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Drug Class Literature Scan: HIV

Date of Review: October 2022

Date of Last Review: August 2021
Literature Search: 05/24/21 – 08/16/22

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

Conclusions:

- Six new randomized controlled trials (RCT) are included (**Appendix 2**) in this literature scan.
- Two RCT support recent approval by the FDA for cabotegravir (APRETUDE) in pre-exposure prophylaxis (PrEP). When compared with tenofovir disoproxil fumarate/emtricitabine, incident human immunodeficiency virus (HIV) infections were reduced in female participants at high risk of HIV acquisition (hazard ratio [HR] 0.12; 95% confidence interval [CI] 0.05 to 0.31; p=<0.0001; superiority design)[1] and in cisgender men who have sex with men (MSM) and transgender women who have sex with men (HR 0.34; 95% CI 0.18 to 0.62; P<0.001; non-inferiority design).[2] Cabotegravir with rilpivirine for HIV-1 treatment has received expanded indications for both population age (12 years and older) and approved dosing regimens (monthly and every two-months), with or without oral-lead in therapy.
- One RCT compared incident HIV infection at 96 weeks in MSM and transgender women who have sex with men with use tenofovir alafenamide fumarate/emtracitabine versus tenofovir disoproxil fumarate/emtracitabine for PrEP (incident rate ratio [IRR] 0.54; 95% CI 0.23 to 1.26; non-inferiority design).[3]
- One RCT found a doravirine-based regimen was non-inferior to an efavirenz-based regimen in treatment-naïve adults for the outcome of viral suppression defined as a HIV RNA less than 50 copies/mL at 96 weeks (77.5% vs. 73.6%, difference 3.8%; 95% CI -2.4% to 10.0%).[4]
- One RCT compared dolutegravir/emtracitabine/(tenofovir disoproxil fumarate or tenofovir alafenamide fumarate) to an efavirenz/emtricitabine/tenofovir disoproxil fumarate regimen in pregnant women. Viral suppression at delivery in the combined dolutegravir (DTG) groups (98%) was compared to the efavirenz group (91%) (est. difference 6.5%; 95% CI 2.0 to 10.7%; P=0.0052; non-inferiority design with prespecified superiority criteria). Composite adverse pregnancy outcomes were lower in the dolutegravir/emtracitabine/ tenofovir alafenamide fumarate (24%) when compared to dolutegravir/emtracitabine/ tenofovir disoproxil fumarate (33%; est. difference -8.8%; 95% CI -17.3 to -0.3; P=0.043) or the efavirenz group (33%; est. difference -8.6%; 95% CI -17.1 to -0.1; P=0.047).[5]
- One RCT compared dolutegravir (DTG) based 3 drug regimens to non-DTG based 3 drug regimens in children requiring 1st or 2nd line therapy. Prespecified non-inferiority criteria were met for the outcome of treatment failure with DTG versus non-DTG based therapy (difference in proportion -0.08; 95% CI -0.14 to -0.03; P=0.004; non-inferiority design).[6]
- Bictegravir/emtricitabine/tenofovir alafenamide fumarate (BIKTARVY) and abacavir/dolutegravir/lamivudine (TRIUMEQ/TRIUMEQ PD) both received expanded indications for pediatric populations and introduced new formulations to accommodate smaller pediatric patients.

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- Several older agents, including stavudine, didanosine, saquinavir and nelfinavir, are no longer recommended in current guidelines. An evaluation of claims data did not identify any current Medicaid patients with claims for these agents.

Recommendations:
- Change stavudine, didanosine, saquinavir, and nelfinavir to non-preferred.

Summary of Prior Reviews and Current Utilization
HIV drugs were added to the PDL in 2015. At the time, all agents were made preferred. Guidelines and literature for HIV drugs were re-evaluated in 2021. Evidence demonstrated variation amongst guidelines related to the recommended initial treatment regimens and alternative regimens in adults. Guideline methodology and quality varies significantly. However, recommendations for initial therapy for most patients consisted of:
- A two-drug nucleoside reverse transcriptase inhibitor backbone combined with:
- An add-on therapy of a non-nucleoside reverse transcriptase inhibitor (NNRTI), integrase strand transfer inhibitor (INSTI), or boosted protease inhibitor (PI)

Guidelines from the Department of Health and Human Services (HHS), also list several agents which are no longer recommended for treatment of HIV. Drugs which are not recommended for use include the following:[7,8]
- Nucleoside reverse transcriptase inhibitors (NRTIs): stavudine, and didanosine. These are older drugs which are no longer recommended because of high rates of serious toxicities, and they have generally been replaced by newer NRTIs with decreased risk of serious adverse events.
- Protease inhibitors (PIs): saquinavir and nelfinavir. These older agents have disadvantages such as greater pill burden, lower efficacy, or increased toxicity. Newer protease inhibitors such as atazanavir and darunavir are more commonly recommended.

