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CADTH COMMON DRUG REVIEW

Clinical Review Report

DOLUTEGRAVIR/LAMIVUDINE (DOVATO)

(ViiV Healthcare ULC)

Indication: As a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and adolescents 12 years of age and older and weighing at least 40 kg.

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Abbreviations

3TC	lamivudine
ABC	abacavir
AE	adverse event
ART	antiretroviral therapy
ARV	antiretroviral
$AUC_{(0-t)}$	area under the curve of the analyte in plasma from time zero to the last quantifiable time
cART	combination antiretroviral therapy
CD4+	cluster of differentiation 4 positive
CDR	CADTH Common Drug Review
C_{max}	maximum measured concentration of the analyte in plasma
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CTAC	Canadian Treatment Action Council
CVR-50	confirmed virologic response of HIV-1 ribonucleic acid less than 50 copies/mL
CVW	confirmed viral withdrawal
DHHS	US Department of Health and Human Services
DRV	darunavir
DTG	dolutegravir
EQ-5D-5L	EuroQoL 5-Dimension 5-Level
EFV	efavirenz
EVG	elvitegravir
FDC	fixed-dose combination
FTC	emtricitabine
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HRQoL	health-related quality of life
INSTI	integrase strand transfer inhibitor
ITC	indirect treatment comparison
ITT	intention-to-treat population
ITT-E	intention-to-treat exposed population
LDL	low-density lipoprotein
MCID	minimal clinically important difference

NMA	network meta-analysis
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
PI	protease inhibitor
PP	per-protocol
RCT	randomized controlled trial
RAL	raltegravir
RNA	ribonucleic acid
RPV	rilpivirine
SAE	serious adverse event
STR	single-tablet regimen
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TLOVR-50	time to loss of virologic response of HIV-1 ribonucleic acid less than 50 copies/mL
WDAE	withdrawal due to adverse event

Drug	dolutegravir/lamivudine (Dovato)
Indication	As a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and adolescents 12 years of age and older and weighing at least 40 kg
Reimbursement Request	As per indication
Dosage Form(s)	Fixed-dose combination oral tablet containing dolutegravir 50 mg/lamivudine 300 mg
NOC Date	August 22, 2019
Manufacturer	ViiV Healthcare ULC

Executive Summary

Introduction

Human immunodeficiency virus type 1 (HIV-1) is one of the two types of viruses that cause HIV infection and is responsible for the majority of HIV infections globally.[1] HIV is transmitted by contact with infected body fluids such as blood, semen, pre-seminal fluid, fluids from the rectum or vagina, and through pregnancy, delivery, or breast feeding.[1,2] HIV infection gradually destroys the immune system by destroying cluster of differentiation 4 positive (CD4+) cells that are critically important in fighting infection.[3] If untreated, HIV infection can progress to AIDS and ultimately, death.[2] The Public Health Agency of Canada estimates that at the end of 2016 there were 63,110 people living with HIV infection (including AIDS) in Canada.[4] This corresponds with a prevalence rate of HIV infection in Canada of 173 per 100,000 people (range, 152 to 194 per 100,000), whereas the incidence rate is estimated to be 6.0 per 100,000 people (range, 3.3 to 8.7 per 100,000).[4]

People with HIV-1 infection can be treated with antiretroviral therapy (ART), which helps to lower the level of HIV-1 in the body, slow the spread of the virus, and helps the immune system respond to other infections.[5] ART has significantly reduced HIV-associated morbidity and mortality and today HIV infection is largely a manageable chronic condition.[5] According to the US Department of Health and Human Services' (DHHS) *Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV*, the initial combination regimen for patients who are ART naive generally consists of two nucleoside reverse transcriptase inhibitors administered in combination with a third active antiretroviral (ARV) drug from one of three drug classes: an integrase strand transfer inhibitor (INSTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a protease inhibitor (PI) with a pharmacokinetic enhancer or booster (e.g., cobicistat and ritonavir).[5] In the setting of patients who are virologically suppressed and are switching from an effective regimen to an alternate regimen, the DHHS guidelines state that the fundamental principle is to maintain viral suppression without jeopardizing future treatment options and to review a patient's full ARV history (i.e., virologic responses, past ARV-associated toxicities and intolerances, and cumulative resistance test results) before selecting a new ART.[5] The DHHS guidelines also state that, given the many excellent options for initial therapy, selection of a particular regimen for a particular patient should take into consideration virologic efficacy, toxicity, pill burden, dose frequency, drug-drug interaction potential, resistance test results, comorbid conditions, access, and cost.[5] ART is a lifelong commitment and high levels of adherence are required. To reduce pill burden and support long-term adherence, numerous single-

tablet regimens (STRs) of two- and three-drug combinations of ART have been developed and are currently marketed in Canada.

The objective of this systematic review was to evaluate the beneficial and harmful effects of dolutegravir (DTG) 50 mg/lamivudine (3TC) 300 mg administered orally in a fixed-dose combination (FDC) as a complete regimen for the treatment of HIV-1 infection in adults and adolescents 12 years of age and older who weigh at least 40 kg.

Results and Interpretation

Included Studies

Three phase III trials met the criteria for inclusion in this review: GEMINI-1 (N = 719) and GEMINI-2 (N = 722), which were identical, double-blind, noninferiority, randomized controlled trials (RCTs) in adult patients with HIV-1 infection who are treatment naive, and the ASPIRE trial (N = 90), which was an open-label, noninferiority, pilot RCT in adult patients with HIV-1 infection who are virologically suppressed. In all three included trials the intervention was DTG + 3TC administered as separate tablets whereas the comparator in the GEMINI trials was DTG + tenofovir disoproxil fumarate (TDF)/emtricitabline (FTC) and in the ASPIRE trial, the comparator was continuation of a patient's ART. All three trials reported results for up to 48 weeks of treatment. The primary outcome in the GEMINI trials was the proportion of patients with an HIV-1 RNA of fewer than 50 copies/mL at week 48, calculated according to the US FDA snapshot algorithm.[6] Noninferiority was concluded in the GEMINI trials if the difference between DTG + 3TC and DTG + TDF/FTC exceeded a noninferiority margin of 10%, which is consistent with the US FDA guidance for ARV drug development.[6] The primary outcome in the ASPIRE trial was the proportion of patients with treatment failure, defined as virologic failure, loss to follow-up, or treatment discontinuation or modification by week 24. Noninferiority was concluded in the ASPIRE trial if the difference between DTG + 3TC and continuation of patients' three-drug ART regimen exceeded a noninferiority margin of 12%, which is inconsistent with the US FDA guidance, which recommends a noninferiority margin of 4% for switch trials of ART drugs; however, the trial was initiated prior to the issuance of the US FDA guidance in 2015 and was not powered for a 4% noninferiority margin.[6]

Limitations of the evidence are the small size, open-label design, and use of an outdated noninferiority margin in the ASPIRE trial; the lack of adjustment for multiplicity of secondary outcomes in the statistical analyses, and use of separate tablet formulations of DTG and 3TC, as opposed to the FDC formulation of DTG/3TC, in all three trials. Further, the comparators used in the included trials are all available in Canada; however, the clinical expert consulted on this review advised that DTG + TDF/FTC (the comparator in the GEMINI trials) is not extensively used in Canada due to the availability of many effective STRs.

A limitation is generalizability to the target patient population. The indication for DTG/3TC includes adults and adolescents 12 years of age or older irrespective of previous ART status. However, inclusion criteria for the GEMINI-1, GEMINI-2, and ASPIRE studies limited study participation to adults 18 years of age and older; thus, there is a lack of data supporting the efficacy and safety of DTG + 3TC in patients with HIV-1 infection who are younger than 18 years of age. However, the expert consulted for this CADTH Common Drug Review review did not express concern regarding drug absorption, metabolism, or toxicity in patients younger than 18 years of age. Further, GEMINI-1 and GEMINI-2 were conducted in

patients who are ART naive only, and while the ASPIRE trial assessed the impact of switching to DTG + 3TC in patients who are virologically suppressed and ART experienced, this trial was associated with numerous limitations and noninferiority has not been established based on a noninferiority margin of 4% as currently recommended by the US FDA for switch trials. However, the clinical expert consulted by CADTH indicated that the data in patients who are treatment naive for DTG + 3TC were likely generalizable to patients who are treatment experienced. Another limitation is the lack of long-term data. Detailed efficacy and safety data for DTG + 3TC beyond 48 weeks were not available for this review. The GEMINI trials are ongoing and the ASPIRE trial was conducted as a pilot for a larger planned trial. The manufacturer provided additional information to CADTH during the review process for outcomes through 96 weeks of treatment. [redacted] In the absence of more compelling long-term data, the durability of the treatment effect and potential for emergence of resistance beyond 48 weeks remain uncertain.

Efficacy

The primary efficacy outcome in the GEMINI trials was the proportion of patients with a plasma HIV-1 RNA of > 50 copies/mL at week 48 in the intention-to-treat exposed population using the US FDA snapshot algorithm.[6] A similar proportion of patients achieved this outcome in both the GEMINI-1 (90% versus 93%) and GEMINI-2 (93% versus 94%) trials, in the DTG + 3TC versus DTG + TDF/FTC groups, respectively. Based on a 10% noninferiority margin, the results demonstrated that DTG + 3TC was noninferior to DTG + TDF/FTC as the lower bound of the 95% confidence interval (CI) of the adjusted treatment difference was greater than –10% in both GEMINI-1 (–2.6% [95% CI, –6.7 to 1.5]) and GEMINI-2 (–0.7% [95% CI, –4.3 to 2.9]). The proportion of patients with an HIV-1 RNA viral load of ≤ 50 copies/mL at week 48 was [redacted] in the DTG + 3TC group and [redacted] in the DTG + TDF/FTC group in GEMINI-1 and [redacted] in each treatment group in GEMINI-2. Subgroups of interest identified in the review protocol were baseline viral load (treatment naive; ≤ 100,000 copies/mL or > 100,000 copies/mL) and baseline CD4+ count (treatment naive; ≤ 200 cells/μL or > 200 cells/μL). The results in patients with a baseline HIV-1 RNA of ≤ 100,000 copies/mL in GEMINI-1 [redacted] and GEMINI-2 [redacted] in the DTG + 3TC and DTG + TDF/FTC groups, respectively, were similar to the primary analysis (i.e., differences in proportion were [redacted] in GEMINI-1 and [redacted] in GEMINI-2). In patients with an HIV-1 RNA of > 100,000 copies/mL, the results were as follows: GEMINI-1 (88% versus 91%) and GEMINI-2 [redacted]; however, the sample sizes in this subgroup were [redacted]. In patients with a baseline CD4+ cell count of > 200 cells/μL, the results were also similar to the primary analysis: GEMINI-1 [redacted] and GEMINI-2 [redacted], respectively, with differences in proportions of [redacted] in GEMINI-1 and [redacted] in GEMINI-2. In patients with a baseline CD4+ cell count of ≤ 200 cells/μL, the proportions of patients were GEMINI-1 [redacted] and GEMINI-2 [redacted], respectively; however, the sample sizes were also [redacted].

In the ASPIRE trial, the primary efficacy outcome was treatment failure, which was defined as a composite of virologic failure (defined as a confirmed HIV-1 RNA of > 50 copies/mL within 35 days of the initial result), loss to follow-up, or treatment discontinuation/modification by week 24. Three patients in each treatment group or 6.8% (DTG + 3TC) versus 6.7% (continued ART) of patients were defined as treatment failures.

The difference in the proportion of patients meeting this outcome was 0.15% (90% CI, –9.8 to 10.2). Based on a 12% noninferiority margin, the results demonstrated that DTG + 3TC was noninferior to continued ART as the lower bound of the 90% CI of the treatment difference was greater than –12%. Overall, 93% of patients treated with DTG + 3TC versus 91% of patients on continued ART (n = 41 patients in each group) achieved HIV-1 RNA levels of < 50 copies/mL at week 24. The corresponding proportions at week 48 were 91% versus 89% (n = 40 patients in each group). Residual viremia was also measured in a substudy of the ASPIRE trial (n = 72) using an ultrasensitive assay with a detection limit of 0.5 copies/mL. At baseline, residual viremia was 5.0 copies/mL in the DTG + 3TC group and 4.2 copies/mL in the continued ART group. There was no statistically significant difference between treatment groups in the change in residual viral load at either week 24 or week 48.

Change from baseline in CD4+ cell count was also assessed at week 48 by the randomization strata of baseline viral load and baseline CD4+ cell count. The change from baseline to week 48 in CD4+ cell count was similar between treatment groups in patients with a baseline viral load of ≤ 100,000 copies/mL: [redacted] in GEMINI-1 and [redacted] in GEMINI-2, whereas in patients with a baseline viral load of > 100,000 copies/mL the treatment differences were [redacted] in GEMINI-1 and [redacted] in GEMINI-2. For patients with a baseline CD4+ cell count of > 200 cells/μL, the differences between treatment groups were [redacted] in GEMINI-1 and [redacted] in GEMINI-2, whereas in patients with a baseline CD4+ count of ≤ 200 cells/μL, the differences between treatment groups were [redacted] in GEMINI-1 and [redacted] in GEMINI-2. The results in the subgroups of baseline HIV-1 RNA of > 100,000 copies/mL and baseline CD4+ cell count of ≤ 200 cells/μL are limited by small sample sizes. The only information reported in the ASPIRE trial was the median change from baseline to week 48 in CD4+ cell count, which was 39 cells/μL (interquartile range, –71 to 188) with DTG + 3TC and 28 cells/μL (interquartile range, –36 to 83) for combined ART.

In the GEMINI trials, health-related quality of life (HRQoL) was measured by the EuroQol 5-Dimensions 5-Levels general health questionnaire at baseline, week 4, week 24, and week 48, and was reported as an exploratory outcome only. In general, the change from baseline in utility scores and Visual Analogue Scale scores were similar throughout the trials in both treatment groups. The only apparent differences in mean (standard error) change from baseline in Visual Analogue Scale scores between treatment groups were reported [redacted] for DTG + TDF/FTC and [redacted]. HRQoL was an exploratory outcome in the GEMINI trials and a key limitation is the lack of evidence for validity, reliability, or responsiveness of the EuroQol 5-Dimensions 5-Levels in patients with HIV infection and that no minimal clinically important difference has been established in this population. There was no information available on HRQoL from the ASPIRE trial.

A key concern with switching from a three-drug regimen to a two-drug regimen of ART or initiating treatment with a two-drug ART regimen is the potential for developing resistance. In the GEMINI-1 and GEMINI-2 trials combined, a total of 10 patients (less than 1%) met pre-specified criteria for confirmed virologic withdrawal to week 48 (i.e., n = 6 in the DTG + 3TC group and n = 4 in the DTG + TDF/FTC group). Genotypic testing of the HIV-1 transcriptase, protease-reverse transcriptase, and integrase genes was successful for baseline and virologic withdrawal samples from all 10 patients with the exception of an integrase genotype assay failure for one patient in the DTG + TDF/FTC group.[7] None of the patients had emergence of resistance mutations to INSTIs or NNRTIs and all patients were classified

as virologic rebounds (not virologic failures). In the ASPIRE trial, one patient was classified as a virologic failure in the DTG + 3TC group at week 24.[8] This patient did not have any emergent reverse transcriptase or INSTI-resistance mutations and the patient remained viremic after switching to darunavir + abacavir/3TC.[8] Furthermore, the patient did not have any missed doses and was confirmed to have DTG concentrations.[8]

There was no information on adherence reported in the GEMINI-1 and GEMINI-2 trials. In the ASPIRE trial, it was reported that 92% of included patients had perfect adherence, although no information on how this was assessed or quantified was provided.

Harms

In the GEMINI-1 and GEMINI-2 trials, the proportion of patients with adverse events (AEs) was numerically less in the DTG + 3TC groups (78% and 74%) than in the DTG + TDF/FTC groups (82% and 79%), respectively. There did not appear to be any major imbalances in AEs between treatment groups or across trials. Overall, the most frequent AEs were headache, diarrhea, nasopharyngitis, and upper respiratory tract infection in both trials. There were limited harms data reported for the ASPIRE trial. The only available data were for laboratory and clinical AEs, of which any one AE was not reported in more than three patients.

The proportion of patients with serious adverse events (SAEs) in the GEMINI-1 and GEMINI-2 trials was similar in the DTG + 3TC groups (6% and 8%) and the DTG + TDF/FTC groups (6% and 9%), respectively. No information on SAEs was provided for the ASPIRE trial. The proportion of patients who withdrew due to AEs was 2% in each treatment group in both GEMINI trials. In the ASPIRE trial, one patient in the DTG + 3TC group withdrew due to an AE. There were no deaths reported in the GEMINI-1 and ASPIRE trials. In the GEMINI-2 trial, two deaths occurred in patients in the DTG + 3TC treatment group. The reasons were Burkitt's lymphoma and acute myocardial infarction.

Notable harms identified in the review protocol included nausea, vomiting, diarrhea, insomnia, depression, birth defects, and effects on lipids, bone, and renal function. In the GEMINI-1 trial, more patients in the DTG + TDF/3TC group appeared to have gastrointestinal AEs (particularly nausea and diarrhea), insomnia, and depression than in the DTG + 3TC group. In comparison, in the GEMINI-2 trial, the frequency of these AEs appeared to be similar between the two treatment groups, making it difficult to draw any conclusions regarding relative frequency of the AES between treatment groups. Mental health outcomes, and particularly depression, were identified as being important to patients based on the input received for this review. In the GEMINI trials, a low percentage of patients [redacted] experienced depression with no apparent imbalances between treatment groups. No information on depression or other mental health outcomes was available from the ASPIRE trial.

In the GEMINI trials, the changes from baseline to week 48 in various lipid parameters (i.e., total, low-density–lipoprotein, and high-density–lipoprotein cholesterol) were larger for DTG + 3TC than for DTG + TDF/FTC. In contrast, changes from baseline to week 48 in bone-related parameters (i.e., serum bone-specific alkaline phosphate, osteocalcin, procollagen 1 N-terminal propeptide, and type-1 collagen C-telopeptide) were larger in the DTG + TDF/FTC group than in the DTG + 3TC group. Similarly, the change from baseline to week 48 in renal-related biomarkers (i.e., serum creatinine, glomerular filtration rate, and urine protein/creatinine ratio) were also larger in the DTG + TDF/FTC group than in the DTG + 3TC group. According to the clinical expert consulted for this review, the magnitude of the

treatment differences in the changes in the lipid, bone, and renal parameters were unlikely to be clinically relevant.

Indirect Treatment Comparison

Based on the trials included in this review, the only direct head-to-head comparison of DTG and 3TC with another ART regimen was with DTG and TDF/FTC. One published network meta-analysis (NMA),[9] which was also submitted as an internal report by the manufacturer,[9,10] was reviewed and critically appraised in Appendix 6. The aim of the NMA was to compare the efficacy and safety of DTG + 3TC with traditional three-drug ART regiments adult patients with HIV-1 infection who are treatment naive. The NMA included 14 RCTs of three-drug ART regimens that comprised either an INSTI, a boosted PI, or a NNRTI as the core drug, combined with two nucleoside reverse transcriptase inhibitors as the treatment backbone. Efficacy outcomes assessed were virologic suppression at week 48 and CD4+ cell count change from baseline to week 48, whereas harms outcomes included AEs and SAEs. Results of the NMA suggest that there was no difference in efficacy or safety between DTG and 3TC and 12 different three-drug regimens of ART that are relevant to Canadian clinical practice. Furthermore, subgroup analysis in patients with a baseline viral load of at least 100,000 copies/mL suggested that DTG + 3TC was no worse than any of the comparators [redacted] for viral suppression at 48 weeks in patients with a high baseline viral load. The sparsity of the evidence networks and the noninferiority design of the primary RCTs precluded the ability of the NMA to establish precise estimates of differences between treatment regimens and thus limit confidence in the results.

Potential Place in Therapy[1]

In Canada, there are 10 STRs available for the treatment of HIV. All except Juluca (DTG/rilpivirine) are based on the paradigm of combining two nucleoside analogues with a third drug (i.e., INSTI, NNRTI, or PI with or without a pharmacokinetic booster). These treatment options can effectively treat most persons infected with HIV with tolerable once-daily doses, with a minimum of short-term and long-term toxicities. Aside from STRs, there remains the potential to combine individual ARV medications, allowing for many more once- or twice-daily treatment options. As such, especially for patients without previous virologic failures, there are few unmet treatment needs.

DTG/3TC, like Juluca, is a two-drug STR. Although one might argue that two-drug regimens are less likely to have short- and long-term toxicities, it would be an overstatement to suggest that more tolerable or safer regimens are needed. Assuming adequate potency to durably suppress HIV, the role of DTG/3TC would be as a smaller, less expensive treatment option than the other STRs (aside from Juluca). Juluca has similar benefits but has not really "caught on" as it must be taken with food and without antacids.

DTG/3TC could be used to treat a wide variety of persons infected with HIV. It would be an acceptable option for anyone not having a drug-resistant virus, either as upfront therapy or as a switch for issues of tolerance, convenience, pill size, or cost. The lower cost would make it a reasonable, and possibly preferred, treatment option for someone paying for a proportion of the cost of therapy out of pocket.

[1] This information is based on information provided in draft form by the clinical expert consulted by CADTH Common Drug Review reviewers for the purpose of this review.

It is estimated that at least 50% of Canadian patients infected with HIV have an un-mutated, wild-type virus, and therefore would qualify for DTG/3TC as a first-line or switch treatment. Even though the RCT data are in patients who are treatment naive, it is likely that DTG/3TC would be most used in those switching for reasons of tolerability, convenience, pill size, or cost. It is conceivable that the number of patients switching to DTG/3TC could be substantial.

Conclusions

Two identical, phase III, double-blind, noninferiority RCTs in adult patients with HIV-1 infection who are treatment naive support that a two-drug regimen of DTG + 3TC administered as separate tablets is noninferior to a three-drug regimen of DTG + TDF/FTC based on the proportion of patients with an HIV-1 viral load of < 50 copies/mL at week 48 using a noninferiority margin of 10%. One phase III, open-label, noninferiority RCT in adult patients with HIV-1 infection who are virologically suppressed demonstrated that switching to separate tablets of DTG + 3TC is noninferior to continued three-drug ART regimens based on the proportion of patients with treatment failure at week 24; however, this trial was associated with numerous limitations and noninferiority has not been established based on a noninferiority margin of 4% as currently recommended by the US FDA for switch trials. Harms were similar between treatment groups in the included trials and any differences in lipid, bone, or renal parameters were not considered to be clinically relevant. An NMA in the treatment-naive population did not provide evidence for a difference in efficacy or safety between DTG and 3TC and 12 different three-drug ART regimens relevant to Canadian clinical practice; however, confidence in the results is limited due to issues in the systematic literature search and the sparsity of the evidence network. Evidence gaps are the lack of evidence in patients younger than 18 years of age, lack of a high-quality trial in patients who are virologically suppressed and switching from a three-drug ART regimen to DTG/3TC, lack of direct evidence for the efficacy and safety of DTG/3TC administered as an FDC or compared with other ARV regimens available in Canada, and lack of long-term data to assess the durability of response and the potential for emergence of resistance mutations beyond 48 weeks.

Table 1: Summary of Results of the GEMINI-1 and GEMINI-2 Trials

Outcomes	GEMINI-1		GEMINI-2	
	DTG + 3TC	DTG + TDF/FTC	DTG + 3TC	DTG + TDF/FTC
Virologic Failures				
HIV-1 RNA ≥ 50 copies/mL at week 48, n/N (%) (ITT-E population)	13/356 (4)	6/358 (2)	7/360 (2)	7/359 (2)
Reasons for virologic failures, n (%): • Data in window and HIV-1 RNA ≥ 50 copies/mL • Discontinued for lack of efficacy • Discontinued for other reason and HIV-1 RNA ≥ 50 copies/mL • Change in ART	[redacted]	[redacted]	[redacted]	[redacted]
Virologic Successes				
HIV-1 RNA < 50 copies/mL at week 48, n/N (%) [95% CI][a] (ITT-E Population)	320/356 (90) [86.8 to 93.0]	332/358 (93) [90.0 to 95.4]	335/360 (93) [90.4 to 95.7]	337/359 (94) [91.4 to 96.4]
Adjusted difference in proportion[b], % (95% CI)	–2.6 (–6.7 to 1.5)		–0.7 (–4.3 to 2.9)	
Change From Baseline in CD4+ Cell Count (cells/μL) at Week 48				
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted mean change (SE)[c]	[redacted]	[redacted]	[redacted]	[redacted]
Difference (95% CI); *P* value	[redacted]		[redacted]	
Change From Baseline in EQ-5D-5L Utility Scores at Week 48				
Baseline score, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Week 48 score, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted mean change (SE)[d]	[redacted]	[redacted]	[redacted]	[redacted]
Difference (95% CI); *P* value	[redacted]		[redacted]	
Change From Baseline in EQ-5D-5L VAS Scores at Week 48				
Baseline score, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Week 48 score, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted mean change (SE)[d]	[redacted]	[redacted]	[redacted]	[redacted]
Difference (95% CI); *P* value	[redacted]		[redacted]	
Harms				
AEs, n/N (%)	276/356 (78)	295/358 (82)	267/360 (74)	284/359 (79)
SAEs, n/N (%)	21/356 (6)	22/358 (6)	29/360 (8)	33/359 (9)
WDAEs, n/N (%)	7/356 (2)	8/358 (2)	8/360 (2)	8/359 (2)
Deaths, n/N (%)	0/356 (0)	0/358 (0)	2/360 (< 1)[e]	0/359 (0)

3TC = lamivudine; AE = adverse event; ART = antiretroviral therapy; CD4+ = cluster of differentiation 4 positive; CI = confidence interval; DTG = dolutegravir; EQ-5D-5L = EuroQoL-5 Dimension-5-Level; FTC = emtricitabine; ITT-E = intention-to-treat exposed population; RNA = ribonucleic acid; SAE = serious adverse event; SD = standard deviation; SE = standard error; TDF = tenofovir disoproxil fumarate; VAS = Visual Analogue Scale; WDAEs = withdrawals due to adverse events.

Note: The primary efficacy outcome in both GEMINI-1 and GEMINI-2 was the proportion of patients with a plasma HIV-1 RNA of < 50 copies/mL at week 48 in the ITT-E population. Noninferiority was concluded if the lower boundary of the two-sided 95% CI for the difference between the treatment groups was greater than –10%.

[a] Using the US FDA snapshot algorithm.

[b] Adjusted difference is as per the Cochran-Mantel-Haenszel -stratified analysis adjusting for baseline stratification factors: HIV-1 RNA (≤ 100,000 copies/mL and > 100,000 copies/mL) and CD4+ cell count (≤ 200 cells/μL and > 200 cells/μL).

