.9% incidence originally reported, and is now estimated at 0.19% compared to 0.09% in women receiving non-DTG containing regimens and 0.12% in women without HIV. These differences were not found to be statistically significant; furthermore, lack of folate consumption due to the uncommon fortification of grains at the location of the initial data may have been an additional confounder. The updated recommendations include:

- Discussion of the benefits of using DTG and the risk of NTDs with the person of childbearing potential, to allow for informed decision making.
- A dual NRTI with DTG or RAL remain preferred options for individuals who are trying to conceive (Grade AIII).
- Cabotegravir with rilpivirine long-acting injectable is not recommended, as it has not been studied, in those trying to conceive (Grade AIII).

Recommendations for ART use in women were updated to note that initiating and changing ART may result in weight gain. Women, and specifically Black women, generally experience more weight gain than men (Grade AI). This may be higher with DTG or BIC based regimens. The quantity of weight gained varied by study; including ≥ 10% weight gain (17.4% female vs 12.2% male; 19.7% Black females vs. 12.4% non-Black females) and 4.2 kg gain in women switching to or adding an INSTI to 0.2 kg for women remaining on non-INSTI regimens after 2 years.

Additional updates include an emphasis on the importance of screening and early diagnosis of HIV, with a recommendation to begin ART immediately or as soon as possible after diagnosis (Grade AII). The regimen of BIC/TAF/FTC was added as an option to treat individuals with acute or recent infection before genotypic drug resistance testing results are available. RAL based regimens have been moved from “Recommended Initial Regimens for Most People with HIV” to one recommended for “certain clinical situations” (Grade BI) due to several reasons. It is no longer necessary to choose RAL over DTG for individuals who may become pregnant, RAL has a lower barrier to resistance than DTB or BIC, and RAL based regimens have a higher pill burden than other INSTI options.

Recommendations related to virologic failure edited the wording that a new regimen "should contain at least 2, and preferably 3, fully active agents (Grade AI)" to "can include 2 fully active agents if at least one with a high resistance barrier is included (e.g., DTG or boosted DRV) (Grade AI)".

Use of Antiretroviral Agents in Pediatric HIV Infection-Update April 7, 2021[4]

The early use of ART has shown benefit in all children living with HIV. These benefits include control of viral replication, fewer drug-resistance mutations, preservation of immune function, prevention of clinical disease progression, possible reduction of inflammation mediated non-AIDS complications (e.g., cardiovascular, kidney, and liver disease, and malignancy), and improved survival. ART should be initiated immediately, or as soon as possible after diagnosis.

Initial preferred therapy in children is dependent on age and weight. Much of the data related to the use of INSTI regimens consists of non-comparative studies of safety, tolerability, and pharmacokinetics of these agents. Clinical effectiveness is commonly extrapolated from adult comparative trials and smaller studies in treatment-naïve adolescents.

Preferred regimens in children (in combination with 2 NRTI backbone):

- Newborns age <14 days: NVP
- Newborns age <4 weeks and weighing ≥ 2kg: RAL
- Neonates age ≥ 14 days to < 4 weeks: LPV/r
- Infants and Children age ≥ 4 weeks and weighing ≥ 3 kg: DTG
- Children age ≥ 6 years and weighing ≥ 25 kg: DTG or BIC
- Adolescents age ≥ 12 years with sexual maturity rating of 4 or 5 should refer to Adult and Adolescent guidelines

The recommended dual NRTI backbone varies by age and most frequently includes ZDV plus (3TC or FTC) for children under 1 month, ABC plus (3TC or FTC) between 1 month and 6 years, and ABC plus (3TC or FTC) or FTC/TAF (in specific circumstances) from 6 to 12 years. Full recommendations and alternative regimens are found in the guidelines.