During the first quarter of 2022, there were over 150 FFS patients with claims for HIV therapy. The most commonly prescribed HIV therapies included:
- Single-tablet 3-drug regimens and
- Combination 2-drug NRTI regimens with indications for PrEP

This trend for commonly prescribed therapies has been consistent over the past few years for both FFS and CCO patients enrolled in Oregon Medicaid. Only a small proportion of patients had claims for 2-drug single-tablet regimens. Overall, about one-third of patients had paid claims for drugs commonly used in multi-tablet regimens. The most common drugs use for multi-tablet regimens from each class were dolutegravir (INSTI), darunavir (PI), and rilpivirine (NNRTI). There was no recent FFS or CCO utilization for drugs which are no longer recommended by U.S. guidelines including saquinavir, nelfinavir, stavudine, and didanosine.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When

necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

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

New Systematic Reviews:

After review, 3 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:
After review, 2 guidelines were excluded due to poor quality or general lack of applicability to PDL assessment.

New Formulations:[9]
Bictegravir/emtricitabine/tenofovir alafenamide (BIKTARVY)-low dose tablet (Oct 2021)
Cabotegravir (APRETUDE)-Extended-release injectable for pre-exposure prophylaxis (Dec 2021)
Abacavir/dolutegravir/lamivudine (TRIUMEQ PD)-tablets for oral suspension (March 2022)

Table 1: New Indications:[9]

Generic Name	Brand Name	Month / Year of Change	New or Expanded Indication
Abacavir/dolutegravir/lamivudine tablet	TRIUMEQ; TRIUMEQ PD	March 2022	Pediatric patients with HIV-1 infection weighing at least 10 kg
Bictegravir; emtricitabine; tenofovir alafenamide tablet	BIKTARVY	Oct 2021	Pediatric patients with HIV-1 infection weighing at least 14 kg
Cabotegravir extended-release intramuscular suspension	APRETUDE	Dec 2021	At-risk adults and adolescents weighing at least 35 kg for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV.
Cabotegravir tablet	VOCABRIA	Dec 2021 March 2022	Expanded to include use as an oral lead-in for APRETUDE for HIV-1 pre-exposure prophylaxis (PrEP) for adults and pediatric patients 12 to less than 19 years of age and weighing at least 35 kg and as short-term oral therapy for HIV-1 PrEP for patients who will miss a planned injection dosing of APRETUDE. Expands use in combination with rilpivirine as an oral, short-term treatment regimen followed by every two-month or monthly CABENUVA injection

			dosing regimen for the treatment of HIV-1 virus infection in adolescents 12 years of age and older and weighing at least 35 kg.
Cabotegravir/rilpivirine extended-release intramuscular suspension	CABENUVA kit	Jan 2022 March 2022 March 2022	Expanded to include every 2-month dosing regimen for treatment of HIV-1 in adults to replace the current antiretroviral regimen in those who are virologically suppressed on a stable antiretroviral regimen with no known or suspected resistance to cabotegravir or rilpivirine. Removal of need for mandatory oral, lead-in therapy. Treatment of HIV-1 infection in adolescents 12 years of age and older and weighing at least 35 kg with use of monthly and every 2-month dosing.
Doravirine tablet Doravirine/lamivudine/tenofovir disoproxil tablet	PIFELTRO DELSTRIGO	Jan 2022	Pediatric patients with HIV-1 infection weighing at least 35 kg
Rilpivirine tablet	EDURANT	March 2022	Expand, in combination with VOCABRIA (cabotegravir), as an oral, short-term treatment regimen, followed by CABENUVA injection dosing regimen for the treatment of HIV-1 virus infection in adolescents 12 years of age and older and weighing at least 35 kg.

References:

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2. Landovitz RJ, Donnell D, Clement ME, et al. Cabotegravir for HIV Prevention in Cisgender Men and Transgender Women. *N Engl J Med.* 2021;385(7):595-608.
3. Ogbuagu O, Ruane PJ, Podzamczer D, et al. Long-term safety and efficacy of emtricitabine and tenofovir alafenamide vs emtricitabine and tenofovir disoproxil fumarate for HIV-1 pre-exposure prophylaxis: week 96 results from a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet HIV.* 2021;8(7):e397-e407.
4. Orkin C, Squires KE, Molina JM, et al. Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate (TDF) Versus Efavirenz/Emtricitabine/TDF in Treatment-naive Adults With Human Immunodeficiency Virus Type 1 Infection: Week 96 Results of the Randomized, Double-blind, Phase 3 DRIVE-AHEAD Noninferiority Trial. *Clin Infect Dis.* 2021;73(1):33-42.

