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Initial Antiretroviral Therapies for Treatment-Naïve Individuals with HIV-1: Update

Rapid Review

August 2020

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Overview

This report update evaluates the effectiveness and harms of initial first-line antiretroviral therapies (ART) for treatment-naïve individuals with human immunodeficiency virus type 1 (HIV-1). The scope of this report focuses on U.S. Food and Drug Administration (FDA)-approved ART that are recommended as initial regimens (first-line therapies) for "most people with HIV" according to recent guidelines from the International Antiviral Society – USA Panel (IAS-USA),[1] the Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents (DHHS),[2] the European AIDS Clinical Society (EACS),[3] and interim guidelines from the World Health Organization (WHO).[4] For this update, we identified 10 studies (in 15 publications). We carried forward 11 studies (in 22 publications) from the prior report for a total of 21 studies (in 37 publications) in this update. We rated all studies as having a moderate or high risk of bias.

Key Findings

Backbone Therapies

2-drug vs. 3-drug regimens

- 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.
  - We rated the quality of evidence for these outcomes as very low to low.

3-drug vs. 3-drug regimens

- Tenofovir alafenamide/emtricitabine (TAF/FTC) vs. TDF/FTC
  - TAF/FTC was noninferior to TDF/FTC in terms of viral suppression, but 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 groups, but no significant differences were observed between them. Further, there were no numerical differences between groups in SAEs; however, TDF/FTC led to significantly greater increases in serum creatinine clearance than TAF/FTC.
  - We rated the quality of evidence for these outcomes as very low.
- TAF/FTC vs. abacavir/lamivudine (ABC/3TC)
  - TAF/FTC was noninferior to ABC/3TC in terms of viral suppression, but 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.
  - We rated the quality of evidence for these outcomes as 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. 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.
    - We rated the quality of evidence for these outcomes as 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, but 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.
    - We rated the quality of evidence for these outcomes as very low to low.

Add-on Therapies

3-drug vs. 3-drug regimens

- Bictegravir (BIC) vs. dolutegravir (DTG)
    - BIC was noninferior to DTG in terms of viral suppression, but 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.
    - We rated the quality of evidence for these outcomes as very low to low.
- Dolutegravir (DTG) vs. raltegravir (RAL)
    - DTG was noninferior to RAL in terms of viral suppression, but 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.
    - We rated the quality of evidence for these outcomes as low to moderate.
- Darunavir/ritonavir (DRV/r) vs. doravirine (DOR)
    - DOR was noninferior to DRV/r in terms of viral suppression, but 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.
    - We rated the quality of evidence for these outcomes as low to moderate.
- DRV/r vs. RAL
    - Statistically significantly fewer participants achieved viral suppression or experienced drug resistance in the DRV/r group compared to the RAL group. 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).
    - We rated the quality of evidence for these outcomes as very low to low.
- DTG vs. efavirenz (EFV)

    - DTG was noninferior to EFV in terms of viral suppression, but 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.
    - We rated the quality of evidence for these outcomes as very low to low.
- RAL vs. EFV
    - RAL was noninferior to EFV in terms of viral suppression at 24, 48, 96, and 156 weeks, but there were no statistically significant differences between groups. RAL led to statistically more people with virologic suppression at weeks 192 and 240 than EFV. 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.
    - We rated the quality of evidence for these outcomes as very low to low.
- Rilpivirine (RPV) vs. EFV
    - RPV was noninferior to EFV in terms of viral suppression, but 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.
    - We rated the quality of evidence for these outcomes as very low to low.

Subgroups

- In a pooled analysis of the ECHO and THRIVE trials, in which participants received either RPV or EFV each co-administered with a nucleoside reverse transcriptase inhibitor (NRTI)/NRTI backbone, 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.

The findings of this update report should be interpreted with caution because of limitations stemming from a lack of generalizability of the study populations. The majority of participants in most studies identified as White males, with few studies including 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.[5] 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. Additionally, no studies focused on or specifically reported findings in Medicaid populations.

List of Brand Names and Generics

Figure 1. Anatomy of an ART Regimen

Abbreviations. ART: antiretroviral therapy; INSTI: integrase strand transfer inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor.

Table 1. Included Drugs by Therapeutic Classification

Generic Drug Name	Mechanism of Action Category	Approval Date	Abbreviation
Backbone			
Abacavir	NRTI	12/17/1998	ABC
Lamivudine	NRTI	11/17/1995	3TC
Tenofovir alafenamide	NRTI	11/10/2016	TAF
Tenofovir disoproxil fumarate	NRTI	10/26/2001	TDF
Emtricitabine	NRTI	7/2/2003	FTC
Add-on			
Bictegravir	INSTI	2/7/2018	BIC
Dolutegravir	INSTI	8/12/2013	DTG
Raltegravir	INSTI	10/12/2007	RAL
Doravirine	NNRTI	8/30/2018	DOR
Efavirenz	NNRTI	9/17/1998	EFV
Rilpivirine	NNRTI	5/20/2011	RPV
Darunavir	PI	6/26/2006	DRV
Booster			
Cobicistat	Pharmacokinetic Enhancer	9/24/2014	c
Ritonavir	PI	3/1/1996	r

Abbreviations. 3TC: lamivudine; ABC: abacavir; BIC: bictegravir; c: cobicistat; DOR: doravirine; DRV: darunavir; DTG: dolutegravir; EFV: efavirenz; FTC: emtricitabine; INSTI: integrase strand transfer inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI:

protease inhibitor; r: ritonavir; RAL: raltegravir; RPV: rilpivirine; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate.

Table 2. Recommended Initial ART Regimens (First-Line Therapy) for Most People with HIV

Regimen	U.S. Trade Name	Guideline Organizations			
		IAS-USA[1]	DHHS[2]	EACS[3]	WHO[4]
3-drug regimens: INSTI + 2 NRTIs					
BIC + TAF/FTC	Biktarvy	✓	✓	✓	
DTG + ABC/3TC	Triumeq	✓	✓	✓	
DTG + TAF/FTC	Tivicay + Descovy	✓	✓	✓	
DTG + TDF/FTC	Tivicay + Truvada		✓	✓	✓
DTG + TDF/3TC	Tivicay + Cimduo or Temixys		✓	✓	✓
DTG + TAF/3TC	Tivicay + Vemlidy + Epivir		✓		
RAL + TDF/FTC	Isentress + Truvada		✓	✓	
RAL + TAF/FTC	Isentress + Descovy		✓	✓	
RAL + TDF/3TC	Isentress + Cimduo or Temixys		✓	✓	
RAL + TAF/3TC	Isentress + Vemlidy + Epivir		✓		
3-drug regimens: NNRTI + 2 NRTIs					
DOR + TDF/3TC	Delstrigo			✓	
DOR + TAF/FTC	Pifeltro + Descovy			✓	
DOR + TDF/FTC	Pifeltro + Truvada			✓	
EFV + TDF/3TC	Symfi or Symfi Lo				✓
EFV + TDF/FTC	Atripla				✓
RPV + TAF/FTC	Odefsey			✓	
RPV + TDF/FTC	Complera			✓	
RPV + TDF/3TC	Edurant + Cimduo or Temixys			✓	
3-drug regimens: PI/r or PI/c + 2 NRTIs					
DRV/c + TAF/FTC	Symtuza			✓	
DRV/c + TDF/FTC	Prezcobix + Truvada			✓	
DRV/c + TDF/3TC	Prezcobix + Cimduo or Temixys			✓	
DRV/r + TAF/FTC	Prezista + Norvir + Descovy			✓	
DRV/r + TDF/FTC	Prezista + Norvir + Truvada			✓	
DRV/r + TDF/3TC	Prezista + Norvir + Cimduo or Temixys			✓	
2-drug regimen: INSTI + NRTI					
DTG + 3TC	Dovato		✓	✓	

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.

Background

In the U.S., the Centers for Disease Control and Prevention (CDC) estimate that 1,173,900 adults and adolescents 13 years of age and older are infected with HIV, including 161,800 persons (13.8%) whose infection has not been diagnosed.[6,7] There are 2 types of the HIV virus: HIV-1 is the most common and HIV-2 is much rarer and less infectious.

HIV attacks the body's immune system, specifically targeting CD4 cells (T cells), which help the immune system combat infections.[8] If left untreated, HIV reduces the number of CD4 cells in the body, making a person more likely to acquire other infections or develop infection-related cancers.[8] Over time, HIV can destroy enough CD4 cells to make the body incapable of fighting off infections and disease, leading to opportunistic infections, cancer, and ultimately transition to acquired immunodeficiency syndrome (AIDS).[8]

Due to advances in treatment and care, HIV has transformed from an acute, life-threatening infection to a more manageable chronic health condition.[9] Antiretroviral drugs first became available in 1987 and have steadily improved over time, with the first potent combination ART becoming available in 1996.[10] These combination therapies have dramatically reduced HIV-associated morbidity and mortality with general life expectancy approaching that of the general population.[10,11]

Medicaid administrators are interested in the efficacy and harms of guideline-recommended initial 2-drug and 3-drug regimens for the treatment of ART-naïve individuals with HIV-1. They are also interested in efficacy and harms by subgroup, such as individuals with co-infection of HCV.

PICOS

Population

- Treatment-naïve adults or adolescents with HIV-1 infection
  - Excluded: pregnant women; children aged 12 years of age and younger

Interventions

- Recommended initial regimens (first-line therapies) for "most people with HIV" according to recent guidelines from the IAS-USA,[1] DHHS,[2] EACS,[3] and interim guidelines from the WHO,[4] enumerated in Table 2.

Comparators

- Head-to-head comparisons between drugs in included classes (each given as part of a recommended regimen):

    - Backbone drug or drug combination (NRTI[s]) vs. another backbone drug or drug combination (NRTI[s])
    - Add-on drug (integrase strand transfer inhibitor [INSTI], non-nucleoside reverse transcriptase inhibitor [NNRTI], or protease inhibitor [PI]) vs. another add-on drug (INSTI, NNRTI, or PI)
    - Booster vs. booster (i.e., cobicistat vs. ritonavir when given with a PI)
- Fixed-dose combination products (multiple drugs combined in 1 tablet) compared with component drugs given in separate tablets

Outcomes

- Effectiveness:
    - Viral suppression, virological failure
    - AIDS-defining illness
- Adherence to prescribed regimen (e.g., proportion of doses taken, proportion taken at prescribed time)
- Persistence (e.g., percentage discontinuing drug, time to discontinuation for either all causes or lack of efficacy/effectiveness)
- Drug resistance
    - Emergence of resistance-associated variants of the HIV virus in the course of treatment
    - Measured by genotypic testing for mutations in viral genes
- SAEs
- Withdrawals due to adverse events and time to withdrawal due to adverse events
- Specific adverse events including:
    - Kidney injury (increased serum creatinine)
    - Hepatotoxicity (elevated transaminases)
    - Cardiovascular events (e.g., myocardial infarction, stroke)
    - Bone marrow suppression (e.g., anemia, neutropenia)
- Combinations of drugs with serious drug interactions including:
    - Contraindicated drug combinations
    - Drugs to treat HCV

Study Designs

- Randomized controlled trials (RCTs)

Key Questions

1. What is the comparative effectiveness of recommended antiretroviral backbone medications for treatment-naïve adults and adolescents infected with HIV-1? Are there differences in effectiveness that would suggest one backbone medication be used over another initially?
2. What are the comparative harms of recommended antiretroviral backbone medications for treatment-naïve adults and adolescents infected with HIV-1? Are there differences in harms that would suggest one drug be used over another initially?
3. What is the comparative effectiveness of recommended antiretroviral add-on medications for treatment-naïve adults and adolescents infected with HIV-1? Are there

differences in effectiveness that would suggest one add-on be used over another initially?
4. What are the comparative harms of recommended antiretroviral add-on medications for treatment-naïve adults and adolescents infected with HIV-1? Are there differences in harms that would suggest one drug be used over another initially?
5. Are there differences in benefits and harms of antiretroviral therapy regimens across subgroups of HIV-infected patients coinfected with HBV, HCV, or tuberculosis?

Methods

We describe our complete methods in Appendix A. Briefly, we searched Ovid MEDLINE and the Cochrane library to identify eligible studies from March 2017 to February 2019. For new drugs not included in the previous Drug Effectiveness Review Project (DERP) report, we searched from database inception. We also reran the Ovid MEDLINE search on June 2020 to capture any studies published since our initial search in February 2019. We checked the studies included in the previous DERP report[12] against our updated inclusion and exclusion criteria and recommended regimens in updated guidelines. We rated the risk of bias of eligible studies using standard instruments adapted from national and international quality standards.[13,14] We rated the quality of the body of evidence for each comparison for major outcomes (i.e., viral suppression, drug resistance, adherence, SAEs, and kidney injury) using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.[15,16]

Findings

Our searches yielded a total of 393 publications that were published since the last DERP report. For this update, we included 10 studies (in 15 publications). We carried forward 11 studies (in 22 publications) from the previous report for a total of 21 studies (in 37 publications) in this update. In general, studies were designed to test whether one drug was noninferior to another as opposed to whether treatments were statistically significantly different from one another for various HIV-related outcomes.

Key Questions 1 and 2: Effectiveness and Harms of Backbone Therapies

We identified evidence for the following comparisons of backbone therapies:

- 2-drug vs. 3-drug combinations:
  - 3TC vs. TDF/FTC (1 RCT)
- 3-drug vs. 3-drug combinations:
  - TAF/FTC vs. TDF/FTC (3 RCTs in 4 publications)
  - TAF/FTC vs. ABC/3TC (1 RCT in 3 publications)
  - ABC/3TC vs. TDF/FTC (1 RCT in 2 publications)
  - TDF/3TC vs. TDF/FTC (1 RCT)

Lamivudine (3TC) vs. Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC): 2-drug vs. 3-drug Regimens

Study Characteristics

We identified 1 publication of 2 eligible RCTs, GEMINI-1 and GEMINI-2, comparing the 2-drug regimen dolutegravir plus lamivudine (DTG + 3TC) with the 3-drug regimen dolutegravir plus co-formulated TDF/FTC in adults (Table 3 and Appendix B Table B1).[17] We assessed this trial as

having a moderate risk of bias because of author conflicts of interest and funding by industry. This study did not report the following outcomes: AIDS-defining illness, adherence, persistence, or drug-drug interactions. GRADE quality of evidence ratings for the outcomes that were reported in this study were assessed as low quality. Additional detail and rationale for these ratings are in Table 4. Additional details pertaining to the outcomes reported in this study are in Appendix B Table B2.

Table 3. Summary Table of Included RCTs of Backbone Therapies 3TC vs. TDF/FTC

Citation Location NCT Number Trial Name Risk of Bias	Patient Characteristics	Intervention	Comparator(s)	Trial Duration
Cahn et al., 2019[17] 192 sites in 21 countries NCT02831673 and NCT02831764 GEMINI-1 and GEMINI-2 Moderate	• Adults (≥ 18 years of age) • Viral load at entry: 1,000 to 500,000 copies/mL • Total N = 1,441 randomized, with 719 in two-drug regimen group (356, GEMINI-1; 360, GEMINI-2) and 722 in three-drug regimen group (358, GEMINI-1; 359, GEMINI-2)	2-drug regimen: DTG 50 mg + 3TC 300 mg orally once daily	3-drug regimen: DTG 50 mg + TDF/FTC 300/200 mg orally once daily	48 weeks

Abbreviations. 3TC: lamivudine; DTG: dolutegravir; FTC: emtricitabine; NCT: national clinical trial; TDF: tenofovir disoproxil fumarate.

Viral Suppression

Overall, fewer participants in the 2-drug regimen group of DTG + 3TC achieved viral suppression at week 48 compared to participants in the 3-drug regimen group of DTG + TDF/FTC in both the GEMINI-1 trial (90% vs. 93%; adjusted treatment difference, -2.6%; 95% CI, -6.7 to 1.5), the GEMINI-2 trial (93% vs. 94%; adjusted treatment difference, -0.7%; 95% CI, -4.3 to 2.9), and pooled results from both trials (91% vs. 93%; adjusted treatment difference, -1.7%; 95% CI, -4.4 to 1.1).[17] However, the differences between groups were not statistically significant. The 2-drug regimen DTG + 3TC was considered noninferior to the 3-drug regimen DTG + TDF/FTC.[17]

Drug Resistance

At week 48, 6 participants in the 2-drug regimen group of DTG + 3TC and 4 participants in the 3-drug regimen group of DTG + TDF/FTC had confirmed virologic withdrawal.[17] However, there was no emergence of mutations conferring resistance to INSTIs or NRTIs.[17]

Adverse Events and Withdrawals Due to Adverse Events

In a pooled analysis of GEMINI-1 and GEMINI-2, there was no numerical difference between DTG + 3TC and DTG + TDF/FTC in terms of percentage of participants experiencing SAEs (7% vs. 8%) or withdrawals due to adverse events (2% vs. 2%) at 48 weeks.[17] At week 48, patients in the DTG + 3TC group experienced statistically significant smaller increases in serum creatinine, a marker for kidney injury, than participants in the DTG + TDF/FTC group (10.4 µmol/L vs. 13.5 µmol/L; $P < .0001$).[17] Similarly, patients in the DTG + 3TC group experienced statistically significant smaller increases in serum bone-specific alkaline phosphatase, a marker of bone turnover, than participants in the DTG + TDF/FTC at week 48 (1.22 vs. 4.07; $P < .0001$).[17]

Table 4. Summary of Findings (GRADE) for Lamivudine vs. Tenofovir Disoproxil Fumarate/Emtricitabine: 2-drug vs. 3-drug Regimens

Outcome	Quality of the Evidence	Relationship	Rationale
Viral Suppression (HIV-1 RNA < 50 copies/mL) (1 RCT with 1,441 total participants[17])	⊕⊕◯◯ LOW	At 48 weeks, more participants had viral suppression on the 3-drug regimen than the 2-drug regimen. However, the 2-drug regimen was considered non-inferior to the 3-drug regimen.	Downgraded 1 level for risk of bias and 1 level for indirectness
Drug Resistance (1 RCT with 1,441 total participants[17])	⊕⊕◯◯ LOW	Confirmed virologic withdrawal at week 48: 6 in 2-drug regimen group vs. 4 in 3-drug regimen group; no emergence of mutations conferring resistance to INSTIs or NRTIs; all 10 participants classified as virologic rebounds	Downgraded 1 level for risk of bias and 1 level for indirectness
Adherence	No evidence		
Serious Adverse Events (1 RCT with 1,441 total participants[17])	⊕⊕◯◯ LOW	No difference between groups	Downgraded 1 level for risk of bias and 1 level for indirectness
Kidney Injury (Increased serum creatinine) (1 RCT with 1,441 total participants[17])	⊕⊕◯◯ LOW	At 48 weeks, 2-drug regimen led to smaller increases in serum creatinine compared to 3-drug regimen.	Downgraded 1 level for risk of bias and 1 level for indirectness

Abbreviations. GRADE: Grading of Recommendations Assessment, Development, and Evaluation; INSTI: integrase strand transfer inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; RCT: randomized controlled trial; RNA: ribonucleic acid.

Tenofovir Alafenamide/Emtricitabine (TAF/FTC) vs. Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC)

Study Characteristics

We identified 3 RCTs (in 4 publications)[18-21] comparing 3-drug regimens including TAF/FTC and TDF/FTC (Table 5 and Appendix B Table B1). We assessed 1 trial[18,21] as having a moderate risk of bias because of author conflicts of interest and funding by industry, and 2 trials[19,20] as having a high risk of bias because of the aforementioned reasons as well as unclear allocation methods, lack of blinding, differences in baseline characteristics between groups, and differential loss to follow-up. Two RCTs (in 3 publications)[18,19,21] focused on adults (≥ 18 years of age) with a moderate to high risk of disease progression based on viral load at study entry (≥ 1,000 copies/mL).[22] One RCT[20] focused on adolescents and adults (≥ 12 years of age) with lower levels of viremia at study entry (≥ 500 copies/mL) and, therefore, lower risk of disease progression.[22] One study was 48 weeks in duration, whereas the other 2 studies were 96 weeks in duration (Table 5). Two studies[18,19,21] compared darunavir/cobicistat (DRV/c) in a single tablet combination with TAF/FTC or TDF/FTC, or administered as separate tablets, while 1 study[20] compared a two-tablet combination of dolutegravir (DTG) with TAF/FTC to a two-tablet regimen of DTG + TDF/FTC, as well as a single tablet regimen of efavirenz (EFV) combined with TDF/FTC. In the two studies that reported dosages of backbone drugs, TDF and FTC were consistently dosed across studies, but the dose of TAF differed (Table 5).[18,20,21] GRADE quality of evidence ratings for the outcomes that were reported in these studies were assessed as low quality. Additional detail and rationale for these ratings are in Table 6. These studies did not report the following outcomes: AIDS-defining illness, persistence, and drug-drug interactions. Additional details pertaining to the outcomes reported in these studies are in Appendix B Table B2.

Table 5. Summary Table of Included RCTs of Backbone Therapies TAF/FTC vs. TDF/FTC

Citation Location NCT Number Trial Name Risk of Bias	Patient Characteristics	Intervention	Comparator(s)	Trial Duration
Eron et al., 2018[18] Rashbaum et al., 2019[21] 121 sites in 10 countries (including U.S.) NCT02431247 AMBER Moderate	• Adults (≥ 18 years of age) • Viral load at entry ≥ 1,000 copies/mL • Total N = 725 randomized with 362 in DRV/c/TAF/FTC group and 363 in DRV/c + TDF/FTC	DRV/c/TAF/FTC 800/150/10/200 mg single tablet daily	DRV/c 800/150 mg FDC + TDF/FTC 300/200 mg FDC daily	96 weeks
Mills et al., 2015[19] Multicenter in the U.S. NCT01565850 High	• Adults (≥ 18 years of age) • Viral load at entry ≥ 5,000 copies/mL	DRV/c/TAF/FTC single tablet regimen once daily	DRV + c + TDF/FTC in separate tablets once daily	48 weeks

Citation Location NCT Number Trial Name Risk of Bias	Patient Characteristics	Intervention	Comparator(s)	Trial Duration
	• Total N = 153 randomized with 103 in DRV/c/TAF/FTC (TAF) group and 50 in DRV + c + TDF/FTC (TDF) group	(DRV dosed at 800 mg)	(DRV dosed in 2, 400-mg tablets)	
Venter et al., 2019[20] South Africa NCT03122262 ADVANCE High	• Adolescents and adults (≥ 12 years of age) • Viral load at entry ≥ 500 copies/mL • Total N = 1,053 randomized with 351 in each group	DTG 50 mg + TAF/FTC 25/200 mg as two tablets daily (TAF group) or TDF/FTC 300/200 mg as two tablets daily (TDF group)	EFV/TDF/FTC 600/300/200 mg as a single tablet daily (standard care group)	96 weeks

Abbreviations. c: cobicistat; DRV: darunavir; DTG: dolutegravir; EFV: efavirenz; FDC: fixed-dose combination; FTC: emtricitabine; NCT: national clinical trial; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate.

Viral Suppression

Studies were mixed in the directionality of the effect of TAF and TDF on viral suppression, but none of the findings were statistically significantly different. TAF was considered noninferior to TDF. One study reported that a greater percentage of participants in the TAF group experienced viral suppression than participants in the TDF group at week 48 (91.4% vs. 88.4%, treatment difference, 2.7%; 95% CI, -1.6 to 7.1),[18,21] while 2 studies found that TDF led to a greater percentage of participants achieving viral suppression than TAF (76.7% vs. 84.0%, weighted difference, -6.2%; 95% CI -19.9 to 7.4;[19] 84.0% vs. 85.0%, treatment difference, -1.1%; 98.3% CI, -7.7 to 5.4[20]).