Use of Antiretroviral Agents in in Pregnant Women with HIV infection and Interventions to Reduce Perinatal HIV transmission in the United States-Update Feb 10, 2021 [5]

All pregnant individuals who are HIV positive and pregnant should initiate ART as soon as possible to maximize health and minimize transmission (Grade AI), and earlier viral suppression has been associated with a lower risk of transmission. Individuals should be counseled on different treatment options to allow for informed decision making. All treatment choices should be individualized, and initial treatment recommendations for pregnant individuals can be found in **Table 8**.

Table 8. Initial ART in Treatment-Naïve Pregnant Individuals[5]

Preferred Regimens in Pregnancy
Preferred Dual-NRTI Backbones
ABC/3TC
TDF/FTC ***or*** TDF/3TC
Preferred INSTI Regimens
DTG/ABC/3TC (FDC) ***or*** DTG plus a Preferred Dual-NRTI Backbone
RAL plus a Preferred Dual-NRTI Backbone
Preferred PI Regimens
ATV/r plus a Preferred Dual-NRTI Backbone
DRV/r plus a Preferred Dual-NRTI Backbone
Alternative Regimens in Pregnancy
Alternative Dual-NRTI Backbones
TAF/FTC
ZDV/3TC
Alternative NNRTI Regimens
EFV/TDF/FTC (FDC) ***or*** EFV/TDF/3TC (FDC) ***or*** EFV plus a Preferred Dual-NRTI Backbone
RPV/TDF/FTC (FDC) ***or*** RPV/TAF/FTC (FDC) RPV plus a Preferred Dual-NRTI Backbone
Insufficient Data in Pregnancy to Recommend for Initial Regimens in ART-Naïve Individuals
BIC/TAF/FTC (FDC)
DOR
IBA
Not Recommended for Initial ART or Use in Pregnancy
ATV/c
DRV/c (FDC) ***or*** DRV/c/FTC/TAF (FDC)
EVG/c/FTC/TAF (FDC)
EVG/c/FTC/TDF (FDC)
Not Recommended for Initial ART in Pregnancy and Not Recommended, Except in Special Circumstances, for Treatment-Experienced Individuals in Pregnancy
ETR
LPV/r plus a Preferred Dual-NRTI Backbone
MVC
NVP
T-20
Any of the follow drugs or combinations: d4T, ddI, FPV, FPV/r, IDV, IDV/r, NFV, RTV (as the sole PI), SQV, SQV/r, TPV, TPV/r, two-drug ARV regimens, or a three-NRTI ARV regimen

Abbreviations: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; CD4 = CD4 T lymphocyte cell; COBI = cobicistat; d4T = stavudine; ddI = didanosine; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDC = fixed-dose combination; FPV = fosamprenavir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; IBA = ibalizumab; IDV = indinavir; IDV/r = indinavir/ritonavir; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NTD = neural tube defect; NVP = nevirapine; the Panel = the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission; PI = protease inhibitor; PK = pharmacokinetic; PPI = proton pump inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQV = saquinavir; SQV/r = saquinavir/ritonavir; T-20 = enfuvirtide; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TPV = tipranavir; TPV/r = tipranavir/ritonavir; ZDV = zidovudine

In newborns of individuals of with HIV, ART use is divided into:

- ART prophylaxis: administration of single agent (typically ZDV), or 2 to 3 drug regimens to reduce risk of HIV acquisition
- Presumptive HIV therapy: administration of 3-drug regimen to newborns at high risk of HIV acquisition; this therapy serves as treatment or prophylaxis
- HIV therapy: administration of 3-drug regimen in newborn with documented infection

These therapies should be initiated as soon as possible after delivery. Recommended regimens can be found in **Table 9.**

Table 9. Drug recommendations for ART in Newborns[5]

Newborns at Low Risk of Perinatal HIV Transmission	
Recommended Regimen	Recommended Duration
ZDV	4 weeks
Newborns at High Risk of Perinatal HIV Transmission	
Recommended Regimen	Recommended Duration
Three-drug HIV therapy: ZDV plus 3TC plus (NVP *or* RAL)	Optimal duration unknown and dependent on many factors. ZDV should be given for 6 weeks 3TC, NVP, and RAL duration may vary from 2 to 6 weeks
Newborns with HIV Infection	
Recommended Regimen	Recommended Duration
Three-drug HIV therapy: ZDV plus 3TC plus (NVP *or* RAL)	Lifelong therapy, agents may change with age per current treatment guidelines
Abbreviations: 3TC=lamivudine; NVP=nevirapine; RAL=raltegravir; ZDV = zidovudine	

No guidelines were excluded due to poor quality, see 2019 DERP report above for full discussion of available guidelines.