[c] Adjusted mean is the estimated mean change from baseline at week 48 in each group calculated from an analysis of covariance model adjusting for the following covariates/factors: baseline plasma HIV-1 RNA (factor) and CD4+ cell count.

[d] Mixed-model repeated measures were run on the last observation carried forward data set, using the observed margins option, adjusted for treatment, and baseline plasma HIV-1 RNA (≤ 100,000 copies/mL versus >100,000 copies/mL), CD4+ cell count (≤ 200 cells/μL versus >200 cells/μL), EQ-5D VAS, treatment × visit and EQ-5D VAS × visit as factors and covariate, with visit as the repeated factor.

[e] Two deaths occurred in GEMINI-2, both in the DTG + 3TC group. One death was due to Burkitt's lymphoma and one death was due to acute myocardial infarction.

Source: GEMINI-1 Clinical Study Report;[11] GEMINI-2 Clinical Study Report.[12]

Table 2: Summary of Results of the ASPIRE trial

Outcomes	ASPIRE	
	DTG + 3TC	DHHS or cART
Virologic Failures		
ITT-E Population at Week 24		
Proportion of patients with treatment failure at week 24, n/N (%)	3/44 (6.8)	3/45 (6.7)
Reasons for treatment failure, n (%): • **Virologic failure**[a] • **Lost to follow-up** • **Treatment discontinuation due to AE**[b] • **Regimen simplifications**	 1 (2.3) 1 (2.3) 1 (2.3) 0 (0)	 0 (0) 1 (2.2) 0 (0) 2 (4.4)
Difference in proportion, % (90% CI)	0.15 (–9.8 to 10.2)	
Virologic Successes		
Proportion of patients with HIV-1 RNA < 50 copies/mL at week 24, n/N (%)[c]	41/44 (93.2)	41/45 (91.1)
Difference in proportion, % (95% CI); *P* value	2.1 (–11.2 to 15.3); *P* = 0.71	
Proportion of patients with HIV-1 RNA < 50 copies/mL at week 48, n/N (%)[c]	40/44 (90.9)	40/45 (88.9)
Difference in proportion, % (95% CI); *P* value	2.0 (–12.6 to 16.5); *P* = 0.76	
Change From Baseline in CD4+ Cell Count (Cells/μL) at Week 48		
Baseline **Median (IQR)**[d]	 680 (498 to 927)	
Median change (IQR)	39 (–71 to 188)	28 (–36 to 83)

3TC = lamivudine; AE = adverse event; cART = combination antiretroviral therapy; CD4+ = cluster of differentiation 4 positive; CI = confidence interval; DHHS = Department of Health and Human Services; DTG = dolutegravir; ITT-E = intention-to-treat exposed; IQR = interquartile range; RNA = ribonucleic acid.

[a] In the one patient with virologic failure, no emergent reverse transcriptase or integrase resistance mutations were identified and the patient remained viremic after switching to darunavir-cobicistat + abacavir/3TC. The patient reported good adherence and had therapeutic DTG concentrations.

[b] One patient discontinued due to grade 2 constipation.

[c] As per the US FDA snapshot algorithm.

[d] Not available by treatment group; only reported for overall patient population.

Note: Noninferiority was concluded if the 90% CI for the difference in proportions calculated with Miettinen-Nurminen (score) CIs excluded a 12% noninferiority margin.

Source: Taiwo et al. (2019).[8]

Introduction

Disease Prevalence and Incidence

Human immunodeficiency virus type 1 (HIV-1) is one of the two types of viruses that cause HIV infection and is responsible for the majority of HIV infections globally.[1] HIV is transmitted by contact with infected body fluids such as blood, semen, pre-seminal fluid, fluids from the rectum or vagina, and through pregnancy, delivery, or breast feeding.[1,2] HIV infection gradually destroys the immune system by destroying cluster of differentiation 4 positive (CD4+) cells.[3] CD4+ cells are white blood cells that are critically important in helping the body fight infection.[3] HIV infection compromises the immune system's ability to mount an effective immunological response to opportunist pathogens and certain cancers.[3] If untreated, HIV infection can progress to AIDS and ultimately, death.[2] People with HIV-1 infection can be treated with antiretroviral (ARV) drugs, which help to lower the level of HIV-1 in the body, slow the spread of the virus, and help the immune system respond to other infections.[5] Antiretroviral therapy (ART) has improved steadily since the introduction of potent combination ART in 1996.[5] Treatment can provide patients with a better opportunity to live a longer, healthier life and decrease their risk of transmitting the virus to others. ART has significantly reduced HIV-associated morbidity and mortality and today HIV infection is largely a manageable chronic condition.[5] If treatment is started early, there is increased probability of living a near-normal lifespan.[2] Patients consulted for this review indicated that stigma, mental health outcomes, and quality of life are of major concern to patients.

The Public Health Agency of Canada estimates that, at the end of 2016, there were approximately 63,110 people (range, 55,500 to 70,720) living with HIV infection (including AIDS) in Canada, an approximate 5% increase from 2014 estimates.[4] The estimated prevalence rate in Canada at the end of 2016 was 173 per 100,000 people (range, 152 to 194 per 100,000).[4] Of those living with HIV, it was further estimated that 86% (range: 78% to 94%) were diagnosed, 81% (range, 75% to 87%) were on treatment, and 91% had a suppressed viral load (range, 87% to 95%).[4] The number of new HIV infections that occurred in Canada in 2016 was 2,165 (range, 1,200 to 3,150), resulting in an estimated incidence rate of 6.0 per 100,000 people (range, 3.3 to 8.7 per 100,000).[4] This reflects a slight increase from 2014 estimates (i.e., 5.5 per 100,000; range, 3.6 to 7.5 per 100,000).[4] In 2017, the Public Health Agency of Canada reported that there were 2,402 new cases of HIV infection in Canada, of which 75.2% were in males and 24.8% in females.[13] Of the new cases, 34.5% were in white people and 20.1% in Indigenous peoples, and most were reported in the 30- to 39-year-old age range.[13]

Standards of Therapy

According to the US Department of Health and Human Services (DHHS) *Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV*, the initial combination regimen for patients who are ART naive generally consists of two nucleoside reverse transcriptase inhibitors (NRTIs) administered in combination with a third active ARV drug from one of three drug classes: an integrase strand transfer inhibitor (INSTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a protease inhibitor (PI) with a pharmacokinetic enhancer or booster (e.g., cobicistat and ritonavir).[5] According to the most recent update of the DHHS guidelines (October 28, 2018), the following are recommended as initial regimens for most people with HIV (listed alphabetically): bictegravir/tenofovir alafenamide/emtricitabine (FTC) (Biktarvy), dolutegravir (DTG)/abacavir/lamivudine (3TC)

(Triumeq), but only for patients who are HLA-B*5701 negative, DTG (Tivicay) + tenofovir/FTC (Truvada), or raltegravir (Isentress) + tenofovir/FTC (Truvada or Descovy).[5] The DHHS guidelines also state that, given the many options for initial therapy, selection of a particular regimen for a particular patient should take into consideration virologic efficacy, toxicity, pill burden, dose frequency, drug-drug interaction potential, resistance test results, comorbid conditions, access, and cost.[5] The clinical expert consulted for this review concurred that the DHHS guidelines are used in Canada.

Drug

Dovato (DTG 50 mg/3TC 300 mg; fixed-dose combination [FDC]) is an oral, two-drug, single-tablet regimen (STR) ART that is the subject of this CADTH Common Drug Review review. The indication for DTG/3TC is as a complete regimen for the treatment of HIV-1 infection in adults and adolescents 12 years of age and older who weigh at least 40 kg.[14] The dosage recommendations are one tablet once daily to be taken orally with or without food.[14] The reimbursement request from the manufacturer is as per the indication.

Dovato consists of DTG, which is an INSTI that acts to inhibit HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral DNA integration.[14] 3TC is an NRTI that is metabolized by intracellular kinases to its active form, which is a substrate and competitive inhibitor of HIV reverse transcriptase which, in turn, is inhibited by viral DNA chain termination after incorporation of the 3TC triphosphate nucleoside analogue.[14] In Canada, DTG is currently available as a two-drug regimen combination with rilpivirine (Juluca), as a three-drug regimen with abacavir and 3TC (Triumeq), and as a single entity (Tivicay). 3TC is currently available in numerous combination products indicated for use in HIV infection, including with doravirine and tenofovir disoproxil fumarate (TDF) (Delstrigo), abacavir (Kivexa), zidovudine (Combivir), nevirapine and zidovudine (generic only), abacavir and zidovudine (Trizivir), and as a single entity (Epivir or 3TC). Various generic formulations of 3TC, alone and in combination (as previously detailed), are also available on the Canadian market.

The key characteristics of STRs and other commonly recommended ART used in Canada are provided in Table 3.

Table 3: Key Characteristics of Single-Table Regimens and Other Commonly Recommended Antiretroviral Therapy Regimens

Comparator Regimens[a]	Brand	Dosage Strengths	Indications[b]	Key Side Effects/Safety Issues
Single-Tablet Regimens				
DRV/TDF/3TC	Delstrigo	**DRV:** 100 mg **TDF:** 300 mg **3TC:** 300 mg	Treatment of HIV-1 infection in adults without past or present evidence of viral resistance to DRV, TDF, or 3TC[15]	**DRV:** Diarrhea, nausea, headache, rash, hyperlipidemia, drug-induced hepatotoxicity in DRV/r (rare); all PIs: risk of ECG abnormalities (i.e., PR interval prolongation)[16] **TDF**: Renal toxicity, decreased BMD, increased osteoporotic fractures; reports of lactic acidosis, hepatotoxicity[16] **3TC**: Generally well tolerated[16]
BTG/FTC/TAF	Biktarvy	**BTG:** 50 mg	Treatment of HIV-1 infection in adults with no known substitution	**BTG:** Diarrhea, nausea, headache, depression[17]

Comparator Regimens[a]	Brand	Dosage Strengths	Indications[b]	Key Side Effects/Safety Issues
		FTC: 200 mg **TAF:** 25 mg	associated with resistance to the individual components of Biktarvy[17]	**FTC**: Discoloration of skin (hands/feet)[16] **TAF:** Similar to TDF, but may have less renal and bone toxicity[18]
DTG/ABC/3TC	Triumeq	**DTG**: 50 mg **ABC**: 600 mg **3TC**: 300 mg	Treatment of HIV-1 infection in adults and adolescents aged ≥ 12 years and weighing ≥ 40 kg	**DTG**: Insomnia, headache, depression, early benign increase in SCr[16] **ABC**: Risk of severe hypersensitivity reaction in genetically susceptible patients, possible increased risk for MI[16] **3TC**: Generally well tolerated[16]
EVG/c/TAF/FTC	Genvoya[c]	**EVG**: 150 mg **c**: 150 mg **FTC**: 200 mg **TAF**: 10 mg	A complete regimen for the treatment of HIV-1 infection in adults and pediatric patients aged ≥ 12 years (and weighing ≥ 35 kg) and with no known RAMs to the individual components of Genvoya[19]	**EVG:** Nausea, diarrhea, insomnia, headache, depression, early benign increase in SCr[16] **c**: Can falsely increase SCr[16] **FTC**: Discoloration of skin (hands/feet)[16] **TAF:** Similar to TDF, but may have less renal and bone toxicity[18]
RPV/TAF/FTC	Odefsey[c]	**RPV**: 25 mg **TAF**: 25 mg **FTC**: 200 mg	A complete regimen for the treatment of adults infected with HIV-1 with no known RAMs to the NNRTI class, tenofovir or FTC, and with a VL ≤ 100,000 copies/mL[20]	**RPV**: Depression, insomnia, rash, headache, early benign increase in SCr [16] **TAF:** Similar to TDF, but may have less renal and bone toxicity[18] **FTC**: Discoloration of skin (hands/feet)[16]
DTG/RPV	Juluca	**DTG:** 50 mg **RPV:** 25 mg	A complete regimen to replace the current antiretroviral regimen for the treatment of HIV-1 infection in adults who are virologically stable and suppressed (HIV-1 RNA < 50 copies/mL)[21]	**DTG**: Insomnia, headache, depression, early benign increase in SCr[16] **RPV**: Depression, insomnia, rash, headache, early benign increase in SCr[16]
DRV/c/TDF/FTC	Symtuza	**DRV:** 800 mg **c**: 150 mg **TAF**: 10 mg **FTC**: 200 mg	Indicated as a complete regimen for the treatment of HIV-1 infection in adults and adolescents (aged 12 years and older with body weight at least 40 kg) and with no known mutations associated with resistance to the individual components of Symtuza[22]	**DRV:** Diarrhea, nausea, headache, rash, hyperlipidemia, drug-induced hepatotoxicity in DRV/r (rare); all PIs: risk of ECG abnormalities (i.e., PR interval prolongation)[16] **c**: Can falsely increase SCr[16] **TAF:** Similar to TDF, but may have less renal and bone toxicity,[18] **FTC**: Discoloration of skin (hands/feet)[16]
EVG/c/TDF/FTC	Stribild[c]	**EVG**: 150 mg **c**: 150 mg **FTC**: 200 mg **TDF**: 300 mg	A complete regimen for the treatment of adults aged ≥ 18 years infected with HIV-1 with no known mutations to the INSTI class, tenofovir, or FTC[23]	**EVG:** Nausea, diarrhea, insomnia, headache, depression, early benign increase in SCr[16] **c**: Can falsely increase SCr[16] **FTC**: Discoloration of skin (hands/feet)[16] **TDF**: Renal toxicity, decreased BMD, increased osteoporotic fractures; reports of lactic acidosis, hepatotoxicity[16]

Comparator Regimens[a]	Brand	Dosage Strengths	Indications[b]	Key Side Effects/Safety Issues
RPV/TDF/FTC	Complera[c]	**RPV**: 25 mg **TDF**: 300 mg **FTC**: 200 mg	A complete regimen for the treatment of adults infected with HIV-1 with no known RAMs to the NNRTI class, tenofovir, or FTC, and with a VL ≤ 100,000 copies/mL[24]	**RPV**: Depression, insomnia, rash, headache, early benign increase in SCr[16] **TDF**: Renal toxicity, decreased BMD, increased osteoporotic fractures; reports of lactic acidosis, hepatotoxicity[16] **FTC**: Discoloration of skin (hands/feet)[16]
EFV/TDF/FTC	Atripla[d]	**EFV**: 600 mg **TDF**: 300 mg **FTC**: 200 mg	For use alone as a complete regimen or in combination with other ARV drugs for the treatment of HIV-1 infection in adults[25]	**EFV**: Insomnia, vivid dreams, depressed mood, dizziness, headache, rash. Avoid in patients with history of anxiety, depression, or psychosis. Contraindicated in first trimester of pregnancy[16] **TDF**: Renal toxicity, decreased BMD, increased osteoporotic fractures; reports of lactic acidosis, hepatotoxicity[16] **FTC**: Discoloration of skin (hands/feet)[16]
Additional Relevant Comparator Regimens				
DRV/c + TAF/FTC	Prezcobix[c] Descovy	**DRV/c**: 800 mg/150 mg **TAF/FTC**: 10 mg/200 mg 25 mg/200 mg	In combination with other ARV drugs for the treatment of HIV infection in patients who are treatment naive and treatment experienced without DRV RAMs[26] In combination with other ARVs (such as NNRTIs or PIs) for the treatment of HIV-1 infection in adults and pediatric patients aged ≥ 12 years (and weighing ≥ 35 kg)[27]	**DRV**: Diarrhea, nausea, headache, rash, hyperlipidemia, drug-induced hepatotoxicity in DRV/r (rare); all PIs: risk of ECG abnormalities (i.e., PR interval prolongation)[16] **c**: Can falsely increase SCr[16] **TAF**: Similar to TDF, but may have less renal and bone toxicity[18] **FTC**: Discoloration of skin (hands/feet)[16]
DTG + TAF/FTC	Tivicay Descovy	**DTG**: 50 mg **TAF/FTC:** 10 mg/200 mg 25 mg/200 mg	Treatment of HIV-1 infection in adults and in INSTI-naive children weighing ≥ 30 kg[28] In combination with other ARVs (such as NNRTIs or PIs) for the treatment of HIV-1 infection in adults and pediatric patients aged ≥ 12 years (and weighing ≥ 35 kg)[27]	**DTG**: Insomnia, headache, depression, early benign increase in SCr[16] **TAF:** Similar to TDF, but may have less renal and bone toxicity[18] **FTC**: Discoloration of skin (hands/feet)[16]
DRV + r + TDF/FTC	Prezista[c]	**DRV**: 800 mg	Co-administered with 100 mg ritonavir and with other ARV drugs for the treatment of HIV-1 infection[29]	**DRV**: Diarrhea, nausea, headache, rash, hyperlipidemia, drug-induced hepatotoxicity in DRV/r (rare); all PIs: risk of ECG abnormalities (i.e., PR interval prolongation)[16] **r**: Diarrhea, nausea, headache, paresthesias, rash, hyperlipidemia, drug-induced hepatotoxicity in DRV/r (rare); all PIs: risk of ECG abnormalities (i.e., PR interval prolongation)[16]
	Norvir[c]	**r**: 100 mg	In combination with other ARV drugs for the treatment of HIV infection when therapy is warranted[30]	
		TDF: 300 mg		

Comparator Regimens[a]	Brand	Dosage Strengths	Indications[b]	Key Side Effects/Safety Issues
	Truvada, generics	**FTC**: 200 mg	In combination with other ARV drugs (such as NNRTIs or PIs) for the treatment of HIV-1 infection in adults[31]	**TDF**: Renal toxicity, decreased BMD, increased osteoporotic fractures; reports of lactic acidosis, hepatotoxicity[16] **FTC**: Discoloration of skin (hands/feet)[16]
DTG + TDF/FTC	Tivicay	**DTG**: 50 mg	Treatment of HIV-1 infection in adults and in INSTI-naive children weighing ≥ 30 kg[28]	**DTG**: Insomnia, headache, depression; early benign increase in SCr[16] **TDF**: Renal toxicity, decreased BMD, increased osteoporotic fractures; reports of lactic acidosis, hepatotoxicity[16] **FTC**: Discoloration of skin (hands/feet)[16]
	Truvada, generics	**TDF**: 300 mg **FTC**: 200 mg	In combination with other ARV drugs (such as NNRTIs or PIs) for the treatment of HIV-1 infection in adults[31]	

3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; BMD = bone mineral density; BTG = bictegravir; c = cobicistat; DRV = darunavir; DTG = dolutegravir; ECG = electrocardiogram; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; MI = myocardial infarction; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; r = low-dose ritonavir; RAM = resistance-associated mutation; RNA = ribonucleic acid; RPV = rilpivirine; SCr = serum creatinine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; VL = viral load.

[a] All regimens are administered orally once daily.[32]

[b] Health Canada indication.

[c] Must be taken with food or a meal.[32]

[d] Must be taken on an empty stomach.[32]

Source: Prezcobix product monograph,[26] Tivicay product monograph,[28] Descovy product monograph,[27] Genvoya product monograph,[19] Odefsey product monograph[20] Triumeq product monograph,[33] Truvada product monograph,[31] Prezista product monograph,[29] Norvir product monograph,[30] Stribild product monograph,[23] Complera product monograph,[24] Atripla product monograph,[25] Juluca product monograph,[21] Symtuza product monograph,[22] Biktarvy product monograph,[17] Delstrigo product monograph,[15] RxFiles.[16]

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of DTG 50 mg/3TC 300 mg administered orally in an FDC as a complete regimen for the treatment of HIV-1 infection in adults and adolescents 12 years of age and older and who weigh at least 40 kg.

Methods

Studies selected for inclusion in the systematic review included key studies provided in the manufacturer's submission to CDR and Health Canada, as well as those meeting the selection criteria presented in Table 4.

Table 4: Inclusion Criteria for the Systematic Review

Patient Population	Adults and adolescents 12 years of age and older who weigh at least 40 kg with HIV-1 infection Subgroups: • Baseline viral load (treatment naive; ≤ 100,000 copies/mL or > 100,000 copies/mL) • Baseline CD4+ count (treatment naive; ≤ 200 cells/μL or > 200 cells/μL) • Treatment naive versus treatment experienced
Intervention	DTG 50 mg/3TC 300 mg administered orally in a FDC once daily
Comparators	Standard of care triple ART regimen for HIV-1 infection: either 2 NRTIs + 1 INSTI; 2 NRTIs + 1 NNRTI; or 2 NRTIs + 1 PI (boosted with ritonavir or cobicistat) or other Health Canada-approved ART, including two-drug ART regimens
Outcomes	**Efficacy outcomes:** • Viral load (e.g., proportion of patients with HIV-1 RNA ≥ and < 50 copies/mL) • Change in CD4+ count • HRQoL[a] • Resistance • Adherence[a] **Harms outcomes:** • Mortality • AEs[a] • SAEs • WDAEs • Notable harms (e.g., NVD, insomnia, depression, birth defects, effects on lipids, bone, and renal function)
Study Design	Published and unpublished phase III and IV RCTs

3TC = lamivudine; AE = adverse event; ART = antiretroviral therapy; CD4+ = cluster of differentiation 4 positive; DTG = dolutegravir; FDC = fixed-dose combination; HRQoL = health-related quality of life; INSTI = integrase strand transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVD = nausea, vomiting, diarrhea; PI = protease inhibitor; RCT = randomized controlled trial; RNA = ribonucleic acid; SAE = serious adverse events; WDAE = withdrawal due to adverse events.

[a] These outcomes were identified as being of particular importance to patients in the input received by CADTH from patient groups.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH

(Medical Subject Headings), and keywords. The main search concepts were Dovato (DTG and 3TC).

No methodological filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results (see Appendix 2 for the detailed search strategies).

The initial search was completed on March 18, 2019. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on July 17, 2019. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters): health technology assessment agencies, health economics, clinical practice guidelines, drug and device regulatory approvals, advisories and warnings, drug class reviews, clinical trial registries, databases (free), Internet search, and background. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 5, excluded studies (with reasons) are presented in Appendix 3.

Results

Findings From the Literature

A total of three studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 5 and Table 6. A list of excluded studies is presented in Appendix 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

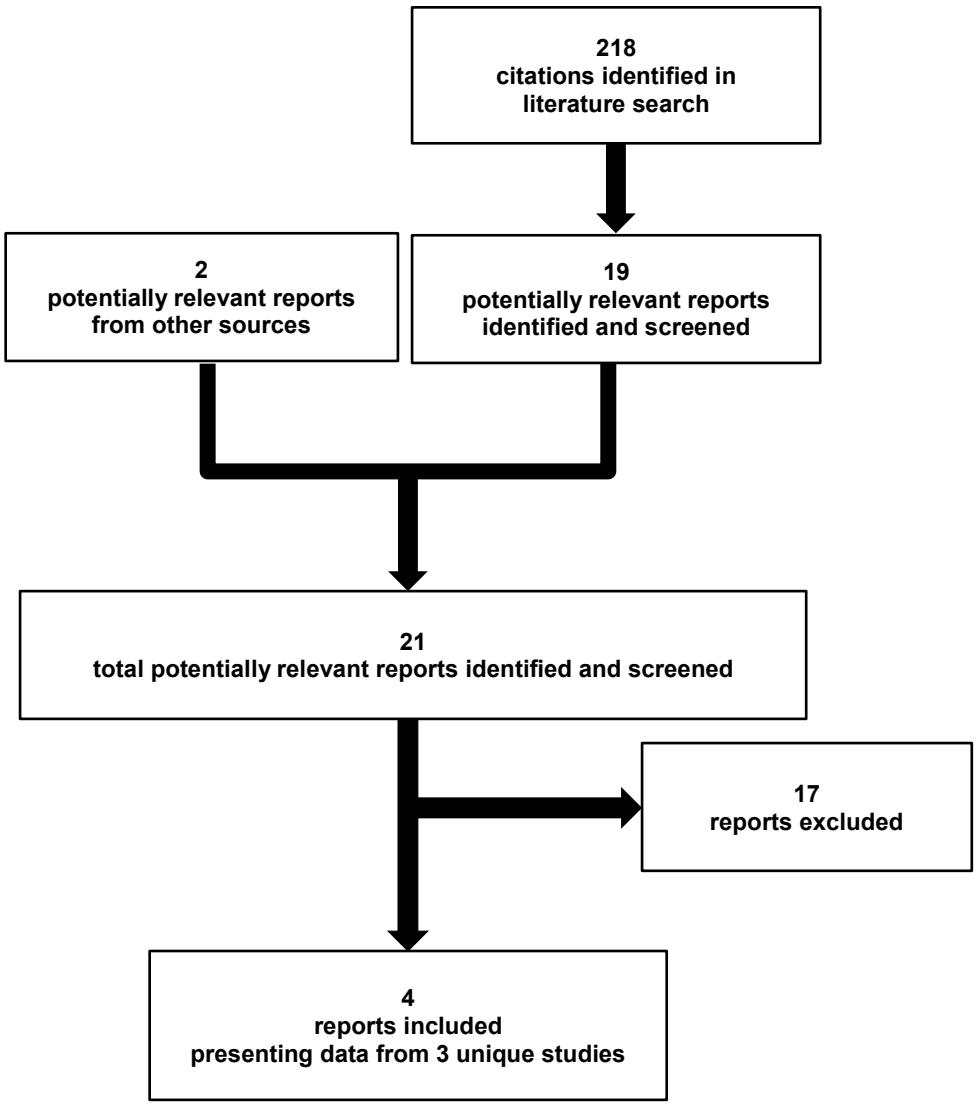


Table 5: Details of the GEMINI-1 and GEMINI-2 trials

		GEMINI-1	GEMINI-2
Designs and Populations	**Study Design**	DB, AC, MC, PG, noninferiority, phase III RCT	
	Locations	87 sites in 18 countries including Europe, South America, Asia, US, and Canada (3 sites)	104 sites in 18 countries including Europe, South America, Asia, US, and Canada (3 sites)
	Randomized (N)	719	722
	Inclusion Criteria	Adult (≥ 18 years of age) patients who are ART naive with HIV-1 infection and screening HIV-1 RNA of 1,000 to ≤ 500,000 copies/mL	
	Exclusion Criteria	Evidence of an active CDC stage 3 disease, hepatic impairment or unstable liver disease, HBV infection, need for HCV therapy in first 48 weeks, treatment with immunosuppressive therapies, evidence of pre-existing resistance, and laboratory abnormalities	
Drugs	**Intervention**	DTG 50 mg tablet + 3TC 300 mg tablet once daily with or without food	
	Comparator(s)	DTG 50 mg tablet + TDF/FTC 300 mg/200 mg FDC tablet once daily with or without food	
Duration	**Phase**		
	Run-in	28-day screening phase	
	Double-blind	96 weeks (DB randomized phase)	
	Follow-up	52 weeks (OL randomized phase) + continuation phase	
Outcomes	**Primary End Point**	Proportion of patients with plasma HIV-1 RNA < 50 copies/mL at week 48 as per the US FDA snapshot algorithm	
	Other End Points	• Proportion of patients with plasma HIV-1 RNA < 50 copies/mL at weeks 24, 96, and 144 as per the US FDA snapshot algorithm • Time to viral suppression (HIV-1 RNA < 50 copies/mL) • Absolute values and changes from baseline in CD4+ cell count at weeks 24, 48, 96, and 144 • Incidence of disease progression (HIV-associated conditions, AIDS and death) • Incidence of treatment-emergent genotypic resistance to DTG and 3TC or TDF/FTC in subjects meeting CVW criteria • Pre-specified subgroup analyses by age, gender, baseline CD4+ cell count • Change from baseline in HRQoL measured by the EQ-5D-5L at week 4, week 24, and week 48	
Notes	**Publications**	Cahn et al. (2019)[7]	

3TC = lamivudine; AC = active controlled; ART = antiretroviral therapy; CD4+ = cluster of differentiation 4 positive; CDC = Centers for Disease Control and Prevention; CVW = confirmed virologic withdrawal; DB = double blind; DTG = dolutegravir; EQ-5D-5L = EuroQoL 5-Dimensions 5-Levels; FDC = fixed-dose combination; FTC = emtricitabine; HBV = hepatitis B virus; HCV = hepatitis C virus; HRQoL = health-related quality of life; MC = multi-centre; OL = open-label; PG = parallel group; RCT = randomized controlled trial; RNA = ribonucleic acid; TDF = tenofovir disoproxil fumarate.