Drug Resistance

Across studies, few patients developed resistance mutations to study drugs. Eron et al.[18,21] and Venter et al.[20] reported that 1 patient each developed resistance mutations to NRTIs or NNRTIs. Mills et al.[19] found that no patients developed resistance to TDF, TAF, FTC, or DRV.

Adherence

Eron et al.[18,21] and Mills et al.[19] reported adherence to study medication as measured by pill count. Both studies reported high adherence (≥ 95% adherent) to study medication in both groups with no significant differences between groups in either study (88.3% vs. 88.3%;[18,21] 98.8% vs. 98.2%[19]).

Persistence

Mills et al.[19] reported persistence on study medications through week 48. Mean duration of study drug exposure was similar between groups (68.0 weeks vs. 69.1 weeks).[19]

Adverse Events and Withdrawals Due to Adverse Events

All 3 studies reported few SAEs, with largely no numerical differences between treatment groups (range 4.6% to 5.0% in TAF groups vs. 4.0% to 6.0% in TDF groups).[18-21] Fewer participants in the TAF groups withdrew from the studies due to adverse events compared to participants in the TDF groups (range 0.28% to 2.0% in TAF groups vs. 2.8% to 4.0%), although few participants withdrew overall.[18-21] Eron et al.[18,21] reported few renal adverse events overall through week 48; however, fewer participants in the TAF group experienced renal adverse events compared to participants in the TDF group (2.0% vs. 6.0%). Fewer participants in the TAF groups experienced increased (4.8 µmol/L vs. 8.2 µmol/L, $P < .0001$)[18,21] or abnormal (0.85% vs. 3.1%) serum creatinine levels compared to participants in the TDF groups.[20] In Mills et al.,[19] the mean change in serum creatinine was smaller in the TAF group than in the TDF group (0.06 mg/dL; 95% CI, 0.04 to 0.08 vs. 0.09 mg/dL; 95% CI, 0.05 to 0.14). Few participants experienced hepatotoxicity, as measured by elevated alanine aminotransferase (ALT, 2.8% vs. 2.0%) and aspartate aminotransferase (AST, 1.7% vs. 1.7%), with no differences between treatment groups.[20] TAF performed better than TDF in terms of bone mineral density (BMD) at week 48, with studies reporting statistically significant smaller percentage changes in BMD in the TAF groups compared with the TDF groups at both the hip (0.21% vs. -2.73%, $P < .0001$;[18,21] -0.84% vs. -3.82; $P < .001$[19]) and lumbar spine (-0.68% vs. -2.38%, $P < .0001$;[18,21] -1.57% vs. -3.62%; $P = .003$[19]).

Table 6. Summary of Findings (GRADE) for Tenofovir Alafenamide/Emtricitabine vs. Tenofovir Disoproxil Fumarate/Emtricitabine

Outcome	Quality of the Evidence	Relationship	Rationale
Viral Suppression (HIV-1 RNA < 50 copies/mL) (3 RCTs with 1,931 participants[18-21])	⊕⊕◯◯ LOW	TAF was noninferior to TDF and the difference between them was not statistically significant.	Downgraded 1 level for risk of bias and 1 level for indirectness
Drug Resistance (3 RCTs with 1,931 participants[18-21])	⊕⊕◯◯ LOW	Few patients developed resistance to the study drugs. Largely no difference was observed between the treatment groups.	Downgraded 1 level for risk of bias and 1 level for indirectness
Adherence (2 RCTs with 878 participants[18,19,21])	⊕⊕◯◯ LOW	High levels of adherence occurred in both groups. No significant differences were observed between groups.	Downgraded 1 level for risk of bias and 1 level for indirectness
Serious Adverse Events (2 RCTs with 878 participants[18,19,21])	⊕⊕◯◯ LOW	No difference between groups	Downgraded 1 level for risk of bias and 1 level for indirectness

Kidney Injury (Increased serum creatinine) (3 RCTs with 1,931 participants[18-21])	⊕⊕◯◯ LOW	TDF led to significantly greater increases in serum creatinine clearance than TAF.	Downgraded 1 level for risk of bias and 1 level for indirectness

Abbreviations. HIV-1: human immunodeficiency virus type 1; RCT: randomized controlled trial; RNA: ribonucleic acid; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate.

Tenofovir Alafenamide/Emtricitabine (TAF/FTC) vs. Abacavir/Lamivudine (ABC/3TC)

Study Characteristics

We identified 1 RCT (in 3 publications)[23-25] comparing 3-drug regimens including TAF/FTC and ABC/3TC in participants over the course of 144 weeks (Table 7 and Appendix B Table B1). We assessed this trial[23-25] as having a moderate risk of bias because of author conflicts of interest and funding by industry. This study included adults with lower levels of viremia at study entry (≥ 500 copies/mL), which represented their lower risk of disease progression.[22-25] This study compared two single-tablet fixed-dosed combinations (FDC), BIC/TAF/FTC and DTG/ABC/3TC.[23-25] GRADE quality of evidence ratings for the outcomes reported in this study were assessed as moderate quality. Additional detail and rationale for these ratings are in Table 8. This study did not report the following outcomes: AIDS-defining illness, adherence, persistence, and drug-drug interactions. Additional details pertaining to the outcomes reported in this study are in Appendix B Table B2.

Table 7. Summary Table of Included RCTs of Backbone Therapies TAF/FTC vs. ABC/3TC

Citation Location NCT Number Trial Name Risk of Bias	Patient Characteristics	Intervention	Comparator(s)	Trial Duration
Gallant et al., 2017[24] Wohl et al., 2019[23] Acosta et al., 2019[25] 122 sites in 9 countries in Europe, Latin America, and North America NCT02607930 Moderate	• Adults (≥ 18 years of age) • Viral load at entry ≥ 500 copies/mL • Total N = 631 randomized with 316 in BIC/TAF/FTC group and 315 in DTG/ABC/3TC group	BIC/TAF/FTC 50/25/200 mg FDC once daily	DTG/ABC/3TC 50/600/300 mg FDC once daily	144 weeks

Abbreviations: 3TC: lamivudine; ABC: abacavir; BIC: bictegravir; DTG: dolutegravir; FDC: fixed-dose combination; FTC: emtricitabine; RCT: randomized controlled trial; TAF: tenofovir alafenamide.

Viral Suppression

The regimen BIC/TAF/FTC was considered noninferior to DTG/ABC/3TC, although the treatment differences between groups were not statistically significant.[23-25] The percentage of participants achieving viral suppression (HIV-1 RNA < 50 copies/mL) was similar between the TAF/FTC and ABC/3TC groups at week 48 (92.4% vs. 93.0%, treatment difference, -0.6%; 95%

CI, -4.8 to 3.6) and week 96 (88.0% vs. 90.0%, treatment difference, -1.9%; 95% CI, -6.9 to 3.1).[23-25]

Drug Resistance

Resistance analysis was conducted for 5 participants (1 in the BIC/TAF/FTC group and 4 in the DTG/ABC/3TC group).[23-25] No treatment-emergent resistance to any component of either treatment regimen had developed at weeks 48 or 96.[23-25]

Adverse Events and Withdrawals Due to Adverse Events

Few participants experienced SAEs and there were largely no differences between groups at both weeks 48 (6.0% vs. 8.0%) and 96 (11.0% vs. 12.0%).[23-25] Similarly, there were few withdrawals due to adverse events and largely no differences between groups at weeks 48 (0.0% vs. 1.0%) and 96 (0.0% vs. 2.0%).[23-25] There was no difference between groups in terms of the mean change in serum creatinine at weeks 48 (0.11 mg/dL, range 0.03 to 0.17 vs. 0.11 mg/dL, range 0.03 to 0.18; *P* = .78) and 96 (0.08 mg/dL, range 0.01 to 0.15] vs. 0.09 mg/dL, range 0.03 to 0.17; *P* = 0.067).[23-25] There were no significant differences between groups in hip or lumbar spine BMD at weeks 48 or 96 (Appendix B Table B2).[23-25]

Table 8. Summary of Findings (GRADE) for Tenofovir Alafenamide/Emtricitabine vs. Abacavir/Lamivudine

Outcome	Quality of the Evidence	Relationship	Rationale
Viral Suppression (HIV-1 RNA < 50 copies/mL) (1 RCT with 631 participants[23-25])	⊕⊕⊕◯ MODERATE	TAF/FTC was noninferior to ABC/3TC and the difference between them was not statistically significant.	Downgraded 1 level for risk of bias
Drug Resistance (1 RCT with 631 participants[23-25])	⊕⊕⊕◯ MODERATE	No difference between groups	Downgraded 1 level for risk of bias
Adherence	No evidence.		
Serious Adverse Events (1 RCT with 631 participants[23-25])	⊕⊕⊕◯ MODERATE	No difference between groups	Downgraded 1 level for risk of bias
Kidney Injury (Increased serum creatinine) (1 RCT with 631 participants[23-25])	⊕⊕⊕◯ MODERATE	No difference between groups	Downgraded 1 level for risk of bias

Abbreviations. 3TC: lamivudine; ABC: abacavir; FTC: emtricitabine; HIV-1: human immunodeficiency virus type 1; RCT: randomized controlled trial; RNA: ribonucleic acid; TAF: tenofovir alafenamide.

Abacavir/Lamivudine (ABC/3TC) vs. Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC)

Study Characteristics

We identified 1 RCT (in 2 publications)[26,27] comparing 3-drug regimens including ABC/3TC and TDF/FTC (Table 9 and Appendix B Table B1). We assessed this trial[26,27] as having a moderate risk of bias because of an unclear allocation concealment method, author conflicts of interest, and

funding by industry. This trial focused on adults with moderate to high viral load at study entry (≥ 1,000 copies/mL), representing a greater risk of disease progression.[22] This study compared a 2-tablet regimen of DTG plus ABC/3TC to a single tablet FDC of EFV/TDF/FTC, both given once daily.[26,27] GRADE quality of evidence ratings for the outcomes reported in this study were assessed as moderate quality. Additional detail and rationale for these ratings are in Table 10. This study did not report the following outcomes: AIDS-defining illness, adherence, persistence, and drug-drug interactions. Additional details pertaining to the outcomes reported in this study are in Appendix B Table B2.

Table 9. Summary Table of Included RCT of Backbone Therapies ABC/3TC vs. TDF/FTC

Citation Location NCT Number Trial Name Risk of Bias	Patient Characteristics	Intervention	Comparator(s)	Trial Duration
Walmsley et al., 2013[26] Walmsley et al., 2015[27] Multiple sites in North America, Europe, and Australia NCT01263015 SINGLE Moderate	• Adults (≥ 18 years of age) • Viral load at entry ≥ 1,000 copies/mL • Total N = 844 randomized with 422 in both treatment group	DTG 50 mg + ABC/3TC + 600/300 mg in two separate tablets once daily	EFV/TDF/FTC 600/300/200 mg FDC once daily	144 weeks

Abbreviations. 3TC: lamivudine; ABC: abacavir; DTG: dolutegravir; EFV: efavirenz; FDC: fixed-dose combination; FTC: emtricitabine; NCT: national clinical trial; TDF: tenofovir disoproxil fumarate.

Viral Suppression

ABC/3TC was found to be noninferior to TDF/FTC, with statistically significantly more participants in the ABC/3TC group achieving viral suppression at week 48 than participants in the TDF/FTC group (88.0% vs. 81.0%, adjusted treatment difference 7.0% [95% CI, 2.0 to 12.0]).[26,27] This finding was consistent over time, at both weeks 96 (80.0% vs. 72.0%; *P* = .006) and 144 (71.0% vs. 63.0%; *P* = .01).[26,27]

Drug Resistance

Through week 48, 4% of participants in each group met criteria for virologic failure.[26,27] No major NRTI or INSTI resistance mutations were found in those in the DTG + ABC/3TC group.[26,27] In the EFV/TDF/FTC group, 1 participant had a TDF-associated resistance mutation and 4 had NNRTI resistance mutations.[26,27] Through week 144, no resistance mutations occurred in the DTG + ABC/3TC group, whereas 7 participants (an additional 2 cases after week 48) in the EFV/TDF/FTC group developed resistance mutations to NNRTIs.[26,27]

Adverse Events and Withdrawals Due to Adverse Events

There were largely no differences between treatment groups in the percentage of participants experiencing SAEs at weeks 48 (9.0% vs. 8.0%), 96 (11.0% vs. 12.0%), and 144 (16.0% vs.

14.0%).[26,27] However, fewer participants in the ABC/3TC group experienced withdrawals due to adverse events compared to participants in the TDF/FTC group at week 48 (2.0% vs. 10.0%).[26,27] Mean serum creatinine level remained stable through week 144 for patients in the DTG + ABC/3TC group, but was not reported for the other group.[26,27] Fewer participants in the ABC/3TC group experienced elevated ALT or AST at week 48 compared to participants in the TDF/FTC group (2.0% vs. 5.0% for both measures).[26,27]

Table 10. Summary of Findings (GRADE) for Abacavir/Lamivudine vs. Tenofovir Disoproxil Fumarate/Emtricitabine

Outcome	Quality of the Evidence	Relationship	Rationale
Viral Suppression (HIV-1 RNA < 50 copies/mL) (1 RCT with 844 participants[26,27])	⊕⊕⊕◯ MODERATE	ABC/3TC was noninferior to and led to a significantly greater percentage of participants achieving viral suppression than TDF/FTC at 48, 96, and 144 weeks.	Downgraded 1 level for risk of bias
Drug Resistance (1 RCT with 844 participants[26,27])	⊕⊕⊕◯ MODERATE	No resistance mutations in the ABC/3TC group; few resistance mutations in the TDF/FTC group; trend consistent at 48 and 144 weeks	Downgraded 1 level for risk of bias
Adherence	No evidence		
Serious Adverse Events (1 RCT with 844 participants[26,27])	⊕⊕⊕◯ MODERATE	No difference between groups	Downgraded 1 level for risk of bias
Kidney Injury (Increased serum creatinine) (1 RCT with 844 participants[26,27])	⊕⊕⊕◯ MODERATE	Mean serum creatinine level remained stable through week 144 for patients in the DTG + ABC/3TC group. Levels were not reported for the other group.	Downgraded 1 level for risk of bias.

Abbreviations. 3TC: emtricitabine; ABC: abacavir; DTG: dolutegravir; FTC: emtricitabine; HIV-1: human immunodeficiency virus type 1; RNA: ribonucleic acid; RCT: randomized controlled trial; TDF: tenofovir disoproxil fumarate.

Tenofovir Disoproxil Fumarate/Lamivudine (TDF/3TC) vs. Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC)

Study Characteristics

We identified 1 RCT comparing 3-drug regimens including TDF/3TC and TDF/FTC (Table 11 and Appendix B Table B1).[28] We assessed this trial as having a high risk of bias because of an unclear allocation concealment method, unclear use of intention-to-treat analysis, author conflicts of interest, and funding by industry. This trial focused on adults (≥ 18 years of age) with moderate to high levels of viremia at study entry (≥ 1,000 copies/mL), representing a greater risk of

disease progression.[22,28] This trial compared 2 single tablet FDC regimens, DOR/TDF/3TF and EFV/TDF/FTC, each administered once daily with a total study duration of 96 weeks.[22] GRADE quality of evidence ratings for the outcomes reported in this study were assessed as low quality. Additional detail and rationale for these ratings are in Table 12. This study did not report the following outcomes: AIDS-defining illness, adherence, persistence, and drug-drug interactions. Additional details pertaining to the outcomes reported in this study are in Appendix B Table B2.

Table 11. Summary Table of Included RCT of Backbone Therapies TDF/3TC vs. TDF/FTC

Citation Location NCT Number Trial Name Risk of Bias	Patient Characteristics	Intervention	Comparator(s)	Trial Duration
Orkin et al., 2019[28] 126 sites worldwide NCT02403674 DRIVE-AHEAD High	• Adults (≥ 18 years of age) • Viral load at entry ≥ 1,000 copies/mL • Total N = 734 randomized with 368 in DOR/TDF/3TC group and 366 in EFV/TDF/FTC group	DOR/TDF/3TC 100/300/300 mg FDC once daily	EFV/TDF/FTC 600/300/200 mg FDC once daily	96 weeks (cut-off for publication was 48 weeks)

Abbreviations. 3TC: lamivudine; DOR: doravirine; EFV: efavirenz; FDC: fixed-dose combination; FTC: emtricitabine; NCT: national clinical trial; TDF: tenofovir disoproxil fumarate.

Viral Suppression

In terms of viral suppression in 1 RCT, TDF/3TC was considered noninferior to TDF/FTC.[28] A slightly greater proportion of participants in the TDF/3TC group achieved viral suppression at week 48 compared to participants in the TDF/FTC group (84.3% vs. 80.8%, treatment difference, 3.5%; 95% CI, -2.0 to 9.0), but the difference was not statistically significant.[28]

Drug Resistance

Through week 48, only 22 participants (6.0%) in the DOR/TDF/3TC group and 14 (3.8%) in the EFV/TDF/FTC group met criteria for virologic failure.[28] Isolates were not obtained from all of these participants. Seven participants in the DOR/TDF/3TC group developed resistance mutations associated with DOR, EFV, or 3TC, while 12 participants in the EFV/TDF/FTC group developed resistance mutations associated with EFV, DOR, or FTC.[28]

Adverse Events and Withdrawals Due to Adverse Events

Fewer participants in the TDF/3TC group experienced SAEs (4.0% vs. 6.0%, treatment difference, -2.2%; 95% CI, -5.5 to 0.9) and withdrawals due to adverse events (3.0% vs. 4.0%, treatment difference, -3.6%; 95% CI, -6.9 to -0.5) compared to participants in the TDF/FTC group at 48 weeks.[28] However, the difference between the groups was only statistically significant for withdrawals due to adverse events.[28] A greater percentage of participants in the TDF/3TC group experienced increases in serum creatinine through week 48 than participants in

the TDF/FTC group (serum creatinine > 1.8 to < 3.5x upper limit of normal (ULN), or increase of 1.5 to < 2.0x above baseline: 1.9% vs. 0.8%, treatment difference, 1.1%; 95% CI, -0.7 to 3.2), but the difference between groups was not statistically significant. Bone fractures occurred in less than 1.0% of each treatment group.

Table 12. Summary of Findings (GRADE) for Tenofovir Disoproxil Fumarate/Lamivudine vs. Tenofovir Disoproxil Fumarate/Emtricitabine

Outcome	Quality of the Evidence	Relationship	Rationale
Viral Suppression (HIV-1 RNA < 50 copies/mL) (1 RCT in 734 participants[28])	⊕⊕◯◯ LOW	TDF/3TC was noninferior to TDF/FTC and the difference between them was not statistically significant.	Downgraded 1 level for risk of bias and 1 level for indirectness
Drug Resistance (1 RCT in 734 participants[28])	⊕⊕◯◯ LOW	Fewer resistance mutations in the TDF/3TC group than the TDF/FTC group	Downgraded 1 level for risk of bias and 1 level for indirectness
Adherence	No evidence		
Serious Adverse Events (1 RCT in 734 participants[28])	⊕⊕◯◯ LOW	No difference between groups	Downgraded 1 level for risk of bias and 1 level for indirectness
Kidney Injury (Increased serum creatinine) (1 RCT in 734 participants[28])	⊕⊕◯◯ LOW	No difference between groups	Downgraded 1 level for risk of bias and 1 level for indirectness

Abbreviations. 3TC: lamivudine; FTC: emtricitabine; HIV-1: human immunodeficiency virus type 1; RCT: randomized controlled trial; RNA: ribonucleic acid; TDF: tenofovir disoproxil fumarate.

Key Questions 3 and 4: Effectiveness and Harms of Add-on Therapies

We identified evidence for the following comparisons of add-on therapies:

- 3-drug vs. 3-drug combinations:
  - BIC vs. DTG (2 RCTs in 3 publications)
  - DTG vs. RAL (1 RCT in 2 publications)
  - DRV/r vs. DOR (1 RCT)
  - DRV/r vs. RAL (1 RCT)
  - DTG vs. EFV (2 RCTs in 3 publications)
  - RAL vs. EFV (3 RCTs in 9 publications)
  - RPV vs. EFV (3 RCTs in 4 publications)

Bictegravir (BIC) vs. Dolutegravir (DTG)

Study Characteristics

We identified 2 RCTs (in 3 publications)[29-31] comparing 3-drug regimens including BIC and DTG in adults (Table 13 and Appendix B Table B1). We assessed 1 trial[30,31] as having a moderate risk of bias because of author conflicts of interest and funding by industry. We assessed the other trial[29] as having a high risk of bias due to the aforementioned reasons as well as an unclear allocation concealment method, unclear use of intention-to-treat analysis, and differences in

baseline characteristics between groups. Sax et al.[30,31] compared the single tablet FDC regimen of BIC/TAF/FTC to a 2-tablet regimen of DTG plus TAF/FTC for 96 weeks in participants with lower levels of viremia at study entry (≥ 500 copies/mL), representing lower risk of disease progression.[22] Sax et al.[29] compared a 2-tablet regimen of BIC plus TAF/FTC with a 2-tablet regimen of DTG + TAF/FTC for 48 weeks in participants with moderate to high levels of viremia at study entry (≥ 1,000 copies/mL), representing a higher risk of disease progression.[22] GRADE quality of evidence ratings for the outcomes reported in these studies ranged from very low to low quality. Additional detail and rationale for these ratings are in Table 14. These studies did not report the following outcomes: AIDS-defining illness and drug-drug interactions. Additional details pertaining to the outcomes reported in these studies are in Appendix B Table B2.

Table 13. Summary Table of Included RCTs of Add-on Therapies BIC vs. DTG

Citation Location NCT Number Trial Name Risk of Bias	Patient Characteristics	Intervention	Comparator(s)	Trial Duration
Sax et al., 2017a[30] Stellbrink et al., 2019[31] 126 sites in 10 countries in Australia, Europe, Latin America, and North America NCT02607956 GS-US-380–1490 Moderate	• Adults (≥ 18 years of age) • Viral load at entry ≥ 500 copies/mL • Total N = 657 randomized with 327 in BIC group and 330 in DTG group	BIC/TAF/FTC 50/25/200 mg FDC once daily	DTG 50 mg + TAF/FTC 25/200 mg, once daily	96 weeks
Sax et al., 2017b[29] 22 sites in the U.S. NCT02397694 High	• Adults (≥ 18 years of age) • Viral load at entry ≥ 1,000 copies/mL • Total N = 98 randomized with 65 in BIC group and 33 in DTG group	BIC 75 mg + TAF/FTC 25/200 mg	DTG 50 mg + TAF/FTC 25/200 mg	48 weeks

Abbreviations. BIC: bictegravir; DTG: dolutegravir; FDC: fixed-dose combination; FTC: emtricitabine; NCT: national clinical trial; TAF: tenofovir alafenamide.

Viral Suppression

Overall, the differences in the included studies comparing BIC and DTG were not statistically significant; however, the directionality of effect was mixed. Further, BIC was considered noninferior to DTG in both studies.[29-31] In Sax et al.,[30,31] fewer participants in the BIC group achieved viral suppression at weeks 48 (89.0% vs. 93.0%, treatment difference, -3.5%; 95% CI, -7.9 to 1.0) and 96 (84.0% vs. 86.0%, treatment difference, -2.3%; 95% CI, -7.9 to 3.2) compared to participants in the DTG group. In Sax et al.,[29] a greater percentage of participants in the BIC

group achieved viral suppression at week 48 compared to participants in the DTG group (97.0% vs. 91.0%, weighted treatment difference, 6.4%; 95% CI, -6.0 to 18.8).