New Formulations or Indications:
See **Table 1** for current list of available formulations for prevention and treatment of HIV.

New FDA Safety Alerts:
None

Randomized Controlled Trials:

A total of 218 citations were manually reviewed from the initial literature search. After further review, 217 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), outcome studied (e.g., non-clinical, extension study of secondary endpoints), or were covered in the accompanying new drug evaluation on cabotegravir. The remaining trial is summarized in the table below. The full abstracts is included in **Appendix 2**.

Table 10. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Mayer et al.[7] MC, DB, DD, RCT, NI 96 weeks, then offered OL enrollment	1. emtricitabine 200mg/ tenofovir alafenamide 25 mg N=2670 FAS 2. emtricitabine 200mg/ tenofovir disoproxil fumarate 300 mg N=2665 FAS FAS=randomized, received at least 1 dose study drug, had a least 1 post-baseline HIV test.	HIV negative cisgender MSM and transgender women at high risk of HIV acquisition	Incident HIV infection in full analysis set once all patients had been treated a minimum of 48 weeks and at least 50% had duration of treatment for 96 weeks.	Group 1 vs. Group 2 IRR 0.47 (95% CI 0.19-1.15); met pre-specified non-inferiority criteria HIV infections 1. 7 infections, 4370 person-years (1 suspected acquisition prior to baseline; tested negative at baseline & positive at week 4) 2. 15 infections, 4386 person-years (4 suspected acquisitions prior to baseline; tested negative at baseline & positive at week 4)
Abbreviations: ART=antiretroviral treatment; CI=confidence interval; DB=double-blind; DD=double dummy; FAS=full analysis set; IRR=incident rate ratio; MC=multicenter; mg = milligram; MSM=men who have sex with men; NI=non-inferiority; OL = open label; RCT = randomized clinical trial				

References:

1. Lazur B, Harrod C. Initial antiretroviral therapies for treatment naïve individuals with HIV-1: Update. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University; 2020.
2. Lazur B, Harrod C. Prevention and treatment of HIV-1 infection: guidelines. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University; 2019.
3. Department for Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. June 3, 2021; https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/AdultandAdolescentGL.pdf. Accessed June 11, 2021.
4. Department for Health and Human Services Panel on Antiretroviral Therapy and Medical Managment of Children Living with HIV. Guidelines for the Use of antiretroviral agents in Pediatric HIV Infection. April 7, 2021; https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/PedARV_GL.pdf. Accessed June 11, 2021.
5. Department for Health and Human Services Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Transmission in the United States. Feb 10, 2021; https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/Perinatal_GL.pdf. Accessed June 11, 2021.
6. DESCOVY (emtricitabine and tenofovir alafenamide) Prescribing Information. Gilead Sciences, Inc; Foster City, CA. March 2021. .
7. Mayer KH, Molina J-M, 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. *The Lancet.* 2020;396(10246):239-254.
8. Centers for Disease Control and Preention. HIV Basics: About HIV. Reviewed June 1, 2021. Available at: https://www.cdc.gov/hiv/basics/whatishiv.html Accessed June 8, 2021.
9. Centers for Disease Control and Prevention. HIV Basics: Basic Statistics. Reviewed April 23, 2021. Available at: https://www.cdc.gov/hiv/basics/statistics.html Accessed June 8, 2021. .
10. Oregon Health Authority. HIV infection in Oregon. OHA 9985 Dec 2019. Available at: https://sharedsystems.dhsoha.state.or.us/DHSForms/Served/le9985.pdf Accessed June 8, 2021.
11. European AIDS Clinical Society. European AIDS Clinical Society Guidelines version 9.1, October 2018. 2018; http://www.eacsociety.org/files/2018_guidelines-9.1-english.pdf.
12. Department for Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. 2018; https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/AA_Recommendations.pdf.
13. Selph S, Holmes R, Blazina I, Stoner R. Antiretroviral Drugs for HIV-1. Small Original Report prepared by the Pacific Northwest Evidence-based Practice Center for the Drug Effectiveness Review Project. Oregon Health & Science University, Portland, Oregon, August 2017.
14. Saag MS, Benson CA, Gandhi RT, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2018 recommendations of the International Antiviral Society-USA Panel. JAMA. 2018;320(4):379-396. doi: 10.1001/jama.2018.8431.
15. Department for Helath and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV, updated December 18, 2019. Weblink no longer available.