Source: GEMINI-1 Clinical Study Report;[11] GEMINI-2 Clinical Study Report.[12]

Table 6: Details of the ASPIRE Trial

		ASPIRE
Designs and Populations	**Study Design**	OL, AC, MC, PG, noninferiority, phase III RCT
	Locations	6 sites in the US
	Randomized (N)	90
	Inclusion Criteria	Adult (≥ 18 years of age) patients with HIV-1 infection and screening HIV-1 RNA < 20 copies/mL and < 50 copies/mL on all measurements within 48 weeks prior to study entry on any DHHS-recommended or alternate 3DR ART, no history of virologic failure after one year of therapy, nadir CD4+ count > 200 cells/μL, pre-treatment genotype documenting no mutations in protease or reverse transcriptase genes and no known resistance to INSTIs, and no evidence of chronic HBV
	Exclusion Criteria	Serious illness or AIDS-related complication, treatment with immune modulators within 30 days or vaccination within 7 days, chronic HBV infection, active HCV treatment, or anticipated need for HCV treatment, unstable liver disease or hepatic impairment
Drugs	**Intervention**	DTG 50 mg tablet + 3TC 300 mg tablet once daily with or without food
	Comparator(s)	Continued current DHHS-recommended or alternate 3DR ART regimen
Duration	**Phase**	
	Run-in	45-day screening phase
	Open-label	48 weeks
	Follow-up	NR
Outcomes	**Primary End Point**	Proportion of patients with treatment failure (defined as HIV-1 RNA > 50 copies/mL, loss to follow-up, or treatment discontinuation/modification) at 24 weeks
	Other End Points	• Proportion of patients with virologic success (defined as HIV-1 RNA < 50 copies/mL as per the US FDA snapshot algorithm) at 24 and 48 weeks • Change in CD4+ count from baseline to week 48 • Change in total cholesterol from baseline to week 48 • Change in LDL cholesterol from baseline to week 48 • Change in creatinine clearance from baseline to week 48 • Drug resistance–associated mutations • Residual viremia by HIV-1 single-copy assay
Notes	**Publications**	Taiwo et al. (2019);[8] Li et al. (2019)[34]

3DR = three-drug regimen; 3TC = lamivudine; AC = active controlled; ART = antiretroviral therapy; CD4+ = cluster of differentiation 4 positive; DHHS = US Department of Health and Human Services; DTG = dolutegravir; HBV = hepatitis B virus; HCV = hepatitis C virus; INSTI = integrase strand transferase inhibitor; LDL = low-density lipoprotein; MC = multi-centre; NR = not reported; OL = open-label; PG = parallel group; RCT = randomized controlled trial; RNA = ribonucleic acid.

Source: Taiwo et al. (2019);[8] Taiwo et al. (2015);[35] US National Library of Medicine Clinicaltrials.gov.[36]

Included Studies

Description of Studies

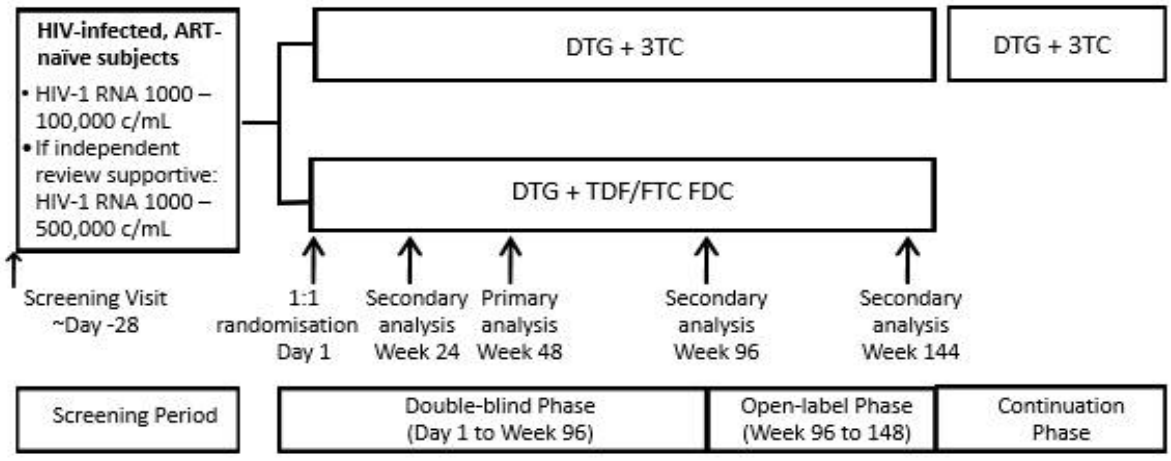
The GEMINI-1 (N = 719) and GEMINI-2 (N = 722) trials are identically designed, ongoing, phase III, randomized, double-blind, active-controlled, multi-centre, noninferiority trials in patients who are ART naive and have HIV-1 infection. The primary objective of both the GEMINI-1 and GEMINI-2 trials was to demonstrate noninferior antiviral activity of the two-drug regimen of DTG + 3TC compared with the three-drug regimen of DTG + TDF/FTC at 48 weeks. Eligible patients were randomized 1:1 in accordance with a computer-generated

randomization schedule using an interactive voice or website response system to either DTG + 3TC or DTG + TDF/FTC, both taken orally once daily with or without food. Patients were stratified at randomization by screening HIV-1 ribonucleic acid (RNA) level (≤ 100,000 copies/mL or > 100,000 copies/mL) and screening CD4+ count (≤ 200 cells/μL or > 200 cells/μL). Patients maintained their randomized treatment assignment throughout the double-blind and open-label randomized phases of the studies.

The GEMINI trials originally enrolled patients with a screening HIV-1 RNA of 1,000 copies/mL to ≤ 100,000 copies/mL, but as permitted by the protocol, the viral load cap was increased to ≤ 500,000 copies/mL following an independent review of accumulated data from other clinical trials investigating the DTG + 3TC regimen, which supported the use of this regimen.

The GEMINI trials included a 28-day screening phase (for viral load assessment, which could be extended to 35 days to allow for receipt of all screening assessment results), a double-blind randomized phase (day 1 to week 96; primary outcome was assessed at week 48), an open-label randomized phase (week 96 to week 148), and a continuation phase (as illustrated in Figure 2). All patients who successfully completed 96 weeks of randomized, double-blind treatment were eligible to continue to receive their originally randomized treatment in the open-label randomized phase through week 148. Patients who were originally randomized to receive DTG + 3TC and successfully completed 148 weeks of treatment were permitted continued access to DTG + 3TC in the continuation phase. With regard to the primary analysis, study visits were planned for baseline, and weeks 4, 8, 12, 16, 24, 36, and 48 with additional re-test visits at weeks 28 and 52 to confirm viral test results in patients with HIV-1 RNA levels of ≥ 50 copies/mL at week 24 or week 48, respectively. The studies are ongoing and study visits are planned every 12 weeks until week 148.

Figure 2: Study Design of the GEMINI-1 and GEMINI-2 Trials



3TC = lamivudine; DTG = dolutegravir; FDC = fixed-dose combination; FTC = emtricitabine; RNA = ribonucleic acid; TDF = tenofovir disoproxil fumarate.

Source: GEMINI-1 Clinical Study Report;[11] GEMINI-2 Clinical Study Report.[12]

The ASPIRE trial (N = 90) was a phase III, randomized, open-label, active-controlled, multi-centre, noninferiority, pilot switch trial in adults infected with HIV-1 who were virologically suppressed with any US DHHS-recommended or alternative three-drug regimen of ART for 48 weeks or more. Patients randomized to the two-drug regimen of DTG + 3TC switched from their three-drug regimen to DTG + 3TC, whereas patients in the comparator group continued their current three-drug regimen ART. The primary objective of the ASPIRE trial was to demonstrate noninferiority of the two-drug regimen of DTG + 3TC to continuation of standard three-drug maintenance ART over 48 weeks. This trial was conducted as a pilot trial in preparation for a planned fully powered clinical trial entitled TANGO (Clinicaltrials.gov identifier, NCT02831673), which is currently recruiting patients. Following a 45-day screening phase, eligible patients were randomized 1:1 to switch to open-label DTG + 3TC given as separate tablets once daily with or without food or to continue their current three-drug regimen ART. The method of randomization was not specified. The primary analysis was conducted at week 24 with supportive analyses conducted at week 48.

A substudy of the ASPIRE trial was conducted in which an ultrasensitive assay was used in a subgroup of patients (n = 72) with undetectable virus by conventional methodology to assess whether the switch to DTG + 3TC led to increased residual viremia. Low-level plasma HIV viremia were measured in a patient's plasma at study entry, and at week 24 and week 48 using a validated ultrasensitive integrase single-copy assay with limit of detection of HIV-1 RNA of 0.5 copies/mL.

Populations

Inclusion and Exclusion Criteria

In the GEMINI-1 and GEMINI-2 studies, eligible patients included adult (18 years of age or older) men and women with screening plasma HIV-1 RNA ranging from 1,000 copies/mL to ≤ 500,000 copies/mL who were ART naive (defined as 10 days or fewer of prior therapy with any ARV drug following a diagnosis of HIV-1 infection). Patients who received past HIV prophylaxis (i.e., either pre- or post-exposure prophylaxis) were permitted if the last pre- or post-exposure dose was more than one year from HIV diagnosis or there was documented HIV seronegativity between the last prophylactic dose and the date of HIV diagnosis.

Key exclusion criteria were any evidence of an active Centers for Disease Control and Prevention stage 3 disease (except cutaneous Kaposi's sarcoma not requiring systemic therapy and historical or current CD4+ cell counts of < 200 cells/μL), severe hepatic impairment or unstable liver disease, evidence of hepatitis B virus (HBV) infection, anticipated need for any hepatitis C virus (HCV) therapy during the first 48 weeks of the study and for HCV therapy based on interferon or any drugs with potential for adverse drug:drug interactions with study treatment throughout the entire study period, and patients with a significant suicidality risk. Patients who had been treated with an HIV-1 immunotherapeutic vaccine within 90 days of screening or received treatment with radiation, cytotoxic chemotherapy, or any systemic immune suppressant within 28 days of screening were also excluded. Finally, patients with any evidence of pre-existing viral resistance based on the presence of any major resistance-associated mutation; any verified grade 4 laboratory abnormality or acute laboratory abnormality at screening; or significant liver, biliary, or renal abnormalities were also excluded.

In the ASPIRE trial, eligible patients included adult (18 years of age or older) patients with HIV-1 infection with a screening HIV-1 RNA of < 20 copies/mL and < 50 copies/mL on all measurements within 48 weeks prior to study entry who were on any US DHHS-

recommended or alternate three-drug regimen ART. Patients were required to have no history of virologic failure after one year of therapy, a nadir CD4+ count of > 200 cells/μL, pre-treatment genotype documenting no mutations in protease or reverse transcriptase genes, no known resistance to INSTIs, and no evidence of chronic HBV. Key exclusion criteria included serious illness or AIDS-related complications, treatment with immune modulators within 30 days or vaccination within seven days, chronic HBV infection, active HCV treatment or anticipated need for HCV treatment, unstable liver disease, or hepatic impairment. A prior switch in ART for simplification or tolerability was permitted.

Baseline Characteristics

In the GEMINI-1 and GEMINI-2 trials, baseline patient demographic and disease characteristics appeared balanced between the treatment groups and across both trials (Table 7). The median age of patients in the intention-to-treat exposed (ITT-E) population ranged from 32 to 33 years. There was a predominance of male patients (83% to 87%) compared with female patients (13% to 17%) in both trials and most patients were white (66% to 69%) in GEMINI-1 and GEMINI-2, respectively. In addition, most patients (39% to 40%) had a baseline HIV-1 RNA viral load in the 10,000 copies/mL to 50,000 copies/mL range. Approximately 20% of patients had a viral load of > 100,000 copies/mL and only 2% to 3% had a viral load of > 500,000 copies/mL. Median CD4+ cell counts at baseline ranged from 427.0 cells/μL to 442.0 cells/μL across treatment groups in both trials. In keeping with the exclusion criteria, there were no patients with HBV infection, whereas approximately 4% to 6% of patients had HCV infection. Approximately 10% to 13% of patients had a history of depression at baseline.

Table 7: Summary of Baseline Characteristics in the GEMINI-1 and GEMINI-2 Trials (Intention-to-Treat Exposed Population)

Characteristic	GEMINI-1		GEMINI-2	
	DTG + 3TC (N = 356)	DTG + TDF/FTC (N = 358)	DTG + 3TC (N = 360)	DTG + TDF/FTC (N = 359)
Age (years), n (%) **Median (range)** **≤ 18[a]** **19 to 64** **≥ 65**	[redacted]	[redacted]	[redacted]	[redacted]
Sex, n (%) **Female** **Male**	[redacted]	[redacted]	[redacted]	[redacted]
Race, n (%) **American Indian or Alaskan Native** **Asian** **Black or African-American** **Native Hawaiian or Pacific Islander** **White** **Multiple heritage**	[redacted]	[redacted]	[redacted]	[redacted]
Baseline HIV-1 RNA (log_{10} copies/mL) **Median (range)**	[redacted]	[redacted]	[redacted]	[redacted]
Baseline HIV-1 RNA (copies/mL), n (%) [redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Characteristic	GEMINI-1		GEMINI-2	
	DTG + 3TC (N = 356)	DTG + TDF/FTC (N = 358)	DTG + 3TC (N = 360)	DTG + TDF/FTC (N = 359)
[redacted]				
Baseline CD4+ count (cells/µL) Median (range)				
Baseline CD4+ count (cells/µL), n (%)				
HBV and HCV test results, n (%)				
CDC category, n (%) HIV infection stage 0 HIV infection stage 1 HIV infection stage 2 HIV infection stage 3				
HIV risk factors[d], n (%)				
Medical history				

3TC = lamivudine; CD4+ = cluster of differentiation 4 positive; CDC = Centers for Disease Control and Prevention; DTG = dolutegravir; FTC = emtricitabine; HBV = hepatitis B virus; HCV = hepatitis C virus; RNA = ribonucleic acid; TDF = tenofovir disoproxil fumarate.

[a] Patients were required to be ≥ 18 years of age to participate in the study.

[redacted]

[d] Patients may have had one or greater risk factor.

Source: GEMINI-1 Clinical Study Report;[11] GEMINI-2 Clinical Study Report.[12]

In the ASPIRE trial, baseline demographic and disease characteristics were only reported for the overall ITT-E population and not specifically by treatment group (Table 8). The median age of patients was older (47 years) than the GEMINI trials; however, similar to the GEMINI trials, there was also a preponderance of male (88%) and white (60%) patients. Included patients had been on prior ART for a median of approximately six years and CD4+ cell counts reflected this (i.e., median 680 cells/µL). There was an approximate equal

distribution of prior ART regimens between INSTIs (37%), PIs (33%), and NNRTIs (30%), whereas 86% of patients were on TDF/FTC and abacavir/3TC prior to randomization.

Table 8: Summary of Baseline Characteristics in ASPIRE (Intention-to-Treat Exposed Population)

Characteristic	ASPIRE	
	DTG + 3TC (N = 44)	DHHS or cART (N = 45)
Age (years)		
Median (IQR)	47 (38 to 54)	
Sex, n (%)		
Male	78 (88)	
Race, n (%)		
White	53 (60)	
Black	34 (38)	
Hispanic	13 (15)	
Past ART exposure (years)		
Median (IQR)	5.7 (3.7 to 7.5)	
CD4+ cell count (cells/μL)		
Median (IQR)	680 (498 to 927)	
Pre-randomization ART regimens, n (%)		
INSTIs	33 (37)	
PIs	29 (33)	
NNRTIs	27 (30)	
TDF/FTC and ABC/3TC	77 (86)	

3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; CD4+ = cluster of differentiation 4 positive; cART = combination antiretroviral therapy; DHHS = Department of Health and Human Services; DTG = dolutegravir; FTC = emtricitabine; INSTI = integrase strand transferase inhibitor; IQR = interquartile range; NNRTI = non-nucleoside reverse transferase inhibitor; PI = protease inhibitor; TDF = tenofovir disoproxil fumarate.

Source: Taiwo et al. (2019).[8]

Interventions

In the GEMINI-1 and GEMINI-2 trials, study treatment comprised DTG 50 mg tablets that were similar in appearance to the commercially available tablets with the exception of a different film coat colour than the commercially supplied tablet. Commercial supply 3TC and TDF/FTC tablets were used but were over-encapsulated to be visually identical to each other. Patients randomized to the two-drug regimen received one DTG 50 mg tablet plus one over-encapsulated 3TC 300 mg tablet once daily and patients randomized to the three-drug regimen received one DTG 50 mg tablet plus one over-encapsulated TDF/FTC 300 mg/200 mg FDC tablet once daily, all with or without food. No dose reductions, modifications in dose, or changes in dose frequency were permitted.

[redacted] A summary of concomitant medications taken by 5% or more of patients in either of the GEMINI-1 or GEMINI-2 trials is provided in Table 9.

Table 9: Summary of Concomitant Medications in GEMINI-1 and GEMINI-2 (≥ 5% of Patients) (Intention-to-Treat Exposed Population)

Medication, n (%)	GEMINI-1		GEMINI-2	
	DTG + 3TC (N = 356)	DTG + TDF/FTC (N = 358)	DTG + 3TC (N = 360)	DTG + TDF/FTC (N = 359)
[redacted]				

Source: GEMINI-1 Clinical Study Report;[11] GEMINI-2 Clinical Study Report.[12]

In the ASPIRE trial, open-label DTG 50 mg + 3TC 300 mg were given as separate tablets once daily with or without food. No information was available on the comparator three-drug regimen ART or regarding concomitant medications used by patients.

Outcomes

In the GEMINI-1 and GEMINI-2 trials, unless otherwise stated, efficacy analyses for the primary week 48 analyses included data up to the data cut-off of May 28, 2018.

The primary efficacy outcome in the GEMINI-1 and GEMINI-2 trials was the proportion of patients with a plasma HIV-1 RNA of < 50 copies/mL at week 48, using the US FDA

snapshot algorithm for the ITT-E population. The snapshot algorithm is an analysis approach that is used for measurement of a virologic outcome at a given time point (e.g., week 48) that also specifies a window period for possible virologic assessments (e.g., the window size may be one-half the duration of time between study visits or the window may be smaller at earlier time points than later time points).[6] For example, the window period for measurement of a virologic outcome at week 48 could range from 42 to 54 weeks (295 to 378 days).[6] This is in contrast to other more complex approaches that have previously been used, such as the time to loss of virologic response analytical approach.[6] Analytical methodology included, but was not limited to, the Abbott RealTime HIV-1 Assay, which has a lower limit of quantitation of 40 copies/mL. In some cases (e.g., where the plasma HIV-1 RNA was below the lower limit of quantification for a given assay), additional exploratory methods may have been used to further characterize plasma HIV-1 RNA levels.

Secondary outcomes in the GEMINI-1 and GEMINI-2 trials relevant to this review included the proportion of patients with a plasma HIV-1 RNA of < 50 copies/mL at week 24 (also using the US FDA snapshot algorithm for the ITT-E population), absolute values and change from baseline in CD4+ cell counts at week 24 and week 48, and incidence of emergence of mutations conferring genotypic and phenotypic resistance to DTG + 3TC or TDF/FTC in patients meeting criteria for confirmed virologic withdrawal (CVW).

Exploratory outcomes in the GEMINI-1 and GEMINI-2 trials relevant to this review included assessment of health-related quality of life (HRQoL) as measured by the EuroQol 5-Dimensions 5-Levels (EQ-5D-5L) questionnaire.[37] The EQ-5D-5L is a standardized, generic, utility-based questionnaire that provides a profile of patient function and a global health state rating.[37] The five-item measure has one question assessing each of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, and five levels for each dimension, including no problems, slight problems, moderate problems, severe problems, and extreme problems.[37] The respondents' rating of each dimension is combined to create a descriptive health profile (health state description), which in turn is used to create an overall index score ranging from 0 (death) to 1.0 (perfect health), reflecting preferability compared with other health profiles according to a US-specific value set. Higher index scores indicate better health. In addition, respondents rate their overall health using a Visual Analogue Scale (VAS) that ranges from 0 (the worst health you can imagine) to 100 (the best health you can imagine); thus, higher VAS scores similarly indicate better overall health statuses. It should be noted that there is no evidence for validity, reliability, or responsiveness of the EQ-5D-5L instrument in patients with HIV infection and that no minimal clinically important difference (MCID) has been established in this population.

[redacted]

Harms outcomes included the monitoring and reporting of the incidence and severity of adverse events (AEs), serious adverse events (SAEs), withdrawals due to adverse events (WDAEs), and laboratory abnormalities. Lipid, bone, and renal parameters were assessed as change from baseline to weeks 24 and 48.

In the ASPIRE trial, the primary outcome was the proportion of patients with treatment failure, which was defined as virologic failure (confirmed virologic load of > 50 copies/mL within 35 days of the initial result), loss to follow-up, or treatment discontinuation or

modification by week 24. In the event of virologic failure, protease-reverse transcriptase and integrase genotyping were performed on the virologic failure confirmation sample, and DTG concentrations were assayed using a validated assay with a dynamic range of 5.0 ng/mL to 10,000 ng/mL.

Secondary outcomes in the ASPIRE trial included the proportion of patients with virologic success, which was defined as an HIV-1 RNA of < 50 copies/mL as per the US FDA snapshot algorithm[6] at 24 and 48 weeks, change from baseline to week 48 in CD4+ cell counts, total cholesterol, low-density–lipoprotein (LDL) cholesterol, creatinine clearance, development of drug resistance–associated mutations, and magnitude of residual viremia by an ultrasensitive HIV-1 single-copy assay with a lower limit of detection of 0.5 copies/mL.

Statistical Analysis

Sample Size

In the GEMINI-1 and GEMINI-2 trials, it was assumed that a true response rate for the DTG + 3TC group would be 87%, whereas for the DTG + TDF/FTC group it would be 89%. Based on these assumptions, the targeted sample size was 347 patients per treatment group, which was based on 90% power, a 2.5% one-sided alpha-level, and a 10% noninferiority margin.

In the ASPIRE trial, a sample size of 41 patients per treatment group provided 80% power to demonstrate noninferiority of DTG + 3TC to continued ART based on a 12% noninferiority margin, assuming an estimated treatment failure rate of 5% per treatment group by week 24 and a 5% one-sided type I error rate. The sample size was increased by 10% to account for potential loss to follow-up, resulting in a target sample size of 45 patients per treatment group.

Noninferiority Margin

In the GEMINI-1 and GEMINI-2 trials, a noninferiority margin of 10% for virologic efficacy was used. Therefore, noninferiority was concluded if the lower bound of the two-sided 95% confidence interval (CI) for the Cochran-Mantel-Haenszel (CMH) adjusted difference in the proportion of patients with a plasma HIV-1 RNA of < 50 copies/mL in the DTG + 3TC group minus the proportion of patients with a plasma HIV-1 RNA of < 50 copies/mL in the DTG + TDF/FTC FDC group was greater than –10%. The use of a 10% to 12% noninferiority margin in patients who are treatment naive is consistent with the US FDA guidance to industry for ART drug development.[6]

In the ASPIRE trial, demonstration of noninferiority was based on a 12% noninferiority margin. Therefore, noninferiority was concluded if the 90% CI for the difference in proportions of patients with treatment failure calculated with Miettinen-Nurminen (score) confidence limits excluded the –12% noninferiority margin. The ASPIRE trial was designed prior to the US FDA guidance to industry for ART drug development (2015), which recommends a stringent noninferiority margin of 4% for virologic failure in switch studies of ART in group 1 patients (i.e., fully susceptible to all approved drugs, treatment naive, or previous treatment with a well-documented treatment history demonstrating no virologic failure).[6]

Missing Data

[redacted]

In the ASPIRE trial, patients with missing data (e.g., lost to follow-up) were considered to be treatment failures. No information was available regarding imputation of missing data for any secondary outcomes.

Multiplicity Adjustment

In the GEMINI-1 and GEMINI-2 trials, there was no adjustment for multiplicity testing of the secondary outcomes. Similarly, in the ASPIRE trial, there was no adjustment for multiplicity in the analysis of any of the secondary outcomes.

Efficacy Analyses

In the GEMINI-1 and GEMINI-2 trials, for the primary comparison at week 48, adjusted estimates of the difference in the proportions of patients with a plasma HIV-1 RNA of < 50 copies/mL between the two treatment groups was calculated along with two-sided 95% CIs based on a stratified analysis using CMH weights in the ITT-E population. For the statistical analysis, four strata (subgroups) were formed according to the combinations of levels of the following categorical variables:

- baseline plasma HIV-1 RNA (≤ 100,000 copies/mL versus > 100,000 copies/mL)
- baseline CD4+ cell count (≤ 200 cells/μL versus >200 cells/μL).

The CMH estimate of the adjusted treatment difference was calculated as the weighted average of strata-specific estimates of the treatment difference between the two groups calculated within each of the four baseline analysis strata. Sensitivity analyses were conducted using the per-protocol (PP) and intention-to-treat (ITT) populations, which were compared for consistency with the results from the primary ITT-E population analysis.