Adherence

In Sax et al.,[29] the median adherence to study medications at week 48 was similar between the BIC and DTG treatment groups (97%, interquartile range [IQR] 94 to 99 vs. 96%, IQR 90 to 99). Similarly, in Sax et al.,[30] there was no difference between BIC and DTG treatment groups in the percentage of participants achieving ≥95% drug adherence at week 48 (94% vs. 94%).

Persistence

In Sax et al.,[30,31] both treatments were well tolerated, with a median exposure of 101 weeks (IQR 98 to 107 for BIC and 98 to 108 for DTG).

Drug Resistance

In Sax et al.,[30,31] no treatment-emergent resistance to the components of either treatment were identified at weeks 48 or 96. In Sax et al.,[29] few participants were eligible for resistance testing (1 in BIC group and 2 in DTG group). Genotypic resistance analysis revealed that 1 patient in the DTG group developed an integrase mutation at week 48 (which was not detected at baseline or at a subsequent timepoint after week 48) but no resistance to emtricitabine or tenofovir.[29]

Adverse Events and Withdrawals Due to Adverse Events

Sax et al.[29] found that no participants in either group experienced SAEs at week 48. However, in Sax et al.[30,31] a greater percentage of participants in the BIC group experienced SAEs at week 96 compared to participants in the DTG group (17.0% vs. 10.0%). Few participants in both studies experienced withdrawals due to adverse events, and the percentages of participants withdrawing was similar in both groups (week 48: 1.5% to 2.0% in BIC vs. 0.0% to < 1.0% in DTG; week 96: 2.0% vs. 2.0%).[29-31] There were no differences between groups in terms of changes in serum creatinine or increases in ALT or AST at week 48 (Appendix B Table B2).[29-31]

Table 14. Summary of Findings (GRADE) for Bictegravir vs. Dolutegravir

Outcome	Quality of the Evidence	Relationship	Rationale
Viral Suppression (HIV-1 RNA < 50 copies/mL) (2 RCTs in 755 participants[29-31])	⊕⊕◯◯ LOW	BIC was noninferior to DTG regimen and the difference between them was not statistically significant.	Downgraded 1 level for risk of bias and 1 level for indirectness
Drug Resistance (2 RCTs in 755 participants[29-31])	⊕⊕◯◯ LOW	Largely no differences between groups	Downgraded 1 level for risk of bias and 1 level for indirectness
Adherence (2 RCTs in 755 participants[29])	⊕⊕◯◯ LOW	No difference between groups	Downgraded 1 level for risk of bias and 1 level for indirectness.
Serious Adverse Events (2 RCTs in 755 participants[29-31])	⊕◯◯◯ VERY LOW	Greater number of participants with SAEs in BIC group than DTG group, but only seen at 96 weeks	Downgraded 1 level for risk of bias, 1 level for indirectness, and 1 level for inconsistency

Outcome	Quality of the Evidence	Relationship	Rationale
Kidney Injury (Increased serum creatinine) (2 RCTs in 755 participants[29-31])	⊕◯◯◯ VERY LOW	Largely no difference between groups	Downgraded 1 level for risk of bias, 1 level for indirectness, and 1 level for inconsistency

Abbreviations. BIC: bictegravir; DTG: dolutegravir; HIV-1: human immunodeficiency virus type 1; RCT: randomized controlled trial; RNA: ribonucleic acid; SAE: serious adverse event.

Dolutegravir (DTG) vs. Raltegravir (RAL)

Study Characteristics

We identified 1 RCT (in 2 publications) comparing 3-drug regimens including DTG and RAL (Table 15 and Appendix B Table B1).[32,33] We assessed this trial[32,33] as having a moderate risk of bias because of author conflicts of interest and funding by industry. This study included adults (≥ 18 years of age) with moderate to high levels of viremia at study entry (≥ 1,000 copies/mL), representing greater risk of disease progression.[32,33] The study compared DTG 50 mg once daily versus RAL 400 mg twice daily, each administered with either tenofovir (TAF or TDF not specified)/FTC or ABC/3TC as a backbone for 96 weeks.[32,33] GRADE quality of evidence ratings for the outcomes reported in this study were assessed as low quality. Additional detail and rationale for these ratings are in Table 16. This study did not report the following outcomes: AIDS-defining illness, adherence, persistence, and drug-drug interactions. Additional details pertaining to the outcomes reported in this study are in Appendix B Table B2.

Table 15. Summary Table of Included RCTs of Add-on Therapies DTG and RAL

Citation Location NCT Number Trial Name Risk of Bias	Patient Characteristics	Intervention	Comparator(s)	Trial Duration
Raffi et al., 2013a[32] Raffi et al., 2013b[33] 100 sites in Canada, U.S., Australia, and Europe NCT01227824 SPRING-2 Moderate	• Adults (≥ 18 years of age) • Viral load at entry ≥ 1,000 copies/mL • Total N = 827 randomized with 411 in both treatment groups	DTG 50 mg once daily + (TAF or TDF)/FTC or ABC/3TC *Dosages of backbones not specified	RAL 400 mg twice daily + (TAF or TDF)/FTC or ABC/3TC *Dosages of backbones not specified	96 weeks

Abbreviations. 3TC: lamivudine; ABC: abacavir; DTG: dolutegravir; FTC: emtricitabine; NCT: national clinical trial; RAL: raltegravir; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate.

Viral Suppression

DTG was found to be noninferior to RAL and the difference between the groups was not statistically significant for viral suppression at weeks 48 (88.0% vs. 85.0%, treatment difference, 2.5%; 95% CI -2.2 to 7.1) and 96 (81.0% vs. 76.0%, treatment difference, 4.5%; 95% CI, -1.1 to 10.0).[32,33]

Drug Resistance

Few participants in each treatment group (DTG n = 20; RAL n = 28) experienced virologic failure at week 48 (5.0% BIC vs. 7.0% RAL).[32,33] Of these, only 5 participants in the RAL group developed drug resistance at week 48.[32,33] A similar percentage of participants in both treatment groups (< 1.0%) experienced virologic failure between weeks 48 and 96, and no additional participants developed drug resistance during this period of time.[32,33]

Adverse Events and Withdrawals Due to Adverse Events

No participants experienced SAEs in either group between weeks 48 and 96, and data were not available prior to week 48.[32,33] Few participants experienced withdrawals due to adverse events at weeks 48 and 96, and there were no numerical differences between groups (2.0% vs. 2.0% for both time points).[32,33] Participants in the DTG group experienced greater changes in serum creatinine clearance at weeks 48 (12.3 µmol/L vs. 4.7 µmol/L) and 96 (14.6 µmol/L vs. 8.2 µmol/L) than participants in the RAL group.[32,33]

Table 16. Summary of Findings (GRADE) for Dolutegravir vs. Raltegravir

Outcome	Quality of the Evidence	Relationship	Rationale
Viral Suppression (HIV-1 RNA < 50 copies/mL) (1 RCT in 827 participants[32,33])	⊕⊕◯◯ LOW	DTG was noninferior to RAL and the difference between them was not statistically significant.	Downgraded 1 level for risk of bias and 1 level for indirectness
Drug Resistance (1 RCT in 827 participants[32,33])	⊕⊕◯◯ LOW	No difference between groups in terms of virologic failure; few overall participants developing resistance, all in RAL group, and only between weeks 0 and 48	Downgraded 1 level for risk of bias and 1 level for indirectness
Adherence	No evidence		
Serious Adverse Events (1 RCT in 827 participants[32,33])	⊕⊕◯◯ LOW	No difference between groups	Downgraded 1 level for risk of bias and 1 level for indirectness
Kidney Injury (Increased serum creatinine) (1 RCT in 827 participants[32,33])	⊕⊕◯◯ LOW	Greater increase in DTG group compared to RAL at both 48 and 96 weeks	Downgraded 1 level for risk of bias and 1 level for indirectness

Abbreviations. DTG: dolutegravir; HIV-1: human immunodeficiency virus type 1; RAL: raltegravir; RCT: randomized controlled trial; RNA: ribonucleic acid.

Darunavir/ritonavir (DRV/r) vs. Doravirine (DOR)

Study Characteristics

We identified 1 RCT (in 2 publications) comparing 3-drug regimens including DRV/r and DOR (Table 17 and Appendix B Table B1).[34,35] We assessed this trial[34,35] as having a moderate risk of bias because of author conflicts of interest and funding by industry. This trial included adults (≥

18 years of age) with moderate to high viremia at study entry (≥ 1,000 copies/mL), representing a higher risk of disease progression.[22,34,35] The study compared DRV/r and DOR, each administered with tenofovir (TAF or TDF not specified)/FTC or ABC/3TC for 96 weeks.[34,35] GRADE quality of evidence ratings for relevant outcomes were assessed as low quality. Additional details and rationale for these ratings are in Table 18. This study did not report the following outcomes: AIDS-defining illness, adherence, persistence, and drug-drug interactions. Additional details pertaining to the outcomes reported in these studies are in Appendix B Table B2.

Table 17. Summary Table of Included RCTs of Add-on Therapies DRV/r and DOR

Citation Location NCT Number Trial Name Risk of Bias	Patient Characteristics	Intervention	Comparator(s)	Trial Duration
Molina et al.,2018[34] Molina et al., 2020[35] 125 sites in 15 countries, including U.S. NCT02275780 DRIVE-FORWARD Moderate	• Adults (≥ 18 years of age) • Viral load at entry ≥ 1,000 copies/mL • Total N = 769 randomized with 384 in DRV/r group and 385 in DOR group	DRV/r 800/100 mg + (TAF or TDF)/FTC 300/200 mg or ABC/3TC 600/300 mg once daily	DOR 100 mg + (TAF or TDF)/FTC 300/200 mg or ABC/3TC 600/300 mg once daily	96 weeks

Abbreviations. 3TC: lamivudine; ABC: abacavir; DOR: doravirine; DRV: darunavir; FTC: emtricitabine; NCT: national clinical trial; r: ritonavir; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate.

Viral Suppression

DOR was considered noninferior to DRV/r.[34,35] A greater percentage of participants in the DOR group achieved viral suppression at week 48 (84.0% vs. 80.0%, treatment difference 3.9% [95% CI, -1.6 to 9.4]) and week 96 (73.0% vs. 66.0%, treatment difference 7.1% [95% CI, 0.5 to 13.7]) compared to participants in the DRV/r group.[34,35] However, the treatment difference was only statistically significant at week 96.[34,35]

Drug Resistance

Similar percentages of participants in the DOR and DRV/r groups experienced virologic failure through weeks 48 (5.0% vs. 6.0%) and 96 (9.0% vs. 11%).[34,35] Resistance testing was conducted in 15 of the 43 (34.9%) participants with virologic failure at week 48, which indicated that 3 participants in the DOR group (vs. 0 in DRV/r group) developed drug resistance.[34,35] At week 96, resistance testing was conducted in 25 of the 77 (32.5%) participants with virologic failure, indicating that 2 participants in the DOR group and 1 participant in the DRV/r group developed drug resistance.[34,35]

Adverse Events and Withdrawals Due to Adverse Events

Similar percentages of participants in the DOR and DRV/r treatment groups experienced SAEs (week 48: 5.0% vs. 6.0%; week 96: 7.0% vs. 9.0%) or withdrawals due to adverse events (week

48: 2.0% vs. 3.0%; week 96: 2.0% vs. 3.0%, *P* = .063).[34,35] There were no significant differences between groups in measures of kidney injury or hepatotoxicity at week 96 (Appendix B Table B2).

Table 18. Summary of Findings (GRADE) for Darunavir/ritonavir vs. Doravirine

Outcome	Quality of the Evidence	Relationship	Rationale
Viral Suppression (HIV-1 RNA < 50 copies/mL) (1 RCT in 769 participants[34])	⊕⊕◯◯ LOW	DOR was noninferior to DRV/r and the difference between them was not statistically significant.	Downgraded 1 level for risk of bias and 1 level for indirectness
Drug Resistance (1 RCT in 769 participants[34])	⊕⊕◯◯ LOW	More DRV/r patients developed resistance than DOR patients.	Downgraded 1 level for risk of bias and 1 level for indirectness
Adherence	No evidence.		
Serious Adverse Events (1 RCT in 769 participants[34])	⊕⊕◯◯ LOW	No difference between groups	Downgraded 1 level for risk of bias and 1 level for indirectness
Kidney Injury (Increased serum creatinine) (1 RCT in 769 participants[34])	⊕⊕◯◯ LOW	No difference between groups	Downgraded 1 level for risk of bias and 1 level for indirectness

Abbreviations. DOR: doravirine; DRV: darunavir; HIV-1: human immunodeficiency virus type 1; r: ritonavir; RCT: randomized controlled trial; RNA: ribonucleic acid.

Darunavir/ritonavir (DRV/r) vs. Raltegravir (RAL)

Study Characteristics

We identified 1 RCT comparing 3-drug regimens including DRV/r and RAL (Table 19 and Appendix B Table B1).[36] We assessed this trial[34-36] as having a high risk of bias because of unclear method of randomization, lack of blinding, loss to follow-up, and author conflicts of interest. This trial included adults with moderate to high viremia at study entry (> 1,000 copies/mL), representing a higher risk of disease progression.[22,36] The trial compared DRV/r versus RAL, each taken once daily with TDF/FTC for 96 weeks.[36] GRADE quality of evidence ratings for the outcomes reported in this study were assessed as low quality. Additional detail and rationale for these ratings are in Table 20. This study did not report the following outcomes: AIDS-defining illness, adherence, persistence, and drug-drug interactions. Additional details pertaining to the outcomes reported in this study are in Appendix B Table B2.

Table 19. Summary Table of Included RCTs of Add-on Therapies DRV/r and RAL

Citation Location NCT Number Trial Name Risk of Bias	Patient Characteristics	Intervention	Comparator(s)	Trial Duration
Lennox et al., 2014[36]	• Adults	DRV/r 800/100 mg once daily +	RAL 400 mg twice daily +	96 weeks

Citation Location NCT Number Trial Name Risk of Bias	Patient Characteristics	Intervention	Comparator(s)	Trial Duration
57 sites in the U.S. and Puerto Rico NCT00811954 ACTG A5257 High	• Viral load at entry > 1,000 copies/mL • Total N = 1,204 randomized with 601 in DRV/r group and 603 in RAL group	TDF/FTC 300/200 mg once daily	TDF/FTC 300/200 mg once daily	

Abbreviations. DRV: darunavir; FTC: emtricitabine; NCT: national clinical trial; r: ritonavir; RAL: raltegravir; TDF: tenofovir disoproxil fumarate.

Viral Suppression

A statistically significant greater percentage of participants in the RAL group achieved viral suppression at week 96 compared to participants in the DRV/r group (93.9% vs. 89.4%; DERP researchers calculated Chi-square, 7.97; *P* = .004).[36]

Drug Resistance

Fewer participants in the RAL group experienced virologic failure at week 96 compared to those in the DRV/r group (9.0% vs. 14.9%, treatment difference, 5.6%; 97.5% CI, 1.3 to 9.9). However, a greater number of participants in the RAL group developed resistance to any study drugs compared to participants in the DRV/r group (3.0% vs. 0.67%).[36]

Adverse Events and Withdrawals Due to Adverse Events

Lennox et al.[36] did not report SAEs. Fewer participants in the RAL group experienced study discontinuation due to toxicity-associated reasons than participants in the DRV/r group (1.3% vs. 5.3%).[36] Hepatic toxicity was rare in this study, but participants in the RAL group experienced fewer events than those in the DRV/r group (0.17% vs. 0.83%).[36]

Table 20. Summary of Findings (GRADE) for Darunavir/ritonavir vs. Raltegravir

Outcome	Quality of the Evidence	Relationship	Rationale
Viral Suppression (HIV-1 RNA < 50 copies/mL) (1 RCT in 1,204 participants[36])	⊕⊕◯◯ LOW	Fewer participants reached viral suppression on DRV/r compared with RAL.	Downgraded 2 levels for risk of bias
Drug Resistance (1 RCT in 1,204 participants[36])	⊕⊕◯◯ LOW	Fewer DRV/r participants developed resistance compared to RAL participants.	Downgraded 2 levels for risk of bias
Adherence	No evidence		
Serious Adverse Events	No evidence		
Kidney Injury	⊕⊕◯◯ LOW	No difference between groups	Downgraded 2 levels for risk of bias.

(Increased serum creatinine) (1 RCT in 1,204 participants[36])			

Abbreviations. DRV: darunavir; HIV-1: human immunodeficiency virus type 1; r: ritonavir; RAL: raltegravir; RCT: randomized controlled trial; RNA: ribonucleic acid.

Dolutegravir (DTG) vs. Efavirenz (EFV)

Study Characteristics

We identified 2 RCTs (in 3 publications) comparing 3-drug regimens including DTG and EFV (Table 21 and Appendix B Table B1).[37-39] We assessed both trials[34,35,37-39] as having a high risk of bias because of an unclear randomization method, lack of blinding, author conflicts of interest, and funding by industry. Both studies compared DTG versus EFV, both in combination with an NRTI/NRTI backbone therapy.[37-39] Koufanack et al.[37] studied a low-dose version of EFV (400 mg) in adult participants in resource-limited settings in Cameroon, Africa, for 48 weeks, while Van Lunzen et al.[38,39] studied a higher dose of EFV (600 mg) in adults in more resource-available settings across North America and Europe for 96 weeks. Both studies included participants with moderate to high levels of viremia at study entry (≥ 1,000 copies/mL), representing a higher risk of disease progression.[37-39] GRADE quality of evidence ratings for the outcomes reported in these studies ranged from very low to low quality. Additional detail and rationale for these ratings are in Table 22. These studies did not report the following outcomes: AIDS-defining illness, persistence, and drug-drug interactions. Additional details pertaining to the outcomes reported in these studies are in Appendix B Table B2.

Table 21. Summary Table of Included RCTs of Add-on Therapies DTG and EFV

Citation Location NCT Number Trial Name Risk of Bias	Patient Characteristics	Intervention	Comparator(s)	Trial Duration
Kouanfack et al., 2019[37] 3 sites in Cameroon, Africa NCT02777229 NAMSAL ANRS 12313 High	• Adults (≥ 18 years of age) • Viral load at entry ≥ 1,000 copies/mL • Total N = 616 randomized with 310 in DTG group and 306 in EFV group	DTG + TDF/3TC *Dosages of study drugs not reported	EFV 400 mg + TDF/3TC *Dosages of other study drugs not reported	48 weeks
Van Lunzen et al., 2012[38] Stellbrink et al., 2013[39]34 sites in France, Germany, Italy, Russia, Spain, and the U.S. NCT00951015 SPRING-1	• Adults (≥ 18 years of age) • Viral load at entry ≥ 1,000 copies/mL • Total N = 208 randomized with 53 in DTG 10 mg group, 51 in DTG 25 mg group, 51 in	DTG 10 mg, 25 mg, or 50 mg + (TAF or TDF)/FTC or ABC/3TC	EFV 600 mg + (TAF or TDF)/FTC or ABC/3TC	96 weeks

Citation Location NCT Number Trial Name Risk of Bias	Patient Characteristics	Intervention	Comparator(s)	Trial Duration
High	DTG 50 mg group, and 50 in EFV group			

Abbreviations. 3TC: lamivudine; ABC: abacavir; DTG: dolutegravir; EFV: efavirenz; FTC: emtricitabine; NCT: national clinical trial; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate.

Viral Suppression

Overall, 2 studies found that DTG was noninferior to EFV, and differences between groups for viral suppression were not statistically significantly different.[37-39] Both studies found that greater percentages of participants receiving DTG achieved viral suppression at weeks 48 (74.5% vs. 69.0%, treatment difference, 5.5%; 95% CI, -1.6 to 12.7;[37] 88.0% to 91.0% across DTG doses vs. 82.0% EFV[38,39]) and 96 (78.0% to 88.0% across DTG doses vs. 72.0% EFV)[38,39] compared to either low-dose EFV (400 mg) or higher dose EFV (600 mg).

Adherence

In Kouanfack et al.[37] adherence to study medication (> 95%), as assessed by questionnaire, was greater in the DTG group than in the low-dose EFV group through week 24 (74.0% vs. 72.0%). However, this trend was not sustained through week 48 (69.0% vs. 70.0%).[37]

Drug Resistance

Kouanfack et al.[37] analyzed predicted drug resistance to study drugs at baseline and found that, while low overall, a greater percentage of participants in the DTG group were predicted to develop resistance mutations to NRTIs/NNRTIs (1.6% vs. 0.7%) or INSTIs (0.3% vs. 0.0%) compared to participants in the low-dose EFV group. In Van Lunzen et al.,[38,39] 4 participants experienced virologic failure through week 48 (2 in DTG 10 mg group, 1 in DTG 25 mg group, 1 in EFV group). Only 1 participant (in the DTG 10 mg group) developed a resistance mutation through 48 weeks and which persisted through 96 weeks.[38,39]

Adverse Events and Withdrawals Due to Adverse Events

In the Kouanfack et al. study[37] of DTG versus low-dose EFV conducted in Cameroon, SAEs were not reported and no withdrawals due to adverse events occurred in either group. Specific adverse events were rare and the occurrence of these events did not differ between treatment groups (renal failure: 1.0% vs. < 1.0%; hepatic failure: 0.0% vs. < 1.0%).[37] In the Van Lunzen et al. study[38,39] of higher dose EFV conducted in North America and Europe, there were largely no significant differences between DTG and EFV groups in terms of SAEs at weeks 48 (DTG groups combined, 5.0% vs. EFV, 8.0%) and 96 (DTG groups combined, 11.0% vs. EFV, 14.0%). However, fewer DTG-treated participants experienced withdrawals due to adverse events at weeks 48 (DTG groups combined, 1.3% vs. EFV, 8.0%) and 96 (DTG groups combined, 3.0% vs. EFV, 10.0%) compared to EFV-treated participants.[38,39] Serum creatinine increased in DTG participants and decreased in EFV participants at weeks 48 (DTG groups combined, 3.4 µmol/L [SD, 9.69] vs. EFV, -6.0 µmol/L [SD, 10.19]) and 96 (DTG groups combined, 5.2 µmol/L [SD,

10.64] vs. EFV, -2.4 µmol/L [SD, 8.79]).[38,39] Fewer DTG-treated participants experienced ALT toxicity (grades 1 through 4) at week 96 compared to EFV-treated participants (DTG groups combined, 13.5% vs. EFV, 38.0%).[38,39]

Table 22. Summary of Findings (GRADE) for Dolutegravir vs. Efavirenz

Outcome	Quality of the Evidence	Relationship	Rationale
Viral Suppression (HIV-1 RNA < 50 copies/mL) (2 RCTs in 824 participants[37-39])	⊕⊕◯◯ LOW	DTG was noninferior to EFV and the difference between them was not statistically significant.	Downgraded 1 level for risk of bias and 1 level for indirectness
Drug Resistance (2 RCTs in 824 participants[37-39])	⊕⊕◯◯ LOW	Few participants with virologic failure and resistance mutations overall; largely no difference between groups	Downgraded 1 level for risk of bias and 1 level for indirectness
Adherence (1 RCT in 616 participants[37])	⊕⊕◯◯ LOW	No difference between groups	Downgraded 1 level for risk of bias and 1 level for indirectness
Serious Adverse Events (1 RCT in 208 participants[38,39])	⊕⊕◯◯ LOW	No difference between groups	Downgraded 1 level for risk of bias and 1 level for indirectness
Kidney Injury (Increased serum creatinine) (2 RCTs in 824 participants[37-39])	⊕◯◯◯ VERY LOW	Mixed findings across studies and over time	Downgraded 1 level for risk of bias, 1 level for inconsistency, and 1 level for indirectness.

Abbreviations. DTG: dolutegravir; EFV: efavirenz; HIV-1: human immunodeficiency virus type 1; RCT: randomized controlled trial; RNA: ribonucleic acid.