16. European AIDS Clinical Society. European AIDS Clinical Society Guidelines version 9.1, October 2018. 2018; http://www.eacsociety.org/files/2018_guidelines-9.1-english.pdf. .
17. World Health Organization. Policy brief. Update of recommendations on first- and second-line antiretroviral regimens. HIV treatment. July 2019. Geneva, Switzerland;2019.
18. Wright E, Grulich A, Roy K, et al. Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine HIV pre-exposure prophylaxis: clinical guidelines. Update April 2018. J Virus Erad. 2018;4(2):143-159.
19. British HIV Association. BHIVA/BASHH guidelines on the use of HIV pre-exposure prophylaxis (PrEP). 2018; https://www.bhiva.org/file/5b729cd592060/2018-PrEP-Guidelines.pdf. .
20. Canadian Medical Association. Canadian guideline on HIV pre-exposure prophylaxis and nonoccupational postexposure prophylaxis. 2018; http://www.cmaj.ca/content/cmaj/189/47/E1448.full.pdf. .
21. Centers for Disease Control and Prevention. Preexposure prophylaxis for the prevention of HIV infection in the United States – 2017 update. 2017; https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf. .
22. U.S. Preventive Services Task Force. Draft recommendation statement: prevention of human immunodeficiency virus (HIV) infection: pre-exposure prophylaxis. 2018; https://www.uspreventiveservicestaskforce.org/Page/Document/draft-recommendation-statement/prevention-of-human-immunodeficiency-virus-hiv-infection-pre-exposure-prophylaxis#Pod6. .

Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
abacavir sulfate	ABACAVIR	ORAL	SOLUTION	Y
abacavir sulfate	ZIAGEN	ORAL	SOLUTION	Y
abacavir sulfate	ABACAVIR	ORAL	TABLET	Y
abacavir sulfate	ZIAGEN	ORAL	TABLET	Y
abacavir sulfate/lamivudine	ABACAVIR-LAMIVUDINE	ORAL	TABLET	Y
abacavir sulfate/lamivudine	EPZICOM	ORAL	TABLET	Y
abacavir/dolutegravir/lamivudi	TRIUMEQ	ORAL	TABLET	Y
abacavir/lamivudine/zidovudine	ABACAVIR-LAMIVUDINE-ZIDOVUDINE	ORAL	TABLET	Y
abacavir/lamivudine/zidovudine	TRIZIVIR	ORAL	TABLET	Y
atazanavir sulfate	ATAZANAVIR SULFATE	ORAL	CAPSULE	Y
atazanavir sulfate	REYATAZ	ORAL	CAPSULE	Y
atazanavir sulfate	REYATAZ	ORAL	POWD PACK	Y
atazanavir sulfate/cobicistat	EVOTAZ	ORAL	TABLET	Y
bictegrav/emtricit/tenofov ala	BIKTARVY	ORAL	TABLET	Y
cabotegravir sodium	VOCABRIA	ORAL	TABLET	Y
cabotegravir/rilpivirine	CABENUVA	INTRAMUSC	SUSER VIAL	Y
cobicistat	TYBOST	ORAL	TABLET	Y
darunavir ethanolate	PREZISTA	ORAL	ORAL SUSP	Y
darunavir ethanolate	PREZISTA	ORAL	TABLET	Y
darunavir/cob/emtri/tenof alaf	SYMTUZA	ORAL	TABLET	Y
darunavir/cobicistat	PREZCOBIX	ORAL	TABLET	Y
didanosine	DIDANOSINE	ORAL	CAPSULE DR	Y
didanosine	VIDEX EC	ORAL	CAPSULE DR	Y
didanosine/sodium citrate	VIDEX	ORAL	PACKET	Y
dolutegravir sodium	TIVICAY PD	ORAL	TAB SUSP	Y
dolutegravir sodium	TIVICAY	ORAL	TABLET	Y
dolutegravir sodium/lamivudine	DOVATO	ORAL	TABLET	Y
dolutegravir/rilpivirine	JULUCA	ORAL	TABLET	Y
doravirine	PIFELTRO	ORAL	TABLET	Y
doravirine/lamivu/tenofov diso	DELSTRIGO	ORAL	TABLET	Y
efavirenz	EFAVIRENZ	ORAL	CAPSULE	Y
efavirenz	SUSTIVA	ORAL	CAPSULE	Y
efavirenz	EFAVIRENZ	ORAL	TABLET	Y
efavirenz	SUSTIVA	ORAL	TABLET	Y
efavirenz/emtricit/tenofovr df	ATRIPLA	ORAL	TABLET	Y
efavirenz/emtricit/tenofovr df	EFAVIRENZ-EMTRIC-TENOFOV DISOP	ORAL	TABLET	Y
efavirenz/lamivu/tenofov disop	EFAVIRENZ-LAMIVU-TENOFOV DISOP	ORAL	TABLET	Y

efavirenz/lamivu/tenofov disop	SYMFI	ORAL	TABLET	Y
efavirenz/lamivu/tenofov disop	SYMFI LO	ORAL	TABLET	Y
elviteg/cob/emtri/tenof alafen	GENVOYA	ORAL	TABLET	Y
elviteg/cob/emtri/tenofo disop	STRIBILD	ORAL	TABLET	Y
emtricita/rilpivirine/tenof DF	COMPLERA	ORAL	TABLET	Y
emtricitab/rilpiviri/tenof ala	ODEFSEY	ORAL	TABLET	Y
emtricitabine	EMTRICITABINE	ORAL	CAPSULE	Y
emtricitabine	EMTRIVA	ORAL	CAPSULE	Y
emtricitabine	EMTRIVA	ORAL	SOLUTION	Y
emtricitabine/tenofov alafenam	DESCOVY	ORAL	TABLET	Y
emtricitabine/tenofovir (TDF)	EMTRICITABINE-TENOFOVIR DISOP	ORAL	TABLET	Y
emtricitabine/tenofovir (TDF)	TRUVADA	ORAL	TABLET	Y
enfuvirtide	FUZEON	SUB-Q	VIAL	Y
etravirine	INTELENCE	ORAL	TABLET	Y
fosamprenavir calcium	LEXIVA	ORAL	ORAL SUSP	Y
fosamprenavir calcium	FOSAMPRENAVIR CALCIUM	ORAL	TABLET	Y
fosamprenavir calcium	LEXIVA	ORAL	TABLET	Y
ibalizumab-uiyk	TROGARZO	INTRAVEN	VIAL	Y
indinavir sulfate	CRIXIVAN	ORAL	CAPSULE	Y
lamivudine	EPIVIR	ORAL	SOLUTION	Y
lamivudine	LAMIVUDINE	ORAL	SOLUTION	Y
lamivudine	EPIVIR	ORAL	TABLET	Y
lamivudine	LAMIVUDINE	ORAL	TABLET	Y
lamivudine/tenofovir disop fum	CIMDUO	ORAL	TABLET	Y
lamivudine/tenofovir disop fum	TEMIXYS	ORAL	TABLET	Y
lamivudine/zidovudine	COMBIVIR	ORAL	TABLET	Y
lamivudine/zidovudine	LAMIVUDINE-ZIDOVUDINE	ORAL	TABLET	Y
lopinavir/ritonavir	KALETRA	ORAL	SOLUTION	Y
lopinavir/ritonavir	LOPINAVIR-RITONAVIR	ORAL	SOLUTION	Y
lopinavir/ritonavir	KALETRA	ORAL	TABLET	Y
maraviroc	SELZENTRY	ORAL	SOLUTION	Y
maraviroc	SELZENTRY	ORAL	TABLET	Y
nelfinavir mesylate	VIRACEPT	ORAL	TABLET	Y
nevirapine	NEVIRAPINE	ORAL	ORAL SUSP	Y
nevirapine	VIRAMUNE	ORAL	ORAL SUSP	Y
nevirapine	NEVIRAPINE ER	ORAL	TAB ER 24H	Y
nevirapine	VIRAMUNE XR	ORAL	TAB ER 24H	Y
nevirapine	NEVIRAPINE	ORAL	TABLET	Y
nevirapine	VIRAMUNE	ORAL	TABLET	Y
raltegravir potassium	ISENTRESS	ORAL	POWD PACK	Y

