Common Drug Review
Clinical Review Report

August 2014

Drug	dolutegravir (Tivicay)
Indication	Used in combination with other antiretroviral agents for the treatment of HIV infection in adults and children 12 years of age and older and weighing at least 40 kg.
Listing request	As per indication
Manufacturer	ViiV Healthcare ULC

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ABBREVIATIONS

3TC	lamivudine
ABC	abacavir
ADC	AIDS-defining conditions
ANCOVA	analysis of covariance
AE	adverse event
AIDS	Acquired Immunodeficiency Syndrome
ARD	antiretroviral drug
ART	antiretroviral therapy
ARV	antiretroviral
ATV	atazanavir
AUC24	area under the curve at 24 hours
b.i.d.	twice daily
C24	24-hour dosing interval
CCR5	chemokine coreceptor type 5
CD4+	helper-inducer T-lymphocyte surface antigen
CDC	Centers for Disease Control and Prevention
CDR	CADTH Common Drug Review
CI	confidence interval
COBI	cobicistat
CVD	cardiovascular disease
DB	double-blind
DHHS	US Department of Health and Human Services
DTG	dolutegravir
EFV	efavirenz
EPHPP	Effective Public Health Practice Project Quality Assessment
EQ-5D	EuroQol 5-dimensions questionnaire
EQ VAS	EuroQol visual analogue scale
EVG	elvitegravir
FDA	Food and Drug Administration
FDC	fixed-dose combination
FTC	emtricitabine
HAART	highly active antiretroviral treatment
HBV	hepatitis B
HCV	hepatitis C
HIV-1	HIV type 1
HDL	high-density lipoprotein
HRQoL	health-related quality of life

INI	integrase inhibitor
INSTI	integrase strand transfer inhibitor
ITT	intention-to-treat population
IQR	interquartile range
LDL	low-density lipoprotein
LOCF	last observation carried forward
MSDF	missing, switch, or discontinuation equals failure analysis
NNH	number needed to harm
NNRTI	non-nucleoside reverse transcriptase inhibitor
NNT	number needed to treat
NRTI	nucleoside reverse transcriptase inhibitor
OBR	optimized background regimen
OR	odds ratio
OBT	optimized background therapy
PI	protease inhibitor
PK	pharmacokinetic
PP	per protocol
q.d.	once daily
RAL	raltegravir
RAMQ	Régie de l'assurance maladie du Québec
RCT	randomized controlled trial
RNA	ribonucleic acid
RPV	rilpivirine
RR	relative risk
SAE	serious adverse event
SD	standard deviation
URTI	upper respiratory tract infection
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
TLOVR	time to loss of virologic response
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

The current standard of care for HIV infection management is to treat with a combination of antiretroviral drugs (ART) with the primary goal of achieving and maintaining maximal suppression of viral load, leading to restoration and preservation of immunologic function, improvement of quality of life, and reduction of HIV-related morbidity and mortality. Treatment modalities for HIV infection have seen considerable changes over the years, with reported improvements in the safety and efficacy profiles of newer drugs. This has resulted in dramatic reductions in HIV-associated morbidity and mortality, and improved health-related quality of life for HIV-infected patients. Nevertheless, ART-resistance mutations, adverse effects, drug interactions, and patient-related factors remain important contributors to suboptimal viral-load suppression and virologic failure.

Clinical practice guidelines recommend the use of ART regimens that include three drugs consisting of two nucleoside reverse transcriptase inhibitors (NRTIs) in combination with another drug from a different antiretroviral drug class. Combination therapy using drugs from different classes increases efficacy and reduces the likelihood of development of resistance mutations.

Dolutegravir (DTG) is an HIV integrase strand transfer inhibitor (INSTI) approved by Health Canada to be used in combination with other antiretroviral drugs for the treatment of HIV infection in adults and children 12 years of age and older and weighing at least 40 kg.

The objective of this review is to evaluate the beneficial and harmful effects of DTG at recommended doses in combination with other antiretroviral drugs for the treatment of HIV infection in ART-naive and ART-experienced patients.

Indication under review
Used in combination with other antiretroviral drugs for the treatment of HIV infection in adults and children 12 years of age and older and weighing at least 40 kg.
Listing criteria requested by sponsor
As per indication.

Results and Interpretation

Included Studies

Two phase III randomized, double-blind, active-controlled, non-inferiority studies (SPRING-2 and SINGLE) were included in the review of efficacy and safety of DTG in ART-naive HIV-infected patients. Between them, a total of 1,671 patients were randomized in a 1:1 ratio to receive DTG or an active drug in combination with two drugs from the NRTI class as backbone treatment. In the SPRING-2 study, 822 patients were randomized to DTG or to raltegravir (RAL). Patients in each treatment group (DTG or RAL) received abacavir plus lamivudine (ABC/3TC) or tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) as backbone NRTI; patients were not randomized to NRTI backbone treatments. In the SINGLE study, 833 patients were randomized to DTG plus ABC/3TC or to efavirenz ([EFV]/TDF/FTC).

Baseline demographic and clinical characteristics were generally well balanced across treatment groups and they were similar in both studies. The majority of patients were white (85% in SPRING-2 and 69% in SINGLE) and predominantly male (86% SPRING-2 and 85% in SINGLE). Mean age was similar across

treatment groups in both SPRING-2 and SINGLE (overall mean of approximately 37 years). Most patients (more than 68%) had baseline viral loads of ≤ 100,000 copies/mL across treatment groups and in both studies. Overall baseline mean CD4+ counts ranged from 349 to 379 cells/mm^3 across the studies.

Another randomized noninferiority trial conducted in treatment-naive HIV-infected adults, FLAMINGO, was submitted by the manufacturer but was excluded from the systematic review because, as per the review protocol, the study was not listed as a pivotal study supporting the Health Canada indication for DTG and it was not double-blinded (it was open-label). The study randomized patients to receive either DTG 50 mg once daily or ritonavir-boosted darunavir (DRV/r) (800 mg/100 mg) once daily. The primary end point was the proportion of patients with plasma HIV RNA of less than 50 copies/mL at week 48 using the FDA Snapshot algorithm.

Two phase III trials, the SAILING and VIKING-3 studies, evaluated DTG in two categories of ART-experienced HIV-infected patients. The SAILING study was a phase III randomized, double-blind, active-controlled trial designed to evaluated non-inferiority of DTG to RAL in HIV-infected patients who were ART-experienced but INSTI-naive. After screening, 715 participants were randomized in a 1:1 ratio to receive DTG 50 mg once daily or RAL 400 mg twice daily both in combination with an optimized background treatment (OBT) regimen consisting of one to two fully active single agents in HIV-infected patients. Baseline demographic and clinical disease characteristics were generally well balanced across treatment groups. The median (range) age of the patients was 43.0 years (18 to 73 years). The majority (68%) of participants were male and half (50%) of the study population was white. Over half of patients in both treatment groups had viral loads of 1,000 to < 10,000 (DTG: 31% and RAL: 29%) or 10,000 to < 50,000 copies/mL (DTG: 26% and RAL: 28%). The mean (SD) of baseline CD4+ counts was 254.0 (207.77) cells/mm^3 in the DTG-treated patients and 246.4 (199.02) cells/mm^3 in RAL-treated patients. The most frequently used OBT was DRV/r plus TDF, with 18% of DTG-treated patients and 20% of RAL-treated patients receiving this regimen.