Treatment heterogeneity across randomization strata was assessed using the weighted least squares chi-squared statistic to test for one-way homogeneity across the levels of each categorical variable, with each categorical variable considered separately. Any heterogeneity found to be statistically significant was to be explored and if necessary, results were reported for each level of the categorical variable. Planned investigation of heterogeneity was confined to the week 24 and week 48 snapshot analyses. Tests of homogeneity were assessed at the one-sided 10% level of significance.

The proportion of patients with an HIV-1 RNA of < 50 copies/mL at week 48 in the ITT-E population was also assessed in various pre-specified subgroups defined by baseline demographic and disease characteristics. The subgroups relevant to this review include baseline plasma viral load and baseline CD4+ cell count, which were randomization strata. No formal statistical comparisons were conducted between subgroups.

Four analyses were planned to evaluate the secondary outcomes at week 24, week 48, week 96, and week 144. Further data cuts and analyses may be conducted after week 144 to support regulatory submissions and publications. The week 48 analysis was the primary analysis to evaluate the primary and secondary objectives of the study protocol.

At weeks 28, 52, 100, and 148, a confirmatory viral load measurement was (or will continue to be) performed for patients presenting with an HIV-1 RNA of ≥ 50 copies/mL at the week 24, 48, 96, and 144 visits, respectively. The primary and secondary efficacy end points correspond to viral load measurements collected within a six or fewer week window around the visits of interest (including data from the visits at weeks 28, 52, 100, and 148), as per the US FDA snapshot algorithm.[6] For this reason, the primary and secondary analyses are denoted as occurring at weeks 24, 48, 96, and 144 with the understanding that respective data from the week 28, 52, 100, and 148 visits may be included.

The change from baseline in CD4+ cell counts at week 48 was analyzed using an analysis of covariance model. The analysis of covariance was adjusted for treatment, baseline CD4+ count as a covariate, and randomization strata (baseline plasma HIV-1 RNA and baseline CD4+ cell count). A mixed-model repeated measures analysis was conducted as a sensitivity analysis.

A sensitivity analysis was performed at week 48 to assess whether bias was introduced by the unblinded analysis performed at week 24. The proportion of patients with a plasma HIV-1 RNA of < 50 copies/mL at week 48 using the US FDA snapshot algorithm was compared between patients who reached week 48 with results before and after the week 24 unblinding. No formal statistical hypothesis testing was performed.

Other data in the GEMINI-1 and GEMINI-2 trials were summarized by treatment group and presented as summary statistics and analyses of change from baseline.

In the ASPIRE trial, the primary analysis was based on the proportion of patients with treatment failure as previously defined. A secondary analysis of treatment failure included only patients with virologic failure. Virologic outcomes were based on the US FDA snapshot algorithm at week 24 and week 48 and were compared with corresponding 95% CIs. Wilcoxon rank sum tests were used to contrast baseline characteristics and assess changes in CD4+ cell counts, lipids, and creatinine clearance. All baseline comparisons and secondary inferences were assessed using a 5% type I error rate.

Analysis Populations

Results are reported for the following populations in the GEMINI-1 and GEMINI-2 trials:

- ITT-E Population: All randomized patients who received at least one dose of the study medication. Patients were assessed according to their randomized treatment, regardless of the treatment they received. Unless otherwise stated, the ITT-E population was used for efficacy analyses.
- ITT Population: All randomized patients. Patients were assessed according to their randomized treatment even if no study treatment was taken or the wrong treatment was received. The ITT population was used for sensitivity analyses.
- PP Population: All patients in the ITT-E population except for significant protocol violators (e.g., violations that could have affected the assessment of antiviral activity). The PP population was used for sensitivity analyses of the primary efficacy outcome.
- Safety Population: All patients who received at least one dose of the study medication. Patients were analyzed according to the actual treatments received. Unless otherwise stated, the safety population was used for all safety analyses.
- CVW Population: All patients in the ITT-E population who met the derived CVW criteria. The CVW algorithm was derived using nominal electronic case report form visit rather than the assessment window, taking unscheduled visits into account. A patient could only be classified as CVW for the analyses if the patient had not withdrawn from the study treatment at the time the HIV-1 RNA sample was taken.

In the ASPIRE trial, all results were reported in the ITT-E population, which was defined as the treatment-exposed population and comprised the ITT population minus one patient who did not initiate the study treatment and was therefore excluded.

Patient Disposition

In the GEMINI-1 and GEMINI-2 trials, similar proportions of patients in each treatment group [redacted] withdrew from the trials (Table 10). The most frequent reasons for discontinuation were loss to follow-up, AEs, and withdrawal of consent by the patient. In GEMINI-1, [redacted] withdrew due to [redacted]. Similarly, in GEMINI-2, [redacted]. In both trials, the proportion of patients who withdrew due to lack of efficacy was lower than 1%.

In the ASPIRE trial, patient disposition was not reported by treatment group (Table 10). Overall, 8% of patients discontinued the trial, mainly due to protocol deviation (5%). In total, two patients (2%) of patients withdrew due to lack of efficacy. Overall, it was reported that of the 89 patients in the ITT-E population, seven (8%) patients discontinued treatment for the reasons detailed in Table 10.

Table 10: Patient Disposition

	GEMINI-1		GEMINI-2		ASPIRE	
	DTG + 3TC	DTG + TDF/FTC	DTG + 3TC	DTG + TDF/FTC	DTG + 3TC	cART
Screened, N	[redacted]		[redacted]		[redacted]	
Randomized, N (%)	[redacted]		[redacted]		45(100)	45(100)
Treated, N (%)	356 (99)	358 (99)	360 (100)	359 (99)	44(98)	45(100)
Discontinued, N (%)	[redacted]		[redacted]		7 (8)[a]	
AE					1 (1)	
Lack of efficacy					2 (2)	
Virologic rebound					*2 (2)*	
Virologic failure					*0 (0)*	
Protocol deviation					4 (5)	
Pregnancy					*0 (0)*	
Non-compliance with protocol procedures					*4 (5)*	
Non-compliance with study treatment					*0 (0)*	
Prohibited medication use					*0 (0)*	
No subreasons					*0 (0)*	
Reached stopping criteria					0 (0)	
Met renal toxicity withdrawal criteria					*0 (0)*	
Met liver toxicity withdrawal criteria					*0 (0)*	
Lost to follow-up					0 (0)	
Physician decision					0 (0)	
Withdrawal by patient					0 (0)	
ITT-E, N	356	358	360	359	44	45
ITT, N	[redacted]		[redacted]		45	45
PP, N	[redacted]		[redacted]		NR	NR
CVW, N	4	2	2	2	NA	NA
Safety, N	356	358	360	359	NR	NR

3TC = lamivudine; AE = adverse event; cART = continued antiretroviral therapy; CVW = confirmed virologic withdrawal; DTG = dolutegravir; FTC = emtricitabine; ITT = intention-to-treat; ITT-E: intention-to-treat exposed; NA = not applicable; NR = not reported; PP = per protocol; TDF = tenofovir disoproxil fumarate.

Note: The difference in numbers of patients between the ITT-E and ITT populations corresponds with those patients who did not receive study treatment. There were n = 3 patients in the DTG + 3TC groups and n = 5 patients in the DTG + TDF/FTC groups who did not receive study treatment. Regarding reasons for discontinuation — not all patients who withdrew due to AEs may be included because only the "primary reason" for withdrawal is included in the above table. If an AE was not the primary reason for withdrawal, it would not be included in this table but would be included in Table 14.

[a] In the ASPIRE trial, discontinuations and reasons for discontinuations were not reported by treatment group but rather for the overall ITT-E population.

Source: GEMINI-1 Clinical Study Report;[11] GEMINI-2 Clinical Study Report;[12] Taiwo et al. (2019);[8] Li et al. (2019).[34]

Suspected virologic withdrawal was defined as a single HIV-1 RNA value as defined by virologic non-response or virologic rebound. In contrast, CVW was defined as a second and consecutive HIV-1 RNA value meeting virologic non-response or virologic rebound. Virologic non-response and virologic rebound were defined as follows:

- **Virologic non-response**: A decrease in plasma HIV-1 RNA of less than 1 log10 copies/mL by week 12, with subsequent confirmation, unless plasma HIV-1 RNA is < 200 copies/mL and confirmed plasma HIV-1 RNA levels are ≥ 200 copies/mL on or after week 24.
- **Virologic rebound:** A confirmed rebound in plasma HIV-1 RNA levels to ≥ 200 copies/mL after prior confirmed suppression to < 200 copies/mL.

Exposure to Study Treatments

In both GEMINI-1 and GEMINI-2, the overall exposure to study treatment was [redacted] between the two treatment groups (as detailed in Table 11). In GEMINI-1, mean exposure was [redacted] in the DTG + 3TC group and [redacted] in the DTG + TDF/FTC group. In GEMINI-2, mean exposure was [redacted] in the DTG + 3TC group and [redacted] in the DTG + TDF/FTC group. In both trials, the exposure is up to the safety data cut-off of May 22, 2018.

There were no exposure data available for the ASPIRE trial.

Table 11: Extent of Exposure in the GEMINI-1 and GEMINI-2 Trials (Safety Population)

Exposure	GEMINI-1		GEMINI-2	
	DTG + 3TC (N = 356)	DTG + TDF/FTC (N = 358)	DTG + 3TC (N = 360)	DTG + TDF/FTC (N = 359)
Days	[redacted]	[redacted]	[redacted]	[redacted]
Weeks, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				

Source: GEMINI-1 Clinical Study Report;[11] GEMINI-2 Clinical Study Report.[12]

Critical Appraisal

Internal Validity

- The GEMINI-1 and GEMINI-2 trials were identically designed, randomized, double-blind, phase III randomized controlled trials (RCTs). Selection bias was minimized by use of appropriate methodology for random allocation of study treatment. Eligible patients were randomized according to a computer-generated randomization schedule using an interactive voice or website response system. Patients were also stratified at randomization by screening HIV-1 RNA level (≤ 100,000 copies/mL or > 100,000 copies/mL) and screening CD4+ count (≤ 200 cells/μL or > 200 cells/μL) and as pre-

specified, subgroup analyses were conducted according to the baseline strata. The methodology for allocation concealment was also appropriate as identical DTG tablets were administered in both treatment groups and the allocation of 3TC or TDF/FTC was concealed by use of the double-dummy technique (i.e., over-encapsulated 3TC or TDF/FTC tablets, which were visually identical to each other). No dose reductions, modifications in dose, or changes in frequency of doses were permitted during the study.

- The ASPIRE trial was a randomized, open-label, phase III, pilot RCT. No information was available on the method of randomization used. Furthermore, baseline demographic and disease characteristics were not available by treatment group, so it is not possible to assess whether the treatment groups were balanced in this regard. Due to the open-label design, treatment allocation was not concealed; therefore, there is potential for high risk of detection and reporting bias for subjective outcomes such as harms, as both patients and study personnel were aware of the treatment allocation.
- The primary outcome in the GEMINI trials was the proportion of patients with an HIV-1 RNA of < 50 copies/mL by week 48, which is a quantitative objective measure that is less susceptible to bias. Furthermore, use of the US FDA snapshot algorithm and the noninferiority margin of 10% is consistent with guidance from the US FDA for ARV drug development in patients who are treatment naive.[6] Although the primary analysis was conducted in the ITT-E population, it was also confirmed in the PP population, as also recommended for noninferiority trials by the US FDA. The GEMINI trials did meet their required sample sizes and appear to have been delivered in optimal fashion. As a result, they appear to have been powered and adequately conducted to find differences if differences truly existed.
- The primary outcome in the ASPIRE trial was treatment failure, which was defined as the proportion of patients with virologic failure (a confirmed virologic load of > 50 copies/mL within 35 days of the initial result), loss to follow-up, or treatment discontinuation or modification by week 24. Although the open-label design of the trial is associated with a high risk of bias, the analysis of the primary outcome may be less so as the individual components of the primary outcome are objective measures. Of note, however, is the use of a noninferiority margin of 12% for the comparison of the treatment groups based on the primary outcome. According to the US FDA guidance for ARV drug development, a noninferiority margin of 4% is recommended in switch trials of ART in patients who are fully susceptible to all of the approved drugs, or who have been on previous treatment with a well-documented treatment history demonstrating no prior virologic failure.[6] However, the ASPIRE trial was initiated prior to the issuance of the US FDA guidance and was powered on the basis of a 12% noninferiority margin.
- In both the GEMINI trials and the ASPIRE trial, the primary efficacy analyses were conducted in the ITT-E population, which was defined as all randomized patients who received at least one dose of the study drug. In the GEMINI trials, eight patients were randomized but did not receive the study treatment (n = 3 in the DTG + 3TC groups and n = 5 in the DTG + TDF/FTC groups), whereas in the ASPIRE trial, one patient in the DTG + 3TC group was randomized but did not receive the study treatment. As a result, the study populations of both trials comprise modified ITT populations. Nonetheless, given that the ITT-E populations include 99% or more of the patients in the ITT populations and that the results were confirmed in the PP population in the GEMINI trials, this is unlikely to have any effect on the study results. The ASPIRE trial did not include a confirmatory analysis in a PP population.
- Discontinuation rates across treatment groups were generally low in the GEMINI trials (7% to 10%) and the ASPIRE trial (8%). In the GEMINI trials, there did not appear to be

evidence of differential attribution between treatment groups. In the ASPIRE trial, patient disposition was only reported for the overall study population (and not by treatment group) so it is not possible to assess between group differences in this regard.

- In the GEMINI trials, the method of imputation for the primary analysis (i.e., patients with missing data were considered to be non-responders) is consistent with the US FDA snapshot approach in that all missing data are considered as treatment failures, regardless of the reason. In the ASPIRE trial, patients with missing data (e.g., lost to follow-up) were also considered to be treatment failures. Therefore, missing data were handled appropriately for the primary analyses in all three included trials. No information was available regarding imputation methods for secondary outcomes in the ASPIRE trial. In the GEMINI trials, various imputation methods were used for secondary outcomes, which all assumed data were missing at random. For the analysis of change from baseline in CD4+ cell count to week 48, multiple imputations were drawn from a multivariate normal model with a Markov chain Monte Carlo approach to impute missing observations, whereas the last observation carried forward method was used for HRQoL outcomes, and a lipids last observation carried forward method (as described in the Statistical Analysis section) was used for the analysis of lipid parameters. It is unclear if the missing at random assumption was satisfied for the various missing data imputations or if the covariates used in the multivariate imputation models were sufficient to ensure appropriate imputation of missing values. However, given the low discontinuation rates in all three trials, it is not expected that the different methods of imputation would have affected the results of the secondary outcomes to a large extent (e.g., results for change in CD4+ cell count from baseline were reported for more than 91% of patients and HRQoL outcomes for more than 97% of patients). It should also be noted that due to the lack of adjustment for multiplicity for the secondary outcomes, the results should be interpreted with consideration of the risk of an inflated type I error.
- There was no control or adjustment for multiplicity in the statistical analysis of secondary outcomes in either the GEMINI trials or the ASPIRE trial. Therefore, treatment differences reported for the harms outcomes of lipid, bone, and renal parameters in the GEMINI trials and for the total cholesterol, LDL cholesterol, triglycerides, and creatinine clearance secondary outcomes in the ASPIRE trial should be considered in the context of the potential for inflated type I error.
- Although subgroup analyses by baseline viral load and baseline CD4+ cell counts were pre-specified and based on stratification variables to maintain randomization, they were not adjusted for multiplicity so it is unclear how they should be interpreted given these are noninferiority trials and no specific noninferiority margins were noted in the protocol for their assessment. Furthermore, in GEMINI-2 [redacted] of an effect of baseline HIV-1 RNA and baseline CD4+ cell count on the treatment difference in the proportion of subjects with an HIV-1 RNA of < 50 copies/mL indicating that [redacted]. This appears to be driven by both a higher response rate in the DTG + 3TC group together with a lower response rate in the DTG + TDF/FTC group in patients with higher baseline plasma HIV-1 RNA (> 100,000 copies/mL) or a lower response rate in the DTG + 3TC group in patients with lower baseline CD4+ counts. However, it should be noted that the numbers of patients in these categories are [redacted] and therefore the results should be interpreted with consideration of the risk of an inflated type I error.

- The ASPIRE trial provided direct evidence for DTG + 3TC in a switch population (i.e., treated patients switching from a stable three-drug regimen to the two-drug regimen of DTG + 3TC). The ASPIRE trial has numerous limitations as it was conducted as a pilot study to inform the design of a larger, adequately powered trial (TANGO; Clinicaltrials.gov identifier, NCT03446573). In addition to the use of an open-label design and outdated noninferiority margin, as previously detailed, the ASPIRE trial was small (N = 90) and the only results available to report in this CDR review were from two brief communications.[8,34] Due to the numerous identified limitations, the results should be interpreted with caution.
- Both HRQoL and adherence were identified as efficacy outcomes in the CDR review protocol. HRQoL was also identified as important to patients based on the patient input received for this review. The ASPIRE trial did not include HRQoL as an outcome. Although the GEMINI trials reported HRQoL as measured by the EQ-5D-5L, it was an exploratory outcome. The lack of evidence for validation, reliability, responsiveness, and a MCID in patients with HIV infection makes interpretation of the HRQoL data difficult. The GEMINI trials did not report any data for adherence and while the ASPIRE trial did report that 92% of patients had perfect adherence, no information was available on how this was assessed or quantified.[8]

External Validity

- The study populations in the GEMINI-1, GEMINI-2, and ASPIRE trials do not appear to adequately represent the entire potential patient population targeted by the indication for DTG/3TC. The indication for DTG/3TC includes adults and adolescents 12 years of age or older irrespective of previous ART status. However, inclusion criteria for the GEMINI-1, GEMINI-2, and ASPIRE studies limited study participation to adults 18 years of age or older; thus, there is a lack of data supporting the efficacy and safety of DTG + 3TC in patients with HIV-1 infection who are younger than 18 years of age. However, the expert consulted for this CDR review did not express concern regarding drug absorption, metabolism, or toxicity in patients younger than 18 years of age. Further, GEMINI-1 and GEMINI-2 were conducted in patients who are ART naive only, and while the ASPIRE trial assessed the impact of switching to DTG + 3TC in patients who are virologically suppressed and ART experienced, this trial was associated with numerous limitations and noninferiority has not been established based on a noninferiority margin of 4% as currently recommended by the US FDA for switch trials. However, the clinical expert consulted by CADTH indicated the data in patients who are treatment naive for DTG + 3TC were likely generalizable to patients who are treatment experienced.
- The GEMINI trials enrolled patients from Europe, South America, Asia, and North America (US and Canada), whereas the ASPIRE trial was conducted only in the US. The GEMINI trials each included three sites in Canada. While all three trials had a preponderance of white (≥ 60%) and male patients (≥ 83%), the clinical expert consulted on this review advised that this would be typical of Canadian patients with HIV-1 infection and that the results should be generalizable to the Canadian population with HIV-1 infection. In fact, the inclusion of 13% to 17% female patients in the GEMINI trials was more than is customary in most trials of ART. The clinical expert did advise that the prior ART regimens of patients included in the ASPIRE trial are inconsistent with what would typically be used in Canada (i.e., the distribution would more likely be 70% INSTIs, 20% NNRTIs, and 10% PIs). In addition, in the ASPIRE trial, the high study entry CD4+ cell count, duration (approximately six years) of prior ART, and exclusion of patients with history of virologic failure or no baseline genotype information could limit the

generalizability of the study findings. Furthermore, the exclusion of patients with HBV infection or those who were expected to require treatment for HCV infection over the duration of the trials in both the GEMINI and ASPIRE trials, and patients with resistance mutations in the GEMINI trials may also limit the generalizability of the results to these patient populations. The exclusion of patients with HIV-1 RNA levels of > 500,000 copies/mL in the GEMINI trials may limit the generalizability of the study results to patients who are treatment naive with very high viral loads. Finally, there was a large proportion of screening failures in the GEMINI-1 [redacted] and GEMINI-2 [redacted] trials, which may have led to the enrolment of a highly selected patient population.

- The intervention used in both the GEMINI trials and in the ASPIRE trial was DTG and 3TC administered as separate tablets, whereas the marketed formulation of DTG/3TC is an FDC. The manufacturer has conducted a bioequivalence study (Study 204994) that compared the FDC and separate tablet formulations of DTG and 3TC under fasting and fed conditions, which is reviewed in Appendix 5.
- The comparators used in the included trials are available in Canada and used in clinical practice. The clinical expert advised that the comparator used in the GEMINI trials (DTG + TDF/FTC) is a valid and effective regimen; however, it is not used extensively in Canada due to the availability of many effective STRs.
- The GEMINI trials and ASPIRE trial all reported results over a treatment duration of 48 weeks. As a result, the durability of the treatment effect of DTG + 3TC beyond this time frame is currently unknown. The ASPIRE trial was a pilot study conducted in preparation for the TANGO trial (Clinicaltrials.gov identifier, NCT03446573), which is designed to provide outcome data for up to 144 weeks (estimated primary completion date: June 14, 2019; estimated study completion date, July 22, 2022). Given that HIV infection is a chronic condition, and patients will require treatment over their lifetimes, the durability of response and the potential for emergence of resistance mutations with the two-drug regimen of DTG + 3TC beyond 48 weeks is unknown at this time.

Efficacy

Efficacy outcomes identified in the CDR review protocol are reported in Table 4. See Appendix 4 for detailed efficacy data.

Viral Load

In the GEMINI-1 trial, 13 patients (4%) in the DTG + 3TC group versus six patients (2%) in the DTG + TDF/FTC group had plasma HIV-1 RNA levels of ≥ 50 copies/mL at week 48, whereas in the GEMINI-2 trial, seven patients (2%) in each treatment group had plasma HIV-1 RNA levels of ≥ 50 copies/mL at week 48 (Table 12).

The primary efficacy outcome in the GEMINI trials was the proportion of patients with viral suppression, defined as a plasma HIV-1 RNA of < 50 copies/mL at week 48 in the ITT-E population using the US FDA snapshot algorithm.[6] A similar proportion of patients achieved this outcome in both GEMINI-1 (90% versus 93%) and GEMINI-2 (93% versus 94%) in the DTG + 3TC versus DTG + TDF/FTC groups, respectively (Table 12). Based on a 10% noninferiority margin, the results demonstrated that DTG + 3TC was noninferior to DTG + TDF/FTC as the lower bound of the 95% CI of the adjusted treatment difference was greater than –10% in both the GEMINI-1 (–2.6% [95% CI, –6.7 to 1.5]) and GEMINI-2 (–0.7% [95% CI, –4.3 to 2.9]) trials. These results were supported by those in the PP population (Table 12) and the ITT population at week 48 and the ITT-E population at week 24 (Table 18).

The proportion of patients with an HIV-1 RNA of < 50 copies/mL by baseline viral load (≤ 100,000 copies/mL and > 100,000 copies/mL) and baseline CD4+ cell count (≤ 200 cells/μL and > 200 cells/μL) are provided in Table 19. The results in patients with a baseline HIV-1 RNA of ≤ 100,000 copies/mL in GEMINI-1 [redacted] and GEMINI-2 [redacted] in the DTG + 3TC and DTG + TDF/FTC groups, respectively, were [redacted] to the primary analysis (i.e., difference in proportion was [redacted] GEMINI-1 and [redacted] in GEMINI-2). In patients with an HIV-1 RNA of > 100,000 copies/mL, the results were [redacted] versus [redacted] (GEMINI-1) and [redacted] (GEMINI-2); however, due to the small sample sizes [redacted] and [redacted], there may be uncertainty associated with these results (although the mean differences in this subgroup were relatively comparable with the main findings). In patients with a baseline CD4+ cell count of > 200 cells/μL, the results are also similar to the primary analysis: [redacted] (GEMINI-1) and [redacted] (GEMINI-2), respectively, with difference in proportions of [redacted] in GEMINI-1 and [redacted] in GEMINI-2. In patients with a baseline CD4+ cell count of ≤ 200 cells/μL, the proportions of patients were [redacted] (GEMINI-1) and [redacted] (GEMINI-2) in the DTG + 3TC and DTG + TDF/FTC groups, respectively; however, the sample sizes were [redacted] and the CIs were [redacted]; thus, the results are uncertain. In GEMINI-2 there was also statistically significant evidence [redacted] for both baseline HIV-1 RNA and baseline CD4+ cell count on the treatment difference in the proportion of subjects with an HIV-1 RNA of < 50 copies/mL. This [redacted]. However, it should be noted that the numbers of patients in these categories are [redacted]; therefore, the results are uncertain.

Table 12: Virologic Efficacy Outcomes in the GEMINI-1 and GEMINI-2 Trials

Virologic Efficacy Outcomes	GEMINI-1		GEMINI-2	
	DTG + 3TC	DTG + TDF/FTC	DTG + 3TC	DTG + TDF/FTC
Failure of Virologic Suppression				
ITT-E Population at Week 48				
HIV-1 RNA ≥ 50 copies/mL at week 48, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Reasons for virologic failures, n (%): • **Data in window and HIV-1 RNA ≥ 50 copies/mL** • **Discontinued for lack of efficacy** • **Discontinued for other reason and HIV-1 RNA ≥ 50 copies/mL** • **Change in ART**	[redacted]	[redacted]	[redacted]	[redacted]
PP Population at Week 48				
HIV-1 RNA ≥ 50 copies/mL at week 48, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Reasons for virologic failures, n (%): • [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Virologic Suppression				
ITT-E Population at Week 48				

Virologic Efficacy Outcomes	GEMINI-1		GEMINI-2	
	DTG + 3TC	DTG + TDF/FTC	DTG + 3TC	DTG + TDF/FTC
HIV-1 RNA < 50 copies/mL at week 48, n/N (%) [95% CI][a]	320/356 (90) [86.8 to 93.0]	332/332 (93) [90.0 to 95.4]	335/360 (93) [90.4 to 95.7]	337/359 (94) [91.4 to 96.4]
Difference in proportion[b], % (95% CI)	–2.8 (–7.0 to 1.3)		–0.8 (–4.4 to 2.8)	
Adjusted difference in proportion[c], % (95% CI)	–2.6 (–6.7 to 1.5)		–0.7 (–4.3 to 2.9)	
PP Population at Week 48				
[redacted]				

3TC = lamivudine; ART = antiretroviral therapy; CI = confidence interval; DTG = dolutegravir; FTC = emtricitabine; HR = hazard ratio; ITT= intention-to-treat population; ITT-E = intention-to-treat exposed population; PP = per-protocol population; RNA = ribonucleic acid; TDF = tenofovir disoproxil fumarate.