raltegravir potassium	ISENTRESS	ORAL	TAB CHEW	Y
raltegravir potassium	ISENTRESS	ORAL	TABLET	Y
raltegravir potassium	ISENTRESS HD	ORAL	TABLET	Y
rilpivirine HCl	EDURANT	ORAL	TABLET	Y
ritonavir	NORVIR	ORAL	POWD PACK	Y
ritonavir	NORVIR	ORAL	SOLUTION	Y
ritonavir	NORVIR	ORAL	TABLET	Y
ritonavir	RITONAVIR	ORAL	TABLET	Y
saquinavir mesylate	INVIRASE	ORAL	TABLET	Y
stavudine	STAVUDINE	ORAL	CAPSULE	Y
tipranavir	APTIVUS	ORAL	CAPSULE	Y
tipranavir/vitamin E TPGS	APTIVUS	ORAL	SOLUTION	Y
zidovudine	RETROVIR	ORAL	CAPSULE	Y
zidovudine	ZIDOVUDINE	ORAL	CAPSULE	Y
zidovudine	RETROVIR	ORAL	SYRUP	Y
zidovudine	ZIDOVUDINE	ORAL	SYRUP	Y
zidovudine	ZIDOVUDINE	ORAL	TABLET	Y
zidovudine	RETROVIR	INTRAVEN	VIAL	Y

Appendix 2: Abstracts of Comparative Clinical Trials

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[7]

Kenneth H Mayer, Jean-Michel Molina, Melanie A Thompson, Peter L Anderson, Karam C Mounzer, Joss J De Wet, Edwin DeJesus, Heiko Jessen, Robert M Grant, Peter J Ruane, Pamela Wong, Ramin Ebrahimi, Lijie Zhong, Anita Mathias, Christian Callebaut, Sean E Collins, Moupali Das, Scott McCallister, Diana M Brainard, Cynthia Brinson, Amanda Clarke, Pep Coll, Frank A Post, C Bradley Hare

Summary

Background Tenofovir alafenamide shows high antiviral efficacy and improved renal and bone safety compared with tenofovir disoproxil fumarate when used for HIV treatment. Here, we report primary results from a blinded phase 3 study evaluating the efficacy and safety of pre-exposure prophylaxis (PrEP) with emtricitabine and tenofovir alafenamide versus emtricitabine and tenofovir disoproxil fumarate for HIV prevention.