5. Lockman S, Brummel SS, Ziemba L, et al. Efficacy and safety of dolutegravir with emtricitabine and tenofovir alafenamide fumarate or tenofovir disoproxil fumarate, and efavirenz, emtricitabine, and tenofovir disoproxil fumarate HIV antiretroviral therapy regimens started in pregnancy (IMPAACT 2010/VESTED): a multicentre, open-label, randomised, controlled, phase 3 trial. *The Lancet.* 2021;397(10281):1276-1292.
6. Turkova A, White E, Mujuru HA, et al. Dolutegravir as First- or Second-Line Treatment for HIV-1 Infection in Children. *N Engl J Med.* 2021;385(27):2531-2543.
7. Department for Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. June 3, 2021; https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/AdultandAdolescentGL.pdf. Accessed June 11, 2021.
8. Department for Health and Human Services Panel on Antiretroviral Therapy and Medical Managment of Children Living with HIV. Guidelines for the Use of antiretroviral agents in Pediatric HIV Infection. April 7, 2021; https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/PedARV_GL.pdf. Accessed June 11, 2021.
9. Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm Accessed Sept 5, 2022. .

Appendix 1: Current Preferred Drug List

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

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

raltegravir potassium	ISENTRESS	ORAL	TABLET	Y
raltegravir potassium	ISENTRESS HD	ORAL	TABLET	Y
rilpivirine	RILPIVIRINE ER	INTRAMUSC	SUSER VIAL	Y
rilpivirine HCl	EDURANT	ORAL	TABLET	Y
ritonavir	NORVIR	ORAL	POWD PACK	Y
ritonavir	NORVIR	ORAL	SOLUTION	Y
ritonavir	NORVIR	ORAL	TABLET	Y
ritonavir	RITONAVIR	ORAL	TABLET	Y
saquinavir mesylate	INVIRASE	ORAL	TABLET	Y
stavudine	STAVUDINE	ORAL	CAPSULE	Y
tipranavir	APTIVUS	ORAL	CAPSULE	Y
zidovudine	RETROVIR	INTRAVEN	VIAL	Y
zidovudine	RETROVIR	ORAL	CAPSULE	Y
zidovudine	ZIDOVUDINE	ORAL	CAPSULE	Y
zidovudine	RETROVIR	ORAL	SYRUP	Y
zidovudine	ZIDOVUDINE	ORAL	SYRUP	Y
zidovudine	ZIDOVUDINE	ORAL	TABLET	Y

Appendix 2: New Comparative Clinical Trials

Since the last review, a total of 609 and 312 citations were identified through PubMed and OVID medline, respectively. After further screening and manual review, all except 6 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). These trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 2. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes
Delany-Moretlwe et al.[1] DB, DD, RCT	Long-acting CAB 600 mg IM every 8 weeks TDF/FTC 300/200mg tablet orally daily 185 weeks	N=3224 total -Patients 18-45 years assigned female sex at birth at high-risk of HIV infection	Incident HIV infection (superiority)	CAB = 4 infections; incidence 0.2/100 person-years TDF/FTC = 36 infections; incidence 1.85/100 person-years CAB vs. TDF/FTC HR 0.12 (95% CI 0.05 to 0.31; p<0.0001)	All patients from sub-Saharan Africa CAB cases: 1 case determined to have been present at enrollment, 2 cases did not receive any CAB injections, 1 occurred in patient with delayed injection visits. TDF-FTC cases: Poor or non-adherence (<2 doses/week) observed in 35 of 36 cases, partial adherence (4-6 doses/week) observed in 1 of 36 cases.
Ladovitz et al.[2] DB, DD, RCT	Long-acting CAB 600 mg IM every 8 weeks TDF/FTC 300/200mg tablet orally daily 153 weeks	N=4566 total -Cisgender MSM -At-risk transgender women who have sex with men (N=570)	Incident HIV infection (non-inferiority) -Non-inferiority margin predetermined HR 1.23	CAB = 13 infections; incidence 0.41/100 person-years TDF/FTC = 39 infections; incidence 1.22/100 person-years CAB vs. TDF/FTC HR 0.34 (95% CI 0.18 to 0.62; p<0.001)	Patients from US, Latin America, Asia, and Africa -96.6% adherence during oral tablet lead-in -74.2% with TDF concentrations consistent with daily use Stopped early for efficacy at preplanned interim analysis.
Lockman et al.[5] RCT	1. DTG/FTC/TAF 2. DTG/FTC/TDF 3. EFV/FTC/TDF	N=643 total -Treatment-naïve pregnant, adult, women with HIV-1 and 14-28 weeks gestation	-Viral suppression (HIV-1 RNA < 200 copies/mL) at or within 14 days of delivery (non-inferiority vs. EFV group) -Composite adverse pregnancy outcome	<u>Viral Suppression</u> Combined DTG groups: 98% EFV group: 91% Est difference 6.5% (95% CI 2.0 to 10.7%; p=0.0052) <u>Composite adverse pregnancy outcome</u> 1. 24%	Open-label Patients from Brazil, India, sub-Saharan Africa, Thailand, & US Stratified by gestation and country Composite adverse pregnancy outcomes include spontaneous abortion, stillbirth,