Note: The primary efficacy outcome in both GEMINI-1 and GEMINI-2 was the proportion of patients with plasma HIV-1 RNA < 50 copies/mL at week 48 using the US FDA snapshot algorithm in the ITT-E population. Noninferiority was concluded if the lower boundary of the two-sided 95% CI for the difference in response between the treatment groups was greater than –10%.

[a] Using the US FDA snapshot algorithm.

[b] Difference is the proportion of patients on DTG + 3TC minus the proportion of patients on DTG + TDF/FTC.

[c] Adjusted difference is based on the Cochran-Mantel-Haenszel-stratified analysis adjusting for baseline stratification factors of plasma HIV-1 RNA (≤ 100,000 copies/mL and > 100,000 copies/mL) and CD4+ cell count (≤ 200 cells/μL and > 200 cells/μL).

Source: GEMINI-1 Clinical Study Report;[11] GEMINI-2 Clinical Study Report.[12]

In the ASPIRE trial, the primary efficacy outcome was treatment failure, which was defined as a composite of virologic failure, loss to follow-up, or treatment discontinuation or modification by week 24. Three patients in each treatment group, or 6.8% (DTG + 3TC) versus 6.7% (combination antiretroviral therapy [cART]), of patients were defined as treatment failures (Table 13). The difference in the proportion of patients meeting this outcome was 0.15% (90% CI, –9.8 to 10.2). Based on a 12% noninferiority margin, the results demonstrated that DTG + 3TC was noninferior to cART as the lower bound of the 90% CI of the treatment difference was greater than –12%. Overall, 41 patients in each group achieved viral suppression or plasma HIV-1 RNA levels of < 50 copies/mL at week 24 (Table 13). The corresponding proportions were 93% versus 91% at week 24 and 91% versus 89% (40 patients in each group) at week 48 in the DTG + 3TC and continued ART groups, respectively.

Table 13: Virologic Efficacy Outcomes in the ASPIRE Trial

Efficacy Outcomes	ASPIRE	
	DTG + 3TC (N = 44)	DHHS or cART (N = 45)
Virologic Failures		
ITT-E Population at Week 24		
Proportion of patients with treatment failure at week 24, n/N (%)	3/44 (6.8)	3/45 (6.7)
Reasons for treatment failure, n (%):		
• **Virologic failure[a]**	1 (2.3)	0 (0)
• **Lost to follow-up**	1 (2.3)	1 (2.2)
• **Treatment discontinuation due to AE[b]**	1 (2.3)	0 (0)
• **Regimen simplifications**	0 (0)	2 (4.4)
Difference in proportion, % (90% CI)	0.15 (–9.8 to 10.2)	
Virologic Successes		

Efficacy Outcomes	ASPIRE	
	DTG + 3TC (N = 44)	DHHS or cART (N = 45)
Proportion of patients with HIV-1 RNA < 50 copies/mL at week 24, n/N (%)[c]	41/44 (93.2)	41/45 (91.1)
Difference in proportion, % (95% CI); *P* value	2.1 (–11.2 to 15.3); *P* = 0.71	
Proportion of patients with HIV-1 RNA < 50 copies/mL at week 48, n/N (%)[c]	40/44 (90.9)	40/45 (88.9)
Difference in proportion, % (95% CI); *P* value	2.0 (–12.6 to 16.5); *P* = 0.76	

3TC = lamivudine; AE = adverse event; cART = combination antiretroviral therapy; CI = confidence interval; DHHS = Department of Health and Human Services; DTG = dolutegravir; ITT-E = intention-to-treat exposed; RNA = ribonucleic acid.

Note: Noninferiority was concluded if the 90% CI for the difference in proportions calculated with Miettinen-Nurminen (score) CIs excluded a 12% noninferiority margin.

[a] In the one patient with virologic failure, no emergent reverse transcriptase or integrase resistance mutations were identified and the patient remained viremic after switching to darunavir-cobicistat + abacavir/3TC. The patient reported good adherence and had therapeutic DTG concentrations.

[b] One patient discontinued due to grade 2 constipation.

[c] As per the US FDA snapshot algorithm.

Source: Taiwo et al. (2019).[8]

In the ASPIRE trial, residual viremia was measured using an ultrasensitive assay with a detection limit of 0.5 copies/mL in a subgroup of 72 patients with undetectable plasma HIV-1 RNA levels (Table 24). At baseline, residual viremia was 5.0 copies/mL in the DTG + 3TC group and 4.2 copies/mL in the cART group. There was no statistically significant difference between treatment groups in the change in mean residual viral load at either week 24 or week 48.

Change in CD4+ Cell Count

In the GEMINI-1 and GEMINI-2 trials, CD4+ cell counts progressively increased from baseline at each study visit to week 48 in both treatment groups (Table 20). [redacted] It should be noted that the statistical analysis was not adjusted for multiplicity and should be interpreted with considerations of inflated type I error. Change from baseline in CD4+ cell count was also assessed at week 48 by the randomization strata of baseline viral load and baseline CD4+ cell count. The change from baseline to week 48 in CD4+ cell count was [redacted] between treatment groups in patients with a baseline viral load of ≤ 100,000 copies/mL: [redacted] in GEMINI-1 and [redacted] in GEMINI-2 whereas in patients with a baseline viral load of > 100,000 copies/mL the treatment differences were [redacted] in GEMINI-1 and [redacted] in GEMINI-2. For patients with a baseline CD4+ cell count of > 200 cells/μL, the differences between treatment groups was [redacted] in GEMINI-1 and [redacted] in GEMINI-2, whereas in patients with a baseline CD4+ count of ≤ 200 cells/μL, the differences between treatment groups were [redacted] in GEMINI-1 and [redacted] in GEMINI-2. The results in the subgroups of a baseline HIV-1 RNA of > 100,000 copies/mL and a baseline CD4+ cell count of ≤ 200 cells/μL are limited by [redacted] across the subgroups. The only information reported in the ASPIRE trial was the median change from baseline to week 48 in CD4+ cell count, which was 39 cells/μL (interquartile range, –71 to 188) with DTG + 3TC and 28 cells/μL (interquartile range, –36 to 83) for combined ART.

Health-Related Quality of Life

HRQoL, as measured by the EQ-5D-5L at baseline, week 4, week 24, and week 48 was reported as an exploratory outcome in the GEMINI-1 and GEMINI-2 trials. The change from baseline in utility scores and VAS scores are provided in Table 22. In general, the change from baseline in utility scores and VAS scores were similar throughout the trials in both treatment groups. [redacted]. HRQoL was an exploratory outcome in the GEMINI trials and a key limitation is the lack of evidence for validity, reliability, or responsiveness of the EQ-5D-5L in patients with HIV infection and that no MCID has been established in this population. There was no information available on HRQoL from the ASPIRE trial.

Resistance

In the GEMINI-1 and GEMINI-2 trials combined, a total of 10 patients (less than 1%) met pre-specified criteria for CVW to week 48 (i.e., six patients in the DTG + 3TC group and four patients in the DTG + TDF/FTC group) as detailed in Table 23. Genotypic testing of the HIV-1 transcriptase, protease-reverse transcriptase, and integrase genes was successful for baseline and virologic withdrawal samples from all 10 patients with the exception of on integrase genotype assay failure for one patient in the DTG + TDF/FTC group.[7] None of the patients had emergence of resistance mutations to INSTIs or NNRTIs and all were classified as virologic rebounds (Table 23).

In the ASPIRE trial, one patient was classified as a virologic failure in the DTG + 3TC group at week 24.[8] This patient did not have any emergent reverse transcriptase or INSTI-resistance mutations and the patient remained viremic after switching to darunavir plus abacavir/3TC.[8] Furthermore, the patient did not have any missed doses and had therapeutic DTG concentrations.[8]

Adherence

There was no information on adherence reported in the GEMINI-1 and GEMINI-2 trials. In the ASPIRE trial, it was reported that 92% of included patients had perfect adherence.

Harms

Harms identified in the review protocol are subsequently reported (see 2.2.1, Protocol). See Table 14 for detailed harms data.

Adverse Events

In the GEMINI-1 and GEMINI-2 trials, the proportion of patients with AEs was numerically less in the DTG + 3TC groups (78% and 74%) than in the DTG + TDF/FTC groups (82% and 79%), respectively (Table 14). Overall, the most frequent AEs were headache 11% and 9% versus 12% and 9%), diarrhea (9% and 10% versus 12% and 10%), nasopharyngitis (9% and 10% versus 6% and 11%), and upper respiratory tract infection (7% and 9% versus 6% in both trials) for GEMINI-1 and GEMINI-2, respectively. There did not appear to be any major imbalances in the frequency of AEs between treatment groups or across the trials.

There were very limited harms data reported for the ASPIRE trial. The only available data were reported for the overall ITT-E population. Grade 3 laboratory AEs affected glucose (n = 2), low-density lipoprotein (n = 1), and alanine transaminase (n = 1) in the DTG + 3TC

group, and bilirubinemia (n = 3) in the continued ART group. Clinical AEs included grade 3 diabetes (n = 2), back pain (n = 1), osteoarthritis (n = 1), fall with loss of consciousness (n = 1), and grade 4 viral syndrome (n = 1) in the DTG + 3TC group and grade 3 diarrhea (n = 1), nephrolithiasis (n = 1), and grade 4 myocardial infarction (n = 2) in the continued ART group.

Serious Adverse Events

In the GEMINI-1 and GEMINI-2 trials, the proportion of patients with SAEs was similar in the DTG + 3TC groups (6% and 8%) and the DTG + TDF/FTC groups (6% and 9%), respectively, as detailed in Table 14.The SAEs that occurred in more than one patient in either treatment group or trial were hepatitis A, [redacted] suicide attempt, suicide ideation, and cholecystitis acute (all 1% or less of patients in each treatment group).

Withdrawals Due to Adverse Events

The proportion of patients who withdrew due to AEs was 2% in each treatment group in the GEMINI-1 and GEMINI-2 trials (Table 14). In the GEMINI trials, the most common reasons for WDAEs were hepatitis A and renal impairment. In the ASPIRE trial, one patient (less than 1%) in the DTG + 3TC group withdrew due to an AE (i.e., grade 2 constipation).

Mortality

There were no deaths reported [redacted] ASPIRE trials. In the GEMINI-2 trial, there were two deaths in the DTG + 3TC treatment group (due to Burkitt's lymphoma and acute myocardial infarction).

Table 14: Harms in the GEMINI-1 and GEMINI-2 Trials (Safety Population)

Harms	GEMINI-1		GEMINI-2	
	DTG + 3TC (N = 356)	DTG + TDF/FTC (N = 358)	DTG + 3TC (N = 360)	DTG + TDF/FTC (N = 359)
AEs				
Patients with > 0 AEs, n (%)	276 (78)	295 (82)	267 (74)	284 (79)
Most common AEs[a]				
Headache	40 (11)	44 (12)	31 (9)	31 (9)
Diarrhea	33 (9)	42 (12)	35 (10)	35 (10)
Nasopharyngitis	33 (9)	37 (10)	22 (6)	41 (11)
URTI	24 (7)	22 (6)	32 (9)	22 (6)
Insomnia	16 (4)	29 (8)	11 (3)	16 (4)
Nausea	12 (3)	30 (8)	15 (4)	23 (6)
Back pain	19 (5)	19 (5)	16 (4)	12 (3)
Pharyngitis	23 (6)	13 (4)	13 (4)	19 (5)
Syphilis	17 (5)	15 (4)	10 (3)	12 (3)
Bronchitis	20 (6)	11 (3)	8 (2)	10 (3)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SAEs				
Patients with > 0 SAEs, n (%)	21 (6)	22 (6)	29 (8)	33 (9)
Most common SAEs[b]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Harms	GEMINI-1		GEMINI-2	
	DTG + 3TC (N = 356)	DTG + TDF/FTC (N = 358)	DTG + 3TC (N = 360)	DTG + TDF/FTC (N = 359)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WDAEs				
Patients with > 0 WDAEs, n (%)	7 (2)	8 (2)	8 (2)	8 (2)
Most common WDAEs[b]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deaths				
Number of deaths, n (%)	0 (0)	0 (0)	2 (<1)[c]	0 (0)

3TC = lamivudine; AE = adverse event; DTG = dolutegravir; FTC = emtricitabine; NR = not reported; SAE = serious adverse event; TDF = tenofovir disoproxil fumarate; URTI = upper respiratory tract infection; WDAE = withdrawal due to adverse event.

[a] Occurring in 5% or more of patients in either treatment group in either trial.

[b] Occurring in one or more patient in either treatment group in either trial.

Source: GEMINI-1 Clinical Study Report;[11] GEMINI-2 Clinical Study Report.[12]

Notable Harms

Notable harms identified in the review protocol included nausea, vomiting, diarrhea, insomnia, depression, birth defects, and effects on lipids, bone, and renal function (Table 4). In the GEMINI-1 trial, more patients in the DTG + TDF/3TC group appeared to have gastrointestinal AEs (particularly nausea [8% versus 3%] and diarrhea [12% versus 9%]), insomnia (8% versus 4%), [redacted] than in the DTG + 3TC group, respectively (Table 15). In the GEMINI-2 trial, the frequency of gastrointestinal AEs (nausea [6% versus 4%], [redacted] diarrhea [10% for both]), insomnia (4% versus 3%), [redacted] (Table 15).

In the GEMINI trials, the changes from baseline to week 48 in lipid parameters (i.e., total, LDL, and high-density–lipoprotein cholesterol) were all larger for DTG + 3TC than for DTG + TDF/FTC (Table 15). In contrast, the changes from baseline to week 48 in bone-related parameters (i.e., serum bone-specific alkaline phosphate, osteocalcin, procollagen 1 N-terminal propeptide, type-1 collagen C-telopeptide, and vitamin D) were all larger in the DTG + TDF/FTC group than in the DTG + 3TC group (Table 15). Similarly, the change from baseline to week 48 in renal-related biomarkers (i.e., serum creatinine, glomerular filtration rate, urine protein/creatinine ratio, and urine albumin/creatinine ratio) were all larger in the DTG + TDF/FTC group than in the DTG + 3TC group (Table 15).

Table 15: Notable Harms in the GEMINI-1 and GEMINI-2 Trials (Safety Population)

Harms	GEMINI-1		GEMINI-2	
	DTG + 3TC (N = 356)	DTG + TDF/FTC (N = 358)	DTG + 3TC (N = 360)	DTG + TDF/FTC (N = 359)
Nausea, n (%)	12 (3)	30 (8)	15 (4)	23 (6)
Vomiting, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhea, n (%)	33 (9)	42 (12)	35 (10)	35 (10)
Insomnia, n (%)	16 (4)	29 (8)	11 (3)	16 (4)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lipid-Related Markers[a]				

Harms	GEMINI-1		GEMINI-2	
	DTG + 3TC (N = 356)	DTG + TDF/FTC (N = 358)	DTG + 3TC (N = 360)	DTG + TDF/FTC (N = 359)
Change From Baseline in Fasting Lipids (Serum or Plasma) (mmol/L) at Week 48 (Multiple Imputed Data Set — MAR)				
Total cholesterol, adjusted mean (SE)[b]	[redacted]	[redacted]	[redacted]	[redacted]
Difference (95% CI); *P* value	[redacted]		[redacted]	
HDL cholesterol, adjusted mean (SE)[b]	[redacted]	[redacted]	[redacted]	[redacted]
Difference (95% CI); *P* value	[redacted]		[redacted]	
LDL cholesterol, adjusted mean (SE)[b]	[redacted]	[redacted]	[redacted]	[redacted]
Difference (95% CI); *P* value	[redacted]		[redacted]	
Total:HDL cholesterol ratio, adjusted mean (SE)[b]	[redacted]	[redacted]	[redacted]	[redacted]
Difference (95% CI); *P* value	[redacted]		[redacted]	
Triglycerides, adjusted mean (SE)[b]	[redacted]	[redacted]	[redacted]	[redacted]
Difference (95% CI); *P* value	[redacted]		[redacted]	
Bone-Related Biomarkers				
Bone Biomarkers (mcg/L) at Week 48 (Multiple Imputed Data Set – MAR)				
Serum Bone-Specific Alkaline Phosphate (µg/L)				
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, adjusted mean (SE)[c]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, difference (95% CI); *P* value	[redacted]		[redacted]	
Serum Osteocalcin (µg/L)				
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Harms	GEMINI-1		GEMINI-2	
	DTG + 3TC (N = 356)	DTG + TDF/FTC (N = 358)	DTG + 3TC (N = 360)	DTG + TDF/FTC (N = 359)
[redacted]				

3TC = lamivudine; ANCOVA = analysis of covariance; BMI = body mass index; CI = confidence interval; DTG = dolutegravir; FTC = emtricitabine; GFR = glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MAR = missing at random; RNA = ribonucleic acid; SD = standard deviation; SE = standard error; TDF = tenofovir disoproxil fumarate.

[a] Baseline values for fasting lipid parameters were not reported.

[b] Adjusted mean is the estimated mean change from baseline in each fasting lipid at week 48 in each treatment group calculated from an ANCOVA model adjusting for the following covariates/factors: treatment, baseline plasma HIV-1 RNA (factor), baseline CD4+ count (factor), age, and fasting lipids at baseline.

[c] Adjusted mean is the estimated mean change from baseline at week 48 in each treatment group calculated from an ANCOVA model adjusting to the following covariates/factors: baseline HIV-1 RNA (factor), baseline CD4+ count (factor), age, sex (factor), race (factor), BMI (factor), smoking status (factor), current vitamin D use (factor), and baseline biomarker value.

[d] Adjusted mean is the estimated mean change from baseline at week 48 in each treatment group calculated from an ANCOVA model adjusting to the following covariates/factors: baseline HIV-1 RNA (factor), baseline CD4+ count (factor), age, sex (factor), presence of diabetes mellitus (factor), and presence of hypertension.

[e] Calculated using the Creatinine-Adjusted Chronic Kidney Disease Epidemiology Collaboration equation.

[f] The estimated ratio of geometric means (week 48/baseline) calculated from an ANCOVA model applied to log-transformed data adjusting for the following covariates/factors: treatment, baseline plasma HIV-1 RNA (factor), baseline CD4+ count (factor), age, sex (factor), race (factor), presence of diabetes mellitus (factor), presence of hypertension (factor), and log-transformed baseline biomarker value.

Source: GEMINI-1 Clinical Study Report;[11] GEMINI-2 Clinical Study Report.[12]

In the ASPIRE trial, no statistically significant differences were identified in the secondary end points of median change from baseline to week 48 in total cholesterol, LDL cholesterol, triglycerides, or creatinine clearance between the DTG + 3TC group and the continued ART group (Table 16).

Table 16: Notable Harms in the ASPIRE Trial (Intention-to-Treat Exposed Population)

Efficacy Outcomes	ASPIRE	
	DTG + 3TC (N = 44)	DHHS or cART (N = 45)
Change From Baseline to Week 48		
Total cholesterol, mg/dL **Median (IQR)**	0 (–31 to 31)	–1 (–13 to 9)
***P* value[a]**	*P* > 0.2	
LDL cholesterol, mg/dL **Median (IQR)**	2 (–19 to 27)	–3 (–16 to 10)
***P* value[a]**	*P* > 0.2	
Triglycerides, mg/dL **Median (IQR)**	–9 (–58 to 37)	4 (–17 to 41)
***P* value[a]**	*P* > 0.2	
Creatinine clearance, mL/min **Median (IQR)**	–4 (–14 to 4)	0 (–6 to 5)
***P* value[a]**	*P* = 0.07	

3TC = lamivudine cART = combination antiretroviral therapy; DHHS = Department of Health and Human Services; DTG = dolutegravir; IQR = interquartile range; LDL = low-density lipoprotein.

[a] *P* value by Wilcoxon rank sum test.

Source: Taiwo et al. (2019).[8]

There was limited information from all three included trials on birth defects. [redacted] In the patient receiving [redacted], the pregnancy ended in spontaneous abortion at seven weeks gestation. In one patient receiving [redacted], the pregnancy also ended in spontaneous abortion at less than 22 weeks gestation with no apparent congenital anomaly present. The second patient in the [redacted] group discontinued the study drug, withdrew from the study, and underwent elective termination of the pregnancy with no medical reasons for the termination. In [redacted], one patient receiving DTG + 3TC became pregnant and the pregnancy was electively terminated by induced abortion at six weeks gestation with no apparent congenital anomaly present. No pregnancies were reported in the ASPIRE trial.

Discussion

Summary of Available Evidence

Three phase III trials met the criteria for inclusion in this review: GEMINI-1 (N = 719) and GEMINI-2 (N = 722), which were identically designed, double-blind, noninferiority RCTs in adult patients with HIV-1 infection who are treatment naive, and the ASPIRE trial (N = 90), which was an open-label, noninferiority, pilot RCT in adult patients with HIV-1 infection who are virologically suppressed. All three trials reported results for up to 48 weeks of treatment. The primary outcome in the GEMINI trials was the proportion of patients with an HIV-1 RNA of < 50 copies/mL at week 48, calculated according to the US FDA snapshot algorithm.[6] Noninferiority was concluded in the GEMINI trials if the difference between DTG + 3TC and DTG + TDF/FTC exceeded a noninferiority margin of 10%, which is consistent with the US FDA guidance for ARV drug development.[6] The primary outcome in the ASPIRE trial was the proportion of patients with treatment failure, defined as virologic failure, loss to follow-up, or treatment discontinuation or modification by week 24. Noninferiority was concluded in the ASPIRE trial if the difference between DTG + 3TC and continuation of patients' three-drug ART regimen exceeded a noninferiority margin of 12%, which is inconsistent with the US FDA guidance that recommends a noninferiority margin of 4% for switch trials of ART drugs.[6] Limitations of the evidence are the small size, open-label design, and use of an outdated noninferiority margin in the ASPIRE trial; the lack of adjustment for multiplicity of secondary outcomes in the statistical analyses, and use of separate tablet formulations of DTG + 3TC, as opposed to the FDC formulation of DTG/3TC, in all three trials. Further, the comparators used in the included trials are all available in Canada; however, the clinical expert consulted on this review advised that DTG + TDF/FTC (the comparator in the GEMINI trials) is not extensively used in Canada due to the availability of many effective STRs.

A limitation of the evidence reviewed is generalizability to the target population. The indication for DTG/3TC includes adults and adolescents 12 years of age and older irrespective of previous ART status. However, inclusion criteria for the GEMINI-1, GEMINI-2, and ASPIRE studies limited study participation to adults 18 years of age and older; thus, there is a lack of data supporting the efficacy and safety of DTG + 3TC in patients with HIV-1 infection who are younger than 18 years of age. However, the expert consulted for this CDR review did not express concern regarding drug absorption, metabolism, or toxicity in patients younger than 18 years of age. Further, GEMINI-1 and GEMINI-2 were conducted only in patients who are ART naive, and while the ASPIRE trial assessed the impact of switching to DTG + 3TC in patients who are virologically suppressed and ART experienced, this trial was associated with numerous limitations, and noninferiority has not been established based on a noninferiority margin of 4% as currently recommended by the US FDA for switch trials. However, the clinical expert consulted by CADTH indicated the data in patients who are treatment naive for DTG + 3TC were likely generalizable to patients who are treatment experienced.

A key evidence gap is the lack of long-term data. The data available from the GEMINI and ASPIRE trials were limited to 48 weeks of treatment. The GEMINI trials are ongoing and the ASPIRE trial was conducted as a pilot for a larger planned trial. The manufacturer provided additional information to CADTH during the review process for outcomes through 96 weeks of treatment. [redacted]

[redacted] In the absence of more compelling long-term data, the durability of the treatment effect and potential for emergence of resistance beyond 48 weeks remain uncertain.

Interpretation of Results

Efficacy

In the GEMINI trials, the primary outcome was the proportion of patients with an HIV-1 RNA of < 50 copies/mL at week 48 in the ITT-E population, as per the US FDA snapshot algorithm.[6] In both trials, noninferiority of the two-drug regimen of DTG + 3TC was compared with the three-drug regimen of DTG + TDF/FTC based on a 10% noninferiority margin, which is consistent with US FDA guidance for industry on ARV drug development.[6] The noninferiority analysis was repeated in the PP population, which supported the primary analyses. Both the two-drug and three-drug regimens were associated with a low proportion of patients with HIV-1 RNA levels of ≥ 50 copies/mL at week 48 [redacted] [GEMINI-1] and [redacted] [GEMINI-2] for patients treated with DTG + 3TC versus DTG + TDF/FTC, respectively). Similarly, both the two-drug and three-drug regimens were associated with low numbers of patients meeting criteria for CVW (i.e., six patients treated with DTG + 3TC and four patients treated with DTG + TDF/FTC). All the CVWs were classified as virologic rebounds and not virologic failures, and neither regimen was associated with emergence of resistance mutations to either INSTIs or NRTIs. It is difficult to interpret if the treatment effect was consistent in pre-specified subgroup analyses based on baseline strata (i.e., baseline viral load [≤ 100,000 copies/mL and > 100,000 copies/mL] and baseline CD4+ cell count [≤ 200 cells/μL and > 200 cells/μL]), which were identified as being relevant in the review protocol. In both GEMINI trials, results for patients with a baseline HIV-1 RNA of ≤ 100,000 copies/mL and baseline CD4+ cell counts of > 200 cells/μL were similar to the results of the primary analysis. [redacted] This appears to be driven by both a higher response rate in the DTG + 3TC group together with a lower response rate in the DTG + TDF/FTC group in patients with higher baseline plasma HIV-1 RNA (> 100,000 copies/mL) or a lower response rate in the DTG + 3TC group in patients with lower baseline CD4+ counts. These data are difficult to interpret because they were not adjusted for multiplicity and the sample sizes in the subgroups were [redacted] therefore, should be considered in this context.

In the ASPIRE trial, the primary efficacy outcome was treatment failure, defined as a composite of virologic failure, loss to follow-up, or treatment discontinuation or modification by week 24. Three patients in each treatment group (DTG + 3TC or continued ART) were defined as treatment failures. The noninferiority margin of 12% for the difference in the proportion of patients meeting this outcome was met; however, the noninferiority margin is outdated as the US FDA guidance for ARV drug development recommends a noninferiority margin of 4% for switch trials of ART in patients who are fully susceptible to all approved drugs or have been on prior treatment with a well-documented treatment history demonstrating no prior virologic failure.[6] As a result, use of the more stringent noninferiority margin would have led to a conclusion of failure to demonstrate noninferiority between the treatment groups. The ASPIRE trial was underpowered for a noninferiority margin of 4% and

is associated with numerous additional limitations (e.g., small size, open-label design, long duration of prior HIV-1 treatment thereby potentially limiting future treatment options, and exclusion of patients with history of virologic failure or unavailable baseline genotype).