The VIKING-3 study was a single-arm, open-label phase III study designed to assess the efficacy of DTG 50 mg administered twice daily with OBT to suppress viral load in HIV-infected patients with extensive ART experience and prior or current virologic failure on an INSTI-containing regimen associated with the emergence of INSTI-resistance mutation. Although the study design was single-arm and open-label, it met the inclusion criteria for the systematic review because it was considered a pivotal study in support of the Health Canada indication for DTG.

In VIKING-3, the median (range) age of the patients was 48.0 years (range: 19 to 67 years). The majority (77%) of participants were male and 77% of the study population was white. The mean (SD) baseline HIV RNA (log_{10} c/mL) for the DTG group was 4.34 (0.95) with a mean (SD) CD4+ cell count of 199.9 (192.43) cell/mm^3.

A key limitation of all the studies is that none of them included adolescents who are between 12 to 18 years old, even though the Health Canada indication includes patients in this age group. Upon Common Drug Review (CDR) reviewers' request for further information concerning this issue, the manufacturer submitted a two-phase open-label, non-comparative study (IMPAACT P1093) investigating the safety of DTG plus OBT in five age-defined cohorts, including 23 adolescents (≥ 12 to < 18 years of age) who had completed a 24-week study (see APPENDIX 5: SUMMARY OF OTHER STUDIES). [redacted] Considering the study design and small size of this cohort of adolescent patients, as well as the short duration of trial, lack of a comparator, and the fact that not all the patients received the approved dose of DTG, evidence

for the use of DTG in patients in this age group seems limited. However, the indication for use of DTG in adolescents infected with HIV is approved by Health Canada, the European Medical Association (EMA), and the US Food and Drug Administration (FDA). The clinical expert involved in the review stated an important difference in efficacy or safety between adolescents and adults would not be expected.

Efficacy

The primary efficacy outcome in the SPRING-2, SINGLE, and SAILING studies was the proportion of patients with plasma HIV RNA < 50 copies/mL through week 48 using the FDA Snapshot algorithm. In the VIKING-3 study, the primary efficacy outcome was plasma HIV RNA < 50 copies/mL at week 24; however, data from week 48 were the focus of this review. Primary efficacy analysis was based on the intention-to-treat-exposed (ITT-E) population in the SPRING-2, SINGLE, and VIKING-3 studies, but the SAILING study used a modified ITT-E population because it excluded data from one site due to issues with non-compliance. A per protocol (PP) analysis was also used in SPRING-2, SINGLE, and SAILING due to the non-inferiority designs. See Table 1 for select efficacy outcome data.

At week 48 in the SPRING-2 study, plasma HIV RNA suppression < 50 copies/mL was achieved in 88% of patients in the DTG group compared with 85% of patients in the RAL group. The adjusted difference was 2.5% (95% confidence interval [CI], –2.2 to 7.1) in the ITT-E population. In the PP analysis 90% and 88% of DTG and RAL patients, respectively, achieved < 50 copies/mL plasma HIV RNA at week 48 with an adjusted difference of 1.6% (95% CI, –2.7 to 5.9). Non-inferiority of DTG to RAL was concluded in accordance with the pre-specified criteria non-inferiority margin of –10%.

At week 48 in the SINGLE study, 88% of the patients in the DTG plus ABC/3TC group achieved the primary efficacy end point compared with 81% in the EFV/TDF/FTC group in the ITT-E population. The adjusted difference was 7.4% (95% CI, 2.5 to 12.3). The respective proportions in the PP analysis were 90% versus 81%. Non-inferiority of DTG plus ABC/3TC to EFV/TDF/FTC was concluded based on the non-inferiority margin of –10%. With non-inferiority met, the investigators then tested for superiority and found that DTG plus ABC/3TC was superior to EFV/TDF/FTC (P = 0.003).

The proportion of patients who achieved the primary efficacy end point in the SAILING study at week 48 was 71% in the DTG plus OBT group compared with and 64% in the RAL plus OBT group using the m-ITT-E population. The adjusted difference was 7.4% (95% CI, 0.7 to 14.2). Using the PP analysis, 73% and 66% of DTG plus OBT and RAL plus OBT patients, respectively, achieved the primary efficacy end point. Non-inferiority could, therefore, be concluded based on the non-inferiority margin of –12%. As well, DTG plus OBT was superior to RAL plus OBT (P = 0.03) at week 48.

In all the comparative studies (SPRING-2, SINGLE, and SAILING), there was no statistically significant difference between treatment groups in the proportion of patients who experienced virologic failure at week 48. In the SPRING-2 and SINGLE studies, the proportion of patients who experienced virologic non-response was less than 10% across all treatment groups at week 48, while in the SAILING study, 20% in the DTG group and 28% in the RAL group experienced virologic non-response at week 48. For all three studies, small and similar improvements from baseline in health-related quality of life were observed in all treatment groups as measured by EQ-5D scores. In all the studies, HIV-related conditions (e.g., opportunistic infections, HIV-related malignancies) occurred infrequently with no appreciable difference between treatment groups. Two deaths occurred in each treatment group of the SPRING-2 study and two deaths occurred in the EFV/TDF/FTC group; no deaths occurred in the DTG plus ABC/3TC group of the SINGLE study; three deaths occurred only in the RAL plus OBT group of the SAILING study.

In the VIKING-3 study, 63% of patients achieved plasma HIV RNA < 50 copies/mL at week 48. This was a single-arm open-label study without a comparator. Quality of life was not assessed and the incidence of morbidity was low but generally higher than in the other studies, which may reflect the highly advanced nature of HIV disease in the study population. Two deaths were reported. They were not suspected to be treatment-related.

Harms

Comparable proportions of patients in the DTG and RAL groups reported adverse events (AE) in the SPRING-2 and SAILING studies at week 48. In the SPRING-2, similar trends between the treatment groups were maintained through week 96. In both the SPRING-2 and SAILING studies, the most commonly reported clinical adverse events (AEs) among patients in both treatment groups included nausea, headache, diarrhea, and upper respiratory tract infections, with no appreciable difference between the DTG and RAL treatment groups in each study. See Table 1 for select harms outcome data.

In the SINGLE study, reported rates of all AEs were similar for DTG plus ABC/3TC and EFV/TDF/FTC except for nervous system disorders and psychiatric disorders. At weeks 48 and 96, 27% and 29%, respectively, of patients receiving DTG plus ABC/3TC experienced nervous system disorders compared with 51% and 54%, respectively, of patients receiving EFV/TDF/FTC. Patients in the EFV/TDF/FTC treatment group were significantly more likely to develop dizziness. With regard to psychiatric disorders, 30% and 40%, respectively, were reported at weeks 48 and 96 in the DTG plus ABC/3TC group, compared with 35% and 42%, respectively, in the EFV/TDF/FTC group at the same time points. However, unlike the other clinical AEs listed under the psychiatric disorders, insomnia occurred at a higher frequency in patients in the DTG plus ABC/3TC treatment group (17%) compared with patients in the EFV/TDF/FTC treatment group (11%). Rates of AEs in the VIKING-3 study were low and similar to the other three studies.