Raltegravir (RAL) vs. Efavirenz (EFV)

Study Characteristics

We identified 3 RCTs (in 9 publications) comparing 3-drug regimens including RAL and EFV (Table 23 and Appendix B Table B1).[40-48] We assessed 1 trial[34,35,42-46] as having a moderate risk of bias because of author conflicts of interest and funding by industry, and 2 trials[40,41,47,48] as having a high risk of bias because of the aforementioned reasons as well as an unclear allocation concealment method, lack of blinding, and differences in baseline characteristics between groups. Grinztejn et al.,[22,40] conducted in Brazil and France, included adults (≥ 18 years of age) with moderate to high levels of viremia at study entry (> 1,000 copies/mL), representing a relatively high risk of disease progression. Lennox et al.[42-46] and Markowitz et al.[41,47,48] included adults (≥ 18 years of age) with higher levels of viremia at study entry (≥ 5,000 copies/mL), representing a potentially higher risk of disease progression than those in the Grinsztejn et al. study.[40] All 3 studies compared various doses of RAL (100 mg, 200 mg, 400 mg, 600 mg, or 800 mg twice daily) versus EFV (600 mg once daily), each administered with a NRTI/NRTI backbone.[40-48] Studies ranged from 48 to 240 weeks in duration.[40-48] GRADE quality of evidence ratings for the outcomes reported in these studies ranged from very low to low quality. Additional detail and rationale for these ratings are in Table 24. These studies did not report the

following outcomes: AIDS-defining illness, persistence, and drug-drug interactions. Additional details pertaining to the outcomes reported in these studies are in Appendix B Table B2.

Table 23. Summary Table of Included RCTs of Add-on Therapies RAL and EFV

Citation Location NCT Number Trial Name Risk of Bias	Patient Characteristics	Intervention(s)	Comparator(s)	Trial Duration
Grinsztejn et al., 2014[40] 8 sites in Brazil and France NCT00822315 ANRS 12180 Reflate TB High	• Adults (≥ 18 years of age) • Viral load at entry > 1,000 copies/mL • Total N = 155 randomized with 52 in EFV group, 51 in RAL 400 mg group, and 52 in RAL 800 mg group	RAL 400 mg or 800 mg twice daily + TDF 245 mg once daily + 3TC 300 mg once daily	EFV 600 mg once daily + TDF 245 mg once daily + 3TC 300 mg once daily (or two half-doses twice daily depending on study site)	48 weeks
Lennox et al., 2009[42] Lennox et al., 2010[44] DeJesus et al., 2012[43] Rockstroh et al., 2011[46] Rockstroh et al., 2013[45] 67 sites on 5 continents, including North America (U.S.) NCT00369941 STARTMRK Moderate	• Adults (≥ 18 years of age) • Viral load at entry > 5,000 copies/mL • Total N = 566 randomized with 262 in RAL group and 284 in EFV group	RAL 400 mg twice daily + (TDF or TAF)/FTC 300/200 mg single tablet once daily	EFV 600 mg once daily + (TDF or TAF)/FTC 300/200 mg single tablet once daily	96 weeks (follow-up through 240 weeks)
Markowitz et al., 2007[41] Markowitz et al., 2009[48] Gotuzzo et al., 2012[47] 29 sites in the U.S., Canada, Latin America, Thailand, and Australia NCT00100048 Protocol 004 High	• Adults (≥ 18 years of age) • Viral load at entry ≥ 5,000 copies/mL • Total N = 201 randomized with 41 in RAL 100 mg group, 40 in RAL 200 mg group, 41 in RAL 400 mg group, 40 in RAL 600 mg group, and 39 in EFV 600 mg group	RAL 100 mg, 200 mg, 400 mg, or 600 mg twice daily + (TAF or TDF) 300 mg once daily + 3TC 300 mg once daily	EFV 600 mg once daily + (TAF or TDF) 300 mg once daily + 3TC 300 mg once daily	240 weeks

Abbreviations. 3TC: lamivudine; EFV: efavirenz; FTC: emtricitabine; NCT: national clinical trial; RAL: raltegravir; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate.

Viral Suppression

Studies were mixed in terms of the effects of RAL and EFV on viral suppression. However, RAL was generally considered noninferior to EFV. In Grinzstejn et al.[40] and Lennox et al.,[42] a greater percentage of RAL-treated participants achieved viral suppression at weeks 48 (RAL 400 mg, 76.0% to 86.1% vs. EFV, 67.0% to 81.9%), 96 (RAL 400 mg, 81.0% vs. EFV 600 mg, 79.0%), and 156 (RAL 400 mg, 75.4% vs. EFV, 68.1%) than EFV-treated participants. However, the differences between groups were not statistically significant for these time points (this trend was not seen for RAL 800 mg).[40,42-46] Nevertheless, a statistically significant greater percentage of RAL 400 mg-treated participants achieved viral suppression at weeks 192 (76.0% vs. 67.0%, treatment difference, 9.0%; 95% CI, 2.0 to 16.0) and 240 (71.0% vs. 61.3%, treatment difference, 9.5%; 95% CI, 1.7 to 17.3) compared to EFV-treated participants.[42-46] Despite this finding, Markowitz et al. observed no significant difference between RAL-treated and EFV-treated participants in terms of achieving viral suppression at weeks 48 (85.6% vs. 86.8%, treatment difference, -1.2%; 95% CI, -11.2 to 13.7), 96 (83.1% vs. 84.2%, treatment difference, -1.1%; 95% CI, -12.0 to 14.5), and 240 (68.8% vs. 63.2%).[41,47,48]

Adherence

Studies were also mixed in terms of adherence to study medications in RAL-treated and EFV-treated participants, although adherence was generally high in all groups. Grinsztejn et al.[40] found that more EFV-treated participants self-reported adherence at week 24 (RAL 400 mg, 87.0%; RAL 800 mg, 84.0% vs. EFV, 95.0%) and week 48 (RAL 400 mg, 92.0%; RAL 800 mg, 79.0% vs. EFV, 94.0%) than RAL-treated participants. However, Lennox et al.[42-46] found no difference between RAL 400 mg and EFV groups in adherence to study medication (≥ 90% of the days during the study) through week 96 (98.0% vs. 97.0%).

Drug Resistance

Studies were also mixed in terms of the effect of RAL or EFV on development of drug resistance. Percentages of participants developing drug resistance varied widely across studies. There were largely no differences between RAL-treated and EFV-treated participants in terms of the percentage of participants who developed resistance at weeks 48 (RAL, 1.4% to 10.0%; EFV, 1.1% to 12.0%), 96 (2.5% vs. 5.3%), 192 (13.2% vs. 16.4%), and 240 (2.5% vs. 7.9%).[40-48]

Adverse Events and Withdrawals Due to Adverse Events

There were no differences between RAL-treated and EFV-treated participants in terms of occurrences of SAEs or withdrawals due to adverse events at weeks 48, 96, 156, and 240 (Appendix B Table B2).[40-48] There were few reported occurrences of kidney injury, hepatotoxicity, and cardiovascular disorders, and there were no differences between RAL-treated and EFV-treated participants in the number or occurrences across all 3 studies (Appendix B Table B2).[40-48]

Table 24. Summary of Findings (GRADE) for Raltegravir vs. Efavirenz

Outcome	Quality of the Evidence	Relationship	Rationale
Viral Suppression (HIV-1 RNA < 50 copies/mL) (3 RCTs in 922 participants[40-48])	⊕⊕◯◯ LOW	RAL was noninferior to EFV over 156 weeks and the difference between them was not statistically significant. RAL led to statistically more people with virologic suppression at weeks 192 and 240 than EFV.	Downgraded 1 level for risk of bias and 1 level for indirectness
Drug Resistance (3 RCTs in 922 participants[40-48])	⊕⊕◯◯ LOW	No difference between groups	Downgraded 1 level for risk of bias and 1 level for indirectness
Adherence (2 RCTs in 721 participants[40,42-46])	⊕◯◯◯ VERY LOW	No difference between group	Downgraded 1 levels for risk of bias, 1 level for indirectness, and 1 level for inconsistency
Serious Adverse Events (3 RCTs in 922 participants[40-48])	⊕◯◯◯ VERY LOW	No difference between groups	Downgraded 1 level for risk of bias, 1 level for indirectness, and 1 level for inconsistency
Kidney Injury (Increased serum creatinine) (3 RCTs in 922 participants[40-48])	⊕◯◯◯ VERY LOW	No difference between groups	Downgraded 1 level for risk of bias, 1 level for indirectness, and 1 level for inconsistency

Abbreviations. EFV: efavirenz; HIV-1: human immunodeficiency virus type 1; RAL: raltegravir; RCT: randomized controlled trial; RNA: ribonucleic acid.

Rilpivirine (RPV) vs. Efavirenz (EFV)

Study Characteristics

We identified 3 RCTs (in 4 publications) that compared 3-drug regimens including RPV and EFV (Table 25 and Appendix B Table B1).[49-52] We assessed 2 RCTs[50,51] as having a moderate risk of bias because of author conflicts of interest and funding by industry, and 1 RCT[49,52] as having a high risk of bias because of the aforementioned reasons as well as an unclear allocation concealment method and unclear use of intention-to-treat analysis. Each trial included adults (≥ 18 years of age) with moderate to high viremia at study entry (> 2,500 copies/mL), representing potentially higher risk of disease progression.[22,49-52] Each study compared RPV 25 mg versus EFV 600 mg in single tablet regimens or co-administered with NRTI/NRTI backbone medications, and each trials was 96 weeks in duration.[22] GRADE quality of evidence ratings for the outcomes reported in these studies were assessed as low quality. Additional detail and rationale for these ratings are in Table 26. These studies did not report the following outcomes: AIDS-defining illness, persistence, and drug-drug interactions. Additional details pertaining to the outcomes reported in these studies are in Appendix B Table B2.

Table 25. Summary Table of Included RCTs of Add-on Therapies RPV and EFV

Citation Location NCT Number Trial Name Risk of Bias	Patient Characteristics	Intervention	Comparator(s)	Trial Duration
Cohen et al., 2011[50] 98 sites in 21 countries, including the U.S. NCT00543725 THRIVE Moderate	• Adults (≥ 18 years of age) • Viral load at entry ≥ 5,000 copies/mL • Total N = 680 randomized with 340 in each treatment group	RPV 25 mg + ABC/3TC or TDF/FTC once daily (Dosages of backbone drugs not specified) (Zidovudine/lamivudine, ZDV/3TC, not included in scope of DERP report)	EFV 600 mg + ABC/3TC or TDF/FTC once daily (Dosages of backbone drugs not specified) (Zidovudine/lamivudine, ZDV/3TC, not included in scope of DERP report)	96 weeks
Cohen et al., 2014[49] Wilkins et al., 2016[52] Multicenter, international GS-US-264–0110 STaR High	• Adults (≥ 18 years of age) • Viral load at entry > 2,500 copies/mL • Total N = 799 randomized with 400 in RPV group and 399 in EFV group	RPV/TDF/FTC 25/300/200 mg single tablet regimen once daily	EFV/TDF/FTC 600/300/200 mg single tablet regimen once daily	96 weeks
Molina et al., 2011[51] 112 sites in 21 countries, including the U.S. NCT00540449 ECHO Moderate	• Adults (≥ 18 years of age) • Viral load at entry ≥ 5,000 copies/mL • Total N = 694 randomized with 346 in RPV group and 348 in EFV group	RPV 25 mg + TDF/FTC 300/200 mg FDC, once daily	EFV 600 mg + TDF/FTC 300/200 mg FDC, once daily	96 weeks

Abbreviations. 3TC: lamivudine; ABC: abacavir; EFV: efavirenz; FDC: fixed-dose combination; FTC: emtricitabine; NCT: national clinical trial; RPV: rilpivirine; TDF: tenofovir disoproxil fumarate; ZDV: zidovudine.

Viral Suppression

Across all 3 RCTs, viral suppression was high in the RPV and EFV groups. RPV was considered noninferior to EFV and found to be not significantly different at week 48 (range, 82.0% to 86.0%; Appendix B Table B2).[49-52]

Adherence

Across all 3 RCTs, adherence to study medications, as measured by the Modified Medication Adherence Self-Report Inventory, was high in both treatment groups (≥ 95 adherence: RPV,

86.0% to 89.0% vs. EFV, 87.0% to 90.0%).[50,51] However, there were no differences between treatment groups.[50,51] One RCT found self-reported adherence (Medication Adherence Self-Report Inventory) to be consistent with adherence based on returned study medications through week 48 (self-report: 97.0% to 99.0% in both groups; returned medications: 97.0% RPV vs. 96.0% EFV).[49,52]

Drug Resistance

Generally, few participants in either treatment group experienced virologic failure at week 48 (RPV, 5.0% to 8.0% vs. EFV, 2.0% to 6.0%).[49,50,52] Of those who did experience virologic failure, a greater percentage of RPV-treated participants developed resistance mutations to study medication compared to EFV-treated participants through week 48 (4.0% vs. 1.0%).[49,50,52] In contrast, 1 RCT reported a much higher percentage of participants in both treatment groups experiencing virologic failure with resistance to any NRTI or NNRTI (RPV, 73.0% vs. EFV, 62.0%).[51]

Adverse Events and Withdrawals Due to Adverse Events

Across all 3 RCTs, there were few occurrences of SAEs and no significant differences between treatment groups (RPV, 7.0% vs. EFV, 7.0% to 9.0%).[49-52] However, fewer RPV-treated participants experienced withdrawals due to adverse events compared to EFV-treated participants (RPV, 2.0% to 4.0% vs. EFV, 7.0% to 8.7%),[49-52] and this difference was statistically significant in 1 RCT (2.5% vs. 8.7%; $P < .001$).[49,52] In terms of kidney injury, 2 RCTs found small increases from baseline in mean serum creatinine at the first on-treatment assessment, with stabilization at 48 weeks in participants treated with RPV (range 4.11 to 7.16 µmol/L;[50] 5.69 to 9.07 µmol/L[51]); however, mean serum creatinine in participants treated with EFV remained relatively stable over time. There were no differences between treatment groups in terms of hepatic toxicity-related measures (Appendix B Table B2).[49-52]

Table 26. Summary of Findings (GRADE) for Rilpivirine vs. Efavirenz

Outcome	Quality of the Evidence	Relationship	Rationale
Viral Suppression (HIV-1 RNA < 50 copies/mL) (3 RCTs in 2,173 participants[49-52])	⊕⊕◯◯ LOW	RPV was noninferior to EFV and the difference between them was not statistically significant.	Downgraded 1 level for risk of bias and 1 level for indirectness
Drug Resistance (3 RCTs in 2,173 participants[49-52])	⊕⊕◯◯ LOW	A greater percentage of RPV patients experienced virologic failure and resistance to study drugs than EFV patients.	Downgraded 1 level for risk of bias and 1 level for indirectness
Adherence (3 RCTs in 2,173 participants[49-52])	⊕⊕◯◯ LOW	No difference between groups	Downgraded 1 level for risk of bias and 1 level for indirectness
Serious Adverse Events (3 RCTs in 2,173 participants[49-52])	⊕⊕◯◯ LOW	No difference between groups	Downgraded 1 level for risk of bias and 1 level for indirectness

Kidney Injury (Increased serum creatinine) (2 RCTs in 1,374 patients[50,51])	⊕⊕◯◯ LOW	Small increase in RPV group, no change over time in EFV group	Downgraded 1 level for risk of bias and 1 level for indirectness

Abbreviations. EFV: efavirenz; HIV-1: human immunodeficiency virus type 1; RCT: randomized controlled trial; RNA: ribonucleic acid; RPV: rilpivirine.

Key Question 5: Effectiveness and Harms in Subgroups of Comorbid Conditions

We identified 1 publication[53] which reported findings from a pooled analysis of 2 RCTs (ECHO[50] and THRIVE[51]) pertaining to efficacy and safety of RPV 25 mg versus EFV 600 mg, each co-administered with a NRTI/NRTI backbone combination once daily, in patients with HIV-1 and co-morbid HBV or HCV. We also identified 1 RCT[40] which reported findings pertaining to the efficacy and safety of RAL 400 mg or 800 mg twice daily versus EFV 600 mg once daily, each co-administered with TDF/3TC in patients co-infected with tuberculosis. Study characteristics and findings are located in Table 27 and Table 28, respectively.

Table 27. Study Characteristics: Initial HIV-1 Regimens in Individuals with Comorbid Conditions

Citation Location NCT Number Trial Name	Patient Characteristics	Intervention(s)	Comparator(s)	Time Period of Analysis
Tuberculosis Coinfection				
Grinsztejn et al., 2014[40] NCT00822315 ANRS 12180 Reflate TB	• Adults (≥ 18 years of age) • Viral load at entry > 1,000 copies/mL • Total N = 155 randomized with 52 in EFV group, 51 in RAL 400 mg group, and 52 in RAL 800 mg group	RAL 400 mg or 800 mg twice daily + TDF 245 mg once daily + 3TC 300 mg once daily	EFV 600 mg once daily + TDF 245 mg once daily + 3TC 300 mg once daily (or two half-doses twice daily depending on study site)	48 weeks
HBV/HCV Coinfection				
Nelson et al., 2012[53] NCT00540449 and NCT00543725 ECHO[51] and THRIVE[50]	• Adults (≥ 18 years of age) • Viral load at entry ≥ 5,000 copies/mL • Total N = 694 randomized with 346 in RPV group and 348 in EFV group	RPV 25 mg + TDF/FTC or ABC/3TC FDC, once daily	EFV 600 mg + TDF/FTC or ABC/3TC FDC, once daily	48 weeks (pooled analysis)

Abbreviations. 3TC: lamivudine; ABC: abacavir; EFV: efavirenz; FDC: fixed-dose combination; FTC: emtricitabine; NCT: national clinical trial; RAL: raltegravir; RPV: rilpivirine; TDF: tenofovir disoproxil fumarate.

Table 28. Findings: Initial HIV-1 Regimens in Individuals with Comorbid Conditions

Citation Location NCT Number Trial Name	Efficacy	Harms
Tuberculosis Coinfection		
Grinsztejn et al., 2014[40] NCT00822315 ANRS 12180 Reflate TB	RAL vs. EFV • Greater viral suppression in RAL-treated participants than EFV-treated participants at week 24 (76% to 78% vs. 63%), but not at week 48 (63% to 76% vs. 67%) • No difference between groups in self-reported adherence to study drugs • No difference between groups in resistance to ART	RAL vs. EFV • No difference between groups in SAEs (33% to 37% across groups) or withdrawals due to adverse events (6.0% in both groups) • Few occurrences of kidney injury, hepatotoxicity, and cardiovascular events, with no differences between treatment groups
HBV/HCV Coinfection		
Nelson et al., 2012[53] NCT00540449 and NCT00543725 ECHO[51] and THRIVE[50]	• A higher percentage of patients achieved viral suppression in the subgroup without HBV/HCV coinfection (RPV, 85.0%; EFV, 82.6%) than in the coinfected subgroup (RPV, 73.5%; EFV, 79.4%) (RPV: $P = 0.04$; EFV: $P = 0.49$, Fisher's exact test).	• Occurrence of hepatic adverse events was low in both groups in the overall population (RPV, 5.5% vs. EFV, 6.6%) and was higher in HBV/HCV-coinfected patients than in those not coinfected (26.7% vs. 4.1%, respectively).

Abbreviations. ART: antiretroviral therapy; EFV: efavirenz; HBV: hepatitis B virus; HCV: hepatitis C virus; NCT: national clinical trial; RAL: raltegravir; RPV: rilpivirine; SAEs: serious adverse events.

Discussion

This focused update of a previous DERP report included 21 RCTs (in 37 publications) evaluating the comparisons displayed in Table 29 for HIV-1. Of the 21 RCTs, we rated none as having a low risk of bias. Instead we determined that all had a moderate or high risk of bias, which reduces our confidence in the findings. Further, in general the studies were designed to test whether one drug was noninferior to another, as opposed to whether they were statistically significantly different from one another for various HIV-related outcomes. In general, the treatments included in this report were noninferior to the drug to which they were being compared. Of note, 3-drug regimens that included the backbone ABC/3TC were found to be noninferior and statistically significantly more effective in achieving viral suppression compared to 3-drug regimens that included TDF/FTC. Similarly, among the comparisons of add-on therapies, RAL was found to be noninferior to EFV and led to statistically significantly more participants achieving viral suppression at long-term follow-up (192 and 240 weeks) compared to EFV participants. Adherence and persistence were generally high across treatment groups, when reported. Finally, there were few occurrences of drug resistance, serious and specific adverse events, and withdrawals due to adverse events, with largely no differences between treatment groups. We rated the quality of the body of evidence for the selected outcomes as very low to moderate with the majority being very low or low.

Table 29. Comparisons Evaluated in this Update Report

Comparisons	Number of RCTs	Risk of Bias
Backbone Therapies		
3TC vs. TDF/FTC[a]	1 RCT	Moderate
TAF/FTC vs. TDF/FTC	3 RCTs (in 4 publications)	Moderate to High
TAF/FTC vs. ABC/3TC	1 RCT (in 3 publications)	Moderate
TDF/FTC vs. ABC/3TC	1 RCT (in 2 publications)	Moderate
TDF/3TC vs. TDF/FTC	1 RCT	High
Add-on Therapies		
BIC vs. DTG	2 RCTs (in 3 publications)	Moderate to High
DTG vs. RAL	1 RCT (in 2 publications)	Moderate
DRV/r vs. DOR	1 RCT	Moderate
DRV/r vs. RAL	1 RCT	High
DTG vs. EFV	2 RCTs (in 3 publications)	High
RAL vs. EFV	3 RCTs (in 9 publications)	Moderate to High
RPV vs. EFV	3 RCTs (in 4 publications)	Moderate to High

Abbreviations. 3TC: lamivudine; ABC: abacavir; BIC: bictegravir; DRV; darunavir; DOR: doravirine; DTG: dolutegravir; EFV: efavirenz; FTC: emtricitabine; r: ritonavir; RAL: raltegravir; RCT: randomized controlled trial; RPV: rilpivirine; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate. Notes. [a] Denotes a 2-drug vs. 3-drug regimen comparison. All other comparisons were of 3-drug vs. 3-drug regimens.

The findings of this update report should be interpreted with some degree of caution due to the level of the risk of bias of the included studies. One consideration is the lack of generalizability of the study populations. The majority of participants in most studies identified as White males, with few studies including participants of other genders, races, and ethnicities. Few studies reported the percentage of participants with specific HIV risk factors, including MSM, transgender individuals, and people who inject drugs. This may lead to underrepresentation of severe adverse effects such as HIVAN, which disproportionately affects Black individuals.[5]

Additionally, no studies focused or specifically reported findings in U.S. Medicaid populations. Most of the included studies were conducted in high-resource countries consistent with the resource level found in the U.S. However, the lack of detailed information on the socioeconomic status and health insurance status of the study participants provides barriers to assessing the generalizability to Medicaid populations.

Another important consideration taken into account when determining the risk of bias ratings for the studies included in this report are issues related to funding and conflicts of interest (COI). Most of the included studies were funded by the pharmaceutical companies responsible for the production and sale of the ART regimens being tested. In some studies, the industry funder played a direct role in the design and conduct of the study as well as the analysis of the data. Furthermore, most of the study authors reported having COIs related to their involvement with industry. Finally, studies were assessed as having a high risk of bias if, in addition to the aforementioned issues, they had any of the following conditions: unbalanced participant characteristics at baseline, high or differential loss to follow-up, and unclear randomization or allocation concealment methods or blinding.