The ASPIRE trial was the only direct evidence from a phase III trial in a switch population that was identified. According to the clinical expert consulted on the review, it is anticipated that the primary place in therapy for DTG/3TC would be in patients who wish to switch from a three-drug to a two-drug ART regimen for reasons of tolerability, convenience, pill size, or cost. The clinical expert advised that clinicians would likely consider the totality of evidence that exists for the combined use of DTG and 3TC in making treatment decisions. Further to this, since it is easier to maintain virologic suppression in a switch study (because patients are already selected for adherence and are generally tolerant to ART) than a study in a treatment-naive population, positive data from a study in patients who are treatment naive would commonly be generalized to imply effectiveness in a switch situation. Although a substudy of the ASPIRE trial that used an ultrasensitive detection method (limit of detection 0.5 copies/mL) reported that there was no difference in residual viremia between patients treated with DTG + 3TC and continued ART, the clinical expert advised that this was of little clinical relevance.

In the GEMINI-1 and GEMINI-2 trials, CD4+ cell counts progressively increased from baseline at each study visit to week 48 with both DTG + 3TC and DTG + TDF/FTC. [redacted] the results should be interpreted with considerations of potential for inflated type I error. Change from baseline in CD4+ cell count at week 48 was also assessed by the baseline strata of viral load and CD4+ cell count. In general, the change from baseline in CD4+ cell count was similar between treatment groups across both trials, although the results in the subgroups of a baseline HIV-1 RNA of > 100,000 copies/mL and baseline CD4+ cell count of ≤ 200 cells/μL are uncertain due [redacted], as discussed previously. In the ASPIRE trial, the median change from baseline to week 48 in CD4+ cell count was similar between DTG + 3TC and combined ART. While the results from the included trials support that CD4+ cell counts increased with the interventions evaluated, the clinical expert advised that other than baseline values, CD4+ cell counts are generally not clinically important in the management of patients with HIV-1 infection.

HRQoL was identified as an efficacy outcome in the review protocol that was important to patients; however, the only available data were from the GEMINI trials where HRQoL was reported as an exploratory outcome. There appeared to be no major changes from baseline in either utility or VAS scores calculated from the EQ-5D-5L in either of the treatment groups over the duration of the trials. As HRQoL was an exploratory outcome, it was not adjusted for multiplicity, and given that the EQ-5D-5L has not been validated in patients with HIV-1 infection, nor has an MCID been identified in this setting, these results should be considered in this context. HRQoL was not included as an outcome in the ASPIRE trial; however, a difference in HRQoL is unlikely in a switch population of patients who are virologically suppressed, as previously noted by the clinical expert, these patients would be selected for adherence and tolerance to prior ART. Adherence was also an efficacy outcome identified in the review protocol and of being important to patients; however, no data were available for adherence from the GEMINI trials, and although the ASPIRE trial reported that 92% of

patients reported perfect adherence, no information on how this was assessed or quantified was provided. A purported benefit of a two-drug regimen as compared with a three-drug regimen is that the two-drug regimen may be associated with improved adherence to ART; however, there is no evidence to substantiate this from the included trials and many three-drug regimens are available as STRs.

A key concern with switching from a three-drug regimen to a two-drug regimen of ART or initiating treatment with a two-drug regimen is the potential for development of resistance. In the GEMINI trials, a total of 10 patients (less than 1% of the study populations) met pre-specified criteria for CVW up to week 48. Genotypic testing of the HIV-1 transcriptase, protease-reverse transcriptase, and integrase genes was successful for baseline and virologic withdrawal samples from all 10 patients with the exception of on integrase genotype assay failure for one patient in the DTG + TDF/FTC group.[7] None of the patients had emergence of resistance mutations to INSTIs or NNRTIs and all were classified as virologic rebounds. In the ASPIRE trial, one patient was classified as a virologic failure in the DTG + 3TC group at week 24. This patient did not have any emergent reverse transcriptase or INSTI-resistance mutations and the patient remained viremic after switching to darunavir + abacavir/3TC. Based on these findings, it does not appear that there is a high risk of resistance up to 48 weeks of treatment with DTG + 3TC; however, the durability of the treatment effect and the potential for resistance development with longer treatment is unknown. As the GEMINI trials are ongoing and a larger study (TANGO; Clinicaltrials.gov identifier, NCT03446573) for which the ASPIRE trial was a pilot for is currently underway, it is anticipated that data for up to 144 weeks of treatment will be available from these trials. Thus, the potential for emergence of resistance mutations will have to be evaluated at that time.

The totality of clinical evidence in support of the two-drug regimen of DTG + 3TC was derived from clinical trials in which DTG and 3TC were administered as separate tablets; however, the marketed formulation of DTG/3TC is an FDC. In order to extrapolate the results of the clinical trials to the FDC formulation, the manufacturer is required to demonstrate bioequivalence of the FDC with the separate tablet formulations of DTG and 3TC, typically via a valid bridging bioequivalence study. The manufacturer has conducted a bioequivalence study that compared the FDC and separate tablet formulations of DTG and 3TC under fasting and fed conditions that is reviewed in Appendix 5.

Harms

In the GEMINI-1 and GEMINI-2 trials, fewer patients experienced AEs in the DTG + 3TC groups (78% and 74%) than in the DTG + TDF/FTC groups (82% and 79%), respectively, and there did not appear to be any major imbalances between treatment groups or across trials. Overall, the most frequent AEs were headache, diarrhea, nasopharyngitis, and upper respiratory tract infection in both trials. There were limited harms data reported for the ASPIRE trial. The only available data were for laboratory and clinical AEs, of which any one reported AE did not occur in more than three patients.

The proportion of patients with SAEs in the GEMINI trials was similar in the DTG + 3TC groups (6% and 8%) compared with the DTG + TDF/FTC groups (6% and 9%), respectively. No information on SAEs was provided for the ASPIRE trial. The proportion of patients who withdrew due to AEs was 2% in each treatment group in the GEMINI trials. In the ASPIRE trial, one patient in the DTG + 3TC group withdrew due to an AE. There were no deaths reported in the GEMINI-1 and ASPIRE trials. In the GEMINI-2 trial, two deaths occurred in

patients in the DTG + 3TC treatment group (due to Burkitt's lymphoma and acute myocardial infarction).

Notable harms identified in the review protocol included nausea, vomiting, diarrhea, insomnia, depression, birth defects, and effects on lipids, bone, and renal function. In the GEMINI-1 trial, more patients in the DTG + TDF/3TC group appeared to have gastrointestinal AEs (particularly nausea and diarrhea), insomnia, [redacted] compared with the DTG + 3TC group. In comparison, in the GEMINI-2 trial, the frequency of these AEs appeared to be similar between the two treatment groups, thus making it difficult to draw any conclusions regarding relative frequency of the AES between treatment groups. Mental health outcomes, and particularly depression, were identified as being important to patients based on the input received. Based on the harms data, a low percentage of patients [redacted] experienced depression as an AE with no apparent imbalances between treatment groups.

In the GEMINI trials, the changes from baseline to week 48 in various lipid parameters (i.e., total, LDL, and high-density–lipoprotein cholesterol) were larger for DTG + 3TC than for DTG + TDF/FTC. In contrast, changes from baseline to week 48 in bone-related parameters (i.e., serum bone-specific alkaline phosphate, osteocalcin, procollagen 1 N-terminal propeptide, and type-1 collagen C-telopeptide) were larger in the DTG + TDF/FTC group than in the DTG + 3TC group. Similarly, the change from baseline to week 48 in renal-related biomarkers (i.e., serum creatinine, glomerular filtration rate, and urine protein/creatinine ratio) were also larger in the DTG + TDF/FTC group than in the DTG + 3TC group. In the ASPIRE trial, there were no statistically significant differences identified in the secondary end points of median change from baseline to week 48 in total cholesterol, LDL cholesterol, triglycerides, or creatinine clearance between the DTG + 3TC group and the continued ART group; however, as they were not adjusted for multiplicity, the results are associated with potential for inflated type I error. Nonetheless, according to the clinical expert consulted on this review, the magnitude of the treatment differences in the changes in the lipid, bone, and renal parameters in the included trials were unlikely to be clinically relevant. No new safety signals were identified with use of the combination of DTG + 3TC in any of the included trials in patients who are either treatment naive (GEMINI-1 and GEMINI-2) or virologically suppressed and switching to DTG + 3TC (ASPIRE). Overall, the safety and tolerability profile of DTG + 3TC appears to be similar to other ART currently available in Canada.

Indirect Treatment Comparisons

Based on the trials included in this review, the only direct head-to-head comparison of DTG and 3TC with another ART regimen was with DTG and TDF/FTC. One published network meta-analysis (NMA),[9,10] for which the manufacturer submitted an internal report,[10] was reviewed and critically appraised in Appendix 6. The aim of the NMA was to compare the efficacy and safety of DTG + 3TC with traditional three-drug ART regimens in adult patients with HIV-1 infection who are treatment naive. The NMA included 14 RCTs of three-drug ART regimens that comprised either an INSTI, a boosted PI, or a NNRTI as the core drug, combined with two NRTIs as the treatment backbone. Efficacy outcomes assessed were viral suppression at week 48 and CD4+ cell count change from baseline to week 48; harms outcomes included AEs and SAEs. Results of the NMA suggest that there was no difference in efficacy or safety between DTG + 3TC and 12 different three-drug ART regimens relevant to Canadian clinical practice. Furthermore, subgroup analyses suggested that DTG + 3TC was no worse than all comparators [redacted] for

viral suppression at 48 weeks in patients with high baseline viral load. The sparsity of the evidence networks and the noninferiority design of the primary RCTs precluded the ability of the NMA to establish precise estimates of differences between treatment regimens thereby limiting confidence in the results.

Potential Place in Therapy[2]

In Canada, we have 10 STRs available for the treatment of HIV. All except Juluca (DTG/rilpivirine) are based upon the paradigm of combining two nucleoside analogues with a third drug (i.e., INSTI, NNRTI, or PI with or without a pharmacokinetic booster). These treatment options can effectively treat most persons infected with HIV with tolerable once-daily doses, with a minimum of short-term and long-term toxicities. Aside from STRs, there remains the potential to combine individual ARV medications, allowing for many more once- or twice-daily treatment options. As such, especially for patients without previous virologic failures, there are few unmet treatment needs.

DTG/3TC, like Juluca, is a two-drug STR. Although one might argue that two-drug regimens are less likely to have short- and long-term toxicities, it would be an overstatement to suggest that we need more tolerable or safer regimens. Assuming adequate potency to durably suppress HIV, the role of DTG/3TC would be as a smaller, less expensive treatment option than the other STRs (aside from Juluca). Juluca has similar benefits but has not really "caught on" as it must be taken with food and without antacids.

DTG/3TC could be used to treat a wide variety of persons infected with HIV. It would be an acceptable option for anyone not having a drug-resistant virus, either as upfront therapy or as a switch for issues of tolerance, convenience, pill size, or cost. The lower cost would make it a reasonable, and possibly preferred, treatment option for someone paying for a proportion of the cost of therapy out of pocket.

It is estimated that at least 50% of patients who are HIV infected in Canada have an un-mutated, wild-type virus, and therefore would qualify for DTG/3TC as a first-line or switch treatment. Even though the RCT data are in patients who are treatment naive, it is likely that DTG/3TC would be most used in those switching for reasons of tolerability, convenience, pill size, or cost. Conceivably, the number of patients switching to DTG/3TC could be substantial.

[2] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

Conclusions

Two identical, phase III, double-blind, noninferiority RCTs in adult patients with HIV-1 infection who are treatment naive support that a two-drug regimen of DTG + 3TC administered as separate tablets is noninferior to a three-drug regimen of DTG + TDF/FTC based on the proportion of patients with an HIV-1 viral load of < 50 copies/mL at week 48 using a noninferiority margin of 10%. One phase III, open-label, noninferiority RCT in adult patients with HIV-1 infection who are virologically suppressed demonstrated that switching to separate tablets of DTG + 3TC is noninferior to continued three-drug ART regimens based on the proportion of patients with treatment failure at week 24; however, this trial was associated with numerous limitations and noninferiority has not been established based on a noninferiority margin of 4% as currently recommended by the US FDA for switch trials. Harms were similar between treatment groups in the included trials and any differences in lipid, bone, or renal parameters were not considered to be clinically relevant. An NMA in the treatment-naive population did not provide evidence for a difference in efficacy or safety between DTG and 3TC and 12 different three-drug ART regimens relevant to Canadian clinical practice; however, confidence in the results is limited due to issues in the systematic literature search and sparsity of the evidence network. Evidence gaps are the lack of evidence in patients younger than 18 years of age, lack of a high-quality trial in patients who are virologically suppressed and switching from a three-drug ART regimen to DTG/3TC, lack of direct evidence for efficacy and safety of DTG/3TC administered as an FDC or compared with other ARV regimens available in Canada, and lack of long-term data to assess the durability of response and the potential for emergence of resistance mutations beyond 48 weeks.

Appendix 1: Patient Input Summary

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input

The Canadian Treatment Action Council (CTAC) is a non-governmental organization that focuses on access to treatment, care, and support for patients living with HIV and hepatitis C (HCV) within the country. CTAC aims to maintain a dialogue with community members, service providers, policy-makers, and other relevant stakeholders to identify, develop, and implement policy and program solutions. Full CTAC membership is reserved for individuals living with HIV (including HCV coinfection), and organizations, groups, or projects with a substantial HIV mandate (including HCV coinfection). Associate CTAC membership is open to any individual, organization, group, or project that supports CTAC's mandate and objective.

In the past two years, CTAC has received funding in excess of $50,000 from ViiV Healthcare. CTAC did not receive help from outside the organization to prepare this submission, or to collect and analyze the data used in this submission.

2. Condition-Related Information

Information for this submission was gathered through a patient input consultation workshop held by CTAC in Toronto on February 7, 2019. People living with HIV who had experience with dolutegravir (DTG), lamivudine (3TC), or a combination of the two were invited to participate in the workshop, where an overview of the CADTH Common Drug Review patient input process was provided along with key findings from the DTG/3TC clinical trials. In addition, a Web-based survey (available February 14, 2019, to March 4, 2019) was emailed to CTAC members and partners and shared on its website. A total of twelve individuals provided information through the workshop (n = 9) and Web-based survey (n = 3), all of whom were HIV positive and on treatment for the disease. Two-thirds of participants identified as male, and the age of participants ranged from "in their 20s" to "in their 60s," with 75% 50 years of age or older. Further, the number of years on treatment varied from five to approximately 34 years. The patient group also indicated that survey data collected for two previous CADTH Common Drug Review submissions (i.e., for DTG and DTG/3TC) have informed the current submission.

HIV is a serious, life-threatening illness that threatens the immune system. If untreated, HIV infection may compromise a person's immune system to the point where they can no longer fight off opportunistic infections. Access, administration of, and adherence to highly active antiretroviral treatment can control progression of HIV such that patients generally manage their condition as a chronic illness. Successful treatment or viral suppression is linked to marked improvement in long-term health outcomes and drastically reduces the possibility of transmitting HIV to sexual partners. However, patients are living longer, which increases susceptibility to inflammation and noninfectious comorbidities, including bone fractures and renal failure, and liver and cardiovascular disease. According to the patient group, the comorbidities are not only a side effect of aging, but due to other factors such as coinfection and antiretroviral treatments themselves.

Many of those living with HIV also experience negative mental health outcomes, whether as a side effect from treatment, or from facing stigma, discrimination, and related stress. One participant explained how their depression can have an effect on whether they adhere to their medication, "When depressed it is sometimes hard to just push yourself to pick up your

pills." Another participant described issues with stigma in the medical community, as they felt that "local doctors feel ill-equipped to treat HIV due to inexperience because of low patient caseloads with the condition." They also noted that "unless they're familiar, doctors still see HIV as something more difficult to live with than it actually is." CTAC also reported that many of those living with HIV experience intersecting vulnerabilities, shaped by social determinants of health. Limited funding or services for addictions, mental health, housing, and food security can impact a patient's HIV treatment. The patient input also noted the loss in labor productivity associated with living with HIV, as well as a loss in quality of life. One respondent stated, "I am worried about the fact that HIV is now viewed as a chronic, manageable disease. I still have good and bad days but, if HIV is now seen as something other than a disability, will I be forced to go back to work, even when I'm not well?"

Regarding caregiver support, respondents highlighted a number of areas where they had support or could benefit from it. They also highlighted the substantial impact that caring for patients living with HIV has on caregivers, with one person noting that "hiding from friends and some of our family members that I am HIV positive" has been extremely difficult and hindered the ability to acquire a social safety net.

3. Current Therapy-Related Information

The twelve workshop/survey respondents who identified as living with HIV were all currently on treatment for HIV. They had been taking current therapies for approximately three to 15 years, with minor changes made due to other health problems, or development of resistance. CTAC noted that the respondents were mostly long-term survivors (up to 34 years with HIV), which demonstrates the relative stability of the new generation of HIV medications. Despite this, individuals living with HIV may need to change their treatment regimen due to advancements in the medication or because of other health complications. Further, treatment adherence is required to maintain efficacy, and nonadherence can lead to a drug class resistance, resulting in a need to try other treatment options.

All of the participants indicated current or past use with one or more of the following: darunavir, DTG, emtricitabine, rilpivirine, ritonavir, tenofovir etravirine, raltegravir, Triumeq (abacavir/DTG/3TC), and/or Atripla (efavirenz/emtricitabine/tenofovir). Participants noted that their current treatment was effective at suppressing their viral load, but that there had been side effects associated with older treatments that were given when they were first diagnosed. One participant noted that "[azidothymidine] made me extremely sick. I became anemic and had extremely low energy. The side effects were so bad, that I wanted to discontinue treatment."

Access to treatment was also mentioned as a challenge, particularly for those residing in rural areas. For example, one respondent noted they had to travel about 100 km each way for doctor's appointments every six months, and that this would be a significant obstacle if appointments were more frequent or if they did not have support from family. Further, others noted service provider knowledge, staff time, funding, transportation, and other associated costs as barriers to providing support for those living with HIV, and its impact on treatment adherence, mental health, and other determinants of health. Respondents also described a number of "challenges associated with lack of knowledge about services and how to access them," including dental care, legal aid, and how to access disability benefits. Others noted the difficulty of navigating HIV-specific social services.

In summary, patients feel that HIV is a complicated illness that requires treatment options that can be tailored to individual needs and delivered in innovative capacities that bolster access to treatment, care, and support, such as treatment outreach programs, low-threshold health care services, adherence programs, and social supports.

4. Expectations About the Drug Being Reviewed

None of the participants, in the workshop or from the online survey, had experience with the fixed-dose combination drug DTG/3TC.

CTAC described DTG/3TC as a novel, once-daily, fixed-dose combination therapy featuring two drugs that are already on the Canadian market: DTG and 3TC. It was noted that the clinical trials for DTG/3TC have shown that switching to this two-drug regimen combination is associated with high HIV suppression rates, has a low potential for drug-drug interactions, and has the potential for reduced long-term drug toxicity. These benefits were considered important for individuals managing lifetime use of HIV antiviral treatment. Many of the participants expressed interest in a drug with a new chemical composition that is potent against variants resistant to non-nucleoside reverse transcriptase inhibitors. One participant noted that “new meds offer hope, especially for those with multiple types of drug resistance.” Other participants, such as one participant from the DTG/3TC survey noted that “I don't see replacing the "devil" I know with the "devil" I don't know - at least on a personal basis.”

5. Additional Information

Not applicable.

Appendix 2: Literature Search Strategy

Clinical Literature Search

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946-present) Embase (1974-present) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	March 18, 2019
Alerts:	Biweekly search updates until project completion
Study Types:	No publication type filters were applied.
Limits:	Publication date limit: none Language limit: none Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.ot	Original title (Medline)
.rn	Registry number
.dq	Candidate term word (Embase)
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings

MULTI-DATABASE STRATEGY	
Line #	**Search Strategy**
1	(Dovato* or "dolutegravir/lamivudine" or "lamivudine/dolutegravir" or "DTG/3TC" or "3TC/DTG" or GSK 3515864 or GSK3515864).ti,ab,kf,ot,hw,rn,nm.
2	(Dolutegravir* or dolutegravirsodium* or Tivicay* or DTG or GSK 1349572* or GSK1349572* or HSDB 8152 or HSDB8152 or S 349572 or S349572 or S GSK 1349572* or SGSK 1349572* or SGSK1349572* or GSK 572 or GSK572 or S 1349572* or S1349572* or 1Q1V9V5WYQ or DKO1W9H7M1 or 0E1T06685X).ti,ab,kf,ot,hw,rn,nm.
3	Lamivudine/
4	(Lamivudin* or 3TC* or Epivir* or hepivir* or heptodin* or Heptovir* or inhavir* or ladiwin* or lamidac* or lamivir or Hepitec or slamivudine* or zefix or Zeffix or CCRIS 9274 or CCRIS9274 or GR 109714X or GR109714X or HSDB 7155 or HSDB7155 or BCH 189 or BCH189 or GR 103665 or GR103655 or nsc 620753 or nsc620753 or 2T8Q726O95).ti,ab,kf,ot,hw,rn,nm.
5	or/3-4
6	2 and 5
7	1 or 6
8	7 use medall
9	(Dovato* or "dolutegravir/lamivudine" or "lamivudine/dolutegravir" or "DTG/3TC" or "3TC/DTG" or GSK 3515864 or GSK3515864).ti,ab,kw,dq.
10	*dolutegravir/
11	(Dolutegravir* or dolutegravirsodium* or Tivicay* or DTG or GSK 1349572* or GSK1349572* or HSDB 8152 or HSDB8152 or S 349572 or S349572 or S GSK 1349572* or SGSK 1349572* or SGSK1349572* or GSK 572 or GSK572 or S 1349572* or S1349572*).ti,ab,kw,dq.
12	or/10-11
13	*lamivudine/
14	(Lamivudin* or 3TC* or Epivir* or hepivir* or heptodin* or Heptovir* or inhavir* or ladiwin* or lamidac* or lamivir or Hepitec or slamivudine* or zefix or Zeffix or CCRIS 9274 or CCRIS9274 or GR 109714X or GR109714X or HSDB 7155 or HSDB7155 or BCH 189 or BCH189 or GR 103665 or GR103655 or nsc 620753 or nsc620753).ti,ab,kw,dq.
15	or/13-14
16	12 and 15
17	9 or 16
18	17 use oemezd
19	18 not conference abstract.pt.
20	8 or 19
21	remove duplicates from 20

CLINICAL TRIAL REGISTRIES		
ClinicalTrials.gov	Produced by the U.S. National Library of Medicine. Targeted search used to capture registered clinical trials. [Search -- dolutegravir AND lamivudine]	
WHO ICTRP	International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials. [Search terms -- dolutegravir AND lamivudine]	
Health Canada Clinical Trails Database	Produced by Health Canada. Targeted search used to capture registered clinical trials. [Search terms -- dolutegravir AND lamivudine]	

OTHER DATABASES		
PubMed	Searched to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.	
Cochrane Central Register of Controlled Trials	Same MeSH, keywords, and limits used as per MEDLINE search, excluding study types and human restrictions. Syntax adjusted for Wiley platform.	

Grey Literature

Dates for Search:	March 11, 2019 – March 18, 2019
Keywords:	Dovato, dolutegravir/lamivudine, DTG/#TC, and HIV
Limits:	Publication years: all

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- health technology assessment agencies
- health technology assessment agencies
- health economics
- clinical practice guidelines
- drug and device regulatory approvals
- advisories and warnings
- drug class reviews
- clinical trial registries
- databases (free)
- health statistics
- Internet search
- uptodate.

Appendix 3: Excluded Studies

Table 17: Excluded Studies

Reference	Reason for Exclusion
Anonymous (2019)[38]	Erratum
Baldin et al. (2019)[39]	Study design
Blanco et al. (2018)[40]	Intervention
Borghetti et al. (2018)[41]	Study design
Borghetti et al. (2016)[42]	Study design
Boswell et al. (2018)[43]	Systematic review
Cahn et al. (2017)[44]	Study design
Cattaneo et al. (2019)[45]	Review
Ciccullo et al. (2018)[46]	Study design
Joly et al. (2019)[47]	Study design
Lanzafame et al. (2018)[48]	Study design
Maggiolo et al. (2017)[49]	Study design
Nyaku et al. (2019)[50]	Study design
Nyaku et al. (2019)[51]	Duplicate
Patel et al. (2014)[52]	Systematic review and network meta-analysis
Reynes et al. (2016)[53]	Conference abstract
Taiwo et al. (2018)[54]	Study design

Appendix 4: Detailed Outcome Data

Table 18: Virologic Efficacy Outcomes in the GEMINI-1 and GEMINI-2 Trials

Virologic Efficacy Outcomes	GEMINI-1		GEMINI-2	
	DTG + 3TC	DTG + TDF/FTC	DTG + 3TC	DTG + TDF/FTC
Virologic Failures				
ITT-E Population at Week 48				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted] [redacted]	[redacted] [redacted]	[redacted] [redacted]	[redacted] [redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted] [redacted]	[redacted] [redacted]	[redacted] [redacted]	[redacted] [redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted] [redacted]	[redacted] [redacted]	[redacted] [redacted]	[redacted] [redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Virologic Efficacy Outcomes	GEMINI-1		GEMINI-2	
	DTG + 3TC	DTG + TDF/FTC	DTG + 3TC	DTG + TDF/FTC
Virologic Successes				
ITT-E Population at Week 48				
HIV-1 RNA < 50 copies/mL at week 48, n/N (%) [95% CI][a]	320/356 (90) [86.8 to 93.0]	332/358 (93) [90.0 to 95.4]	335/360 (93) [90.4 to 95.7]	337/359 (94) [91.4 to 96.4]
Difference in proportion[b], % (95% CI)	–2.8 (–7.0 to 1.3)		–0.8 (–4.4 to 2.8)	
Adj. difference in proportion[c], % (95% CI)	–2.6 (–6.7 to 1.5)		–0.7 (–4.3 to 2.9)	
Time to Viral Suppression in ITT-E Population				
[redacted]				

3TC = lamivudine; Adj = adjusted; AE = adverse event; ART = antiretroviral therapy; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; DTG = dolutegravir; FTC = emtricitabine; ITT= intention-to-treat population; ITT-E = intention-to-treat exposed population; PP = per-protocol population; RNA = ribonucleic acid; TDF = tenofovir disoproxil fumarate.

Note: The primary efficacy outcome in both GEMINI-1 and GEMINI-2 was the proportion of patients with plasma HIV-1 RNA < 50 copies/mL at week 48 using the US FDA snapshot algorithm in the ITT-E population. Noninferiority was concluded if the lower boundary of the two-sided 95% CI for the difference in response between the treatment groups was greater than –10%.

[a] Using the US FDA snapshot algorithm.

[b] Difference is the proportion of patients on DTG + 3TC minus the proportion of patients on DTG + TDF/FTC.