Serious adverse events (SAEs) occurred rarely in all the studies, and discontinuation of study drug due to AE was low, with no discernible patterns of individual events in the SPRING-2, SAILING, and VIKING-3 studies. In the SINGLE study, withdrawal due to adverse events (WDAEs) were generally reported at a higher rate in the EFV/TDF/FTC treatment group (10% at 48 weeks and 12% at 96 weeks) than the DTG plus ABC/3TC group (2% at 48 weeks and 3% at 96 weeks). The most common AEs leading to premature discontinuation were nervous system disorders and psychiatric disorders.

All the listed AEs under notable harms occurred infrequently across treatment groups and rates were similar in all the reviewed studies. However, in the SINGLE study, the rate of insomnia was higher in the DTG +ABC/3TC treatment group (15%) than in the EFV/TDF/FTC treatment group (10%) at week 48. At week 96, the rate of insomnia was 17% in the DTG +ABC/3TC treatment group compared with 11% in the EFV/TDF/FTC treatment group. For all the studies reviewed, there were only small changes in lipid parameters in both the DTG and RAL groups, with none of the reported changes in the lipid profiles for total cholesterol, LDL cholesterol, HDL cholesterol, total HDL cholesterol ratio, or triglycerides indicating clinically impairment. Changes in glucose were small and cardiac disorders were reported rarely.

Pharmacoeconomic Summary

The manufacturer submitted a cost-utility analysis for DTG, in both treatment-naive and treatment-experienced patients. In the TN analysis, the manufacturer compared DTG to commonly used regimens (Atripla, RAL, darunavir boosted with ritonavir [DRV/r] and atazanavir boosted with ritonavir [ATZ/r]) or alternative regimens (Complera, Stribild, lopinavir boosted with ritonavir [LPV/r]). Efficacy and safety estimates were derived from head-to-head trials (SINGLE, SPRING-2, FLAMINGO) and a network meta-

analysis. In the TE analysis, the manufacturer compared DTG relative to RAL with OBT in integrase inhibitor–naive TE patients, with efficacy data from the SAILING clinical trial. AEs were considered only if treatment was discontinued due to AEs, as no difference was observed between RAL and DTG in SAILING. The reference case time horizon was lifetime with monthly cycle, and used the Canadian public payer perspective.

Patients transition through mutually exclusive health states defined in terms of HIV with or without opportunistic infections, combined with cardiovascular disease (CVD) health state. As patients pass through the model, they experienced the natural progression of HIV infection. Successive antiretroviral therapies (ARTs) were followed in the model depending on treatment history and resistance status. Patients could switch treatment after an acute AE, or when a treatment was failing. HIV utilities were derived from a Canadian study that examined the relationship between Health Utilities Index 3-derived health preference score and HIV health status as measured by CD4+ cell count. Utility decrements associated with CVD were derived from a US study. The costs for ART and OI prophylaxis treatment were obtained from the RAMQ List of Medications. Health care resource utilization costs (costs of HIV, opportunistic infections, CVD, and death) were based on Canadian studies.

Results of Manufacturer's Analysis

- For TN, the manufacturer reported DTG being the dominant strategy (less cost and more effective) when compared with Atripla, RAL, DRV/r, and other indirect comparators (Complera, Stribild, ATZ/r, LPV/r).
- For TE, the manufacturer reported DTG being the dominant strategy when compared with RAL.

Interpretations and Key Limitations

The following limitations with the manufacturer's pharmacoeconomic analysis were noted:

- The model uses surrogate end points of viral suppression and CD4+ count to predict clinical outcomes, including opportunistic infection, resistance, and mortality: however, these are well-accepted indicators of clinical outcomes, and an accepted standard to adjudicate relative efficacy.
- The incremental QALYs with DTG compared with other relevant treatment strategies are small: additional 15 to 48 days of perfect life for treatment-naive patients, and an additional 81 days of perfect life for treatment-experienced. However, this does not alter conclusions, as DTG is less costly in most analyses.
- While RCTs of some relevant comparators are available, the FLAMINGO trial is an open-label study, and there are no head-to-head trials for DTG versus Complera, Stribild, ATZ/r and LPV/r. An NMA was conducted in a matter appropriate for estimating relative efficacy. In the CDR reanalysis, assuming no difference in viral suppression at 48 weeks between comparators did not alter overall conclusions.
- The cost of antiretroviral therapy is the key driver of costs (comprising approximately 87% of total costs). ART costs are lower for DTG, driven by either lower drug-acquisition costs for DTG (in some but not all comparators), as well as lower likelihood of treatment failure or resistance.
- No economic information was provided for TE integrase–naive patients.

Results of CDR Analysis

For TN, to explore the uncertainty around virologic suppression, when equivalent virological suppression is assumed for DTG versus Complera, Stribild, ATZ/r, and LPV/r, DTG remains the dominant strategy (less costly and more effective).

In general, DTG is more effective at viral suppression than many of the comparators, which leads to a very minor increase in incremental QALYs. Also, due to a reduced probability of requiring regimens further down the treatment algorithm (e.g., second- through sixth-line agents, which are more costly) due to treatment failure, net ART costs (the primary driver of costs in the model) are lower for DTG. When considered ART costs alone, if more expensive agents along the treatment algorithm are required, DTG remains less costly than most of the comparators considered (five or seven of the eight comparators, depending on the NRTI backbone used). The economic attractiveness of DTG is driven by its pricing; it is priced lower than some (but not all) comparators, including the other integrase inhibitor (RAL).

At the recommended oral dose of 50 mg daily, the daily cost of DTG is $18.50, which is less than RAL (400 mg twice daily, $27).

Conclusions

The included studies demonstrated the efficacy and safety of DTG or DTG-containing regimens to be noninferior or superior to RAL and EFV/TDF/FTC regimens for HIV-infected ART-naive and ART-experienced patients. The SPRING-2 and SAILING studies demonstrated non-inferiority of DTG to RAL in ART-naive patients and the ART-experienced (but INSTI-naive populations), respectively, in achieving sustained viral-load suppression. DTG also demonstrated superiority to RAL in the SAILING study at week 48. In the SINGLE study, DTG plus ABC/3TC was noninferior and superior to EFV/TDF/FTC at week 48 and at week 96. The majority (63%) of treatment-experienced and INSTI-resistant HIV-infected patients in the VIKING-3 study who received DTG 50 mg twice daily with OBT achieved HIV RNA of less than 50 copies/mL at week 48. DTG appeared to be well tolerated in the included studies, including the VIKING-3 study where the patients received a 100 mg (50 mg twice daily) dose instead of the usual 50 mg once daily. In the SINGLE study, the safety and tolerability profile of DTG plus ABC/3TC was generally better than that of EFV/TDF/FTC over the period of the study, with a higher rate of patients in the EFV/TDF/FTC group withdrawing from the study drug due to AE.