The findings of this update report differ from those of systematic reviews published elsewhere, likely because of a differing scope and type of analyses utilized. For example, in a systematic review and network meta-analysis conducted by the WHO and published in 2016, Kanters et al. found a statistically significant greater achievement of viral suppression at 48 weeks with DTG (OR, 1.87; 95% credible interval [CrI], 1.34 to 2.64) and RAL (OR, 1.40; 95% CrI, 1.02 to 1.96) compared with EFV.[54] However, the authors found that low-dose EFV was similar to other ART regimens in terms of viral suppression, which is consistent with the findings of this update report.[54]

Another 2-drug regimen, DTG + RPV (Juluca), was approved on November 21, 2017, but has not yet been included in the clinical practice guidelines reviewed in this report.[55] Future analysis is needed to assess the efficacy of this regimen compared to DTG + 3TC and 3-drug regimens.

Medicaid administrators should consider the few differences in clinical outcomes between guideline-recommended initial treatment regimens for adolescents and adults with HIV-1, including the noninferiority of 2-drug versus 3-drug regimens and newly approved therapies, such as BIC and DOR, when making coverage decisions for beneficiaries infected with HIV-1. The findings of this report indicate that Medicaid programs have flexibility in their evidence-based decision-making process, given the few differences in efficacy and harms between therapies.

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Appendix A. Clinical Evidence Methods

Search Strategy

We searched Ovid MEDLINE and the Cochrane Library to identify randomized controlled trials (RCTs) using terms for human immunodeficiency virus-1 (HIV-1) and individual study drugs. We limited searches of evidence sources to studies published in English in 2017 and later.

We searched the following Drug Effectiveness Review Project (DERP) evidence sources:

- Cochrane Library (Wiley Interscience)
- Ovid MEDLINE

Ovid MEDLINE Search Strategy

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to June 26, 2020>

Search Strategy:

1 HIV/ or Anti-HIV Agents/ or HIV-1/

2 abacavir.mp.

3 bictegravir.mp.

4 darunavir.mp.

5 dolutegravir.mp.

6 doravirine.mp.

7 efavirenz.mp.

8 emtricitabine.mp.

9 lamivudine.mp.

10 raltegravir.mp.

11 rilpivirine.mp.

12 tenofovir*.mp.

13 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12

14 1 and 13

15 limit 14 to english language

16 limit 15 to animals/

17 15 not 16

18 limit 17 to (comment or editorial or interview or letter or personal narrative)

19 17 not 18

20 limit 19 to yr="2019 -Current"

Cochrane Library Search Strategy

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <May 2020>

Search Strategy:

1 HIV/ or Anti-HIV Agents/ or HIV-1/

2 abacavir.mp.

3 bictegravir.mp.

4 darunavir.mp.

5 dolutegravir.mp.

6 doravirine.mp.

7 efavirenz.mp.

8 emtricitabine.mp.

9 lamivudine.mp.

10 raltegravir.mp.

11 rilpivirine.mp.

12 tenofovir*.mp.

13 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12

14 1 and 13

15 limit 14 to yr="2019 -Current"

Screening and Data Abstraction

One experienced researcher independently screened all titles and abstracts of the identified documents. This method was repeated for full-text review of documents that could not be excluded by title and abstract screening. One experienced researcher abstracted and entered data from eligible studies into a standardized form using Microsoft Word.

Risk of Bias of Included Studies

We assessed the risk of bias of the included RCTs using standard instruments developed and adapted by DERP that are modifications of instruments used by national and international standards for quality.[13,14] One experienced researcher independently rated the risk of bias of the

included studies. A second experienced researcher reviewed each assessment. Disagreement was managed by discussion.

Randomized Controlled Trials

Low-risk-of-bias RCTs include a clear description of the population, setting, intervention, and comparison groups; a random and concealed allocation of patients to study groups; low dropout rates; and intention-to-treat analyses. Low-risk-of-bias RCTs also have low potential for bias from conflicts of interest and funding source(s). Moderate-risk-of-bias RCTs have incomplete information about methods that might mask important limitations or a meaningful conflict of interest. High-risk-of-bias RCTs have clear flaws that could introduce significant bias.

Quality of Evidence Assessment

Overall Quality of Evidence

We assigned each outcome a summary judgment for the overall quality of evidence based on the system developed by the Grading of Recommendations, Assessment, Development, and Evaluation Working Group (GRADE).[15,16] Two independent experienced researchers assigned ratings, with disagreements resolved by a third rater. The GRADE system defines the overall quality of a body of evidence for an outcome in the following manner:

- **High:** Raters are very confident that the estimate of the effect of the intervention on the outcome lies close to the true effect. Typical sets of studies are RCTs with few or no limitations, and the estimate of the effect is likely stable.
- **Moderate:** Raters are moderately confident in the estimate of the effect of the intervention on the outcome. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is different. Typical sets of studies are RCTs with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.
- **Low:** Raters have little confidence in the estimate of the effect of the intervention on the outcome. The true effect may be substantially different from the estimate of the effect. Typical sets of studies are RCTs with serious limitations or nonrandomized studies without special strengths.
- **Very low:** Raters have no confidence in the estimate of the effect of the intervention on the outcome. The true effect is likely to be substantially different from the estimate of the effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.
- **Not applicable:** Researchers did not identify any eligible articles.

Appendix B. Full Evidence Tables

Study Characteristics

Table B1. Study Characteristics of Eligible Randomized Controlled Trials

Citation Location NCT Number Name	Study Aim Study Duration	Key Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)
Backbone Therapies					
3TC vs. TDF/FTC					
Cahn et al., 2019[17] 192 sites in 21 countries NCT02831673 and NCT02831764 GEMINI-1 and GEMINI-2	Evaluate the efficacy and safety of a 2-drug regimen compared to a 3-drug regimen 48 weeks	Inclusion: Adults (aged 18 years and older), HIV-1 infection, naïve to ART (≤ 10 days of previous ART therapy), entry viral load of 1,000 to 500,000 copies/mL. Exclusion: Individuals with pre-existing major viral resistance mutations to NRTIs, NNRTIs, or PIs; active CDC stage 3 HIV disease; HBV.	Total N = 1,441 randomized, with 719 in 2-drug regimen group (356, GEMINI-1; 360, GEMINI-2) and 722 in 3-drug regimen group (358, GEMINI-1; 359, GEMINI-2) Mean age (range): 32 years (26 to 40) 2-drug; 33 years (26 to 42) 3-drug Sex: 16% female, 2-drug; 14% female, 3-drug Ethnicity: 30% Hispanic or Latino, 2-drug; 32% Hispanic or Latino, 3-drug Race: 67% White, 2-drug; 69% White, 3-drug	2-drug regimen: dolutegravir + lamivudine (DTG + 3TC)	3-drug regimen: dolutegravir + tenofovir disoproxil fumarate + emtricitabine (DTG + TDF + FTC)

Citation Location NCT Number Name	Study Aim Study Duration	Key Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)
			HIV-1 RNA ≤ 100,000 copies/mL: 80%, 2-drug; 79%, 3-drug CD4+ cell count > 200 cells/µL: 91%, 2-drug; 92% 3-drug HIV infection category: 55% Stage 2, 2-drug; 55% Stage 2, 3-drug HCV infection: 5%, 2-drug; 7%, 3-drug		
TAF/FTC vs. TDF/FTC					
Eron et al., 2018[18] Rashbaum et al., 2019[21] 121 sites in 10 countries (including U.S.) NCT02431247 AMBER	To investigate the efficacy and safety of a single-tablet regimen of DRV/c/TAF/FTC vs. DRV/c + TDF/FTC 96 weeks	Inclusion: Adults (aged 18 years and older), HIV-1 infection, naïve to ART, entry viral load of at least 1,000 copies/mL. Exclusion: Diagnosis of new AIDs-defining condition within 30 days	Total N = 725 randomized with 362 in DRV/c/TAF/FTC group and 363 in DRV/c + TDF/FTC Mean age (range): 34 years (27 to 42) in DRV/c/TAF/FTC group; 34 years (27 to 42) in DRV/c + TDF/FTC group Sex: 12% female in DRV/c/TAF/FTC group; 11% female in DRV/c + TDF/FTC group	Darunavir/cobicistat/tenofovir alafenamide/emtricitabine (DRV/c/TAF/FTC) 800/150/10/200 mg single tablet daily	Darunavir/cobicistat (DRV/c) 800/150 mg FDC + tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) 300/200 mg FDC daily

Citation Location NCT Number Name	Study Aim Study Duration	Key Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)
		prior to screening, HBV or HCV infection, clinically significant disease (e.g., malignancy, severe infections), pregnancy or breastfeeding in women.	Ethnicity: 14% Hispanic or Latino in DRV/c/TAF/FTC group; 12% Hispanic or Latino in DRV/c + TDF/FTC group Race: 83% White in DRV/c/TAF/FTC group; 83% White in DRV/c + TDF/FTC group HIV-1 RNA ≥ 100,000 copies/mL: 17% in DRV/c/TAF/FTC group; 19% in DRV/c + TDF/FTC group CD4+ cell count < 200 cells/µL: 6% in DRV/c/TAF/FTC group; 8% in DRV/c + TDF/FTC group HIV infection category (WHO): 87% Stage 1, DRV/c/TAF/FTC group; 82% Stage 1, DRV/c + TDF/FTC group HCV infection: not reported		

Citation Location NCT Number Name	Study Aim Study Duration	Key Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)
Mills et al., 2015[19] Multicenter in U.S. NCT01565850	To evaluate the safety and efficacy of TAF as part of a single-tablet regimen compared to TDF 48 weeks	Inclusion: Adults (older than 18 years), HIV positive, treatment naïve, HIV-1 RNA ≥ 5,000 copies/mL, CD4+ cell count > 50 cells/µL, genotype sensitivity to DRV, TDF, and FTC, eGFR ≥ 70 mL/min. Exclusion: Patients who were pregnant, those with HBV, HCV, or new AIDS-defining condition within 30 days of screening.	Total N = 153 randomized with 103 in DRV/c/TAF/FTC (TAF) group and 50 in DRV + c + TDF/FTC (TDF) group Mean age (range): 31 years (25 to 42) in TAF group; 36 years (28 to 44) in TDF group Sex: 7.8% female in TAF group; 6% female in TDF group Ethnicity: 22.3% Hispanic or Latino in TAF group; 18.0% Hispanic or Latino in TDF group Race: 60.2% White in TAF group; 60.0% White in TDF group HIV-1 RNA ≥ 100,000 copies/mL: 22.3% in TAF group; 14.0% in TDF group CD4+ cell count ≤ 200 cells/mm^3: 10.7% in TAF group; 20.0% in TDF group	Darunavir/cobicistat/tenofovir alafenamide/emtricitabine (DRV/c/TAF/FTC) single tablet regimen once daily (DRV dosed at 800 mg)	Darunavir + cobicistat + tenofovir disoproxil fumarate/emtricitabine (DRV + c + TDF/FTC) in separate tablets once daily (DRV dosed in 2, 400-mg tablets)

Citation Location NCT Number Name	Study Aim Study Duration	Key Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)
			HIV infection category: not reported HCV infection: Not applicable eGFR (range): 116.0 mL/min (97.0 to 137.6) in TAF group; 109.6 mL/min (92.5 to 131.4) in TDF group		

Citation Location NCT Number Name	Study Aim Study Duration	Key Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)
Venter et al., 2019[20] South Africa NCT03122262 ADVANCE	To evaluate the efficacy and safety of 2 tenofovir prodrugs, TAF and TDF, in combination with DTG compared with EFV as standard care in low- and middle-income countries 96 weeks	Inclusion: Adolescents and adults (12 years and older), weight of 40 kg or more, HIV RNA ≥ 500 copies/mL, creatinine clearance > 60 mL/min (19 years or older) or > 80 mL/min (< 19 years of age) Exclusion: More than 30 days of treatment with any form of ART, any ART within last 6 months, pregnancy, or current TB treatment	Total N = 1,053 randomized with 351 in each group Mean age (SD): 33 years (7.8) in TAF group; 32 years (8.1) in TDF group; 32 years (7.4) in standard care group Sex: 61% female in TAF group; 59% female in TDF group; 57% female in standard care group Ethnicity (country of origin): 61% South Africa in TAF group; 64% South Africa in TDF group;62% South Africa in standard care group Race: 99% Black in TAF group; 100% Black in TDF group; 100% Black in standard care group HIV-1 RNA ≤ 100,000 copies/mL: 78% in TAF group; 80% in TDF group; 77% in standard care group	DTG 50 mg + TAF/FTC 25/200 mg as two tablets daily (TAF group) or TDF/FTC 300/200 mg as two tablets daily (TDF group)	Efavirenz/tenofovir disoproxil fumarate/emtricitabine (EFV/TDF/FTC) 600/300/200 mg as a single tablet daily (standard care group)

Citation Location NCT Number Name	Study Aim Study Duration	Key Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)
			CD4+ cell count (SD): 349 cells/mm^3 (225.3) in TAF group; 323 cells/mm3 (234.3) in TDF group; 337 cells/mm3 (221.6) in standard care group HIV infection category: not reported HCV infection: not reported		
TAF/FTC vs. ABC/3TC					

Citation Location NCT Number Name	Study Aim Study Duration	Key Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)
Gallant et al., 2017[24] Wohl et al., 2019[23] Acosta et al., 2019[25] 122 sites in 9 countries in Europe, Latin America, and North America NCT02607930	To assess the efficacy and safety of BIC/TAF/FTC co-formulated in an FDC versus co-formulated DTG/ABC/3TC 144 weeks	Inclusion: Adults (≥ 18 years old), HIV-1 infected, previously untreated, plasma HIV-1 RNA ≥ 500 copies/mL, HLA-B*5701-negative, eGFR ≥ 50 mL/min, no resistance to FTC, TAF, TDF, ABC, or 3TC. Exclusion: HBV infection.	Total N = 631 randomized with 316 in BIC/TAF/FTC group and 315 in DTG/ABC/3TC group Mean age (range): 31 years (18 to 71) in BIC/TAF/FTC group; 32 years (18 to 68) in DTG/ABC/3TC group Sex: 9% female in BIC/TAF/FTC group; 10% female in DTG/ABC/3TC group Ethnicity: 23% Hispanic or Latino in BIC/TAF/FTC group; 21% in DTG/ABC/3TC group Race: 57% White in both groups HIV-1 RNA > 100,000 copies/mL: 17% in BIC/TAF/FTC group; 16% in DTG/ABC/3TC group	Bictegravir/tenofovir alafenamide/emtricitabine (BIC/TAF/FTC) 50/25/200 mg FDC once daily	Dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) 50/600/300 mg FDC once daily

Citation Location NCT Number Name	Study Aim Study Duration	Key Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)
			CD4+ cell count ≥ 200 cells/µL: 88.5% in BIC/TAF/FTC group; 89.8% in DTG/ABC/3TC group HIV disease status: Asymptomatic: 91% in both groups Symptomatic: 5% in BIC/TAF/FTC group; 4% in DTG/ABC/3TC group AIDS: 4% in BIC/TAF/FTC group; 5% in DTG/ABC/3TC group HIV risk factors: Heterosexual sex: 19% in BIC/TAF/FTC group; 20% in DTG/ABC/3TC group Homosexual sex: 80% in BIC/TAF/FTC group; 79% in DTG/ABC/3TC group IV drug use: 2% in BIC/TAF/FTC group; 1% in DTG/ABC/3TC group HCV infection: not reported		
ABC/3TC vs. TDF/FTC					

Citation Location NCT Number Name	Study Aim Study Duration	Key Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)
Walmsley et al., 2013[26] Walmsley et al., 2015[27] Multiple sites in North America, Europe, and Australia NCT01263015 SINGLE	To compare the efficacy and safety of DTG/ABC/3TC to EFV/TDF/FTC 144 weeks (weeks 48 and 96 blinded, week 144 unblinded)	Inclusion: Adults (≥ 18 years old), HIV-1 infection, no previous ART, HIV-1 RNA ≥ 1,000 copies/mL, no resistance, HLA-B*5701 negative Exclusion: Women who were pregnant or breastfeeding, persons with moderate or severe hepatic impairment, and those with estimated creatinine clearance of < 50 mL/min.	Total N = 844 randomized with 422 in both treatment group Median age (range): 36 years (18 to 68) in ABC/3TC group; 35 years (18 to 85) in TDF/FTC group Sex: 16% in ABC/3TC group; 15% TDF/FTC group Ethnicity: 14% Hispanic or Latino in ABC/3TC group; 13% Hispanic or Latino in TDF/FTC group Race: 69% White in ABC/3TC group; 68% White in TDF/FTC group HIV-1 RNA ≤ 100,000 copies/mL: 68% in ABC/3TC group; 69% in TDF/FTC group Median CD4+ cell count: 334.5 cells/mm^3 in ABC/3TC group; 339.0 cells/mm^3 in TDF/FTC group	Dolutegravir (DTG) 50 mg + abacavir/lamivudine (ABC/3TC) + 600/300 mg in two separate tablets once daily	Efavirenz/tenofovir disoproxil fumarate/emtricitabine (EFV/TDF/FTC) 600/300/200 mg FDC once daily

Citation Location NCT Number Name	Study Aim Study Duration	Key Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)
			HIV infection category (CDC): 83% Category A in ABC/3TC group; 84% Category A in TDF/FTC group HCV infection: 7% in both groups HIV Risk Factors: Homosexual contact: 67% in ABC/3TC group; 71% in TDF/FTC group Heterosexual contact: 33% in ABC/3TC group; 27% in TDF/FTC group Injectable drug use: 5% in ABC/3TC group; 2% in TDF/FTC group		
TDF/3TC vs. TDF/FTC					
Orkin et al., 2019[28] 126 sites worldwide NCT02403674 DRIVE-AHEAD	To compare the efficacy and safety of DOR/TDF/3TC to EFV/TDF/FTC 96 weeks (data cut-off for report 48 weeks)	Inclusion: Adults (≥ 18 years old), HIV-1 infection, naïve to ART, HIV-1 RNA ≥ 1,000 copies/mL, no resistance to study drugs, creatinine	Total N = 734 randomized with 368 in DOR/TDF/3TC group and 366 in EFV/TDF/FTC group Mean age (range): 32 years (18 to 70) in DOR/TDF/3TC group; 30 years (18 to 69) in EFV/TDF/FTC group	Doravirine/tenofovir disoproxil fumarate/lamivudine (DOR/TDF/3TC) 100/300/300 mg FDC once daily	Efavirenz/tenofovir disoproxil fumarate/emtricitabine (EFV/TDF/FTC) 600/300/200 mg FDC once daily

Citation Location NCT Number Name	Study Aim Study Duration	Key Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)
		clearance ≥ 50 mL/min. Exclusion: Resistance to study drugs, creatinine clearance < 50 mL/min.	Sex: 16% female in DOR/TDF/3TC group; 15% female in EFV/TDF/FTC group Ethnicity: 35% Hispanic or Latino in DOR/TDF/3TC group; 33% Hispanic or Latino in EFV/TDF/FTC group Race: 49% White in DOR/TDF/3TC group; 47% White in EFV/TDF/FTC group HIV-1 RNA ≤ 100,000 copies/mL: 80% in DOR/TDF/3TC group; 77% in EFV/TDF/FTC group CD4+ cell count > 200 cells/µL: 88% in DOR/TDF/3TC group; 87% in EFV/TDF/FTC group HIV infection category: not reported HBV or HCV infection: 3% in DOR/TDF/3TC		

Citation Location NCT Number Name	Study Aim Study Duration	Key Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)
			group; 2% in EFV/TDF/FTC group History of AIDS: 13% in DOR/TDF/3TC group; 15% in EFV/TDF/FTC group		
Add-on Therapies					
RPV vs. EFV					
Cohen et al., 2011[50] 98 sites in 21 countries, including the U.S. NCT00543725 THRIVE	To assess the noninferiority of RPV to EFV with common background NRTIs 96 weeks	Inclusion: Adults (≥ 18 years old), naïve to ART, HIV-1 RNA ≥ 5,000 copies/mL, viral sensitivity to the background NRTIs. Exclusion: HIV-2 infection, resistance to NNRTIs, active clinically significant disease, renal impairment, pregnancy or breastfeeding.	Total N = 680 randomized with 340 in each treatment group Median age (IQR): 36 years (29 to 42) in RPV group; 36 years (29 to 43) in EFV group Sex: 26% female in RPV group; 28% female in EFV group Ethnicity: not reported Race: 61% White in RPV group; 60% White in EFV group HIV-1 RNA ≤ 100,000 copies/mL: 55% in RPV group; 49% in EFV group	Rilpivirine (RPV) 25 mg + abacavir/lamivudine (ABC/3TC) or tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) once daily (Dosages of backbone drugs not specified) (Zidovudine/lamivudine, ZDV/3TC, not included in scope of DERP report)	Efavirenz (EFV) 600 mg + abacavir/lamivudine (ABC/3TC) or tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) once daily (Dosages of backbone drugs not specified) (Zidovudine/lamivudine, ZDV/3TC, not included in scope of DERP report)

Citation Location NCT Number Name	Study Aim Study Duration	Key Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)
			Median CD4+ cell count (IQR): 263 cells/µL (177 to 342) in RPV group; 263 cells/µL (171 to 353) in EFV group HIV infection category (CDC): 70% Category A in RPV group; 69% Category A in EFV group HBV infection: 4% in both groups HCV infection: 5% in RPV group; 6% in EFV group NRTIs in background regimen: TDF/FTC: 60% in both groups ZDV/3TC: 30% in both groups ABC/3TC: 10% in both groups		
Cohen et al., 2014[49] Wilkins et al., 2016[52] Multicenter, international	To compare the efficacy, safety, and tolerability of single-tablet regimens RPV/TDF/FTC	Inclusion: Adults (≥ 18 years old), HIV-1 infected, HIV-1 RNA > 2,500 copies/mL at	Total N = 799 randomized with 400 in RPV group and 399 in EFV group Median age (IQR): 37 years (29 to 45) in RPV	Rilpivirine/tenofovir disoproxil fumarate/emtricitabine (RPV/TDF/FTC) 25/300/200 mg single tablet regimen once daily	Efavirenz/tenofovir disoproxil fumarate/emtricitabine (EFV/TDF/FTC) 600/300/200 mg single tablet regimen once daily

Citation Location NCT Number Name	Study Aim Study Duration	Key Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)
GS-US-264–0110 STaR	and EFV/TDF/FTC 96 weeks	screening, no prior use of ART, no resistance to EFV, FTC, TDF, and RPV, eGFR ≥ 50 mL/min. Exclusion: Resistance to study drugs, use of proton pump inhibitors	group vs. 35 years (28 to 45) in EFV group Sex: 7% female in both groups Ethnicity: 15% Latino in RPV group; 19% Latino in EFV group Race: 68% White in RPV group; 67% White in EFV group HIV-1 RNA ≤ 100,000 copies/mL: 66% in RPV group; 64% in EFV group Mean CD4+ cell count (SD): 396 cells/µL (180) in RPV group; 385 cells/µL (187) in EFV group HIV infection category: not reported HCV infection: not reported		
Molina et al., 2011[51]	To assess the efficacy, safety, and tolerability of RPV versus	Inclusion: Adults (≥ 18 years old), no prior ART, HIV-	Total N = 694 randomized with 346 in RPV group and 348 in EFV group	Rilpivirine (RPV) 25 mg + tenofovir disoproxil fumarate/emtricitabine	Efavirenz (EFV) 600 mg + tenofovir disoproxil fumarate/emtricitabine