[c] Adjusted difference is based on the CMH-stratified analysis adjusting for baseline stratification factors of plasma HIV-1 RNA (≤ 100,000 copies/mL and > 100,000 copies/mL) and CD4+ cell count (≤ 200 cells/μL and > 200 cells/μL).

Source: GEMINI-1 Clinical Study Report;[11] GEMINI-2 Clinical Study Report.[12]

Table 19: Proportion of Patients With HIV-1 RNA < 50 Copies/mL at Week 48 by Subgroup (Baseline HIV-1 RNA and Baseline CD4+ Cell Count) in the GEMINI-1 and GEMINI-2 Trials (Intention-to-Treat Exposed Population)

Characteristic	GEMINI-1		GEMINI-2	
	DTG + 3TC (N = 356)	DTG + TDF/FTC (N = 358)	DTG + 3TC (N = 360)	DTG + TDF/FTC (N = 359)
[redacted]				

Source: GEMINI-1 Clinical Study Report;[11] GEMINI-2 Clinical Study Report.[12]

Table 20: Change From Baseline in CD4+ Cell Count (Cells/µL) in the GEMINI-1 and GEMINI-2 Trials (Intention-to-Treat Exposed Population)

Characteristic	GEMINI-1		GEMINI-2	
	DTG + 3TC (N = 356)	DTG + TDF/FTC (N = 358)	DTG + 3TC (N = 360)	DTG + TDF/FTC (N = 359)
Baseline, Mean (SD)				
Change From Baseline in CD4+ Cell Count (cells/µL)				
[redacted]				
n/N (%)				
Adjusted mean (SE)[a]				
Difference (95% CI); *P* value[b]				
[redacted]				
n/N (%)				
Adjusted mean (SE)[a]				
Difference (95% CI); *P* value				
[redacted]				

Characteristic	GEMINI-1		GEMINI-2	
	DTG + 3TC (N = 356)	DTG + TDF/FTC (N = 358)	DTG + 3TC (N = 360)	DTG + TDF/FTC (N = 359)
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted mean (SE)[a]	[redacted]	[redacted]	[redacted]	[redacted]
Difference (95% CI); *P* value	[redacted]		[redacted]	
[redacted]				
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted mean (SE)[a]	[redacted]	[redacted]	[redacted]	[redacted]
Difference (95% CI); *P* value	[redacted]		[redacted]	
[redacted]				
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted mean (SE)[a]	[redacted]	[redacted]	[redacted]	[redacted]
Difference (95% CI); *P* value	[redacted]		[redacted]	
[redacted]				
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted mean (SE)[a]	[redacted]	[redacted]	[redacted]	[redacted]
Difference (95% CI); *P* value	[redacted]		[redacted]	
[redacted]				
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted mean (SE)[a]	[redacted]	[redacted]	[redacted]	[redacted]
Difference (95% CI); *P* value	[redacted]		[redacted]	
[redacted]				
n	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted mean (SE)[c]	[redacted]	[redacted]	[redacted]	[redacted]
Difference[b] (95% CI); *P* value	[redacted]		[redacted]	

[redacted]

[redacted]

[redacted]

[redacted]

Source: GEMINI-1 Clinical Study Report;[11] GEMINI-2 Clinical Study Report.[12]

Table 21: Analysis of Change From Baseline in CD4+ Cell Count (Cells/µL) at Week 48 by Subgroup — Observed Case (Baseline HIV-1 RNA and CD4+ Cell Count) in the GEMINI-1 and GEMINI-2 Trials (Intention-to-Treat Exposed Population)

Characteristic	GEMINI-1		GEMINI-2	
	DTG + 3TC (N = 356)	DTG + TDF/FTC (N = 358)	DTG + 3TC (N = 360)	DTG + TDF/FTC (N = 359)
Baseline HIV-1 RNA ≤ 100,000 Copies/mL				
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted mean (SE)[a]	[redacted]	[redacted]	[redacted]	[redacted]
Difference in proportion[b], % (95% CI)	[redacted]		[redacted]	
Baseline HIV-1 RNA > 100,000 Copies/mL				
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]

Characteristic	GEMINI-1		GEMINI-2	
	DTG + 3TC (N = 356)	DTG + TDF/FTC (N = 358)	DTG + 3TC (N = 360)	DTG + TDF/FTC (N = 359)
Adjusted mean (SE)	[redacted]			
Difference in proportion, % (95% CI)	[redacted]			
Baseline CD4+ Count ≤ 200 cells/μL				
n/N (%)	[redacted]			
Adjusted mean (SE)	[redacted]			
Difference in proportion, % (95% CI)	[redacted]			
Baseline CD4+ Count > 200 cells/μL				
n/N (%)	[redacted]			
Adjusted mean (SE)	[redacted]			
Difference in proportion, % (95% CI)	[redacted]			

3TC = lamivudine; CD4+ = cluster of differentiation 4 positive; CI = confidence interval; DTG = dolutegravir; FTC = emtricitabine; ITT-E = intention-to-treat exposed population; RNA = ribonucleic acid; SE = standard error; TDF = tenofovir disoproxil fumarate.

[a] For each subgroup, adjusted mean is the estimated mean change from baseline at week 48 in each arm calculated from an analysis of covariance model adjusting for the following covariates/factors: treatment, baseline plasma HIV-1 RNA (factor), baseline CD4+ cell count, subgroup, and treatment and relevant subgroup interaction. For CD4+ cell count subgroup, baseline CD4+ cell count group is included as a factor only.

[b] Difference is the proportion of DTG + 3TC minus the proportion of DTG+ TDF/FTC.

Source: GEMINI-1 Clinical Study Report;[11] GEMINI-2 Clinical Study Report.[12]

Table 22: Change From Baseline in EQ-5D-5L Utility Scores and VAS Scores [redacted] in the GEMINI-1 and GEMINI-2 Trials (Intention-to-Treat Exposed Population)

Characteristic	GEMINI-1		GEMINI-2	
	DTG + 3TC (N = 356)	DTG + TDF/FTC (N = 358)	DTG + 3TC (N = 360)	DTG + TDF/FTC (N = 359)
Utility Score				
Baseline score, mean (SD)	[redacted]			
[redacted]				
n/N (%)	[redacted]			
Mean (SD)	[redacted]			
Adjusted mean change (SE)[a]	[redacted]			
Difference (95% CI); *P* value[b]	[redacted]			
[redacted]				
n/N (%)	[redacted]			
Mean (SD)	[redacted]			
Adjusted mean (SE)[a]	[redacted]			
Difference (95% CI); *P* value[b]	[redacted]			
[redacted]				
n/N (%)	[redacted]			
Mean (SD)	[redacted]			
Adjusted mean (SE)[a]	[redacted]			
Difference (95% CI); *P* value[b]	[redacted]			
Visual Analogue Scale				
Baseline score, Mean (SD)	[redacted]			
[redacted]				
n/N (%)	[redacted]			
Mean (SD)	[redacted]			

Characteristic	GEMINI-1		GEMINI-2	
	DTG + 3TC (N = 356)	DTG + TDF/FTC (N = 358)	DTG + 3TC (N = 360)	DTG + TDF/FTC (N = 359)
Adjusted mean (SE)[a]	[redacted]	[redacted]	[redacted]	[redacted]
Difference (95% CI); *P* value[b]	[redacted]		[redacted]	
[redacted]				
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted mean (SE)[a]	[redacted]	[redacted]	[redacted]	[redacted]
Difference (95% CI); *P* value[b]	[redacted]		[redacted]	
[redacted]				
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted mean (SE)[a]	[redacted]	[redacted]	[redacted]	[redacted]
Difference (95% CI); *P* value[b]	[redacted]		[redacted]	

[redacted]

Source: GEMINI-1 Clinical Study Report;[11] GEMINI-2 Clinical Study Report.[12]

Table 23: Cumulative Summary of Confirmed Virologic Withdrawals by Visit Through Week 48 in the GEMINI-1 and GEMINI-2 trials (Intention-to-Treat Exposed Population)

Week	GEMINI-1		GEMINI-2	
	DTG + 3TC (N = 356)	DTG + TDF/FTC (N = 358)	DTG + 3TC (N = 360)	DTG + TDF/FTC (N = 359)
Any time, n (%) Virologic non-response Rebound	4 (1) 0 (0) 4 (1)	2 (< 1) 0 (0) 2 (< 1)	2 (< 1) 0 (0) 2 (< 1)	2 (< 1) 0 (0) 2 (< 1)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

3TC = lamivudine; CVW = confirmed virologic withdrawal; DTG = dolutegravir; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; ITT-E = intention-to-treat exposed population; NRTI = nucleoside reverse transcriptase inhibitor; RNA = ribonucleic acid; TDF = tenofovir disoproxil fumarate; VAS = Visual Analogue Scale.

Note: CVW was defined as a second and consecutive HIV-1 RNA value meeting the definition for virologic non-response or virologic rebound. Genotypic testing of the HIV-1 reverse transcriptase, protease-reverse transcriptase, and integrase genes was successful for baseline and virologic withdrawal samples from all 10 patients, except for one patient who received DTG + TDF/FTC. All 10 patients were classified as virologic rebounds and none of the patients with successful amplified and sequenced samples had emergence of mutations conferring resistance to INSTI or NRTIs.

Source: GEMINI-1 Clinical Study Report;[11] GEMINI-2 Clinical Study Report;[12] Cahn et al. (2019).[7]

Table 24: Longitudinal Changes in Residual Viremia in a Substudy of the ASPIRE Trial

Efficacy Outcomes	ASPIRE	
	DTG + 3TC (N = 36)	DHHS or cART (N = 36)
Residual Viremia		
Baseline HIV-1 RNA copies/mL **Mean**[a]	5.0	4.2
***P* value**[b]	*P* = 0.64	
Week 24 HIV-1 RNA copies/mL **Mean viral load change, copies/mL (95% CI)** ***P* value**[b]	1.6 (–1.9 to 5.2) *P* = 0.37	
Week 48 HIV-1 RNA copies/mL **Mean viral load change, copies/mL (95% CI)** ***P* value**[b]	0.5 (–3.0 to 4.1) *P* = 0.76	

3TC = lamivudine; cART = combination antiretroviral therapy; CI = confidence interval; DHHS = Department of Health and Human Services; DTG = dolutegravir; RNA = ribonucleic acid.

[a] No measure of variation was reported (e.g., standard deviation).

[b] Differences between groups were analyzed by fitting a linear model using a generalized least squares fit including study time point and treatment arm in the model.

Source: Li et al. (2019).[34]

Appendix 5: Summary of Pivotal Bioequivalence Study

Aim

To summarize the details and findings of Study 204994 related to the evaluation of bioequivalence between a fixed-dose combination (FDC) tablet of dolutegravir (DTG) and lamivudine (3TC) in comparison with DTG + 3TC administered as individual tablets under fasted and fed conditions.

Methods

The manufacturer conducted one phase I, single-centre, open-label, single-dose, randomized, two-part, crossover study (Study 204994) that evaluated the bioequivalence and food effect of the DTG/3TC FDC in both a monolayer (part 1) and bilayer (part 2) tablet. Only information from part 2 that evaluated the bioequivalence and food effect of the bilayer FDC of DTG 50 mg/3TC 300 mg (which is the marketed formulation) and the co-administration of its two single-entity components have been included in this summary (Table 25). Study 204944 used a crossover design consisting of two treatment periods in which healthy adult volunteers received either the test (FDC of DTG 50 mg/3TC 300 mg) or reference (DTG 50 mg + 3TC administered as separate tablets) product under fasting conditions, separated by a washout period of at least seven days. The first 16 volunteers who completed the crossover phase and provided consent to continue entered a third treatment period during which they received a single dose of the FDC tablet administered with a high fat meal to evaluate any food effect on the FDC.

Table 25: Study Design

Description	Study 204994
Study design	Phase I, single-centre, open-label, single-dose, randomized, crossover bioequivalence study under fasted conditions followed by evaluation of any food effect under fed conditions
Test	FDC (DTG 50 mg/3TC 300 mg)
Reference	DTG 50 mg tablet and Epivir (3TC 300 mg) tablet administered separately

3TC = lamivudine; DTG = dolutegravir; FDC = fixed-dose combination.

Source: Study 204994 Clinical Study Report.[55]

End Points

As per the guidance from Health Canada relating to comparative bioavailability standards, two pharmacokinetic parameters are generally used to assess bioequivalence, which were both measured and used as end points in this study. These include the area under the curve of the analyte in plasma from time zero to the last quantifiable time point ($AUC_{(0-t)}$) and the maximum measured concentration of the analyte in plasma (C_{max}), for both DTG and 3TC.

Statistical Analyses

[redacted] in Canada, the bioequivalence standards outlined by Health

Canada are that the 90% confidence interval of the geometric means ratio of $AUC_{(0-t)}$ of the test to reference product and the geometric mean ratio of the C_{max} of the test to reference product must fall within 0.800 to 1.250 inclusive under fasting conditions.[56]

[redacted]

Results

Study Population

A total of [redacted] healthy adult male and female volunteers were screened and randomized. Of the [redacted] randomized volunteers, [redacted] had pharmacokinetic data that were deemed evaluable and were therefore included in the pharmacokinetic and statistical analyses. Details regarding the subject disposition and demographics of the included volunteers have been summarized in Table 26.

Table 26: Study Population — Disposition and Demographics

	Study 204994
Subject Disposition	[redacted]
Planned, N	[redacted]
Randomized, N	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Completed as planned, n (%)	[redacted]
Withdrawn for any reason, n (%)	[redacted]
Lost to follow-up, n (%)	[redacted]
Adverse events, n (%)	[redacted]
Demographics	
Age, mean (SD)	[redacted]
Sex, n (%)	
Female	[redacted]
Male	[redacted]
BMI (kg/m^2), mean (SD)	[redacted]
Weight (kg), mean (SD)	[redacted]
Race, n (%)	
African-American	[redacted]
American Indian or Alaskan Native	[redacted]
Asian	[redacted]
White/Caucasian	[redacted]

[redacted]

Source: Study 204994 Clinical Study Report.[55]

Pharmacokinetic Results

The key results from the bioequivalence assessment have been summarized in Table 27.

[redacted]

Table 27: Pharmacokinetic Parameters — Key Results [redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Source: Study 204994 Clinical Study Report.[55]

The results of the assessment of food effect on the FDC are summarized in Table 28.

[redacted]

[redacted]

Table 28: Pharmacokinetic Parameters — Key Results [redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	

[redacted]

Source: Study 204994 Clinical Study Report.[55]

Conclusion

As noted in the CADTH Common Drug Review systematic review, the randomized controlled trials supporting the efficacy and safety of DTG/3TC were conducted using DTG + 3TC administered as separate tablets, whereas the marketed formulation is a FDC. The results of the bioequivalence assessment have been presented in this summary.

Appendix 6: Summary of Indirect Comparisons

Introduction

The aim of this section is to assess the indirect evidence available for the efficacy and harms of the combination of dolutegravir (DTG) and lamivudine (3TC) as a complete regimen for the treatment of HIV-1 infection compared with any of the comparators listed in the CADTH Common Drug Review systematic review protocol (see Table 4). The randomized controlled trials (RCTs) included in the CADTH Common Drug Review systematic review compared DTG + 3TC with the combination of DTG and tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC). There were no trials directly comparing the combination of DTG + 3TC administered as separate components or DTG/3TC as a single-tablet regimen with any of the other relevant comparators.

Methods

A published network meta-analysis (NMA)[9] that was also submitted by the manufacturer as an internal report[10] was reviewed. No additional indirect comparisons (ITCs) comparing DTG + 3TC or DTG/3TC with other antiretroviral treatment (ART) regimens for the treatment of HIV-1 infection were identified in a literature search of published ITCs.

Description of the Network Meta-Analysis

Review of the Network Meta-Analysis

Objectives and Rationale for the Network Meta-Analysis

The aim of the NMA was to compare the efficacy and safety of DTG + 3TC with European and US guideline-recommended three-drug ART regimens in patients with HIV-1 who are treatment naive. The rationale provided for comparing DTG + 3TC with three-drug regimens was [redacted]

The study selection process for the NMA indicated that guideline-recommended first-line regimens were to be compared in patients who are treatment naive and at least 13 years of age with HIV-1 infection for virologic suppression, increase in cluster of differentiation 4 positive (CD4+) cell count, and adverse events (AEs).

Methods for the Network Meta-Analysis

Study Eligibility and Selection Process

The eligibility criteria for study inclusion and exclusions were appropriate for achieving the aim of the NMA. A systematic literature search in the PubMed, Embase, and Cochrane databases was supplemented by systematic searching of the National Institute of Health clinical trial registry, and publicly available regulatory reports. Clinical study reports (CSRs) were also added to the search. The search terms included “HIV” and excluded “pregnancy” and treatment search terms appeared to include all ARTs recommended by the US Department of Health and Health Services (DHHS) and/or the European AIDS Clinical Society that were not nucleoside reverse transcriptase inhibitors. The search was limited to English-language publications of studies in human adults and adolescents with one of the following study designs: RCTs, systematic reviews, and meta-analyses. The search was

performed on December 4, 2018, and was an update of the search performed for a previous systematic literature review conducted in 2013 and published by Patel et al.[52]

Two independent reviewers screened titles and abstracts and selected potentially relevant articles. During full-text review, the reviewers resolved discrepancies by consensus.

The NMA included primary studies that were phase III or IV RCTs of 48- or 96-weeks' duration and published in English. The patient population of interest was patients at least 13 years of age with HIV-1 infection and wholly ART naive. To be included, the RCTs had to use at least one regimen of interest and report at least one outcome of interest. RCTs solely comparing more than one dosage of the same drug were excluded. [redacted]

[redacted] The regimens of interest were those composed of either an integrase strand transfer inhibitor, a boosted protease inhibitor, or a non-nucleoside reverse transcriptase inhibitor as the core drug, combined with two nucleoside reverse transcriptase inhibitors as the treatment backbone. Treatment regimens were considered regimens of interest if they were recommended by the US DHHS[57] as initial treatment regimens for most people with HIV and/or recommended by the European AIDS Clinical Society[58] as initial treatment regimens for adults with HIV. [redacted]

The primary outcome was the proportion of patients with virologic suppression at week 48 and the secondary efficacy outcome was mean increase in CD4+ cell count from baseline to week 48. The proportions of patients with AEs, drug-related AEs, and serious AEs (SAEs) were also outcomes of interest.

[redacted] reasons for exclusion were not provided for the final step after data extraction.

Data Extraction

A total of 14 RCTs were included in the NMA. [redacted] For each study, the sample size and the following baseline characteristics were reported for each arm: sex, [redacted] age, CD4+ cell count, viral load, [redacted]. The results for each outcome were also reported for each arm. [redacted]

Comparators

The components of the regimens included: DTG, darunavir (DRV), elvitegravir (EVG), efavirenz (EFV), raltegravir (RAL), rilpivirine (RPV), 3TC, abacavir (ABC), tenofovir alafenamide (TAF), TDF, FTC, cobicistat (c), and ritonavir (r). The following 13 comparators for DTG + 3TC were part of the evidence network for virologic suppression, CD4+ cell count change from baseline, AEs, and SAEs: DTG with ABC/3TC, TDF/FTC, or TAF/FTC; BIC + TAF/FTC; DRV/r or DRV/c (boosted DRV) with TDF/FTC; DRV/r with ABC/3TC; DRV/c with TAF/FTC; EFV + TDF/FTC; EVG/c with TDF/FTC or TAF/FTC; RAL with ABC/3TC or TDF/FTC; RPV with TDF/FTC.

There was no distinction made between treatment regimens that were combinations of two tablets (core drug and backbone) or single-tablet regimens containing the same drugs. The dose of each drug was consistent across RCTs. The dose for the combination of TAF/FTC was 10 mg/200 mg when combined with DRV or EVG and 25 mg/200 mg when combined with BIC or DTG. Patients took medications once or twice daily depending on the dosage regimen of the treatments and a double-dummy design was used to mask treatment assignment in most RCTs.

In two RCTs, patients were randomized to one of two core drugs and the treatment backbone was left up to the investigators' discretion. Dosages were not specified for the backbone in either RCT. Each of the RCTs contributed data to four treatment groups.

Outcomes

The efficacy outcomes analyzed were virologic suppression at week 48 and CD4+ cell count change from baseline to week 48. For virologic suppression results to be included, RCTs reporting virologic suppression had to use the FDA snapshot algorithm, the time to loss of virologic response of HIV-1 ribonucleic acid (RNA) less than 50 copies/mL (TLOVR-50), confirmed virologic response of HIV-1 RNA less than 50 copies/mL (CVR-50), or HIV RNA of less than 50 copies/mL in an intention-to-treat population. If more than one of these methods were used to determine virologic suppression, the method closest to the beginning of the list took precedence.

Among the 14 RCTs, 12 evaluated virologic suppression using the snapshot algorithm, one used the TLOVR-50 method, and one RCT analyzed viral load of less than 50 copies/mL in the per-protocol population. For the latter, the NMA authors extracted the population of patients in the intention-to-treat population who received the study drug as the denominator for determining the percentage of patients achieving virologic suppression. This is consistent with the snapshot algorithm and TLOVR-50 method. The FDA has found high concordance between snapshot and TLOVR results and considers the differences between the two to be minimal.[6] The definition of viral load of less than 50 copies/mL appeared to be similar to the other two methods.

Mean change from baseline in CD4+ cell count [redacted] was included for all RCTs. The methods for determining mean change from baseline in CD4+ cell count varied among the RCTs. Extracted mean values were a mixture of unadjusted means and means adjusted for baseline factors and/or covariates. Methods for imputing missing data varied across the trials. Seven RCTs excluded patients with missing data from CD4+ cell count analysis, five RCTs imputed data, and two did not specify how missing data were handled. Methods for data imputation consisted of non-completer equals failure (baseline observation carried forward), last observation carried forward, and a Markov chain Monte Carlo approach. Two RCTs did not specify how missing data were handled. Finally, for RCTs reporting standard

deviation and not standard error, the method for deriving the [redacted] was not specified.

The safety outcomes analyzed were AEs and SAEs. [redacted] In at least two RCTs, the data appeared to be erroneously extracted by calculating the percentage of patients with at least one SAE plus percentage of patients with at least one other (non-serious) AE.

Data for all outcomes were extracted at baseline, 48 weeks, [redacted] where available.

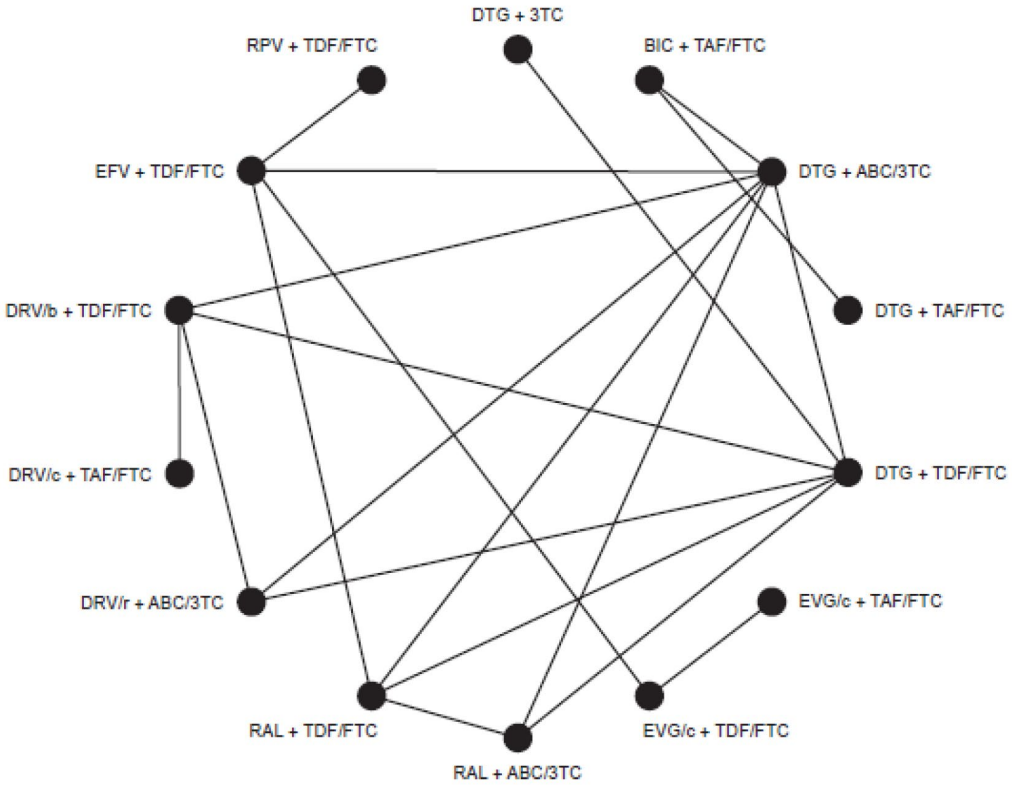
Quality Assessment of Included Studies

The Effective Public Health Practice Project quality assessment tool for quantitative studies was used to assess the quality of the included primary RCTs. For each RCT, ratings of strong, moderate, or weak were assigned to each of six components (selection bias, study design, confounders, blinding, data collection methods, and withdrawals and dropouts) and a global rating (strong [no weak components], moderate [one weak component], or weak [two or more weak components]) was assigned based on the component ratings. It was not specified whether quality assessment was performed by more than one reviewer and no sensitivity analyses were performed to assess the effects of excluding RCTs of lower quality. [redacted]

Evidence Network

The evidence network (Figure 3) was the same for all of the outcomes, except for the subgroup analysis of virologic suppression in patients with a baseline viral load of at least 100,000 copies/mL. In the former, 13 comparators were included while 11 comparators were included for the subgroup analysis (EVG/c + TAF/FTC and EVG/c + TDF/FTC were excluded). All network connections were informed by one trial, except for three comparisons that were informed by two trials each: DTG + 3TC versus DTG + TDF/FTC, DTG + TDF/FTC versus DTG + ABC/3TC, and RPV + TDF/FTC versus EFV + TDF/FTC.

Figure 3: Evidence Network for Virologic Suppression, CD4+ Change From Baseline, Adverse Events, and Serious Adverse Events



3TC = lamivudine; ABC = abacavir; AEs = adverse events; BIC = bictegravir; CSRs = clinical study reports; DRV/b = cobicistat- or ritonavir-boosted darunavir; DRV/c = cobicistat-boosted darunavir; DRV/r = ritonavir-boosted darunavir; DTG = dolutegravir; EFV = efavirenz; EVG/c = cobicistat-boosted elvitegravir; FTC = emtricitabine; NCTs = National Institute of Health Clinical Trials results published on ClinicalTrials.gov; NMA = network meta-analysis; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; pubs = published articles; RAL = raltegravir; RCT = randomized controlled trial; RPV = rilpivirine; SAEs = serious adverse events; SLR = systematic literature review; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TN = treatment naive; VS = virologic suppression.