TABLE 1: SUMMARY OF 48-WEEK RESULTS

	SPRING-2		SINGLE		SAILING		VIKING-3
	DTG 50 mg q.d. + OBT N = 411	RAL 400 mg b.i.d. + OBT N = 411	DTG 50 mg q.d. + OBT N = 414	EFV/TDF/ FTC N = 419	DTG 50 mg + OBT N = 354	RAL 400 mg + OBT N = 361	DTG 50 mg b.i.d. + OBT N = 183
HIV RNA < 50 copies/mL n (%)	361 (88)	351 (85)	364 (88)	338 (81)	251 (71)	230 (64)	116 (63)
Diff. (95% CI)	2.4 (–2.2, 7.1)		7.3 (2.3, 12.2)		7.2 (0.3, 14.0)		
Adjusted diff. (95% CI)	2.5 (–2.2, 7.1)		7.4 (2.5, 12.3)		7.4 (0.7, 14.2)		
PP < 50 copies/mL n (%)	348/387 (90)	342/387 (88)	362/403 (90)	335/412 (81)	238/325 (73)	225/340 (66)	NA
Diff. (95% CI)	1.6 (–2.8, 5.9)		8.5 (3.7, 13.3)		7.1 (0.1, 14.0)		
Adjusted diff. (95% CI)	1.6 (–2.7, 5.9)		8.7 (3.9, 13.4)		7.5 (0.6, 14.3)		
P value (superiority)	NR		0.003		0.030		
Virologic Non-response[a] n (%)	20 (5)	31 (8)	21 (5)	26 (6)	71 (20)	100 (28)	58 (32)
HIV RNA ≥ 50 copies/mL n (%)	8 (2)	5 (1)	6 (1)	5 (1)	35 (10)	48 (13)	18 (10)

	SPRING-2		SINGLE		SAILING		VIKING-3
	DTG 50 mg q.d. + OBT N = 411	RAL 400 mg b.i.d. + OBT N = 411	DTG 50 mg q.d. + OBT N = 414	EFV/TDF/ FTC N = 419	DTG 50 mg + OBT N = 354	RAL 400 mg + OBT N = 361	DTG 50 mg b.i.d. + OBT N = 183
Morbidity[b] n (%)	7 (2)	7 (2)	12 (3)	16 (4)	20 (6)	19 (5)	16 (9)
Mortality n (%)	1 (< 1)	1 (< 1)	0	2 (< 1)	0	3 (< 1)	2 (1)
Health-Related Quality of Life (EQ-5D)							
Baseline, mean ± SD	[redacted]						NA
Adjusted mean change (SE)	[redacted]						
Diff. (95% CI)	[redacted]						
P value	[redacted]						
Discontinued, n (%)	47 (11)	56 (14)	51 (12)	84 (20)	68 (19)	82 (23)	46 (25)
SAEs	29 (7)	31 (8)	37 (9)	35 (8)	33 (9)	42 (12)	39 (21)
WDAEs	10 (2)	7 (2)	10 (2)	42 (10)	7 (2)	13 (4)	8 (4)
Notable Harms n (%)							
Metabolic disorders	18 (4)	21 (5)	22 (5)	37 (9))	18 (5)	14 (4)	25 (14)
Cardiac disorders	5 (1)	6 (1)	9 (2)	6 (1)	8 (2)	13 (4)	8 (4)
CNS/cognitive							
Headache	51 (12)	48 (12)	55 (13)	56 (13)	39 (9)	31 (9)	21 (11)
Fatigue	20 (5)	18 (4)	54 (13)	50 (12)	15 (4)	24 (7)	16 (9)
Nausea	59 (14)	53 (13)	59 (14)	57 (14)	28 (8)	(8)	23 (13)
Insomnia	21 (5)	17 (4)	64 (15)	43 (10)	12 (3)	14 (4)	12 (7)
Dizziness	23 (6)	23 (6)	37 (9)	148 (35)	13 (4)	14 (4)	7 (4)
Depression	21 (5)	14 (3)	23 (6)	26 (6)	11 (3)	7 (2)	6 (3)
Anxiety	14 (3)	20 (5)	14 (3)	27 (6)	5 (1)	6 (2)	7 (4)

ART = antiretroviral therapy; b.i.d. = twice daily; CI = confidence interval; CNS = central nervous system; diff. = difference; DTG = dolutegravir; EFV = efavirenz; EQ-5D = EuroQol 5-dimensions questionnaire; FTC = emtricitabine; HIV-1 = HIV type 1; INI = integrase inhibitor; PP = per protocol; q.d. = once daily; RNA = ribonucleic acid; SAE = serious adverse event; TDF = tenofovir; WDAE = withdrawal due to adverse events.

[a] Virologic failure = viral load not at threshold (HIV RNA ≥ 50 copies/mL), or discontinuation due to lack of efficacy or for other reasons while not < 50 copies/mL, or change in ART.

[b] HIV-associated conditions.

Source: SPRING-2 weeks 48 and 96 Clinical Study Reports (CSRs);[1,2] SINGLE weeks 48 and 96 CSRs.[3,4]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

The estimated number of people living with HIV (including AIDS) in Canada in 2011 was approximately 71,300 (range: 58,600 to 84,000),[5] an increase of 11.4% from the 2008 estimate of 64,000. In 2012, there were 2,062 incident cases of HIV infection compared with 2,237 in 2011, which represents a 7.8% decrease in incidence between 2011 and 2012. This also represents the lowest number of new cases of HIV infection since reporting began in 1985.[6] Men who have sex with men account for 50.3% of all adults (≥ 15 years) with positive HIV test reports with known exposure category in 2012, followed by heterosexuals (32.6%), and injection drug users (14.0%).[6]

As in previous years, Ontario had the highest number of incident cases (843) in 2012, followed by Quebec (450), Alberta (239), British Columbia (238) and Saskatchewan (184). Both Ontario and British Columbia noted a decrease in their annual number of new cases from 2011 to 2012 — a 10.8% decrease in Ontario and a 17.4% decrease in British Columbia.[6]

1.2 Standards of Therapy

The current standard of care for HIV management is to treat with antiretroviral therapy (ART) with the primary goal of achieving and maintaining maximal suppression of viral load, which leads to restoration and preservation of immunologic function, improvement of quality of life, and reduction of HIV-related morbidity and mortality.[7] These can be achieved by using effective ART regimens to suppress HIV replication so that plasma HIV RNA levels (viral load) are below assay-detectable limits — usually less than 50 copies/mL. Virologic failure occurs when viral suppression to less than 50 copies/mL does not occur, or when the viral load rises to more than 50 copies/mL consistently.[7]

The choice of ART regimen for an individual patient must take into account drug potency, tolerability, convenience, and known or potential drug interactions, as well as patient comorbidities, ART history, concomitant medication use, and cost.

Available ART drugs are categorized into six classes according to mechanism of action: nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors (FIs), chemokine coreceptor type 5 (CCR5) antagonists, and integrase strand transfer inhibitors (INSTIs). The most commonly used regimens include three drugs consisting of two NRTIs in combination with another drug from a different class. When a drug is selected from the PI class, it is usually boosted with another PI, ritonavir (RTV). Combination therapy using drugs from different classes increases efficacy and reduces the likelihood of development of resistant viruses.[7]

In general, clinical practice guidelines (such as those by the US Department of Health and Human Services[7]) recommend use of ART regimens that include three drugs consisting of two NRTIs in combination with a drug from a different antiretroviral drug class. This approach has been shown to increase efficacy and reduce the likelihood of resistance mutations developing.[7] Tenofovir plus emtricitabine (TDF/FTC) are recommended as the preferred NRTI backbone with efavirenz (EFV), ritonavir-boosted atazanavir (ATV/r), ritonavir-boosted darunavir (DRV/r) or raltegravir (RAL) as the third drug when initiating ART in treatment-naive people. Alternative NRTI backbone pairs include abacavir with lamivudine (ABC/3TC).