Citation Location NCT Number Name	Study Aim Study Duration	Key Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)
112 sites in 21 countries, including the U.S. NCT00540449 ECHO	EFV, each combined with TDF/FTC 96 weeks	1 RNA at screening ≥ 5,000 copies/mL, viral sensitivity to TDF and FTC. Exclusion: HIV-2 infection, resistance to NNRTIs, active clinically significant disease, renal impairment, pregnancy or breastfeeding.	Median age (range): 36 years (18 to 78) in RPV group; 36 years (19 to 67) in EFV group Sex: 23% female in RPV group; 20% women in EFV group Ethnicity: not reported Race: 62% White in RPV group; 60% White in EFV group HIV-1 RNA ≤ 100,000 copies/mL: 52% in RPV group; 47% in EFV group Median CD4+ cell count (range): 240 cells/µL (1 to 888) in RPV group; 257 cells/µL (1 to 757) in EFV group HIV infection category (CDC): 72% Category A in RPV group; 70% Category A in EFV group	(TDF/FTC) 300/200 mg FDC, once daily	(TDF/FTC) 300/200 mg FDC, once daily

Citation Location NCT Number Name	Study Aim Study Duration	Key Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)
			HBV infection: 3% in RPV group; 6% in EFV group HCV infection: 2% in RPV group; 3% in EFV group		
RAL vs. EFV					
Grinsztejn et al., 2014[40] 8 sites in Brazil and France NCT00822315 ANRS 12180 Reflate TB	To explore the safety and efficacy of multiple strengths of RAL as an alternative to EFV for patients co-infected with HIV and TB 48 weeks	Inclusion: Adults (≥ 18 years old), previously untreated HIV-1 infection or had been treated with Art for less than 34 months, HIV RNA > 1,000 copies/mL, receiving rifampicin-based treatment for pulmonary or extra-pulmonary TB for 2 to 8 weeks, no mutations to tenofovir or lamivudine.	Total N = 155 randomized with 52 in EFV group, 51 in RAL 400 mg group, and 52 in RAL 800 mg group Median age (IQR): 35 years (29 to 45) in EFV group; 37 years (31 to 44) in RAL 400 mg group; 38 years (33 to 43) in RAL 800 mg group Sex: 24% female in EFV group; 31% female in RAL 400 mg group; 25% female in RAL 800 mg group Ethnicity: not reported Race: 41% White in EFV group; 41% White in RAL 400 mg group; 14%	Raltegravir (RAL) 400 mg or 800 mg twice daily + tenofovir disoproxil fumarate (TDF) 245 mg once daily + lamivudine (3TC) 300 mg once daily	Efavirenz (EFV) 600 mg once daily + tenofovir disoproxil fumarate (TDF) 245 mg once daily + lamivudine (3TC) 300 mg once daily (or two half-doses twice daily depending on study site)

Citation Location NCT Number Name	Study Aim Study Duration	Key Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)
		Exclusion: Women who were pregnant or breastfeeding, refused contraception, or individuals with HIV-2 infection.	White in RAL 800 mg group HIV-1 RNA ≥ 100,000 copies/mL: 51% in EFV group; 39% in RAL 400 mg group; 47% in RAL 800 mg group Median CD4+ cell count (IQR): 129 cells/µL (45 to 308) in EFV group; 115 cells/µL (50 to 213) in RAL 400 mg group; 166 cells/µL (80 to 367) in RAL 800 mg group HIV infection category: not reported HBV or HCV infection: 4% in EFV group; 16% in RAL 400 mg group; 12% in RAL 800 mg group		
Lennox et al., 2009[42] Lennox et al., 2010[44] DeJesus et al., 2012[43] Rockstroh et al., 2011[46]	To compare the safety and efficacy of RAL with EFV as part of combination ART 96 weeks (follow-up	Inclusion: Adults (≥ 18 years old), no prior ART, HIV RNA > 5,000 copies/mL Exclusion: Patients with	Total N = 566 randomized with 262 in RAL group and 284 in EFV group Median age (IQR): 37 years (32 to 43) in RAL group; 36 years (30 to 42) in EFV group	Raltegravir (RAL) 400 mg twice daily + tenofovir (TDF or TAF not specified)/emtricitabine (FTC) 300/200 mg single tablet once daily	Efavirenz (EFV) 600 mg once daily + tenofovir (TDF or TAF not specified)/emtricitabine (FTC) 300/200 mg single tablet once daily

Citation Location NCT Number Name	Study Aim Study Duration	Key Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)
Rockstroh et al., 2013[45] 67 sites on 5 continents, including North America (U.S.) NCT00369941 STARTMRK	through 240 weeks)	acute or decompensated chronic hepatitis, renal insufficiency, or medical disorder that could impact study participation.	Sex: 19% female in RAL group; 18% female in EFV group Ethnicity: 21% Hispanic in RAL group; 24 Hispanic in EFV group Race: 41% White in RAL group; 44% White in EFV group History of AIDS: 14% in RAL group; 15% in RFV group HIV-1 RNA ≤ 100,000 copies/mL: 45% in RAL group; 49% in EFV group CD4+ cell count > 200 cells/µL: 53% in RAL group; 51% in EFV group HIV infection category: not reported HBV or HCV infection: 6% in both groups		

Citation Location NCT Number Name	Study Aim Study Duration	Key Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)
Markowitz et al., 2007[41] Markowitz et al., 2009[48] Gotuzzo et al., 2012[47] 29 sites in the U.S., Canada, Latin America, Thailand, and Australia NCT00100048 Protocol 004	To explore the ART activity and safety of RAL compared with EFV 240 weeks	Inclusion: Adults (≥ 18 years old), HIV-1 infected, HIV-1 RNA ≥ 5,000 copies/mL, CD4+ cell count ≥ 100 cells/mm^3 Exclusion: Prior ART for more than 7 days, resistance to tenofovir, lamivudine, and/or efavirenz	Total N = 201 randomized with 41 in RAL 100 mg group, 40 in RAL 200 mg group, 41 in RAL 400 mg group, 40 in RAL 600 mg group, and 39 in EFV 600 mg group Mean age (range): 35 years (19 to 68) in RAL 100 mg group; 31 years (21 to 57) in RAL 200 mg group; 35 years (19 to 55) in RAL 400 mg group; 37 years (20 to 49) in RAL 600 mg group; 35 years (22 to 54) in EFV 600 mg group Sex: 15.4% female in RAL 100 mg group; 27.5% female in RAL 200 mg group; 9.8% female in RAL 400 mg group; 27.5% female in RAL 600 mg group; 23.7% in EFV 600 mg group Ethnicity: not reported Race: 82.1% non-White in RAL 100 mg group; 65.0% non-White in RAL 200 mg group; 65.9%	Raltegravir (RAL) 100 mg, 200 mg, 400 mg, or 600 mg twice daily + tenofovir (TAF or TDF not specified) 300 mg once daily + lamivudine (3TC) 300 mg once daily	Efavirenz (EFV) 600 mg once daily + tenofovir (TAF or TDF not specified) 300 mg once daily + lamivudine (3TC) 300 mg once daily

Citation Location NCT Number Name	Study Aim Study Duration	Key Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)
			non-White in RAL 400 mg group; 65.0% non-White in RAL 600 mg group; 68.4% non-White in EFV 600 mg group HIV-1 RNA > 100,000 copies/mL: 33.3% in RAL 100 mg group; 30.0% in RAL 200 mg group; 29.2% in RAL 400 mg group; 40.0% in RAL 600 mg group; 36.8% in EFV 600 mg group Mean CD4+ cell count (SD): 314 cells/mm^3 (171) in RAL 100 mg group; 296 cells/mm^3 (149) in RAL 200 mg group; 338 cells/mm^3 (191) in RAL 400 mg group; 271 cells/mm^3 (156) in RAL 600 mg group; 280 cells/mm^3 in EFV 600 mg group HIV infection category: not reported History of AIDS: 33.3% in RAL 100 mg group; 32.5% in RAL 200 mg group; 29.3% in RAL 400		

Citation Location NCT Number Name	Study Aim Study Duration	Key Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)
			mg group; 42.5% in RAL 600 mg group; 36.8% in EFV 600 mg group HCV infection: not reported		
DTG vs. EFV					
Kouanfack et al., 2019[37] 3 sites in Cameroon NCT02777229 NAMSAL ANRS 12313	To evaluate DTG-based and low-dose EFV-based ART combinations in resource-limited settings 48 weeks	Inclusion: Adults (≥ 18 years old), no prior ART, HIV-1 group M infection with HIV RNA ≥ 1,000 copies/mL. Exclusion: Pregnancy, breastfeeding, severe hepatic impairment, renal failure, severe psychiatric illness, and unstable TB coinfection.	Total N = 616 randomized with 310 in DTG group and 306 in EFV group Median age (IQR): 38 years (31 to 46) in DTG group; 36 years (29 to 43) in EFV group Sex: 63.5% female in DTG group; 68.3% female in EFV group Ethnicity: not reported Race: not reported HIV-1 RNA ≥ 100,000 copies/mL: 66.8% in DTG group; 66.0% in EFV group Median CD4+ cell count (IQR): 289 cells/mm^3 in	Dolutegravir (DTG) + tenofovir disoproxil fumarate/lamivudine (TDF/3TC)	Low-dose efavirenz (EFV) 400 mg + tenofovir disoproxil fumarate/lamivudine (TDF/3TC)

Citation Location NCT Number Name	Study Aim Study Duration	Key Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)
			DTG group; 271 cells/mm^3 in EFV group HIV infection category (WHO stage): 57.9% Stage 1 in DTG group; 60.7% Stage 1 in EFV group HBV infection (positive for surface antigen): 8.1% in DTG group; 11.2% in EFV group		
Van Lunzen et al., 2012[38] Stellbrink et al., 2013[39] 34 sites in France, Germany, Italy, Russia, Spain, and the U.S. NCT00951015 SPRING-1	To assess the efficacy and safety of 3 doses of DTG and a standard EFV-based regimen. 96 weeks	Inclusion: Adults (≥ 18 years old), HIV-1 positive, HIV RNA ≥ 1,000 copies/mL, and CD4 cell count ≥ 200 cells/µL at screening. Exclusion: Prior ART (> 10 days), resistance to ART, pregnancy, active CDC-defined category c disease, recent	Total N = 208 randomized with 53 in DTG 10 mg group, 51 in DTG 25 mg group, 51 in DTG 50 mg group, and 50 in EFV group Median age (range): 32 years (21 to 61) in DTG 10 mg group; 38 years (20 to 64) in DTG 25 mg group; 37 years (22 to 55) in DTG 50 mg group; 40 years (20 to 79) in EFV group Sex: 21% female in DTG 10 mg group; 10% female in DTG 25 mg group; 12% in DTG 50	Dolutegravir (DTG) 10 mg, 25 mg, or 50 mg + tenofovir (TAF or TDF not specified)/emtricitabine (FTC) or abacavir (ABC)/lamivudine (3TC)	Efavirenz (EFV) 600 mg + tenofovir (TAF or TDF not specified)/emtricitabine (FTC) or abacavir (ABC)/lamivudine (3TC)

Citation Location NCT Number Name	Study Aim Study Duration	Key Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)
		pancreatitis, or hepatitis.	mg group; 12% in EFV group Ethnicity: not reported Race: 77% White in DTG 10 mg group; 82% White in DTG 25 mg group; 75% White in DTG 50 mg group; 86% White in EFV group HIV-1 RNA > 100,000 copies/mL: 21% in DTG 10 mg group; 20% in DTG 25 mg group; 24% in DTG 50 mg group; 22% in EFV group Median CD4+ cell count: 289 in DTG 10 mg group; 330 in DTG 25 mg group; 305 in DTG 50 mg group; 308 in EFV group HIV infection category (CDC): 100% Category A or B in DTG 10 mg group; 98% Category A or B in DTG 25 mg group; 100% Category A or B in DTG 50 mg		

Citation Location NCT Number Name	Study Aim Study Duration	Key Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)
			group; 98% Category A or B in EFV group HCV infection: not reported Background NRTI selection: 67% to 68% of participants received tenofovir/ Emtricitabine; 32% to 33% received abacavir/lamivudine		
DRV/r vs. RAL					
Lennox et al., 2014[36] 57 sites in the U.S. and Puerto Rico NCT00811954 ACTG A5257	To assess the efficacy and tolerability of DRV/r versus RAL. 96 weeks	Inclusion: Adults infected with HIV-1, HIV RNA > 1,000 copies/mL, fewer than 10 days of ART, absence of resistance to NRTIs and PIs Exclusion: Greater than 10 days of prior ART, presence of resistance mutations	Total N = 1,204 randomized with 601 in DRV/r group and 603 in RAL group Median age: 37 years in DRV/r group, 36 years in RAL group Sex: 23.8% female in DRV/r group, 24.5% female in RAL group Ethnicity: 25% Hispanic in DRV/r group, 19.4% Hispanic in RAL group	Darunavir/ritonavir (DRV/r) 800/100 mg once daily + tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) 300/200 mg once daily	Raltegravir (RAL) 400 mg twice daily + tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) 300/200 mg once daily

Citation Location NCT Number Name	Study Aim Study Duration	Key Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)
			Race: 32% White in DRV/r group; 35.2% White in RAL group HIV-1 RNA < 100,000 copies/mL: 72.2% in DRV/r group; 68.0% in RAL group Median CD4+ cell count: 0.310 x 10^9 cells/L in DRV/r group; 0.304 x 10^9 cells/L in RAL group HIV infection category: not reported HBV antibody positive: 3.0% in DRV/r group; 2.7% in RAL group HCV infection: 7.5% in DRV/r group; 8.1% in RAL group Mode of transmission: Male same-sex sexual contact: 53.7% in both groups Heterosexual contact: 33.1% in DRV/r group; 31.5% in RAL group		

Citation Location NCT Number Name	Study Aim Study Duration	Key Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)
			Injection drug use: 1.2% in DRV/r group; 2.5% in RAL group Transfusion/occupational exposure: 1.0% in DRV/r group; 1.5% in RAL group		
DRV/v vs. DOR					
Molina et al., 2018[34] Molina et al., 2020[35] 125 sites in 15 countries, including U.S. NCT02275780 DRIVE-FORWARD	To compare DRV/r to DOR in treatment naïve HIV-1 adults 96 weeks	Inclusion: Adults (≥ 18 years old), HIV-1 infected, ART naïve, HIV RNA ≥ 1,000 copies/mL, liver enzyme levels within 5 times ULN Exclusion: not reported	Total N = 769 randomized with 384 in DRV/r group and 385 in DOR group Median age (IQR): 34.0 years (27 to 43) in DRV/r group; 33.0 years (27 to 41) in DOR group Sex: 15% female in DRV/r group; 17% female in DOR group Ethnicity: 22% Hispanic or Latino in DRV/r group; 24% Hispanic or Latino in DOR group Race: 73% White in both groups HIV-1 RNA ≤ 100,000 copies/mL: 80% in	Darunavir/ritonavir (DRV/r) 800/100 mg + tenofovir (TAF or TDF not specified)/emtricitabine (FTC) 300/200 mg or abacavir/lamivudine (ABC/3TC) 600/300 mg once daily	Doravirine (DOR) 100 mg + tenofovir (TAF or TDF not specified)/emtricitabine (FTC) 300/200 mg or abacavir/lamivudine (ABC/3TC) 600/300 mg once daily

Citation Location NCT Number Name	Study Aim Study Duration	Key Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)
			DRV/r group; 78% in DOR group Median CD4+ cell count (IQR): 393 cells/µL (257 to 547) in DRV/r group; 410 cells/µL (299 to 550) in DOR group HIV infection category: not reported HBV or HCV positive: 5% in DRV/r group; 3% in DOR group Previous AIDS diagnosis: 10% in DRV/r group; 9% in DOR group NRTI component: Tenofovir/emtricitabine: 87% in both groups Abacavir/lamivudine: 13% in both groups		
DTG vs. RAL					
Raffi et al., 2013a[32] Raffi et al., 2013b[33] 100 sites in Canada, U.S.,	To compare DTG to RAL as initial treatment for adults with HIV-1 96 weeks	Inclusion: Adults (≥ 18 years old), HIV-1 positive, HIV RNA ≥ 1,000 copies/mL, no ART resistance	Total N = 827 randomized with 411 in both treatment groups Median age (IQR): 37 years (18 to 68) in DTG	Dolutegravir (DTG) 50 mg once daily + tenofovir (TAF or TDF not specified)/emtricitabine (FTC) or abacavir (ABC)/lamivudine (3TC)	Raltegravir (RAL) 400 mg twice daily + tenofovir (TAF or TDF not specified)/emtricitabine (FTC) or abacavir (ABC)/lamivudine (3TC) *Dosages of backbones not specified

Citation Location NCT Number Name	Study Aim Study Duration	Key Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)
Australia, and Europe NCT01227824 SPRING-2		Exclusion: CDC HIV Category C disease, pregnancy, moderate to severe hepatic impairment, anticipated need for HCV treatment	group; 35 years (18 to 75) in RAL group Sex: 15% female in DTG group; 14% female in RAL group Ethnicity: not reported Race: 84% White in DTG group; 86% White in RAL group HIV-1 RNA > 100,000 copies/mL: 28% in both groups Median CD4+ cell count (IQR): 359 cells/µL (276 to 470) in DTG group; 362 cells/µL (267 to 469) in RAL group HIV infection category: not reported HBV infection: 2% in both groups HCV infection: 10% in DTG group; 9% in RAL group	*Dosages of backbones not specified	

Citation Location NCT Number Name	Study Aim Study Duration	Key Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)
			Dual NRTI assignment: Tenofovir/emtricitabine: 59% in DTG group; 60% in RAL group Abacavir/lamivudine: 41% in DTG group; 40% in RAL group		
BIC vs. DTG					
Sax et al., 2017a[30] Stellbrink et al., 2019[31] 126 sites in 10 countries in Australia, Europe, Latin America, and North America NCT02607956 GS-US-380–1490	To compare BIC/TAF/FTC to DTG + TAF/FTC 96 weeks	Inclusion: Adults (≥ 18 years old), HIV-1 infection, no prior ART, HIV-1 RNA ≥ 500 copies/mL, eGFR ≥ 30 mL/min, no resistance to FTC and TAF. Exclusion: Not meeting above criteria.	Total N = 657 randomized with 327 in BIC group and 330 in DTG group Median age (IQR): 33 years (27 to 46) in BIC group; 34 years (27 to 46 in DTG group) Sex: 13% female in BIC group; 11% female in DTG group Ethnicity: 26% Hispanic or Latino in BIC group; 25% Hispanic or Latino in DTG group Race: 57% White in BIC group; 60% White in DTG group HIV-1 RNA ≤ 100,000 copies/mL: 79% in BIC	Bictegravir/tenofovir alafenamide/emtricitabine (BIC/TAF/FTC) 50/25/200 mg FDC once daily (BIC regimen)	Dolutegravir (DTG) 50 mg + tenofovir alafenamide/emtricitabine (TAF/FTC) 25/200 mg once daily (DTG regimen)

Citation Location NCT Number Name	Study Aim Study Duration	Key Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)
			group; 83% in DTG group Median CD4+ cell count (IQR): 440 cells/µL (289 to 591) in BIC group; 441 cells/µL (297 to 597) in DTG group HIV infection category: not reported HIV risk factor: Heterosexual sex: 25% in BIC group; 24% in DTG group Homosexual sex: 74% in BIC group; 77% in DTG group Intravenous drug use: 1% in BIC group; 2% in DTG group Prior AIDS diagnosis: 8% in both groups HBV infection: 3% in BIC group; 2% in DTG group HCV infection: 2% in both groups		

Citation Location NCT Number Name	Study Aim Study Duration	Key Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)
Sax et al., 2017b[29] 22 sites in the U.S. NCT02397694	To compare BIC to DTG. 48 weeks	Inclusion: Adults (≥ 18 years old), HIV-1 infection, no prior ART, HIV-1 RNA ≥ 1,000 copies/mL, CD4 count ≥ 200 cells/µL, eGFR ≥ 70 mL/min, no resistance to TAF and FTC. Exclusion: HBV or HCV co-infection, new AIDs-defining condition within 30 days of screening, pregnant.	Total N = 98 randomized with 65 in BIC group and 33 in DTG group Median age (IQR): 30 years (25 to 41) in BIC group; 36 years (26 to 51) in DTG group Sex: 2% in BIC group; 9% in DTG group Ethnicity: not reported Race: 58% White in BIC group; 55% White in DTG group HIV-1 RNA ≤ 100,000 copies/mL: 85% in BIC group; 79% in DTG group Median CD4+ cell count (IQR): 441 cells/µL (316 to 574) in BIC group; 455 cells/µL (273 to 677) in DTG group HIV infection category: not reported	Bictegravir (BIC) 75 mg + tenofovir alafenamide/emtricitabine (TAF/FTC) 25/200 mg (BIC regimen)	Dolutegravir (DTG) 50 mg + tenofovir alafenamide/emtricitabine (TAF/FTC) 25/200 mg (DTG regimen)

Citation Location NCT Number Name	Study Aim Study Duration	Key Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)
			HBV or HCV infection: not reported		

*Abbreviations. 3TC: lamivudine; ABC: abacavir; AIDS: acquired immunodeficiency syndrome; ART: antiretroviral therapy; BIC: bictegravir; c: cobicistat; CDC: U.S. Centers for Disease Control and Prevention; DERP: Drug Effectiveness Review Project; DOR: doravirine; DRV: darunavir; DTG: dolutegravir; EFV: efavirenz; eGFR: estimated glomerular filtration rate; FDC: fixed-dose combination; FTC: emtricitabine; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV-1: human immunodeficiency virus type 1; HLA-B*5701: human leukocyte antigen-B*5701; IQR: interquartile range; NCT: national clinical trial; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor; r: ritonavir; RAL: raltegravir; RNA: ribonucleic acid; RPV: rilpivirine; SD: standard deviation; TAF: tenofovir alafenamide; TB: tuberculosis; TDF: tenofovir disoproxil fumarate; ULN: upper limit of normal; WHO: World Health Organization; ZDV: zidovudine.*

Study Findings

Table B2. Findings from Eligible Randomized Controlled Trials

Citation Location NCT Number Name	Effectiveness	Harms
Backbone Therapies		
3TC vs. TDF/FTC		
Cahn et al., 2019[17] 192 sites in 21 countries NCT02831673 and NCT02831764 GEMINI-1 and GEMINI-2	2-drug vs. 3-drug regimen <u>Viral suppression:</u> Achieving HIV-1 RNA < 50 copies/mL at week 48: GEMINI-1 (ITT): 320 of 356 (90%) vs. 332 of 358 (93%); adjusted treatment difference -2.6% (95% CI, -6.7 to 1.5) GEMINI-2 (ITT): 335 of 360 (93%) vs. 337 of 359 (94%); adjusted treatment difference -0.7% (95% CI, -4.3 to 2.9)	2-drug vs. 3-drug regimen <u>Serious adverse events:</u> Pooled analysis: 50 of 716 (7%) vs. 55 of 717 (8%) <u>Withdrawals due to adverse events:</u> Pooled analysis: 15 of 716 (2%) vs. 16 of 717 (2%) <u>Specific adverse events:</u>

Citation Location NCT Number Name	Effectiveness	Harms
	Pooled analysis (ITT): 655 of 716 (91%) vs. 669 of 717 (93%); adjusted treatment difference -1.7% (95% CI, -4.4 to 1.1) Response rates analyzed by demographic and baseline characteristics were generally consistent with overall response in pooled analysis. AIDS-defining illness: Not reported Adherence: Not reported Persistence: Not reported Drug resistance: Confirmed virologic withdrawal at week 48: 6 in two-drug regimen group vs. 4 in three-drug regimen group; no emergence of mutations conferring resistance to INSTIs or NRTIs; all 10 participants were classified as virologic rebounds	Kidney injury (increased serum creatinine): 10.4 µmol/L vs. 13.5 µmol/L; *P* < .0001 Hepatotoxicity: not reported Cardiovascular events (e.g., MI, stroke): not reported Bone turnover (serum bone-specific alkaline phosphatase): 1.22 vs. 4.07; *P* < .0001 Drug-drug interactions: Not reported
TAF/FTC vs. TDF/FTC		
Eron et al., 2018[18] Rashbaum et al., 2019[21] 121 sites in 10 countries (including U.S.) NCT02431247	DRV/c/TAF/FTC vs. DRV/c + TDF/FTC Viral suppression: Achieving HIV-1 RNA < 50 copies/mL at week 48: 331 of 362 (91.4%) vs. 321 of 363 (88.4%); treatment difference 2.7% (95% CI -1.6 to 7.1) Similar across demographic and clinical characteristic subgroups. AIDS-defining illness:	DRV/c/TAF/FTC vs. DRV/c + TDF/FTC Serious adverse events: 17 of 362 (5%) vs. 21 of 363 (6%) Similar across subgroups Withdrawals due to adverse events: 7 of 362 (2%) vs. 16 of 363 (4%) Similar across subgroups