			-Occurrence of grade 3 or higher maternal and infant adverse events	2. 33% 3. 33% 1 vs. 2 Est difference -8.8% (95% CI -17.3 to -0.3; p=0.043) 1 vs. 3 Est difference -8.6% (95% CI -17.1 to -0.1; p=0.047) 2 vs. 3 NS <u>Grade 3 or higher maternal and infant adverse events</u> 1. 21% 2. 26% 3. 22% NS between groups	preterm delivery, or the infant being born small for gestational age.
Ogbuagu et al.[3] DB, RCT	TAF/FTC (25/200mg) TDF/FTC (300/200mg) 96 weeks	N=5387 total -Cisgender MSM -At-risk transgender women who have sex with men	Incident HIV infection at 96 weeks (non-inferiority)	TAF/FTC: 8 infections incidence 0.16/100 person-years TDF/FTC: 15 infections incidence 0.3/100 person-years TAF/FTC vs TDF/FTC IRR 0.54 (95% CI 0.23 to 1.26)	Patients from Europe and North America Adherence was similar between groups and assessed by dry blood spot, self-report, and pill count.
Orkin et al.[4] DRIVE-AHEAD DB, RCT	DOR/3TC/TDF (100/300/300mg FDT) EFV/FTC/TDF (600/200/300mg FDT) 96 weeks	N=728 total Treatment naïve adults	HIV-1 RNA levels <50 copies/mL at week 96 (non-inferiority)	DOR/3TC/TDF: 77.5% EFV/FTC/TDF: 73.6% Treatment difference 3.8% (95% CI -2.4% to 10.0%)	Participants from Africa, Asia/Pacific, Europe, Latin America, and North America. Neuropsychiatric adverse events more common in EFV based group.

Turkova et al.[6] RCT	DTG based 3-drug ART Non-DTG based 3-drug ART standard care 96 weeks	N=707 total Children 4 weeks to < 18 years old weighing at least 14kg with HIV-1 Requiring 1st or 2nd line ART	Virologic or clinical treatment failure by 96 weeks (non-inferiority)	DTG based: 47 failure (estimated probability 0.14) Non-DTG based: 75 failure (estimated probability 0.22) Difference in proportion -0.08 (95% CI -0.14 to -0.03, P=0.004)	Open-label Those <14 kg enrolled in different, ongoing trial cohort. Most participants from sub-Saharan Africa, some sites in Thailand and Europe. 1st and 2nd line cohort enrollments similar (44% vs. 56%)
Abbreviations: ART = antiretroviral treatment; CAB = cabotegravir; CI = confidence interval; DB = double-blind; DD = double-dummy; DOR = doravirine; DTG = dolutegravir; EFV = efavirenz; FDT = fixed-dose tablet; FTC = emtricitabine; HIV = human immunodeficiency virus; HR = hazard ratio; IM = intramuscular; IRR = incidence rate ratio; MSM = men who have sex with men; NS = not significant; RCT = randomized clinical trial; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate; US = United States; 3TC = lamivudine.					

Appendix 3: Abstracts of Comparative Clinical Trials

Cabotegravir for the prevention of HIV-1 in women: results from HPTN 084, a phase 3, randomised clinical trial[1]