Treatment guidelines have recently recommended that ART be initiated for all HIV-infected individuals — regardless of CD4 cell counts — to reduce the risk of disease progression.[7] The recommendation is supported by growing evidence that uncontrolled viremia is associated with development of non–AIDS-defining diseases, including cardiovascular disease (CVD), kidney disease, liver disease, neurologic complications, and malignancies.[7] Some concerns about the early initiation of ART include possible complications related to extended cumulative exposure to ART, impaired adherence due to medication fatigue, earlier development of resistance, and cost.

Antiretroviral drug resistance is an important contributor to suboptimal viral-load suppression and virologic failure. Therefore, baseline genotypic and phenotypic HIV drug–resistance testing are also recommended to assess viral strains and inform selection of treatment strategies when initiating ART in treatment-naive patients.[7] Guidelines also recommend drug-resistance testing be performed in treatment-experienced patients who are not achieving or maintaining viral-load suppression.[7] Approximately 25% of patients receiving ART are not virologically suppressed.[7] Virologic failure is patient-related (e.g., ART non-adherence) and regimen-related factors (e.g., medication intolerance).[7] If virologic failure persists despite correcting these factors, the ART regimen should be changed to avoid further development of resistance mutations.[7]

ART-experienced patients with drug resistance who are experiencing virologic failure should receive a new regimen that includes at least two, and preferably three, expected to have antiretroviral activity drugs on the basis of the patient's treatment history and drug-resistance testing results (optimized background therapy [OBT]).[7] As in ART-naive patients, the goal of treatment in ART-experienced patients is to establish virologic suppression below the lower limits of detection of currently used assays. However, achieving this goal is impossible for some highly ART-experienced patients. For such patients, ART regimens should be designed to minimize toxicity, preserve CD4+ cell counts, and at least delay clinical progression.

1.3 Drug

Dolutegravir (DTG) is an INSTI which blocks the integration of retroviral DNA into the host cell genome, thereby inhibiting HIV replication.[8] It has a Health Canada indication for use in combination with other antiretroviral drugs for the treatment of HIV infection in adults and children 12 years of age and older and weighing at least 40 kg. According to information in the Health Canada reviewers report, the use of dolutegravir in pediatric patients aged 12 years and older is based on evaluation of safety, pharmacokinetics, and efficacy through 24 weeks in a multi-centre, open-label trial in patients without integrase inhibitor-resistance (n = 23)[9] (APPENDIX 5: SUMMARY OF OTHER STUDIES).

Dolutegravir is available as 50 mg oral tablets. The usual dose is one tablet daily for all HIV-infected patients, except for those who have demonstrated resistance to other INSTI drugs, in which case 50 mg twice daily is the recommended dose. Similarly, dolutegravir 50 mg twice daily is recommended in INSTI-naive patients who are being treated concomitantly with potent cytochrome P450 inducers such as efavirenz (EFV), etravirine (ETR), ritonavir-boosted tipranavir (TPV/r), ritonavir-boosted fosamprenavir (FPV/r) or rifampin should take DTG 50 mg twice daily. The Health Canada Reviewers' report on dolutegravir states that there is insufficient data to recommend a dosing regimen for adolescents between 12 and 18 who are ART-experienced and INSTI-resistant.[9]

Indication under review
Used in combination with other antiretroviral drugs for the treatment of HIV infection in adults and children 12 years of age and older and weighing at least 40 kg.
Listing criteria requested by sponsor
As per indication.

TABLE 2: KEY CHARACTERISTICS OF NNRTI-, PI/R-, AND INSTI-BASED REGIMENS

	NNRTI-Based	PI/r-Based	INSTI-Based
Regimen(s)	Efavirenz/tenofovir/ emtricitabine (EFV/TDF/FTC)	Ritonavir-boosted atazanavir/tenofovir/ emtricitabine (ATV/r + TDF/FTC) Ritonavir-boosted darunavir/tenofovir/ emtricitabine (DRV/r + TDF/FTC)	Dolutegravir plus abacavir/lamivudine or tenofovir/emtricitabine (DTG + ABC/3FT or TDF/FTC Raltegravir plus abacavir/lamivudine or tenofovir/emtricitabine (RAL + ABC/3FT or TDF/FTC
Mechanism of Action	**N(t)RTI** (e.g., 3TC, ABC,TDF, FTC) and **NNRTI** (e.g., EFV): inhibit HIV reverse transcriptase to prevent early-cycle viral replication. **PI** (e.g., ATV, DRV, r): inhibits HIV protease to prevent late-cycle viral replication. **INSTI** (e.g., RAL): inhibits HIV integrase to prevent entry of viral DNA into host cell genome.		
Indication[a]	**EFV/TDF/FTC**: alone as a complete regimen or in combination with other ARTs for the treatment of HIV infection in adults.	**ATV:** in combination with other ARTs for treatment of HIV infection. **DRV**: co-administered with 100 mg ritonavir (**r**), and with other ARTs, for treatment of HIV infection. **TDF/FTC**: in combination with other ARTs (e.g., NNRTIs, PIs) for the treatment of HIV infection in adults.	**DTG:** in combination with other antiretroviral drugs, is indicated for the treatment of HIV infection in adults and children 12 years of age and older and weighing at least 40 kg. **RAL**: in combination with other ARTs for treatment of HIV infection in adult patients. **ABC/3TC:** indicated in antiretroviral combination therapy for the treatment of HIV infection in adults. **TDF/FTC**: in combination with other ARTs (e.g., NNRTIs, PIs) for the treatment of HIV infection in adults.
Route of Administration	Oral		
Recommended Dose	**EFV/TDF/FTC**: 600/ 300/200 mg once daily	**ATV/r + TDF/FTC:** ATV/r 300/100 mg once daily; TDF/FTC 300/200 mg once daily **DRV/r + TDF/FTC**: DRV/r 800/100 mg once daily (treatment-naive) **or** DRV/r 600/100 mg b.i.d. (treatment-experienced); TDF/FTC 300/200 mg once daily	**DTG + ABC/3TC:** DTG 50 mg q.d. + ABC/3TC 600/300 mg q.d. **or** DTG 50 mg once + TDF/FTC 300/200 mg once daily **RAL + TDF/FTC**: RAL 400 mg b.i.d. + ABC/3TC 600/300 mg q.d. **or** RAL 400 mg b.i.d.; TDF/FTC 300/200 mg q.d.