Citation Location NCT Number Name	Effectiveness	Harms
AMBER	Not reported Adherence: (pill count) At least 95% adherent through week 48: 264 of 299 (88.3%) vs. 271 of 307 (88.3%) Persistence: Not reported Drug resistance: Through week 48, 8 vs. 6 participants had virologic failure. No DRV, PI, or TDF/TAF resistance mutations were found in any patient. One mutation to FTC and 3TC found in one patient, but this patient was discontinued from study.	Specific adverse events: Kidney injury: Renal adverse events: 7 of 362 (2%) vs. 21 of 363 (6%) Increased serum creatinine: 4.8 µmol/L vs. 8.2 µmol/L; *P* < .0001 Similar across subgroups Hepatotoxicity: not reported Cardiovascular events: not reported Bone events: Osteopenia: 17 of 362 (5%) vs. 27 of 363 (7%) Hip BMD % change at week 48: 0.21% vs. -2.73%; *P* < .0001 Lumbar spine BMD % change at week 48: -0.68% vs. -2.38%; *P* < .0001 Femoral neck BMD % change at week 48: -0.26% vs. -2.97%; *P* = .004 Fractures: 4 of 362 (1.1%) vs. 2 of 363 (0.6%); *P* = .451 Similar across subgroups Drug-drug interactions: Not reported
Mills et al., 2015[19] Multicenter in U.S. NCT01565850	TAF group vs. TDF group Viral suppression: At week 48: 76.7% vs. 84.0%;* weighted difference in response rate -6.2% (95% CI, -19.9 to 7.4) * Study does not report raw numbers No difference by pre-specified subgroup analyses by demographics, disease characteristics, or adherence AIDS-defining illness: Not reported Adherence: (pill count) At week 48: 98.8% vs. 98.2%	TAF group vs. TDF group Serious adverse events: 5 of 103 (4.9%) vs. 2 of 50 (4.0%) Withdrawals due to adverse events: 2 of 103 (1.9%) vs. 2 of 50 (4.0%) Specific adverse events: Kidney injury: Mean change in serum creatinine from baseline to week 48: 0.06 mg/dL (95% CI 0.04 to 0.08) vs. 0.09 mg/dL (95% CI 0.05 to 0.14) Median change in eGFR from baseline to week 48: -2.9 mL/min vs. -10.6 mL/min; *P* = .017

Citation Location NCT Number Name	Effectiveness	Harms
	Persistence: Mean duration of study drug exposure: 68.0 weeks vs. 69.1 weeks Drug resistance: Among those with virologic failure, none experienced resistance. Through week 48, 8 participants met criteria for resistance analysis because of virologic rebound; 7 were confirmed with virologic rebound, 1 was lost to follow-up. Genotypic analysis showed no resistance to TDF, TAF, FTC, or DRV.	Hepatotoxicity: not reported Cardiovascular events: 0 vs. 0 Bone events: Decline in hip BMD at week 48: -0.84% vs. -3.82; *P* < .001 Decline in lumbar spine BMD at week 48: -1.57% vs. -3.62%; *P* = .003 Drug-drug interactions: Not reported
Venter et al., 2019[20] South Africa NCT03122262 ADVANCE	TAF group vs. TDF group vs. standard care group Viral suppression: HIV-1 RNA < 50 copies/mL at week 48: 84% vs. 85% vs. 79% Difference in prevalence of viral suppression between groups: TAF vs. standard care: 5.1% (98.3% CI, -1.9 to 12.2; *P* = .08) TDF vs. standard care: 6.3% (98.3% CI, -0.1 to 13.2; *P* = .03) TAF vs. TDF: -1.1% (98.3% CI, -7.7 to 5.4; *P* = .68) In a multivariate analysis of response, younger age (≤ 32 years) and unemployment were significant predictors of treatment failure at week 48 (*P* < .01 for both comparisons). Baseline HIV-1 RNA level, baseline CD4 count, and sex were not significant predictors of response. AIDS-defining illness: Not reported	TAF group vs. TDF group vs. standard care group Serious adverse events: 16 of 351 (4.6%) vs. 20 of 351 (5.7%) vs. 24 of 351 (6.8%) Withdrawals due to adverse events: 1 of 351 (0.28%) vs. 0 vs. 10 of 351 (2.8%) Specific adverse events: Kidney injury: Renal disorder leading to discontinuation: 0 vs. 0 vs. 2 of 351 (0.57%) Abnormal creatinine clearance: 3 of 351 (0.85%) vs. 11 of 351 (3.1%) vs. 6/351 (1.7%) Hepatotoxicity: Elevated liver enzymes leading to discontinuation: 1 of 351 (0.28%) vs. 0 vs. 5 of 351 (1.4%) Elevated alanine aminotransferase: 10 of 351 (2.8%) vs. 7 of 351 (2.0%) vs. 18/351 (5.1%) Elevated aspartate aminotransferase: 6 of 351 (1.7%) vs. 6 of 351 (1.7%) vs. 14 of 351 (4.0%) Cardiovascular events: not reported

Citation Location NCT Number Name	Effectiveness	Harms
	Adherence: Not reported Persistence: Not reported Drug resistance: After virologic failure, no resistance to INSTIs were observed in patients receiving DTG-containing regimens; 4 patients receiving EFV and 1 patient receiving DTG showed new resistance to NRTIs or NNRTIs during viremic episodes.	Bone events: New osteopenia Whole body: 4 of 279 (1%) vs, 6 of 295 (2%) vs. 2 of 262 (1%) Spine: 37 of 203 (18%) vs. 50 of 220 (23%) vs. 45 of 202 (22%) Hip: 15 of 227 (7%) vs. 38 of 234 (16%) vs. 40 of 225 (18%) New osteoporosis Spine: 9 of 200 (4%) vs. 15 of 213 (7%) vs. 15 of 196 (8%) Hip: 3 of 223 (1%) vs. 2 of 229 (1%) vs. 10 of 216 (5%) Drug-drug interactions: Drug interactions between TAF and rifampin and between DTG and rifampin are an ongoing concern, but not assessed in this study. There was a low incidence of TB in this study, likely due to the use of isoniazid preventive therapy.
TAF/FTC vs. ABC/3TC		
Gallant et al., 2017[24] Wohl et al., 2019[23] Acosta et al., 2019[25] 122 sites in 9 countries in Europe, Latin America, and North America NCT02607930	BIC/TAF/FTC vs. DTG/ABC/3TC Viral suppression: HIV-1 RNA < 50 copies/mL at week 48: 290 of 314 (92.4%) vs. 293 of 315 (93.0%); difference -0.6% (95.002% CI -4.8 to 3.6) Between-group efficacy did not differ significantly among various subgroups. HIV-1 RNA < 50 copies/mL at week 96: 276 of 314 (88%) vs. 283 of 315 (90%); difference -1.9% (95% CI -6.9 to 3.1) Differences existed between treatment groups in the subgroups with cumulative adherence < 95% and those who were older than 50 years. In both cases, the difference was driven by participants who did not have available data in the analysis window and whose last on-treatment assessment of HIV-1 RNA was less than 50 copies/mL rather than any evidence of virological	BIC/TAF/FTC vs. DTG/ABC/3TC Serious adverse events: Week 48: 19 of 314 (6%) vs. 25 of 315 (8%) Week 96: 36 of 314 (11%) vs. 39 of 315 (12%) Withdrawals due to adverse events: Week 48: 0 vs. 4 of 315 (1%) Week 96: 0 vs. 5 of 315 (2%) Specific adverse events: Kidney injury: Median change in serum creatinine at week 48 (range): 0.11 mg/dL (0.03 to 0.17) vs. 0.11 mg/dL (0.03 to 0.18); *P* = .78 Median change in eGFR at week 48 (range): -10.5 mL/min (19.5 to 0.2) vs. -10.8 mL/min (-21.6 to -2.4); *P* = 0.20 Median change in serum creatinine at week 96 (range): 0.08 mg/dL (0.01 to 0.15) vs. 0.09 mg/dL (0.03 to 0.17); *P* = 0.067

Citation Location NCT Number Name	Effectiveness	Harms
	failure. No significant differences were detected between the two treatments in other subgroups and no interactions between treatment and subgroup for other prespecified subgroups, including baseline viral load and CD4 strata. <u>AIDS-defining illness:</u> Not reported <u>Adherence:</u> Not reported <u>Persistence:</u> Not reported <u>Drug resistance:</u> Resistance analysis was conducted for 5 participants (1 in BIC/TAF/FTC group and 4 in DTG/ABC/3TC group). No treatment-emergent resistance developed to any component of either treatment regimen at weeks 48 or 96.	Median change in eGFR at week 96 (range): -7.8 mL/min (-16.4 to 3.6) vs. -9.6 mL/min (-19.9 to -0.4); *P* = .01 Renal failure at week 96: 0 vs. 1 of 315 (0.32%) Hepatotoxicity: not reported Cardiovascular events: not reported Bone events: Mean % change in hip BMD at week 48 (SD): -0.78% (2.22) vs. -1.02% (2.31); least-squares mean difference 0.238% (95% CI -0.151 to 0.626) Mean % change in lumbar spine BMD at week 48 (SD): -0.83% (3.19) vs. -0.60% (3.10); least-squares mean difference -0.235 (95% CI -0.766 to 0.297) Mean % change in hip BMD at week 96 (SD): -1.13% (2.77) vs. -1.26% (2.85); *P* = .59 Mean % change in lumbar spine BMD at week 96 (SD): -0.71% (3.87) vs. -0.22% (3.52); *P* = .14 <u>Drug-drug interactions:</u> Not reported
ABC/3TC vs. TDF/FTC		
Walmsley et al., 2013[26] Walmsley et al., 2015[27] Multiple sites in North America, Europe, and Australia NCT01263015	DTG + ABC/3TC vs. EFV/TDF/FTC <u>Viral suppression:</u> HIV-1 RNA < 50 copies/mL at week 48 (ITT): 364 of 414 (88%) vs. 339 of 419 (81%); adjusted treatment difference 7% (95% CI, 2 to 12) Treatment differences were observed across clinical (i.e., HIV-1 RNA level) and demographic (i.e., race, sex, and age) subgroups consistent with the overall analysis.	DTG + ABC/3TC vs. EFV/TDF/FTC <u>Serious adverse events:</u> Week 48: 37 of 414 (9%) vs. 35 of 419 (8%) Week 96: 44 of 414 (11%) vs. 51 of 419 (12%) Week 144: 65 of 414 (16%) vs. 60 of 419 (14%) <u>Withdrawals due to adverse events:</u> At week 48: 10 of 414 (2%) vs. 42 of 419 (10%) <u>Specific adverse events:</u>

Citation Location NCT Number Name	Effectiveness	Harms
SINGLE	Differences in response in ITT analysis were due primarily to discontinuations because of adverse events. HIV-1 RNA < 50 copies/mL at week 96: 273 of 342 (80%) vs. 223 of 310 (72%); *P* = .006 HIV-1 RNA < 50 copies/mL at week 144: 242 of 341 (71%) vs. 194 of 309 (63%); *P* = .01 <u>AIDS-defining illness:</u> Not reported <u>Adherence:</u> Not reported <u>Persistence:</u> Not reported <u>Drug resistance:</u> Through week 48: 4% of participants in each group met criteria for virologic failure. No major NRTI or INSTI resistance mutations in those in the DTG + ABC/3TC group. In EFV/TDF/FTC group, 1 participant had a TDF-associated resistance mutation and 4 had NNRTI resistance mutations. Through week 144: No resistance mutations occurred in the DTG + ABC/3TC group, whereas 7 participants (an additional 2 cases after week 48) in the EFV/TDF/FTC group developed resistance mutations to NNRTIs.	Kidney injury: Mean serum creatinine level remained stable through week 144 for patients in DTG + ABC/3TC group. Not reported for another group. Hepatotoxicity: Elevated alanine aminotransferase at week 48: 10 of 414 (2%) vs. 22 of 419 (5%) Elevated aspartate aminotransferase at week 48: 7 of 414 (2%) vs. 23 of 419 (5%) Low rate of elevated liver enzymes in both treatment groups through week 144 (6 vs. 3 participants with Grade 3/4 ALT elevations). Cardiovascular events (i.e., MI or ischemic coronary events) through week 48: 0 vs. 0 Bone events: not reported <u>Drug-drug interactions:</u> Not reported
TDF/3TC vs. TDF/FTC		

Citation Location NCT Number Name	Effectiveness	Harms
Orkin et al., 2019[28] 126 sites worldwide NCT02403674 DRIVE-AHEAD	DOR/TDF/3TC vs. EFV/TDF/FTC <u>Viral suppression:</u> HIV-1 RNA < 50 copies/mL at week 48: 307 of 364 (84.3%) vs. 294 of 364 (80.8%); treatment difference 3.5% (95%, CI -2.0 to 9.0) Virologic response rates were similar between treatment groups at each time point throughout the study and across all baseline prognostic and demographic factors except age, with response rates favoring EFV/TDF/FTC in participants ≤ 31 years old and DOR/TDF/3TC in those older than 31 years. Among participants with high baseline HIV-1 RNA (> 100,000 copies/mL), 56/69 (81.2%) in the DOR/TDF/3TC group and 59/73 (80.8%) in the EFV/TDF/FTC group achieved HIV-1 RNA of < 50 copies/mL at week 48. <u>AIDS-defining illness:</u> Not reported <u>Adherence:</u> Not reported <u>Persistence:</u> Not reported <u>Drug resistance:</u> Through week 48: Only 22 participants (6.0%) in the DOR/TDF/3TC group and 14 (3.8%) in the EFV/TDF/FTC group met criteria for virologic failure. Isolates were not obtained from all of these participants.	DOR/TDF/3TC vs. EFV/TDF/FTC <u>Serious adverse events:</u> Week 48: 13 of 364 (4%) vs. 21 of 364 (6%); treatment difference -2.2% (95% CI, -5.5 to 0.9) <u>Withdrawals due to adverse events:</u> Week 48: 11 of 364 (3%) vs. 24 of 364 (7%); treatment difference -3.6% (95% CI, -6.9 to -0.5) <u>Specific adverse events:</u> Kidney injury: Serum creatinine > 1.8 to < 3.5x ULN, or increase of 1.5 to < 2.0x above baseline: 7 of 363 (1.9%) vs. 3 of 359 (0.8%); difference 1.1% (95% CI, -0.7 to 3.2) Hepatotoxicity: not reported Cardiovascular events: not reported Bone events: Fractures occurred in < 1% of each treatment group <u>Drug-drug interactions:</u> Not reported

Citation Location NCT Number Name	Effectiveness	Harms
	DOR/TDF/3TC group: 7 participants had resistance mutations associated with DOR, EFV, or 3TC. EFV/TDF/FTC group: 12 participants had resistance mutations associated with EFV, DOR, or FTC.	
Add-on Therapies		
RPV vs. EFV		
Cohen et al., 2011[50] 98 sites in 21 countries, including the U.S. NCT00543725 THRIVE	RPV vs. EFV <u>Viral suppression:</u> HIV-1 RNA < 50 copies/mL at week 48: 291 of 340 (86%) vs. 276 of 338 (82%); treatment difference 3.9% (95% CI, -1.6 to 9.5) <u>AIDS-defining illness:</u> Not reported <u>Adherence (measured by Modified Medication Adherence Self-Report Inventory):</u> > 95% adherence: 243 of 272 (89%) vs. 206 of 230 (90%) ≤ 95% adherence: 23 of 36 (64%) (median adherence 92.2%) vs. 24 of 39 (62%) (median adherence 91.5%) <u>Persistence:</u> Not reported <u>Drug resistance:</u> Virologic failure at 48 weeks: 27 of 340 (8%) vs. 20 of 338 (6%)	RPV vs. EFV <u>Serious adverse events:</u> At 48 weeks: 22 of 340 (7%) vs. 24 of 338 (7%) <u>Withdrawals due to adverse events:</u> At 48 weeks: 15 of 340 (4%) vs. 25 of 338 (7%) <u>Specific adverse events:</u> Kidney injury: Small increase from baseline in mean serum creatinine at first on-treatment assessment, which remained stable over 48 weeks with RPV (range 4.11 to 7.16 µmol/L), but no change with EFV. Treatment-associated changes in GFR varied depending on method of measurement. Hepatotoxicity: not reported Increased alanine aminotransferase: 6 of 340 (2%) vs. 11 of 330 (3%) Increased aspartate aminotransferase: 6 of 340 (2%) vs. 7 of 330 (2%) Cardiovascular events: not reported Bone events: not reported <u>Drug-drug interactions:</u> Not reported

Citation Location NCT Number Name	Effectiveness	Harms
Cohen et al., 2014[49] Wilkins et al., 2016[52] Multicenter, international GS-US-264–0110 STaR	RPV vs. EFV <u>Viral suppression:</u> HIV-1 RNA < 50 copies/mL at week 48: 338 of 394 (85.5%) vs. 320 of 392 (81.6%); *P* = .12 Baseline HIV-1 RNA ≤ 100,000 copies/mL: 231 of 260 (88.8%) vs. 204 of 250 (81.6%); treatment difference 7.2% (95% CI, 1.1 to 13.4) Baseline HIV-1 RNA > 100,000 copies/mL: 107 of 134 (79.9%) vs. 116 of 142 (81.7%); treatment difference -1.8% (95% CI, -11.1 to 7.5) Baseline HIV-1 RNA 100,001 to 500,000 copies/mL: 81 of 98 (82.7%) vs. 96 of 117 (82.1%); treatment difference 0.6% (95% CI, -9.6 to 10.8) Baseline HIV-1 RNA > 500,000 copies/mL: 26 of 36 (72.2%) vs. 20 of 25 (80.0%); treatment difference -7.8% (95% CI, -29.2 to 13.7) <u>AIDS-defining illness:</u> Not reported <u>Adherence:</u> Medication Adherence Self-Report Inventory Patients reporting having never missed a dose: 49% vs. 48% High overall treatment adherence in both groups: 97% to 99% Adherence Based on Returned Study Medications Through Week 48: 97% vs. 96% <u>Persistence:</u> Not reported	RPV vs. EFV <u>Serious adverse events:</u> 1 in study overall (treatment arm not specified) <u>Withdrawals due to adverse events:</u> 10 of 394 (2.5%) vs. 34 of 392 (8.7%); *P* < .001 <u>Specific adverse events:</u> Kidney injury: Change from baseline to week 48 in eGFR: -5.4 mL/min vs. +4.6 mL/min; *P* < .001 Renal failure (n): 1 vs. 1 Hepatotoxicity: not reported Cardiovascular events: not reported Bone events: not reported <u>Drug-drug interactions:</u> Not reported

Citation Location NCT Number Name	Effectiveness	Harms
	Drug resistance: Participants with resistance data: 20 of 394 (5%) vs. 7 of 392 (2%) Participants with resistance to ART through week 48: 17/394 (4%) vs. 3/392 (1%)	

Citation Location NCT Number Name	Effectiveness	Harms
Molina et al., 2011[51] 112 sites in 21 countries, including the U.S. NCT00540449 ECHO	RPV vs. EFV <u>Viral suppression:</u> HIV-1 RNA < 50 copies/mL at week 48 (ITT): 287 of 346 (83%) vs. 285 of 344 (83%); treatment difference 0.1% (95% CI, -5.5 to 5.7) <u>AIDS-defining illness:</u> Not reported <u>Adherence:</u> Medication Adherence Self-Report Inventory Patients reporting > 95% adherence: 236 of 275 (86%) vs. 229 of 262 (87%) <u>Persistence:</u> Not reported <u>Drug resistance:</u> Virologic failure with resistance to any NRTI or NNRTI: 29 of 40 (73%) vs. 8 of 13 (62%)	RPV vs. EFV <u>Serious adverse events:</u> 23 of 346 (7%) vs. 31 of 344 (9%) <u>Withdrawals due to adverse events:</u> 6 of 346 (2%) vs. 25 of 344 (7%) <u>Specific adverse events:</u> Kidney injury: Small increase from baseline in mean serum creatinine concentration for RPV at first on-treatment assessment, but then concentration remained stable over the 48-week treatment period (range 5.69 to 9.07 µmol/L), whereas values remained around baseline for EFV (range 0.10 to 2.38 µmol/L) eGFR: Remained slightly below baseline levels with RPV, but were within normal limits (mean decreases 8 to 11 mL/min), and at about baseline levels with EFV. Hepatotoxicity: not reported Increased aspartate aminotransferase: 8 of 345 (2%) vs. 12 of 339 (4%) Increased alanine aminotransferase: 4 of 345 (1%) vs. 12 of 340 (4%) Cardiovascular events: not reported Bone events: not reported <u>Drug-drug interactions:</u> Not reported
RAL vs. EFV		

Citation Location NCT Number Name	Effectiveness	Harms
Grinsztejn et al., 2014[40] 8 sites in Brazil and France NCT00822315 ANRS 12180 Reflate TB	RAL 400 mg vs. RAL 800 mg vs. EFV <u>Viral suppression:</u> HIV RNA < 50 copies/mL at week 24 (ITT): 39 of 51 (76%) vs. 40 of 51 (78%) vs. 32 of 51 (63%) HIV RNA < 50 copies/mL at week 48 (ITT): 39 of 51 (76%) vs. 32 of 51 (63%) vs. 34 of 51 (67%) <u>AIDS-defining illness:</u> Not reported <u>Adherence:</u> Self-reported adherence to ART at week 24: 40 of 46 (87%) vs. 32 of 38 (84%) vs. 38 of 40 (95%) Self-reported adherence to ART at week 48: 36 of 39 (92%) vs. 27 of 34 (79%) vs. 31 of 33 (94%) <u>Persistence:</u> Not reported <u>Drug resistance:</u> Resistance analysis population: 11 of 51 (22%) vs. 10 of 51 (20%) vs. 9 of 51 (18%) Developed resistance to ART: 5 of 51 (10%) vs. 4 of 51 (8%) vs. 6 of 51 (12%)	RAL 400 mg vs. RAL 800 mg vs. EFV <u>Serious adverse events:</u> 17 of 51 (33%) vs. 17 of 51 (33%) vs. 19 of 51 (37%) <u>Withdrawals due to adverse events:</u> 0 vs. 3 of 51 (6.0%) vs. 3 of 51 (6.0%) <u>Specific adverse events:</u> Kidney injury: Creatinine > 3 ULN: 0 vs. 0 vs. 1 of 51 (2.0%) Hepatotoxicity: Leading to drug discontinuation: 0 vs. 2 of 51 (3.9%) vs. 0 Aspartate aminotransferase > 5 ULN: 3 of 51 (6.0%) vs. 3 of 51 (6.0%) vs. 3 of 51 (6.0%) Alanine aminotransferase > 5 ULN: 1 of 51 (2.0%) vs. 1 of 51 (2.0%) vs. 3 of 51 (6.0%) Cardiovascular disorders related to ART: 1 of 51 (2.0%) vs. 1 of 51 (2.0%) vs. 1 of 51 (2.0%) Bone events: not reported <u>Drug-drug interactions:</u> Not reported
Lennox et al., 2009[42] Lennox et al., 2010[44] Rockstroh et al., 2011[46] DeJesus et al., 2012[43]	RAL 400 mg twice daily vs. EFV 600 mg once daily <u>Viral suppression:</u> Failures as non-completers (primary analysis): HIV RNA < 50 copies/mL at week 48: 241 of 280 (86.1%) vs. 230 of 281 (81.9%); treatment difference 4.2% (95% CI, -1.9 to 10.3)	RAL 400 mg twice daily vs. EFV 600 mg once daily <u>Serious adverse events:</u> Week 48: 28 of 281 (10%) vs. 27 of 282 (9.6%); difference 0.4% (95% CI, -4.6 to 5.4) Week 96: 40 of 281 (14.0%) vs. 34 of 282 (12.0%); difference 2.0% (95% CI, -4 to 8) Week 156: 47 of 281 (17%) vs. 47 of 282 (17%); difference 0 (95% CI, -6 to 6)