Methods This study is an ongoing, randomised, double-blind, multicentre, active-controlled, phase 3, noninferiority trial done at 94 community, public health, and hospital-associated clinics located in regions of Europe and North America, where there is a high incidence of HIV or prevalence of people living with HIV, or both. We enrolled adult cisgender men who have sex with men and transgender women who have sex with men, both with a high risk of acquiring HIV on the basis of their self-reported sexual behaviour in the past 12 weeks or their recent history (within 24 weeks of enrolment) of bacterial sexually transmitted infections. Participants with current or previous use of PrEP with emtricitabine and tenofovir disoproxil fumarate were not excluded. We used a computer-generated random allocation sequence to randomly assign (1:1) participants to receive either emtricitabine (200 mg) and tenofovir alafenamide (25 mg) tablets daily, with matched placebo tablets (emtricitabine and tenofovir alafenamide group), or emtricitabine (200 mg) and tenofovir disoproxil fumarate (300 mg) tablets daily, with matched placebo tablets (emtricitabine and tenofovir disoproxil fumarate group). As such, all participants were given two tablets. The trial sponsor, investigators, participants, and the study staff who provided the study drugs, assessed the outcomes, and collected the data were masked to group assignment. The primary efficacy outcome was incident HIV infection, which was assessed when all participants had completed 48 weeks of followup and half of all participants had completed 96 weeks of follow-up. This full analysis set included all randomly assigned participants who had received at least one dose of the assigned study drug and had at least one postbaseline HIV test. Non-inferiority of emtricitabine and tenofovir alafenamide to emtricitabine and tenofovir disoproxil fumarate was established if the upper bound of the 95·003% CI of the HIV incidence rate ratio (IRR) was less than the prespecified non-inferiority margin of 1·62. We prespecified six secondary bone mineral density and renal biomarker safety endpoints to evaluate using the safety analysis set. This analysis set included all randomly assigned participants who had received at least one dose of the assigned study drug. This trial is registered with ClinicalTrials.gov, NCT02842086, and is no longer recruiting.

Findings Between Sept 13, 2016, and June 30, 2017, 5387 (92%) of 5857 participants were randomly assigned and received emtricitabine and tenofovir alafenamide (n=2694) or emtricitabine and tenofovir disoproxil fumarate (n=2693). At the time of the primary efficacy analysis (ie, when all participants had completed 48 weeks and 50% had completed 96 weeks) emtricitabine and tenofovir alafenamide was non-inferior to emtricitabine and tenofovir disoproxil fumarate for HIV prevention, as the upper limit of the 95% CI of the IRR, was less than the prespecified non-inferiority margin of 1·62 (IRR 0·47 [95% CI 0·19–1·15]). After 8756 person-years of follow-up, 22 participants were diagnosed with HIV, seven participants in the emtricitabine and tenofovir alafenamide group (0·16 infections per 100 person-years [95% CI 0·06–0·33]), and 15 participants in the emtricitabine and tenofovir disoproxil fumarate group (0·34 infections per 100 person-years [0·19–0·56]). Both regimens were well tolerated, with a low number of participants reporting adverse events that led to discontinuation of the study drug (36 [1%] of 2694 participants in the emtricitabine and tenofovir alafenamide group vs 49 [2%] of 2693 participants in the emtricitabine and tenofovir

disoproxil fumarate group). Emtricitabine and tenofovir alafenamide was superior to emtricitabine and tenofovir disoproxil fumarate in all six prespecified bone mineral density and renal biomarker safety endpoints.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to November Week 3 2014, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations May 24, 2021