	NNRTI-Based	PI/r-Based	INSTI-Based
Serious Side Effects/Safety issues	**EFV/TDF/FTC:** Contraindicated: multiple drugs (e.g., voriconazole; ergot derivatives; midazolam, triazolam; pimozide). **TDF/FTC:** Lactic acidosis; severe hepatomegaly with steatosis (including fatal cases) have been reported with nucleoside analogues (e.g., TDF); safety and efficacy not established in patients co-infected with HBV and HIV; renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia) has been reported with TDF.	**ATV:** Contraindicated with drugs that are highly dependent on CYP3A4 or UGT1A1 for clearance. **DRV**: Contraindications: severe (Child-Pugh Class C) hepatic insufficiency: drug-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis), including fatal cases, have been reported; drugs that are highly dependent on CYP3A4 for clearance. Must be administered with low-dose ritonavir to ensure its therapeutic effect. **TDF/FTC**: Lactic acidosis; severe hepatomegaly with steatosis (including fatal cases) have been reported with nucleoside analogues (e.g., TDF); safety and efficacy not established in patients co-infected with HBV and HIV; renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia) has been reported with TDF.	**DTG:** Hepatitis, hypersensitivity reactions, and IRS. Stop medication and contact your doctor or pharmacist immediately in case of skin rash, fever, lack of energy, or fatigue, difficulty breathing, joint or muscle pain, redness, rash, swelling, yellowing of skin or whites of the eyes, or any new symptoms. **RAL**: Severe, potentially life-threatening and fatal skin reactions have been reported (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis).Caution with concomitant strong inducers of UGT1A1 (e.g., rifampin). **ABC/3TC:** Serious and sometimes fatal hypersensitivity reactions have been associated with therapy with abacavir sulphate and other products containing abacavir. **TDF/FTC**: Lactic acidosis; severe hepatomegaly with steatosis (including fatal cases) have been reported with nucleoside analogues (e.g., TDF); safety and efficacy not established in patients co-infected with HBV and HIV; renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia) has been reported with TDF.

3TC = lamivudine; ABC = abacavir; ART = antiretroviral treatment; ATV/r = ritonavir-boosted atazanavir; b.i.d. = twice daily; CYP3A4 = Cytochrome P450 3A4; DRV/r = ritonavir-boosted darunavir; EFV = efavirenz; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; HBV = hepatitis B; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; N(t)RTI = nucleoside and nucleotide reverse transcriptase inhibitors; PI/r = ritonavir-boosted protease inhibitor; q.d. = once daily; RAL = raltegravir; TDF = tenofovir; UGT1A1 = uridine diphosphate glucuronosyltransferase 1A1.

[a] Health Canada indication.

2. OBJECTIVES AND METHODS

2.1 Objectives

To evaluate the beneficial and harmful effects of dolutegravir (Tivicay) in combination with other antiretroviral drugs at recommended doses for the treatment of HIV infection in adults and children 12 years of age or older and weighing at least 40 kg.

2.2 Methods

Studies selected for inclusion in the systematic review included the pivotal studies in support of the Health Canada indication provided in the manufacturer's submission to CDR as well as those meeting the selection criteria presented in Table 3.

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adults and children 12 years of age or older and weighing at least 40 kg who have been diagnosed with HIV infection and who are either treatment-naive or treatment-experienced.	
	Subgroups	
	Treatment-naive: Baseline VL (≤ or > 100,000 copies/mL; ≤ or > 500,000 copies/mL) Age: 12 to < 18 years; ≥ 18 years;	**Treatment-experienced:** Baseline VL (≤ or > 100,000 copies/mL; ≤ or > 500,000 copies/mL) Antiretroviral drug resistance at baseline Age: 12 to < 18 years; ≥ 18 years; INSTI-naive INSTI resistance
Intervention	Dolutegravir 50 mg orally once daily + TDF/FTC or ABC/3TC	Dolutegravir 50 mg orally once or twice daily[a] in combination with OBT[b]
Comparators	**Treatment-naive:** EFV/TDF/FTC EFV/COBI/TDF/FTC RAL/TDF/FTC RPV/TDF/FTC DRV/r + TDF/FTC ATV/r + TDF/FTC	**Treatment-naive:** RAL + OBT PI + OBT
Outcomes	**Key efficacy outcomes** Percentage of patients with VL < 50 copies/mL at end of trial Percentage of patients with VL > 50 copies/mL at end of trial Quality of life by validated scale Morbidity (opportunistic infections, HIV-associated malignancies, or ADC) Mortality (all-cause and HIV- and AIDS-specific) **Other efficacy outcomes** Change in CD4+ cell count from baseline Development of resistance mutations (any antiretroviral drug or INSTI-specific) **Harms outcomes** AEs, SAEs, WDAEs **Notable harms:** Metabolic complication (e.g., changes in blood lipids, glucose) Cardiac complications CNS/cognitive effects (e.g., headache, fatigue, nausea, insomnia, dizziness, depression, anxiety)	

Study Design	Published and unpublished double-blind RCTs ≥ 48 weeks duration

3TC = lamivudine; ABC = abacavir; ADC = AIDS-defining conditions; AE = adverse event; AIDS = acquired immunodeficiency syndrome; ART = antiretroviral therapy; ATV/r = ritonavir-boosted atazanavir; CNS = central nervous system; COBI = cobicistat; DRV/r = ritonavir-boosted darunavir; EFV = efavirenz; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; IRS = immune reconstitution syndrome; NRTI = nucleoside/nucleotide reverse transcriptase inhibitor; OBT = optimized background therapy; PI = protease inhibitor; RAL = raltegravir; RCT = randomized controlled trial; RPV = rilpivirine; SAE = serious adverse event; WDAE = withdrawal due to adverse event; TDF = tenofovir; VL = viral load; WDAE = withdrawal due to adverse event.

[a] Recommended dosing in treatment-experienced patients is 50 mg once daily if INSTI-naive, and twice daily if INSTI-resistant.[8]

[b] Per genotyping results: OBT includes at least two optimally active drugs from class of protease inhibitors (PI), INSTI, or non-nucleoside reverse transcriptase inhibitors (NNRTI).

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 (1946–) with in-process records and daily updates 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 concept was Tivicay (dolutegravir).

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or language. Conference abstracts were excluded from the search results.

The initial search was completed on March 13th, 2014. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee (CDEC) on July 16th, 2014. 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 (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Databases (free), Internet Search, and Open Access Journals. 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 regarding unpublished studies.

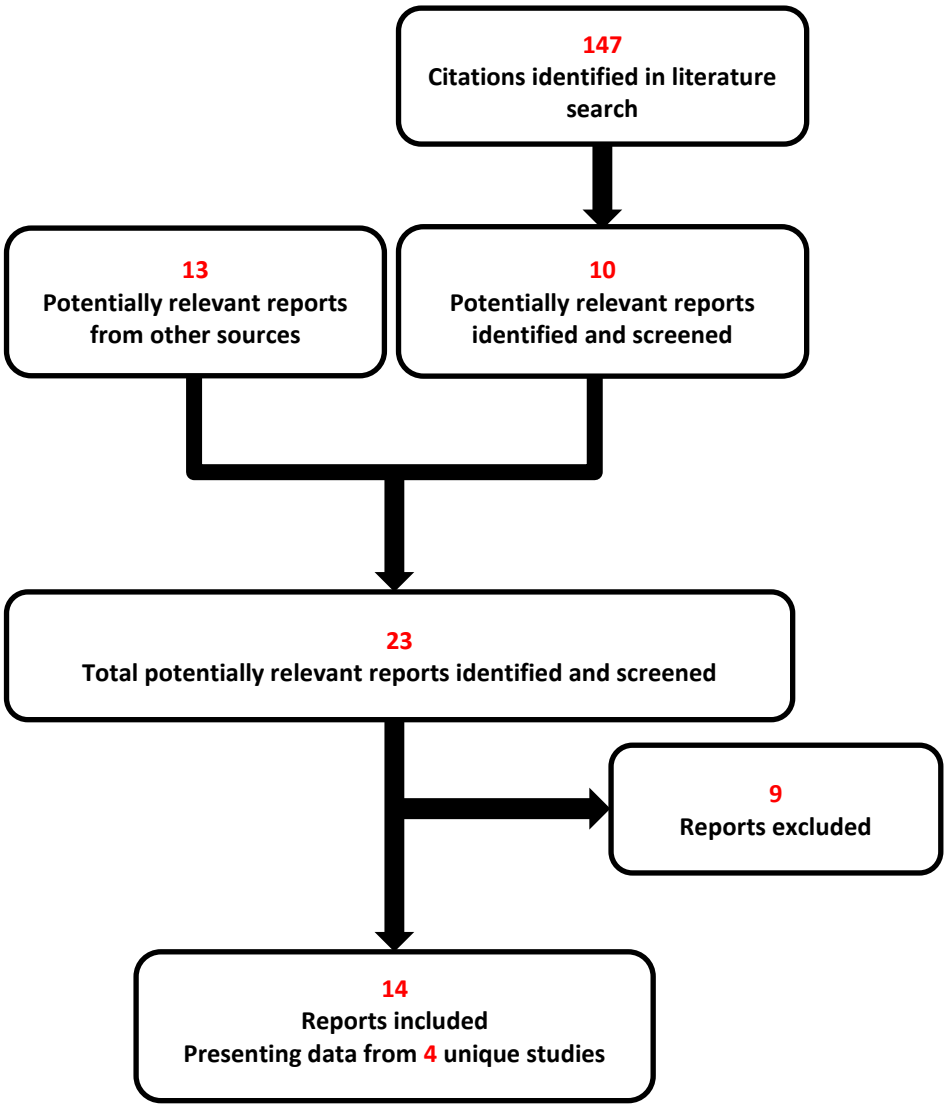
Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4; excluded studies (with reasons) are presented in APPENDIX 3: EXCLUDED STUDIES.