BACKGROUND: Oral pre-exposure prophylaxis has been introduced in more than 70 countries, including many in sub-Saharan Africa, but women experience considerable barriers to daily pill-taking, such as stigma, judgement, and the fear of violence. Safe and effective long-acting agents for HIV prevention are needed for women. We aimed to evaluate the safety and efficacy of injectable cabotegravir compared with daily oral tenofovir diphosphate plus emtricitabine (TDF-FTC) for HIV prevention in HIV-uninfected women. METHODS: HPTN 084 was a phase 3, randomised, double-blind, double-dummy, active-controlled, superiority trial in 20 clinical research sites in seven countries in sub-Saharan Africa. Participants were eligible for enrolment if they were assigned female sex at birth, were aged 18-45 years, reported at least two episodes of vaginal intercourse in the previous 30 days, were at risk of HIV infection based on an HIV risk score, and agreed to use a long-acting reversible contraceptive method. Participants were randomly assigned (1:1) to either active cabotegravir with TDF-FTC placebo (cabotegravir group) or active TDF-FTC with cabotegravir placebo (TDF-FTC group). Study staff and participants were masked to study group allocation, with the exception of the site pharmacist who was responsible for study product preparation. Participants were prescribed 5 weeks of daily oral product followed by intramuscular injections every 8 weeks after an initial 4-week interval load, alongside daily oral pills. Participants who discontinued injections were offered open-label daily TDF-FTC for 48 weeks. The primary endpoints of the study were incident HIV infection in the intention-to-treat population, and clinical and laboratory events that were grade 2 or higher in all women who had received at least one dose of study product. This study is registered with ClinicalTrials.gov, NCT03164564. FINDINGS: From Nov 27, 2017, to Nov 4, 2020, we enrolled 3224 participants (1614 in the cabotegravir group and 1610 in the TDF-FTC group). Median age was 25 years (IQR 22-30); 1755 (54·7%) of 3209 had two or more partners in the preceding month. 40 incident infections were observed over 3898 person-years (HIV incidence 1·0% [95% CI 0·73-1·40]); four in the cabotegravir group (HIV incidence 0·2 cases per 100 person-years [0·06-0·52]) and 36 in the TDF-FTC group (1·85 cases per 100 person-years [1·3-2·57]; hazard ratio 0·12 [0·05-0·31]; p<0·0001; risk difference -1·6% [-1·0% to -2·3%]. In a random subset of 405 TDF-FTC participants, 812 (42·1%) of 1929 plasma samples had tenofovir concentrations consistent with daily use. Injection coverage was 93% of the total number of person-years. Adverse event rates were similar across both groups, apart from injection site reactions, which were more frequent in the cabotegravir group than in the TDF-FTC group (577 [38·0%] of 1519 vs 162 [10·7%] of 1516]) but did not result in injection discontinuation. Confirmed pregnancy incidence was 1·3 per 100 person-years (0·9-1·7); no congenital birth anomalies were reported. INTERPRETATION: Although both products for HIV prevention were generally safe, well tolerated, and effective, cabotegravir was superior to TDF-FTC in preventing HIV infection in women.

Cabotegravir for HIV Prevention in Cisgender Men and Transgender Women[2]

BACKGROUND: Safe and effective long-acting injectable agents for preexposure prophylaxis (PrEP) for human immunodeficiency virus (HIV) infection are needed to increase the options for preventing HIV infection. METHODS: We conducted a randomized, double-blind, double-dummy, noninferiority trial to compare long-acting injectable cabotegravir (CAB-LA, an integrase strand-transfer inhibitor [INSTI]) at a dose of 600 mg, given intramuscularly every 8 weeks, with daily oral tenofovir disoproxil fumarate-emtricitabine (TDF-FTC) for the prevention of HIV infection in at-risk cisgender men who have sex with men (MSM) and in at-risk transgender women who have sex with men. Participants were randomly assigned (1:1) to receive one of the two regimens and were followed for 153 weeks. HIV testing and safety evaluations were performed. The primary end point was incident HIV infection. RESULTS: The intention-to-treat population included 4566 participants who underwent randomization; 570 (12.5%) identified as transgender women, and the median age was 26 years (interquartile range, 22 to 32). The trial was stopped early for efficacy on review of the results of the first preplanned interim end-point analysis. Among 1698 participants from the United States, 845 (49.8%) identified as Black. Incident HIV infection occurred in 52 participants: 13 in the cabotegravir group (incidence, 0.41 per 100 person-years) and 39 in the TDF-FTC group (incidence, 1.22 per 100 person-years) (hazard ratio, 0.34; 95% confidence interval, 0.18 to 0.62). The effect was consistent across prespecified subgroups. Injection-site reactions were reported in 81.4% of the participants in the cabotegravir group and in 31.3% of those in the TDF-FTC group. In the participants in whom HIV infection was diagnosed after exposure to CAB-LA, INSTI resistance and delays in the detection of HIV infection were noted. No

safety concerns were identified. CONCLUSIONS: CAB-LA was superior to daily oral TDF-FTC in preventing HIV infection among MSM and transgender women. Strategies are needed to prevent INSTI resistance in cases of CAB-LA PrEP failure. (Funded by the National Institute of Allergy and Infectious Diseases and others; HPTN 083 ClinicalTrials.gov number, NCT02720094.).