Citation Location NCT Number Name	Effectiveness	Harms
Rockstroh et al., 2013[45] 67 sites on 5 continents, including North America (U.S.) NCT00369941 STARTMRK	HIV RNA < 50 copies/mL at week 96: 227 of 281 (81%) vs. 222 of 282 (79%); treatment difference 2.0% (95% CI, -4 to 9) HIV RNA < 50 copies/mL at week 156: 212 of 281 (75.4%) vs. 192 of 282 (68.1%); treatment difference 7.3% (95% CI, -0.2 to 14.7) HIV RNA < 50 copies/mL at week 192: 214 of 281 (76%) vs. 189 of 282 (67%); treatment difference 9.0% (95% CI, 2 to 16) HIV RNA < 50 copies/mL at week 240: 198 of 279 (71.0%) vs. 171 of 279 (61.3%); treatment difference 9.5% (95% CI, 1.7 to 17.3) <u>AIDS-defining illness:</u> Not reported <u>Adherence:</u> Patients taking medication ≥ 90% of the days on study through week 96: 276 of 281 (98%) vs. 273 of 282 (97%) <u>Persistence:</u> Not reported <u>Drug resistance:</u> Patients with virologic failure through week 48: 27 of 281 (9.6%) vs. 39 of 282 (13.8%) Patients with resistance to any study drugs through week 48: 4 of 281 (1.4%) vs. 3 of 282 (1.1%) Patients with virologic failure through week 192: 21 of 53 (39.6%) vs. 17 of 55 (30.9%)	Week 240: 57 of 281 (20.3%) vs. 57 of 282 (20.2%); difference 0.1 (95% CI, -6.6 to 6.7) <u>Withdrawals due to adverse events:</u> Week 48 (≥ 1 adverse event): 9 of 281 (3.2%) vs. 17 of 282 (6.0%); difference -2.8% (95% CI, -6.6 to 0.7) Week 96: 11 of 281 (4.0%) vs. 17 of 282 (6.0%); difference -2.0% (95% CI, -6 to 2) Week 156: 13 of 281 (5%) vs. 21 of 282 (7%); difference -3.0% (95% CI, -7 to 1) Week 240: 14 of 281 (5.0%) vs. 25 of 282 (8.9%); difference -3.9% (95% CI, -8.3 to 0.3) <u>Specific adverse events:</u> Kidney injury: Creatinine clearance ≥ 1.9x ULN at week 156: 0 vs. 1 of 279 (0.4%) Hepatotoxicity: Aspartate aminotransferase > 5x ULN at week 48: 6 of 281 (2%) vs. 5 of 282 (2%) Aspartate aminotransferase > 5x ULN at week 96: 9 of 281 (3.2%) vs. 8 of 279 (2.9%) Aspartate aminotransferase > 5x ULN at week 156: 12 of 281 (4.3%) vs. 8 of 279 (2.9%) Alanine aminotransferase > 5x ULN at week 48: 5 of 281 (2%) vs. 6 of 262 (2%) Alanine aminotransferase > 5x ULN at week 96: 5 of 281 (1.8%) vs. 7 of 279 (2.5%) Alanine aminotransferase > 5x ULN at week 156: 6 of 281 (2.2%) vs. 7 of 279 (2.5%) Cardiovascular events: not reported Bone events: not reported

Citation Location NCT Number Name	Effectiveness	Harms
	Patients with resistance to any study drugs through week 192: 7 of 53 (13.2%) vs. 9 of 55 (16.4%)	Drug-drug interactions: Not reported
Markowitz et al., 2007[41] Markowitz et al., 2009[48] Gotuzzo et al., 2012[47] 29 sites in the U.S., Canada, Latin America, Thailand, and Australia NCT00100048 Protocol 004	RAL 100 mg BID vs. RAL 200 mg BID vs. RAL 400 mg BID vs. RAL 600 mg BID vs. EFV 600 mg QD Viral suppression: HIV RNA < 50 copies/mL et week 24: 34 of 39 (87%) vs. 34 of 40 (85%) vs. 38 of 41 (93%) vs. 38 of 40 (95%) vs. 34/37 (92%) HIV RNA < 50 copies/mL at week 48: 33 of 39 (85%) vs. 33 of 40 (83%) vs. 36 of 41 (88%) vs. 35 of 40 (88%) vs. 33/38 (87%) HIV RNA < 50 copies/mL at week 48 (pooled to RAL 400 mg BID vs. EFV): 137 of 160 (85.6%) vs. 33 of 38 (86.8%); treatment difference -1.2% (95% CI, -11.2 to 13.7) HIV RNA < 50 copies/mL at week 96 (pooled to RAL 400 mg BID vs. EFV): 133 of 160 (83.1%) vs. 32 of 38 (84.2%); treatment difference -1.1% (95% CI, -12.0 to 14.5) HIV RNA < 50 copies/mL at week 240 (pooled to RAL 400 mg BID vs. EFV): 160 of 232 (68.8%) vs. 38 of 60 (63.2%) AIDS-defining illness: Not reported Adherence: Not reported Persistence:	RAL 100 mg BID vs. RAL 200 mg BID vs. RAL 400 mg BID vs. RAL 600 mg BID vs. EFV 600 mg QD Serious adverse events: Week 48: 5.1% vs. 12.5% vs. 0 vs. 5.0% vs. 5.3% Week 96 (RAL 400 mg BID vs. EFV 600 mg QD): 16 of 160 (10.0%) vs. 3 of 38 (7.9%) Week 240 (RAL 400 mg BID vs. EFV 600 mg QD): 25 of 160 (15.6%) vs. 4 of 38 (10.5%) Withdrawals due to adverse events: Week 96 (RAL 400 mg BID vs. EFV 600 mg QD): 2 of 160 (1.3%) vs. 1 of 38 (2.6%) Week 240 (RAL 400 mg BID vs. EFV 600 mg QD): 3/160 (1.9%) vs. 1/38 (2.6%) Specific adverse events: Kidney injury: Creatine kinase ≥ 10x ULN at week 96: 10 of 160 (6.3%) vs. 1 of 38 (2.6%) Creatine kinase ≥ 10x ULN at week 240: 15 of 159 (9.4%) vs. 2 of 37 (5.4%) Hepatotoxicity: Alanine aminotransferase increase at week 48: 0 vs. 10.0% vs. 0 vs. 5.0% vs. 5.3% Alanine aminotransferase increase at week 96: 6 of 160 (3.8%) vs. 2 of 38 (5.3%) Aspartate aminotransferase increase at week 96: 7 of 160 (4.4%) vs. 2 of 38 (5.3%)

Citation Location NCT Number Name	Effectiveness	Harms
	Not reported <u>Drug resistance:</u> Virologic failure at week 48: Occurred in 5 (3%) of 160 patients receiving a RAL regimen and in 1 (3%) of 38 patients receiving the EFV regimen. Patients with resistance (n): 4 (2.5%) vs. 1 (2.6%) Virologic failure at week 96: Occurred in 6 (4%) of 160 patients receiving RAL and in 2 (5%) of 38 patients receiving EFV. Patients with resistance (n): 4 (2.5%) vs. 2 (5.3%) Virologic failure at week 240: Occurred in 10 (6%) of the 160 RAL patients and 5 (13%) of the 38 EFV patients. Patients with resistance (n): 4 (2.5%) vs. 3 (7.9%)	Aspartate aminotransferase > 5x ULN at week 96: 4 of 160 (2.5%) vs. 1 of 38 (2.6%) Alanine aminotransferase > 5x ULN at week 96: 2 of 160 (1.3%) vs. 2 of 38 (5.3%) Aspartate aminotransferase > 5x ULN at week 240: 6 of 159 (3.8%) vs. 2 of 37 (5.4%) Alanine aminotransferase > 5x ULN at week 240: 5 of 159 (3.1%) vs. 2 of 37 (5.4%) Cardiovascular events: not reported Bone events: not reported <u>Drug-drug interactions:</u> Not reported
DTG vs. EFV		
Kouanfack et al., 2019[37] 3 sites in Cameroon NCT02777229 NAMSAL ANRS 12313	DTG regimen vs. low-dose (400 mg) EFV regimen <u>Viral suppression:</u> HIV RNA < 50 copies/mL at week 48: 231 of 310 (74.5%) vs. 209 of 303 (69.0%); treatment difference 5.5% (95% CI, -1.6 to 12.7) Subgroup analysis by demographic and disease characteristics largely favored the DTG regimen. <u>AIDS-defining illness:</u> Not reported <u>Adherence: (score from questionnaire)</u> Week 24:	DTG regimen vs. low-dose (400 mg) EFV regimen <u>Serious adverse events:</u> Not reported <u>Withdrawals due to adverse events:</u> 0 vs. 0 <u>Specific adverse events:</u> Kidney injury: Unspecified or acute renal failure: 3 of 310 (1%) vs. 1 of 303 (< 1%) Hepatotoxicity: Hepatic failure: 0 vs. 1 of 303 (< 1%) Cardiovascular events: not reported Bone marrow suppression: not reported

Citation Location NCT Number Name	Effectiveness	Harms
	Adherence > 95%: 209 of 283 (74%) vs. 197 of 275 (72%) Week 48: Adherence > 95%: 194 of 283 (69%) vs. 187 of 275 (70%) <u>Persistence:</u> Not reported <u>Drug resistance:</u> Predicted drug resistance at baseline to study drugs: NRTI/NNRTI mutations: 5 of 309 (1.6%) vs. 2 of 302 (0.7%) INSTI mutations: 1 of 307 (0.3%) vs. 0	<u>Drug-drug interactions:</u> Not reported
Van Lunzen et al., 2012[38] Stellbrink et al., 2013[39] 34 sites in France, Germany, Italy, Russia, Spain, and the U.S. NCT00951015 SPRING-1	DTG 10 mg vs. DTG 25 mg vs. DTG 50 mg vs. EFV 600 mg <u>Viral suppression:</u> HIV RNA < 50 copies/mL at week 48: 48 of 53 (91%) vs. 45 of 51 (88%) vs. 46 of 51 (90%) vs. 41 of 50 (82%) HIV RNA < 50 copies/mL at week 96: 42 of 53 (79%) vs. 40 of 51 (78%) vs. 45 of 51 (88%) vs. 36 of 50 (72%) <u>AIDS-defining illness:</u> Not reported <u>Adherence:</u> Not reported <u>Persistence:</u> Not reported	DTG 10 mg vs. DTG 25 mg vs. DTG 50 mg vs. EFV 600 mg <u>Serious adverse events:</u> Week 48: 3 of 53 (6%) vs. 1 of 51 (2%) vs. 4 of 51 (8%) vs. 4 of 50 (8%) Week 48 (DTG combined vs. EFV): 8 of 155 (5%) vs. 4 of 50 (8%) Week 96: 5 of 53 (9%) vs. 5 of 51 (10%) vs. 7 of 51 (14%) vs. 7 of 50 (14%) Week 96 (DTG combined vs. EFV): 17 of 155 (11%) vs. 7 of 50 (14%) <u>Withdrawals due to adverse events:</u> Week 48 (DTG combined vs. EFV): 2 of 155 (1.3%) vs. 4 of 50 (8%) Week 96: 1 of 53 (2%) vs. 1 of 51 (2%) vs. 2 of 51 (4%) vs. 5 of 50 (10%) Week 96 (DTG combined vs. EFV): 4 of 155 (3%) vs. 5 of 50 (10%) <u>Specific adverse events:</u>

Citation Location NCT Number Name	Effectiveness	Harms
	Drug resistance: Through week 48, 4 participants experienced virologic failure (2 in DTG 10 mg group, 1 in DTG 25 mg group, 1 in EFV group). Resistance mutation found only in 1 of the DTG 10 mg participants (this was consistent at 96 weeks).	Kidney injury: Change in serum creatinine at week 48, mean (SD), µmol/L (DTG combined vs. EFV): 3.4 (9.69) vs. -6.0 (10.19) Change in serum creatinine at week 96, mean (SD), µmol/L (DTG combined vs. EFV): 5.2 (10.64) vs. -2.4 (8.79) Hepatotoxicity: Any (Grade 1-4) alanine aminotransferase toxicity at week 96 (DTG combined vs. EFV): 21 of 155 (13.5%) vs. 19 of 50 (38.0%) Cardiovascular events: not reported Bone marrow suppression: not reported Drug-drug interactions: Not reported
DRV/r vs. RAL		
Lennox et al., 2014[36] 57 sites in the U.S. and Puerto Rico NCT00811954 ACTG A5257	DRV/r vs. RAL Viral suppression: HIV RNA < 50 copies/mL at week 96: 537 of 601 (89.4%) vs. 566 of 603 (93.9%) AIDS-defining illness: Not reported Adherence: Not reported Persistence: Not reported Drug resistance:	DRV/r vs. RAL Serious adverse events: Not reported Withdrawals due to adverse events: Toxicity-associated reason for discontinuation: 32 of 601 (5.3%) vs. 8 of 603 (1.3%) Specific adverse events: Kidney injury: Renal toxicity: 0 vs. 0 Hepatotoxicity: Hyperbilirubinemia: 0 vs. 0 Other hepatic toxicity: 5 of 601 (0.83%) vs. 1 of 603 (0.17%) Cardiovascular events: not reported Bone events: not reported

Citation Location NCT Number Name	Effectiveness	Harms
	Cumulative incidence of virologic failure at week 96: 14.9% vs. 9.0%; treatment difference 5.6% (97.5% CI, 1.3 to 9.9) Any resistance detected (n): 4 of 601 (0.67%) vs. 18 of 603 (3.0%)	Drug-drug interactions: Not reported
DRV/r vs. DOR		
Molina et al.,2018[34] Molina et al., 2020[35] 125 sites in 15 countries, including U.S. NCT02275780 DRIVE-FORWARD	DRV/r vs. DOR Viral suppression: HIV RNA < 50 copies/mL at week 48: 306 of 383 (80.0%) vs. 321 of 383 (84.0%); treatment difference 3.9% (95% CI, -1.6 to 9.4) HIV RNA < 50 copies/mL at week 96: 248 of 383 (66%) vs. 277 of 383 (73%); treatment difference 7.1% (95% CI, 0.5 to 13.7). AIDS-defining illness: Not reported Adherence: Not reported Persistence: Not reported Drug resistance: Virologic failure through week 48: 24 of 383 (6%) vs. 19 of 383 (5%) Resistance testing conducted in 15 of the 43 participants with virologic failure at week 48. Patients with drug resistance (n): 3 vs. 0 Virologic failure through week 96: 43 of 383 (11.0%) vs. 34 of 383 (9.0%)	DRV/r vs. DOR Serious adverse events: Week 48: 23 of 383 (6%) vs. 19 of 383 (5%) Week 96: 33 of 383 (9%) vs. 27 of 383 (7%) Withdrawals due to adverse events: Week 48: 12 of 383 (3%) vs. 6 of 383 (2%) Week 96: 13 of 383 (3%) vs. 6 of 383 (2%); *P* = .063 Specific adverse events (all week 96): Kidney injury: Serum creatinine (Grade 2) > 1·3x ULN to 1·8x ULN or increase of > 0·3 mg/dL above baseline: 22 of 378 (6%) vs. 15 of 380 (4%); treatment difference -1.9 (95% CI -5.1 to 1.2) Serum creatinine (Grade 3) > 1·8x ULN to < 3·5x ULN or increase of 1·5x above baseline to < 2·0x above baseline: 15 of 378 (4%) vs. 11 of 380 (3%); treatment difference -1.1 (95% CI -3.9 to 1.6) Hepatotoxicity: AST increase > 5.0x baseline: 14 of 378 (3.7%) vs. 17 of 380 (5%); treatment difference 0.8 (95% CI -2.2 to 3.8) ALT increase > 5.0x baseline: 15 of 378 (4%) vs. 15 of 380 (4%); treatment difference -0.0 (95% CI -2.9 to 2.9) Cardiovascular events: not reported Bone events: not reported

Citation Location NCT Number Name	Effectiveness	Harms
	Resistance testing conducted in 25 of the 77 participants with virologic failure at week 96. Patients with drug resistance (n): 1 vs. 2	Drug-drug interactions: Not reported
DTG vs. RAL		
Raffi et al., 2013a[32] Raffi et al., 2013b[33] 100 sites in Canada, U.S., Australia, and Europe NCT01227824 SPRING-2	DTG vs. RAL Viral suppression: HIV RNA < 50 copies/mL at week 48: 361 of 411 (88%) vs. 351 of 411 (85%); treatment difference 2.5% (95% CI, -2.2 to 7.1) HIV RNA < 50 copies/mL at week 96: 332 of 411 (81%) vs. 314 of 411 (76%); treatment difference 4.5% (95% CI, -1.1 to 10.0) AIDS-defining illness: Not reported Adherence: Not reported Persistence: Not reported Drug resistance: Virologic failure through week 48: 20 of 411 (5%) vs. 28 of 411 (7%) Patients with drug resistance at week 48 (n): 0 vs. 5 Virologic failure between weeks 48 and 96: 2 of 411 (< 1.0%) vs. 1 of 411 (< 1.0%) Patients with drug resistance between weeks 48 and 96 (n): 0 vs. 0	DTG vs. RAL Serious adverse events: Between weeks 48 and 96: 0 vs. 0 Withdrawals due to adverse events: Week 48: 10 of 411 (2%) vs. 7 of 411 (2%) Week 96: 10 of 411 (2%) vs. 10 of 411 (2%) Specific adverse events: Kidney injury: Mean change in creatinine clearance at week 48 (SD): -16.5 mL/min (14.17) vs. -5.4 mL/min (13.88) Mean change in creatinine clearance at week 48: 12.3 µmol/L vs. 4.7 µmol/L Mean change in creatinine clearance at week 96: 14.6 µmol/L vs. 8.2 µmol/L Mean change in eGFR at 96 weeks: -19.6 mL/min vs. -9.3 mL/min Hepatotoxicity: not reported Cardiovascular events: not reported Bone events: not reported Drug-drug interactions: Not reported
BIC vs. DTG		

Citation Location NCT Number Name	Effectiveness	Harms
Sax et al., 2017a[30] Stellbrink et al., 2019[31] 126 sites in 10 countries in Australia, Europe, Latin America, and North America NCT02607956 GS-US-380–1490	BIC regimen vs. DTG regimen <u>Viral suppression:</u> HIV RNA < 50 copies/mL at week 48: 286 of 320 (89%) vs. 302 of 325 (93%); treatment difference -3.5% (95% CI, -7.9 to 1.0) HIV RNA < 50 copies/mL at week 96: 269 of 320 (84%) vs. 281 of 325 (86%); treatment difference -2.3% (95% CI, -7.9 to 3.2) <u>AIDS-defining illness:</u> Not reported <u>Adherence:</u> ≥95% adherence at week 48: 301 of 320 (94%) vs. 306 of 325 (94%) <u>Persistence:</u> Both treatments were well tolerated with a median exposure of 101 weeks (IQR 98 to 107 for BIC and 98 to 108 for DTG). <u>Drug resistance:</u> No treatment emergent resistance to the components of either treatment were identified at weeks 48 or 96.	BIC regimen vs. DTG regimen <u>Serious adverse events:</u> Week 96: 55 of 320 (17%) vs. 33 of 325 (10%) <u>Withdrawals due to adverse events:</u> Through week 48: 5 of 320 (2%) vs. 1 of 325 (< 1%) Through week 96: 6 of 320 (2%) vs. 5 of 325 (2%) <u>Specific adverse events:</u> Kidney injury: Creatinine increase: 2 of 320 (1%) vs. 0 Median change in serum creatinine at week 48 (IQR): 0.10 (0.03 to 0.18) vs. 0.11 (0.04 to 0.19); *P* = .10 Median change in eGFR at week 48 (IQR): -7.3 (-17.3 to 0.1) vs. -10.8 (-20.0 to -1.7); *P* = .018 Hepatotoxicity: ALT increase: 7 of 320 (2%) vs. 3 of 325 (1%) AST increase: 4 of 320 (1%) vs. 8 of 325 (2%) Cardiovascular events: not reported Bone events: not reported <u>Drug-drug interactions:</u> Not reported
Sax et al., 2017b[29] 22 sites in the U.S. NCT02397694	BIC regimen vs. DTG regimen <u>Viral suppression:</u> HIV-1 RNA < 50 copies/mL at week 24: 63 of 65 (97%) vs. 31 of 33 (94%); weighted treatment difference 2.9% (95% CI, -8.5 to 14.2) HIV-1 RNA < 50 copies/mL at week 48: 63 of 65 (97%) vs. 30 of 33 (91%); weighted treatment difference 6.4% (95% CI, -6.0 to 18.8)	BIC regimen vs. DTG regimen <u>Serious adverse events:</u> Week 48: 0 vs. 0 <u>Withdrawals due to adverse events:</u> Week 48: 1 vs. 0 <u>Specific adverse events:</u>

Citation Location NCT Number Name	Effectiveness	Harms
	AIDS-defining illness: Not reported Adherence: Median adherence at week 48 (IQR): 97% (94 to 99) vs. 96% (90 to 99) Persistence: Not reported Drug resistance: Patients eligible for resistance testing (n): 1 vs. 2 Genotypic resistance analysis revealed that 1 patient in the DTG group developed an integrase mutation at week 48 (which was not detected at baseline or a subsequent timepoint after week 48) and no resistance to emtricitabine or tenofovir.	Kidney injury: Change in creatinine clearance at week 48: -7.0 mL/min vs. -11.3 mL/min Hepatotoxicity: AST concentration elevation: 6 of 64 (9%) vs. 1 of 32 (3%) ALT concentration elevation: 4 of 64 (6%) vs. 0 Cardiovascular events: Bone events: Drug-drug interactions: Not reported

Abbreviations. 3TC: lamivudine; ABC: abacavir; AIDS: acquired immunodeficiency syndrome; ALT: alanine aminotransferase; ART: antiretroviral therapy; AST: aspartate aminotransferase; BIC: bictegravir; BID: twice-daily; BMD: bone mineral density; c: cobicistat; CI: confidence interval; DOR: doravirine; DRV: darunavir; DTG: dolutegravir; EFV: efavirenz; eGFR: estimated glomerular filtration rate; FTC: emtricitabine; HIV-1: human immunodeficiency virus type 1; INSTI: integrase strand transfer inhibitor; IQR: interquartile range; ITT: intention-to-treat; NCT: national clinical trial; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor; QD: once-daily; r: ritonavir; RAL: raltegravir; RNA: ribonucleic acid; RPV: rilpivirine; SD: standard deviation; TAF: tenofovir alafenamide; TB: tuberculosis; TDF: tenofovir disoproxil fumarate; ULN: upper limit of normal.

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