3. RESULTS

3.1 Findings from the Literature

A total of four studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 2 and described in Section 3.2. A list of excluded studies is presented in APPENDIX 3: EXCLUDED STUDIES.

FIGURE 1: QUOROM FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES



3.2 Included Studies

3.2.1 Description of Studies

a) Studies in ART-Naive Patients

SPRING-2[1,2] and SINGLE[3,4] were phase III randomized, double-blind, active-controlled, multi-centre, non-inferiority studies involving adult patients 18 years or older with HIV infection who were ART-naive (Table 4). In both studies, a central computer randomization system was used to randomize patients to treatment group, including stratification. In SPRING-2,[1,2] 822 HIV patients were randomized 1:1 to receive DTG 50 mg once daily or raltegravir (RAL) 400 mg twice daily, both administered either abacavir/lamivudine (ABC/3TC) or TDF/FTC. The SINGLE study[3,4] randomized 833 HIV patients 1:1 to receive DTG 50 mg plus ABC/3TC, or efavirenz (EFV) plus TDF/FTC. Each regimen was administered once daily.

The SPRING-2 study[1,2] stratified randomization by screening plasma HIV RNA (≤ 100,000 copies/mL or > 100,000 copies/mL) and backbone NRTI selection (ABC/3TC or TDF/FTC) to achieve balance across the two treatment groups. In the SINGLE study,[3,4] randomization was stratified by screening plasma HIV RNA (≤ 100,000 copies/mL or > 100,000 copies/mL) and screening CD4 cell count (≤ or > 200 cells/mm^3).

In both studies,[1-4] randomized patients attended clinic visits at day 1 and weeks 2, 4, 8, 12, 16, 24, 32, 40, and 48, and then every 12 weeks thereafter through the double-blind phase, which lasted 96 weeks.

In the SINGLE study, patients with any ongoing adverse events or lab abnormalities were required to participate in a follow-up evaluation performed four weeks after permanent discontinuation of the investigational product. Though the SPRING-2 study[1,2] did not specify a duration for the safety follow-up, in both SPRING-2 and SINGLE,[1-4] patients received study drugs plus matching placebo tablets during the randomized phase.

TABLE 4: DETAILS OF INCLUDED STUDIES IN ART-NAIVE PATIENTS

		SPRING-2[1,2]	SINGLE[3,4]
Designs & Populations	Study Design	Phase III randomized, double-blind, double-dummy, active-controlled, multi-centre, parallel group, non-inferiority study.	Phase III randomized, double-blind, double-dummy, active-controlled, multi-centre, parallel group, non-inferiority study
	Locations	Canada, France, Germany, Italy, Spain, UK, US, Australia, and Russia	Belgium, Canada, France, Germany, Italy, Spain, UK, US, and Russia
	Randomized (N)[a]	827	844
	Inclusion Criteria	• HIV-infected adults ≥ 18 • Plasma HIV RNA ≥ 1,000 copies/mL at screening • ART-naive (10 days or less of prior therapy with any ART drug) • Negative for HLA-B*5701 allele at screening	
	Exclusion Criteria	• Women who are pregnant or breastfeeding • Any evidence of an active CDC Category C[b] disease, except cutaneous Kaposi's sarcoma not requiring systemic therapy, or historic or current CD4+ cell levels < 200 cells/mm^3 • Moderate-to-severe hepatic impairment • History of (within last five years) or ongoing malignancy (other than cutaneous Kaposi's sarcoma, basal cell carcinoma, or resected, non-invasive cutaneous squamous cell carcinoma)	

		SPRING-2[1,2]	SINGLE[3,4]
		• HIV vaccination within 90 days of screening, or treatment with radiation therapy, cytotoxic chemotherapeutic agents, or any immunomodulator within 28 days of screening • Any current or historical evidence of primary viral resistance • CrCl < 50 mL/min • Any upper or lower GI bleed within the past three months, with the exception of anal or rectal bleeding	
Drugs	Intervention	DTG 50 mg q.d. tablet plus ABC/3TC (600/300 mg FDC) tablet, or TDF/FTC (200/300 mg FDC) tablet q.d.	DTG 50 mg q.d. plus ABC/3TC (600/300 mg FDC) tablet
	Comparator(s)	RAL 400 mg b.i.d. plus ABC/3TC (600/300 mg FDC) tablet or TDF/FTC (200/300 mg FDC) tablet q.d.	EFV/TDF/FTC (600/200/300 mg FDC) q.d.
Duration	Phase		
	Run-in	2 weeks	3 weeks
	Double-blind	96 weeks	96 weeks
	Safety follow-up	NR	4 weeks
Outcomes	Primary end point	Proportion of patients with HIV RNA < 50 copies/mL at week 48 using the FDA Snapshot algorithm.	
	Other end points	Protocol-defined virological failure at week 48; time to viral suppression; health-related quality of life; change from baseline in the CD4+ T-cell count; and incidence of the development of genotypic and phenotypic resistance	
Notes	Publications	Raffi et al. 2013[10,11]	Walmsley et al. 2013[12]

3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; b.i.d. = twice daily; CDC = Centers for Disease Control and Prevention; CrCl = creatinine clearance; DTG = dolutegravir; EFV = efavirenz; FDC = fixed-dose combination; GI = gastrointestinal; TDF = tenofovir; FTC = emtricitabine; FDC = fixed-dose combination; GI = gastrointestinal; ITT = intention-to-treat, PP = per protocol; q.d. = once daily.

[a] Not all randomized patients received the study medication.

[b] CDC Category C implies AIDS and associated disease.