Efficacy and safety of dolutegravir with emtricitabine and tenofovir alafenamide fumarate or tenofovir disoproxil fumarate, and efavirenz, emtricitabine, and tenofovir disoproxil fumarate HIV antiretroviral therapy regimens started in pregnancy (IMPAACT 2010/VESTED): a multicentre, open-label, randomised, controlled, phase 3 trial[5]

BACKGROUND: Antiretroviral therapy (ART) during pregnancy is important for both maternal health and prevention of perinatal HIV-1 transmission; however adequate data on the safety and efficacy of different ART regimens that are likely to be used by pregnant women are scarce. In this trial we compared the safety and efficacy of three antiretroviral regimens started in pregnancy: dolutegravir, emtricitabine, and tenofovir alafenamide fumarate; dolutegravir, emtricitabine, and tenofovir disoproxil fumarate; and efavirenz, emtricitabine, and tenofovir disoproxil fumarate. METHODS: This multicentre, open-label, randomised controlled, phase 3 trial was done at 22 clinical research sites in nine countries (Botswana, Brazil, India, South Africa, Tanzania, Thailand, Uganda, the USA, and Zimbabwe). Pregnant women (aged ≥18 years) with confirmed HIV-1 infection and at 14–28 weeks' gestation were eligible. Women who had previously taken antiretrovirals in the past were excluded (up to 14 days of ART during the current pregnancy was permitted), as were women known to be pregnant with multiple fetuses, or those with known fetal anomaly or a history of psychiatric illness. Participants were randomly assigned (1:1:1) using a central computerised randomisation system. Randomisation was done using permuted blocks (size six) stratified by gestational age (14–18, 19–23, and 24–28 weeks' gestation) and country. Participants were randomly assigned to receive either once-daily oral dolutegravir 50 mg, and once-daily oral fixed-dose combination emtricitabine 200 mg and tenofovir alafenamide fumarate 25 mg; once-daily oral dolutegravir 50 mg, and once-daily oral fixed-dose combination emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg; or once-daily oral fixed-dose combination of efavirenz 600 mg, emtricitabine 200 mg, and tenofovir disoproxil fumarate 300 mg. The primary efficacy outcome was the proportion of participants with viral suppression, defined as an HIV-1 RNA concentration of less than 200 copies per mL, at or within 14 days of delivery, assessed in all participants with an HIV-1 RNA result available from the delivery visit, with a prespecified non-inferiority margin of −10% in the combined dolutegravir-containing groups versus the efavirenz-containing group (superiority was tested in a pre-planned secondary analysis). Primary safety outcomes, compared pairwise among treatment groups, were the occurrence of a composite adverse pregnancy outcome (ie, either preterm delivery, the infant being born small for gestational age, stillbirth, or spontaneous abortion) in all participants with a pregnancy outcome, and the occurrence of grade 3 or higher maternal and infant adverse events in all randomised participants. This trial was registered with ClinicalTrials.gov, NCT03048422. FINDINGS: Between Jan 19, 2018, and Feb 8, 2019, we enrolled and randomly assigned 643 pregnant women: 217 to the dolutegravir, emtricitabine, and tenofovir alafenamide fumarate group, 215 to the dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group, and 211 to the efavirenz, emtricitabine, and tenofovir disoproxil fumarate group. At enrolment, median gestational age was 21·9 weeks (IQR 18·3–25·3), the median HIV-1 RNA concentration among participants was 902·5 copies per mL (152·0–5182·5; 181 [28%] of 643 participants had HIV-1 RNA concentrations of <200 copies per mL), and the median CD4 count was 466 cells per µL (308–624). HIV-1 RNA concentrations at delivery were available for 605 (94%) participants. Of these, 395 (98%) of 405 participants in the combined dolutegravir-containing groups had viral suppression at delivery compared with 182 (91%) of 200 participants in the efavirenz, emtricitabine, and tenofovir disoproxil fumarate group (estimated difference 6·5% [95% CI 2·0 to 10·7], p=0·0052; excluding the non-inferiority margin of −10%). Significantly fewer participants in the dolutegravir, emtricitabine, and tenofovir alafenamide fumarate group (52 [24%] of 216) had a composite adverse pregnancy outcome than those in the dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group (70 [33%] of 213; estimated difference −8·8% [95% CI −17·3 to −0·3], p=0·043) or the efavirenz, emtricitabine, and tenofovir disoproxil fumarate group (69 [33%] of 211; −8·6% [–17·1 to −0·1], p=0·047). The proportion of participants or infants with grade 3 or higher adverse events did not differ among the three groups. The proportion of participants who had a preterm delivery was significantly lower in the dolutegravir, emtricitabine, and tenofovir alafenamide fumarate group (12 [6%] of 208) than in the efavirenz, emtricitabine, and tenofovir disoproxil fumarate group (25 [12%] of 207; −6·3% [–11·8 to −0·9], p=0·023). Neonatal mortality was significantly higher in the efavirenz, emtricitabine, and tenofovir