Note: Network of treatment comparisons presented for the primary outcome of VS at week 48, and the secondary outcomes of CD4+ cell count change from baseline, AEs, and SAEs at week 48. The network represents the connections between treatments of interest based on the studies included in the NMA.

Source: Figure 1B from Radford M et al. Dolutegravir and lamivudine vs other antiviral regimens in patients with HIV-1 who are treatment naive: a systematic review and network meta-analysis. AIDS. 2019. doi: 10.1097/QAD.0000000000002285. Distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND). https://creativecommons.org/licenses/by-nc-nd/4.0/legalcode. Disclaimer.

Indirect Comparison Methods

Each outcome was analyzed using a Bayesian approach with Markov chain Monte Carlo simulation. Both fixed-effects and random-effects models were used. The proportion of patients achieving virologic suppression and the mean CD4+ cell count change from baseline were modelled as continuous variables with normal distributions. [redacted] A normal likelihood and an identity link function were used for the continuous variables. The treatment effects were summarized as mean differences in proportions of patients achieving virologic suppression or in change from baseline in CD4+ cell count. A subgroup analysis for virologic suppression was performed for patients with a

baseline viral load of at least 100,000 copies/mL. For AEs and SAEs, [redacted] and the treatment effects were summarized as odds ratios.

[redacted] The results were based on three chains with 50,000 iterations each and a burn-in of 20,000 iterations. [redacted]

[redacted] the choice between a fixed- or random-effects model for each outcome was based on convergence criteria, total residual deviance, and deviance information criterion. [redacted]

[redacted]

Results

Population

According to the eligibility criteria in the RCTs, patients had to be at least 18 years of age and ART naive. In most RCTs, patients also had to have a viral load of greater than 1,000 copies/mL or 5,000 copies/mL. According to the extracted baseline characteristics, the percentage of male patients ranged from 59% to 93% and the mean or median age ranged from 31 to 38 years. Mean or median baseline CD4+ cell count ranged from 217 copies/mL to 463 cells/mL and mean or median baseline viral load in $\log_{10}$ copies/mL ranged from 4.42 to 5. There were no notable imbalances in baseline characteristics between treatment groups in each RCT. Some RCTs excluded patients with hepatitis C or with either hepatitis B or C. Where reported, patients coinfected with hepatitis B or C virus comprised 10% or less of each RCT population. The percentage of patients discontinuing ranged from 5% to 20% and the percentage of patients discontinuing due to an AE ranged from 0% to 10% in each treatment group.

Efficacy

[redacted] The fixed-effects model results were reported as the main results for all of the outcomes [redacted]

Virologic Suppression at Week 48

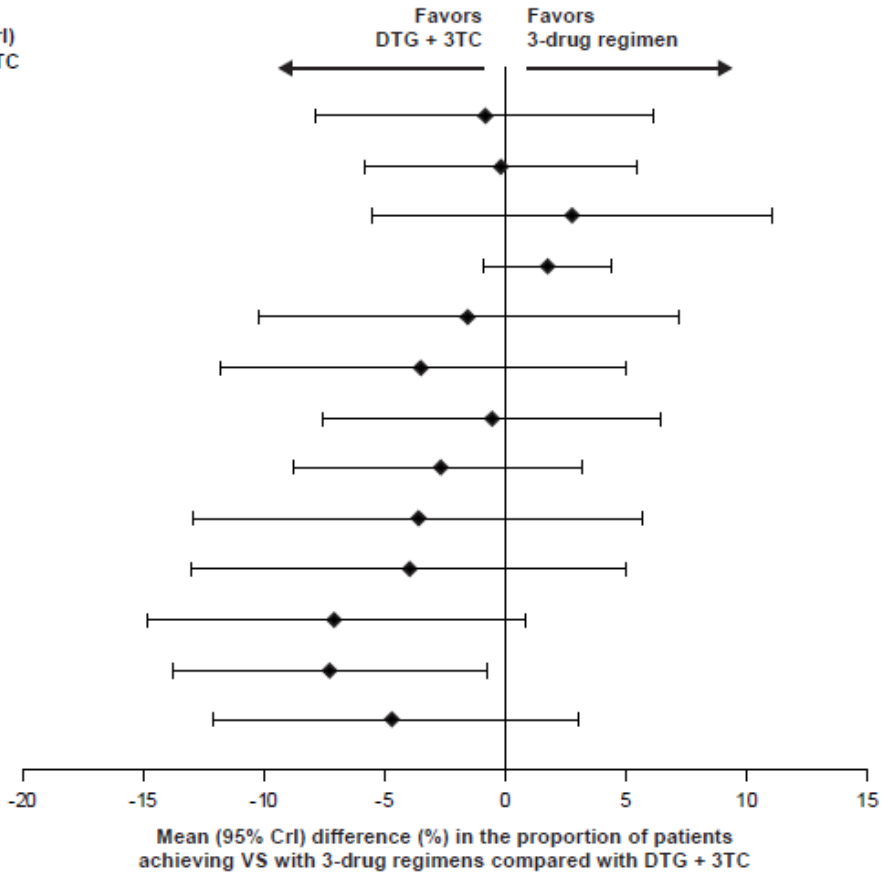
The NMA fixed-effects model results for mean difference in the proportion of patients achieving virologic suppression at week 48 are presented in Figure 4A. All of the 95% credible intervals included 0 aside from the comparison between DTG + 3TC and EFV + TDF/FTC, which was in favour of DTG + 3TC. [redacted]

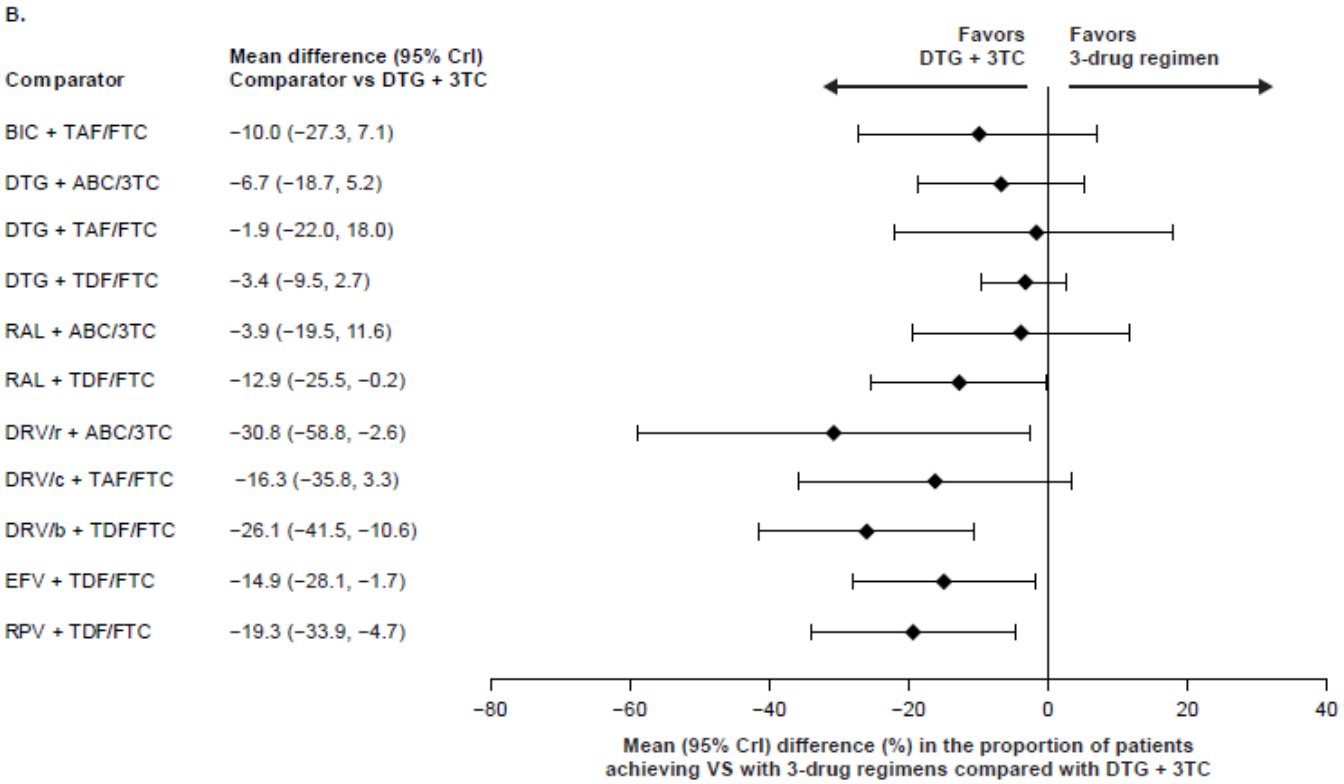
The fixed-effects model results from the subgroup analysis in patients with baseline viral load of at least 100,000 copies/mL showed significant differences in favour of DTG + 3TC against DRV/r + ABC/3TC, boosted DRV + TDF/FTC, EFV + TDF/FTC, RAL + TDF/FTC, and RPV + TDF/FTC (Figure 4B). [redacted]

Figure 4: Mean Difference in Percentage of Patients Achieving Virologic Suppression at Week 48 in (A) All Patients and in (B) Patients with Baseline Viral Load of at Least 100,000 Ribonucleic Acid Copies/mL (Fixed-Effects Model)

A.

Comparator	Mean difference (95% CrI) Comparator vs DTG + 3TC
BIC + TAF/FTC	−0.9 (−7.9, 6.1)
DTG + ABC/3TC	−0.2 (−5.8, 5.4)
DTG + TAF/FTC	2.7 (−5.6, 11.0)
DTG + TDF/FTC	1.7 (−1.0, 4.4)
EVG/c + TAF/FTC	−1.6 (−10.3, 7.2)
EVG/c + TDF/FTC	−3.5 (−11.8, 4.9)
RAL + ABC/3TC	−0.6 (−7.6, 6.4)
RAL + TDF/FTC	−2.7 (−8.8, 3.2)
DRV/r + ABC/3TC	−3.6 (−12.9, 5.7)
DRV/c + TAF/FTC	−4.0 (−13.0, 4.9)
DRV/b + TDF/FTC	−7.1 (−14.9, 0.8)
EFV + TDF/FTC	−7.3 (−13.8, −0.8)
RPV + TDF/FTC	−4.7 (−12.1, 3.0)





3TC = lamivudine; ABC = abacavir; BIC = bictegravir; crl = credible interval; DRV/b = boosted darunavir (cobicistat or ritonavir); DRV/c = cobicistat-boosted darunavir; DRV/r = ritonavir-boosted darunavir; DTG = dolutegravir; EFV = efavirenz; EVG/c = cobicistat-boosted elvitegravir; FTC = emtricitabine; RAL = raltegravir; RNA = ribonucleic acid; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; VL = viral load.

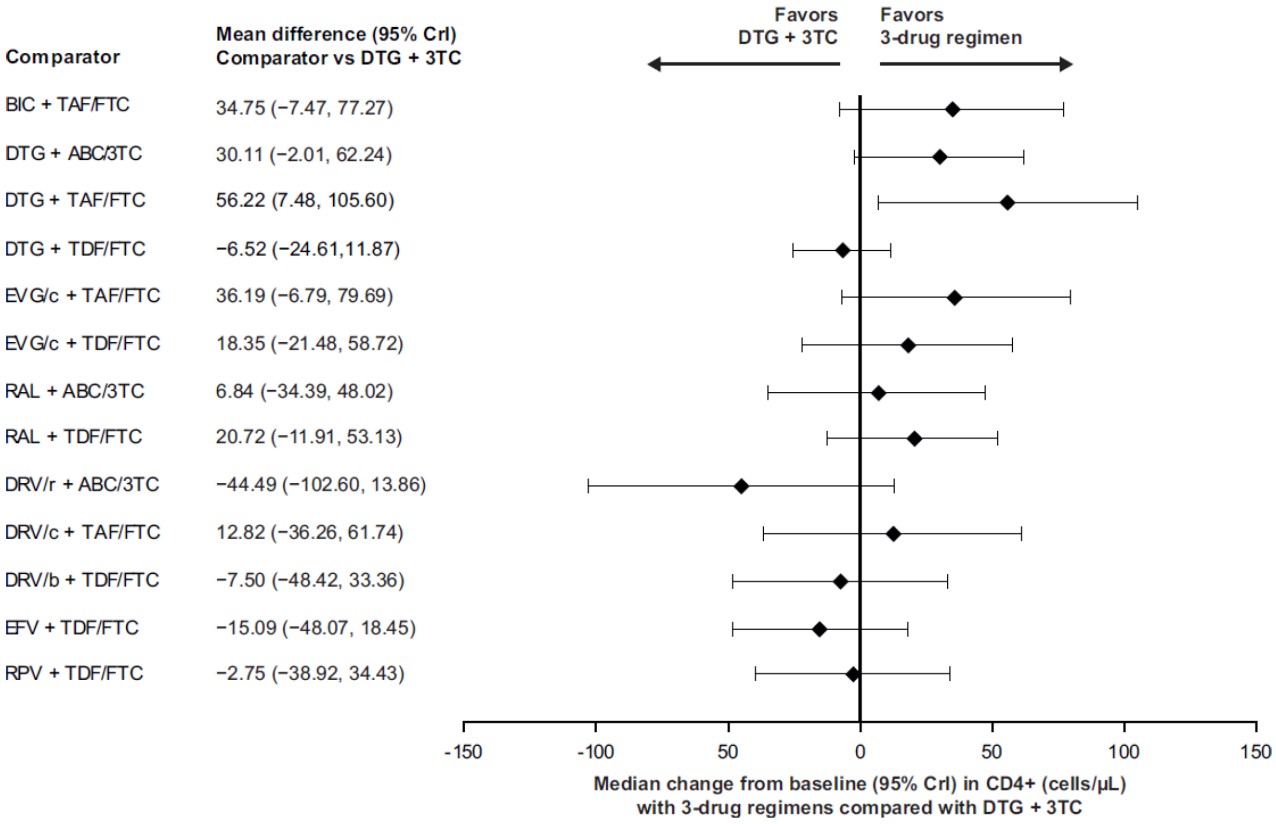
Note: Mean difference (%) in the proportion of (A) all patients, and (B) patients with baseline VL greater than 100,000 RNA copies/mL achieving VS at week 48 with three-drug regimens (comparator) versus DTG + 3TC (fixed-effects model).

Source: Figure 2 from Radford M et al. Dolutegravir and lamivudine vs other antiviral regimens in patients with HIV-1 who are treatment naive: a systematic review and network meta-analysis. *AIDS*. 2019. doi: 10.1097/QAD.0000000000002285. Distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND). https://creativecommons.org/licenses/by-nc-nd/4.0/legalcode. Disclaimer.

Change in CD4+ Cell Count From Baseline to Week 48

The NMA fixed-effects model results for mean change in CD4+ cell count from baseline to week 48 are presented in Figure 5. All of the 95% credible intervals included zero, aside from the comparison between DTG + 3TC and DTG + TAF/FTC, which was in favour of DTG + TAF/FTC. [redacted]

Figure 5: Change From Baseline at Week 48 in CD4+ Cell Count (Fixed-Effects Model)



3TC = lamivudine; ABC = abacavir; BIC = bictegravir; crI = credible interval; DRV/b = boosted darunavir (cobicistat or ritonavir); DRV/c = cobicistat-boosted darunavir; DRV/r = ritonavir-boosted darunavir; DTG = dolutegravir; EFV = efavirenz; EVG/c = cobicistat-boosted elvitegravir; FTC = emtricitabine; RAL = raltegravir; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.

Note: CD4+ change from baseline at week 48 with DTG + 3TC versus three-drug regimens (fixed-effects model).

Source: Figure 3 from Radford M et al. Dolutegravir and lamivudine vs other antiviral regimens in patients with HIV-1 who are treatment naive: a systematic review and network meta-analysis. *AIDS*. 2019. doi: 10.1097/QAD.0000000000002285. Distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND). https://creativecommons.org/licenses/by-nc-nd/4.0/legalcode. Disclaimer.

Safety

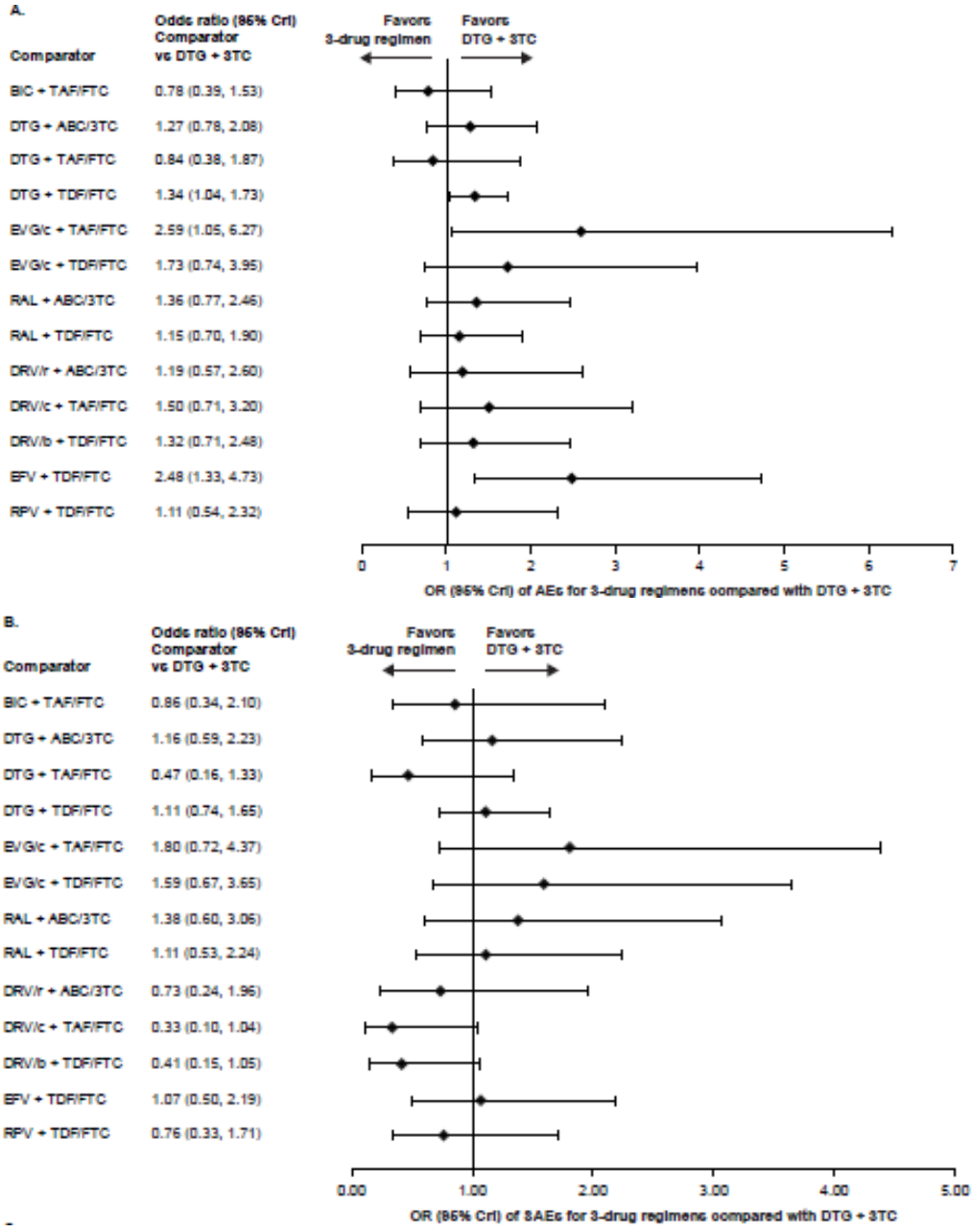
Adverse Events up to Week 48

The NMA fixed-effects model results for the proportion of patients with AEs up to week 48 are presented in Figure 6A. All of the 95% credible intervals for the odds ratios included one, aside from the comparisons with DTG + TDF/FTC, EFV + TDF/FTC, and EVG/c + TAF/FEC, which were in favour of DTG + 3TC. [redacted]

Serious Adverse Events up to Week 48

The NMA fixed-effects model results for the proportion of patients with SAEs up to week 48 are presented in Figure 6B. All of the 95% credible intervals for the odds ratios included one, and no differences were found. [redacted]

Figure 6: (A) Adverse Events and (B) Serious Adverse Events up to Week 48 (Fixed-Effects Model)



3TC = lamivudine; ABC = abacavir; AEs = adverse events; BIC = bictegravir; crI = credible interval; DRV/b = boosted darunavir (cobicistat or ritonavir); DRV/c = cobicistat-boosted darunavir; DRV/r = ritonavir-boosted darunavir; DTG = dolutegravir; EFV = efavirenz; EVG/c = cobicistat-boosted elvitegravir; FTC = emtricitabine; OR = odds ratio; RAL = raltegravir; RPV = rilpivirine; SAEs = serious adverse events; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.

Note: (A) AEs, (B) SAEs, and (C) drug-related AEs by week 48 with three-drug regimens versus DTG + 3TC (fixed-effects model).

Source: Figure 4 parts A and B from Radford M et al. Dolutegravir and lamivudine vs other antiviral regimens in patients with HIV-1 who are treatment naive: a systematic review and network meta-analysis. *AIDS*. 2019. doi: 10.1097/QAD.0000000000002285. Distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND). https://creativecommons.org/licenses/by-nc-nd/4.0/legalcode. Disclaimer.

Critical Appraisal

Systematic Review

- Overall, the methods used for the systematic review were appropriate given the aim of the NMA. However, the following limitations were identified:
- [redacted] As well, reasons for excluding studies following data extraction were not reported. Therefore, it was not possible to fully assess the risk of bias from study selection.
- It was unclear whether quality assessment of the primary RCTs was performed in duplicate and there was no mention of how lower-quality RCTs would be handled. [redacted] Therefore, it is difficult to assess the potential impact of including lower-quality RCTs.

Network Meta-Analysis

The following limitations of the NMA as a whole were identified:

- There was potentially clinically significant heterogeneity between RCTs in baseline viral load. Therefore, the subgroup analysis of virologic suppression according to baseline viral load is important for demonstrating consistency across categories of baseline viral load.
- Noninferiority margins in ART trials in patients who are treatment naive are typically 10% to 13%.[59] Given the noninferiority design of all of the primary RCTs and the sparsity of the evidence networks, the ability of the NMA to establish precise estimates for between-treatment differences was limited.
- The sparsity of the evidence network decreased the CADTH Common Drug Review reviewers' confidence in the results. Most network connections were informed by a single RCT and some comparators (EVG/c + TAF/FTC, EVG/c + TDF/FTC, DTG + TAF/FTC, and EFV + TDF/FTC) were separated from DTG + 3TC by more than two intermediate comparators. [redacted]

The following limitations of the NMA were identified for specific outcomes:

- The results for change in CD4+ cell count from baseline to week 48 may be less reliable than those for the primary efficacy end point. There was variation between RCTs in the methods for determining change in CD4+ cell count. Also, there was potentially clinically significant heterogeneity among the RCTs in baseline VL and there was no subgroup or meta-regression analysis performed for this outcome.
- The results for AEs may be less reliable than those for the primary efficacy end point. Despite the presence of three open-label RCTs (two contributing data to four treatment groups each), no sensitivity analyses were performed to handle RCTs of low quality. While lack of blinding was likely not a cause for concern in the efficacy outcomes, AE reporting can be subjective and therefore at risk of bias. As well, AE data were not extracted in an appropriate manner for at least two RCTs.

The studied populations appeared to have similar characteristics to the adult treatment-naive Canadian population with HIV-1. The most commonly used ART regimens in Canada were included as comparators and the dosages are standard for each drug combination. Therefore, the results are highly relevant to the Canadian setting. The studied efficacy outcomes were those commonly used in ART trials with patients who are treatment naive, though they only inform efficacy during the first 48 months of treatment.

Discussion

The aim of the NMA was to compare the efficacy and safety of DTG + 3TC with European and US guideline-recommended three-drug ART regimens in patients with HIV-1 who are treatment naive. While the results of the NMA found no differences between DTG + 3TC and most of the three-drug regimens in terms of efficacy and safety, these results should be considered within the context of the limitations identified in the systematic review and evidence network.

For the primary end point (virologic suppression at week 48), the fixed-effects model results showed no evidence for a difference between DTG + 3TC and the three-drug regimens, other than a difference with EFV + TDF/FTC in favour of DTG + 3TC. However, the limitations regarding the systematic literature search and the sparsity of the network introduce the potential for bias in the results and make it difficult to conclude that there were true differences between DTG + 3TC and other treatment regimens. The subgroup analysis in patients with a high viral load at baseline suggested that DTG + 3TC was superior to boosted DRV + TDF/FTC, DRV/r + ABC/3TC, EFV + TDF/FTC, and RPV + TDF/FTC in terms of virologic suppression at week 48, [redacted] Overall, the subgroup results suggested that high viral load at treatment initiation was not detrimental to the comparative efficacy of DTG + 3TC versus the three-drug regimens.

As in the critical appraisal, the change in CD4+ cell count and safety outcomes had limitations in addition to those for virologic suppression. These limitations suggest that the results for these secondary outcomes were at greater risk of bias than the results for virologic suppression and that the underlying differences between the treatment regimens remain unknown.

NMAs of first-line, three-drug ART regimens for the treatment of patients with HIV-1 have previously been published — one funded by the manufacturer (Patel et al. [2014])[52] and one funded by the World Health Organization (Kanters et al. [2016]).[60] Both NMAs concluded that three-drug ART regimens containing DTG were superior to those containing DRV/r, EFV, and RPV as the core drug in achieving virologic suppression at week 48, with no evidence of a difference between regimens with DTG and those with RAL or EVG/c. In contrast to the present NMA, the previously published NMAs pooled together ART regimens containing the same core drug and adjusted for the treatment backbone. These findings, combined with the pivotal trials for DTG + 3TC, suggest that DTG + 3TC is at least as effective in virologic suppression 48 weeks after treatment initiation as three-drug ART regimens in the patients population that is ART naive.

Conclusion

The NMA did not provide any evidence for a difference in efficacy or safety between DTG + 3TC and 12 different three-drug ART regimens relevant to Canadian clinical practice. Subgroup analyses suggested that DTG + 3TC was no worse than all comparators [redacted] for virologic suppression at week 48 in patients with a high baseline viral load. Overall, the sparsity of the evidence networks and the noninferiority design of the primary RCTs precluded the ability to establish precise estimates of differences between treatment regimens. No ITCs were identified that included a virologically suppressed patient population.

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