		Searches	Results
○	1	abacavir.mp.	2443
○	2	atazanavir.mp. or Atazanavir Sulfate/	1908
○	3	bictegravir.mp.	148
○	4	cabotegravir.mp.	174
○	5	Cobicistat/ or cobicistat.mp.	600
○	6	darunavir.mp. or Darunavir/	1812
○	7	didanosine.mp. or Didanosine/	2830
○	8	dolutegravir.mp.	1346
○	9	doravirine.mp.	116
○	10	efavirenz.mp. or Efavirenz, Emtricitabine, Tenofovir Disoproxil Fumarate Drug Combination/	4854
○	11	elvitegravir.mp. or Elvitegravir, Cobicistat, Emtricitabine, Tenofovir Disoproxil Fumarate Drug Combination/	738
○	12	Efavirenz, Emtricitabine, Tenofovir Disoproxil Fumarate Drug Combination/ or Emtricitabine, Rilpivirine, Tenofovir Drug Combination/ or Emtricitabine/ or Elvitegravir, Cobicistat, Emtricitabine, Tenofovir Disoproxil Fumarate Drug Combination/ or Emtricitabine, Tenofovir Disoproxil Fumarate Drug Combination/ or emtricitabine.mp.	3117
○	13	enfuvirtide.mp. or Enfuvirtide/	1033
○	14	etravirine.mp.	791
○	15	fosamprenavir.mp.	286
○	16	ibalizumab.mp.	71
○	17	indinavir.mp. or Indinavir/	2772
○	18	lamivudine.mp. or Lamivudine/	10341
○	19	lopinavir.mp. or Lopinavir/	3850
○	20	maraviroc.mp. or Maraviroc/	1184
○	21	nelfinavir.mp. or Nelfinavir/	1912
○	22	nevirapine.mp. or Nevirapine/	4706
○	23	raltegravir.mp. or Raltegravir Potassium/	2031
○	24	Emtricitabine, Rilpivirine, Tenofovir Drug Combination/ or Rilpivirine/ or rilpivirine.mp.	792
○	25	ritonavir.mp. or Ritonavir/	8062
○	26	saquinavir.mp. or Saquinavir/	2135
○	27	stavudine.mp. or Stavudine/	3012
○	28	tipranavir.mp.	483
○	29	zidovudine.mp. or Zidovudine/	12584
○	30	Efavirenz, Emtricitabine, Tenofovir Disoproxil Fumarate Drug Combination/ or Emtricitabine, Rilpivirine, Tenofovir Drug Combination/ or Tenofovir/ or Elvitegravir, Cobicistat, Emtricitabine, Tenofovir Disoproxil Fumarate Drug Combination/ or Emtricitabine, Tenofovir Disoproxil Fumarate Drug Combination/ or tenofovir.mp.	8072
○	31	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30	46949
○	32	limit 31 to yr="2015 -Current"	12598
○	33	limit 32 to english language	12322
○	34	limit 33 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or multicenter study or practice guideline or randomized controlled trial or "systematic review")	2149
○	35	COVID-19/	79953
○	36	SARS Virus/ or SARS-CoV-2/ or SARS.mp.	95070
○	37	Middle East Respiratory Syndrome Coronavirus/	1620
○	38	35 or 36 or 37	110646
○	39	34 not 38	2011
◉	40	limit 39 to yr="2020 -Current"	227

Appendix 4: Key Inclusion Criteria

Population	Adults and children with HIV-1 or at risk of acquiring HIV-1
Intervention	See Appendix 1
Comparator	See Appendix 1, placebo
Outcomes	HIV RNA copies, HIV acquisition
Timing	Prophylaxis or Treatment
Setting	Outpatient

Appendix 5: Abbreviations for Antiretroviral Drug Names[12]

3TC	lamivudine
ABC	abacavir
APV	amprenavir
ATV	atazanavir
BIC	bictegravir
CAB	cabotegravir
COBI or c	cobicistat
d4T	stavudine
ddI	didanosine
DLV	delavirdine
DOR	doravirine
DRV	darunavir
DTG	dolutegravir
EFV	efavirenz
ETR	etravirine
EVG	elvitegravir
FPV	fosamprenavir
FTC	emtricitabine
IBA	ibalizumab
IDV	indinavir
LPV	lopinavir
MVC	maraviroc

NFV	nelfinavir
NVP	nevirapine
RAL	raltegravir
RPV	rilpivirine
RTV or r	ritonavir
SQV	saquinavir
T-20	enfuvirtide
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TPV	tipranavir
ZDV	zidovudine