disoproxil fumarate group (ten [5%] of 207 infants) than in the dolutegravir, emtricitabine, and tenofovir alafenamide fumarate group (two [1%] of 208; p=0·019) or the dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group (three [2%] of 202; p=0·050). INTERPRETATION: When started in pregnancy, dolutegravir-containing regimens had superior virological efficacy at delivery compared with the efavirenz, emtricitabine, and tenofovir disoproxil fumarate regimen. The dolutegravir, emtricitabine, and tenofovir alafenamide fumarate regimen had the lowest frequency of composite adverse pregnancy outcomes and of neonatal deaths.

Long-term safety and efficacy of emtricitabine and tenofovir alafenamide vs emtricitabine and tenofovir disoproxil fumarate for HIV-1 pre-exposure prophylaxis: week 96 results from a randomised, double-blind, placebo-controlled, phase 3 trial[3]

BACKGROUND: In DISCOVER, a multinational, randomised controlled trial, emtricitabine and tenofovir alafenamide compared with emtricitabine and tenofovir disoproxil fumarate showed non-inferior efficacy for HIV prevention and improved bone mineral density and renal safety biomarkers at week 48. We report outcomes analysed after all participants had completed 96 weeks of follow-up. METHODS: This study is an ongoing, randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial done at 94 community, public health, and hospital-associated clinics located in Europe and North America. Adult cisgender men and transgender women who have sex with men, both with a high risk of acquiring HIV as determined by self-reported sexual behaviour or recent sexually transmitted infections, were randomly assigned (1:1) to receive either emtricitabine and tenofovir alafenamide (200/25 mg) tablets daily, with matched placebo tablets (emtricitabine and tenofovir alafenamide group), or emtricitabine and tenofovir disoproxil fumarate (200/300 mg) tablets daily, with matched placebo tablets (emtricitabine and tenofovir disoproxil fumarate group). The primary efficacy outcome was incident HIV infection. Incidence of HIV-1 infection per 100 person-years was assessed when the last participant had completed 96 weeks of follow-up. This trial is registered with ClinicalTrials.gov , number NCT02842086 .FINDINGS: Between Sept 13, 2016, and June 30, 2017, 5387 participants were randomly assigned to receive emtricitabine and tenofovir alafenamide (n=2694) or emtricitabine and tenofovir disoproxil fumarate (n=2693), contributing 10 081 person-years of follow-up. At 96 weeks of follow-up, there were eight HIV infections in participants who had received emtricitabine and tenofovir alafenamide (0·16 infections per 100 person-years [95% CI 0·07–0·31]) and 15 in participants who had received emtricitabine and tenofovir disoproxil fumarate (0·30 infections per 100 person-years [0·17–0·49]). Emtricitabine and tenofovir alafenamide maintained its non-inferiority to emtricitabine and tenofovir disoproxil fumarate for HIV prevention (IRR 0·54 [95% CI 0·23–1·26]). Approximately 78–82% of participants reported taking study medication more than 95% of the time across all study visits. Rates of sexually transmitted infections remained high and similar across groups (21 cases per 100 person-years for rectal gonorrhoea and 28 cases per 100 person-years for rectal chlamydia). Emtricitabine and tenofovir alafenamide continued to show superiority over emtricitabine and tenofovir disoproxil fumarate in all but one of the six prespecified bone mineral density and renal biomarkers. There was more weight gain among participants who had received emtricitabine and tenofovir alafenamide (median weight gain 1·7 kg vs 0·5 kg, p<0·0001). INTERPRETATION: Emtricitabine and tenofovir alafenamide is safe and effective for longer-term pre-exposure prophylaxis in cisgender men and transgender women who have sex with men.

Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate (TDF) Versus Efavirenz/Emtricitabine/TDF in Treatment-naive Adults With Human Immunodeficiency Virus Type 1 Infection: Week 96 Results of the Randomized, Double-blind, Phase 3 DRIVE-AHEAD Noninferiority Trial[4]

BACKGROUND: Doravirine (DOR) is a nonnucleoside reverse-transcriptase inhibitor. In the phase 3 DRIVE-AHEAD trial in treatment-naive adults with human immunodeficiency virus type 1 (HIV-1) infection, DOR demonstrated noninferior efficacy compared with efavirenz (EFV) and superior profiles for neuropsychiatric tolerability and lipids at 48 weeks. We present data through week 96. METHODS: DRIVE-AHEAD is a phase 3, multicenter, double-blind, noninferiority trial in antiretroviral treatment-naive adults with HIV-1 RNA >/=1000 copies/mL. Participants were randomized to a daily fixed-dose tablet of DOR (100 mg), lamivudine (3TC; 300 mg) and tenofovir disoproxil fumarate (TDF; 300 mg) (DOR/3TC/TDF) or EFV (600 mg), emtricitabine (FTC; 200 mg) and TDF (300 mg) (EFV/FTC/TDF). The efficacy end point of interest at week 96 was the proportion of participants with HIV-1 RNA levels <50 copies/mL (Food and Drug Administration Snapshot Approach) with a predefined noninferiority margin of 10% to support week 48 results. Safety end points of interest included

prespecified neuropsychiatric adverse events and the mean change in fasting lipids at week 96. RESULTS: Of 734 participants randomized, 728 received study drugs and were included in analyses. At week 96, HIV-1 RNA <50 copies/mL was achieved by 77.5% of DOR/3TC/TDF vs 73.6% of EFV/FTC/TDF participants, with a treatment difference of 3.8% (95% confidence interval, -2.4% to 10%). Virologic failure rates were low and similar across treatment arms, with no additional resistance to DOR observed between weeks 48 and 96. Prespecified neuropsychiatric adverse events and rash were less frequent in DOR/3TC/TDF than in EFV/FTC/TDF participants through week 96. At week 96, fasting low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol (HDL-C) levels increased in the EFV/FTC/TDF group but not in the DOR/3TC/TDF group; the mean changes from baseline in total cholesterol/HDL-C ratio were similar. CLINICAL TRIALS REGISTRATION: NCT02403674.

Dolutegravir as First- or Second-Line Treatment for HIV-1 Infection in Children[6]

BACKGROUND: Children with human immunodeficiency virus type 1 (HIV-1) infection have limited options for effective antiretroviral treatment (ART). METHODS: We conducted an open-label, randomized, noninferiority trial comparing three-drug ART based on the HIV integrase inhibitor dolutegravir with standard care (non-dolutegravir-based ART) in children and adolescents starting first- or second-line ART. The primary end point was the proportion of participants with virologic or clinical treatment failure by 96 weeks, as estimated by the Kaplan-Meier method. Safety was assessed. RESULTS: From September 2016 through June 2018, a total of 707 children and adolescents who weighed at least 14 kg were randomly assigned to receive dolutegravir-based ART (350 participants) or standard care (357). The median age was 12.2 years (range, 2.9 to 18.0), the median weight was 30.7 kg (range, 14.0 to 85.0), and 49% of the participants were girls. By design, 311 participants (44%) started first-line ART (with 92% of those in the standard-care group receiving efavirenz-based ART), and 396 (56%) started second-line ART (with 98% of those in the standard-care group receiving boosted protease inhibitor-based ART). The median follow-up was 142 weeks. By 96 weeks, 47 participants in the dolutegravir group and 75 in the standard-care group had treatment failure (estimated probability, 0.14 vs. 0.22; difference, -0.08; 95% confidence interval, -0.14 to -0.03; P = 0.004). Treatment effects were similar with first- and second-line therapies (P = 0.16 for heterogeneity). A total of 35 participants in the dolutegravir group and 40 in the standard-care group had at least one serious adverse event (P = 0.53), and 73 and 86, respectively, had at least one adverse event of grade 3 or higher (P = 0.24). At least one ART-modifying adverse event occurred in 5 participants in the dolutegravir group and in 17 in the standard-care group (P = 0.01). CONCLUSIONS: In this trial involving children and adolescents with HIV-1 infection who were starting first- or second-line treatment, dolutegravir-based ART was superior to standard care. (Funded by ViiV Healthcare; ODYSSEY ClinicalTrials.gov number, NCT02259127; EUDRACT number, 2014-002632-14; and ISRCTN number, ISRCTN91737921.).

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to August 16, 2022
1 exp HIV/ or exp Anti-HIV Agents/ or exp HIV-1/ 155430
2 limit 1 to (yr="2021 -Current" and (clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial)) 312

PubMed.gov:
(HIV infection) AND (randomized controlled trial[Publication Type] OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract]))
Filters applied: from 2021/6/1 - 2022/8/16
609 results

After manual review of results above, 2 guidelines, 3 systematic reviews, and 10 comparative trials were identified for additional quality assessment.

Appendix 5: Key Inclusion Criteria

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