Source: SPRING-2 weeks 48 and 96 CSRs;[1,2] SINGLE weeks 48 and 96 CSRs.[3,4]

b) Studies in ART-Experienced Patients

The SAILING study[13] was a phase III randomized, double-blind, active-controlled, multi-centre, non-inferiority study to establish the safety and efficacy of DTG at 50 mg once daily compared with RAL at 400 mg twice daily in HIV-infected ART-experienced but INSTI-naive patients (Table 5). A total of 724 patients aged 18 years or older were randomized 1:1 into either a DTG 50 mg once daily or RAL 400 mg twice daily treatment group. The study was conducted on 715 patients (DTG n = 354, RAL n = 361) who received treatment with a study drug. Both DTG and RAL were administered in combination with an investigator-selected background regimen consisting of one fully active single drug plus no more than one second single drug that may or may not have been active. Recruitment of patients treated with highly potent regimens including ritonavir-boosted darunavir (DRV/r) was limited to 170 to ensure the contribution of DTG to successful suppression could be demonstrated in a patient population similar to the BENCHMRK-1 and 2 trials. The BENCHMRK trials were phase III studies conducted to evaluate the efficacy and safety of RAL in HIV patients with triple-class–resistant virus.[14]

According to the investigators, limiting the number of patients receiving treatment with a highly potent background regimen was necessary because a placebo and a potent drug would appear identical when neither can improve upon the response generated by potent background regimen alone.

Randomization was conducted via a central randomization procedure and was stratified by screening: plasma HIV RNA (≤ 50,000 copies/mL versus > 50,000 copies/mL); DRV/r treatment without primary PI resistance; and number of fully active drugs in investigator-selected background regimen (2 versus < 2). Patients received double-blinded DTG or RAL plus matching placebo tablets during the randomized phase. SAILING was a 48-week study in which randomized patients attended clinic visits at day 1 and weeks 2, 4, 8, 12, 16, 20, 24, 32, 40 and 48. During that time, investigators and patients remained blinded to allocation. A follow-up evaluation was required four weeks after permanent discontinuation of investigational product if a patient had ongoing adverse events (AEs) or laboratory abnormalities at the last on-study visit.[13]

The VIKING-3 study[15] was a 48-week multi-centre, single-group, open-label phase III study (N = 183) to demonstrate the antiviral activity and safety of DTG 50 mg administered twice daily with OBT in adults 18 years or older with extensive ART experience, who had experienced virologic failure while on an ART regimen containing an INSTI. DTG 50 mg twice daily was administered with the failing-background therapy for 7 days, but with OBT consisting of at least one fully active beginning on day 8 and continuing through to week 24, when the primary efficacy outcome was determined (Table 5). Recruitment of patients continued while the first cohort of patients had already begun treatment with study drug.

TABLE 5: DETAILS OF INCLUDED STUDIES IN ART-EXPERIENCED PATIENTS

		SAILING[13]	VIKING-3[15]
DESIGNS & POPULATIONS	**Study Design**	Phase III randomized, double-blind, double-dummy, active-controlled, multi-centre, parallel group, non-inferiority study	Phase III, single-arm, open-label study
	Locations	Australia, Canada, Europe, Latin America, Taiwan, South Africa, and the USA	Canada, US, and Europe
	Randomized (N)	724	183
	Inclusion Criteria	• HIV-infected adults ≥ 18 years old • Two consecutive plasma HIV RNA assessments of ≥ 400 copies/mL (only 1 assay if > 1,000 copies/mL at screening) • Resistance to ≥ 2 ART classes • One to two fully active drugs[b] for OBT • INSTI-naive	• HIV-infected adults ≥ 18 years old • Plasma HIV RNA ≥ 500 copies/mL • Resistance to RAL and/or EVG and to ≥ 2 other ART classes • ≥ 1 fully active drug option for OBT
	Exclusion Criteria	• Active US CDC Category C disease[a] (except Kaposi's sarcoma) • Defined laboratory values, pregnancy, moderate or severe hepatic impairment • Expected need for hepatitis C virus therapy • Malignancy • Recent (90 days) treatment with HIV vaccines, radiation therapy, cytotoxic chemotherapy, or immunomodulators	• Active US CDC Category C disease[a] (except Kaposi's sarcoma) • Moderate to severe hepatic impairment (Child-Pugh criteria) • Anticipated need for hepatitis C therapy during the first 24 weeks • Defined exclusionary laboratory values and medical conditions, including pregnancy • Treatments including EFV or nevirapine within 14 days of DTG first dose and during the study • Etravirine was permitted only if co-administered with LPV/r or DRV/r • Tipranavir/ritonavir or fosamprenavir/ritonavir were only allowed from day 8 for patients

		SAILING[13]	VIKING-3[15]
			harbouring virus without Q148 + ≥ 2 associated mutations
DRUGS	**Intervention**	DTG 50 mg q.d. + OBT (investigator-selected)	DTG 50 mg b.i.d. + OBT (investigator-selected)
	Comparator(s)	RAL 400 mg b.i.d. + OBT (investigator-selected)	NA
DURATION	**Phase**		
	Run-in	NA	Functional monotherapy phase (day 1 to day 7),where DTG 50 mg b.i.d. replaced RAL or EVG in the previously failing ART regimen
	Double-blind	48 weeks	NA
	Unblinded	NA	48 weeks Optimized phase: day 8 to week 24
	Follow-up	Open-label phase after 48 weeks for DTG only, or RAL in South Africa	Every 12 weeks
OUTCOMES	**Primary End Point**	Proportion of patients with HIV RNA < 50 copies/mL at week 48	Proportion of patients with HIV RNA < 50 copies/mL at week 24
	Other End Points	• Mortality • Morbidity (HIV-associated conditions, AIDS) • Health-related quality of life (EQ-5D) • Change from baseline in CD4 cell counts • Treatment-emergent INSTI resistance	• Proportion of patients with HIV RNA < 50 copies/mL at week 48 • Mortality • Morbidity (HIV-associated conditions, AIDS) • Change from baseline in CD4 cell counts • Treatment-emergent INSTI resistance
NOTES	**Publications**	Cahn et al. 2013[16]	Castagna et al. 2014[17]

3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; CDC = Centers f or Disease Control and Prevention; DRV = darunavir; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; FDC = fixed-dose combination; FTC = emtricitabine INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; NA = not applicable; OBT = optimized background therapy; q.d. = once daily; TDF = tenofovir.

[a] CDC Category C represents AIDS and associated diseases.

[b] A fully active drug is one that is expected to have antiretroviral activity on the basis of the patient's treatment history and drug-resistance testing results and/or the drug's novel mechanism of action.[7]

Source: SAILING weeks 24 and 48 CSRs;[13,18] VIKING-3 weeks 24 and 48 CSRs.[15,19]

3.2.2 Populations

a) Inclusion and Exclusion Criteria

Studies in ART-Naive Patients

In both the SPRING-2 and SINGLE studies,[1-4] patients were included if they were 18 years or older and diagnosed with HIV infection with plasma HIV RNA ≥ 1,000 copies/mL at screening and had not received therapy with any antiretroviral agent following a diagnosis. Patients also had to be HLA-B*5701 negative to avoid hypersensitivity to ABC. Patients were excluded from both studies if they were pregnant or breastfeeding, if they had hepatic impairment or if they received an HIV immunotherapeutic vaccine within 90 days of screening (Table 4).

Studies in ART-Experienced Patients

The main inclusion criteria of the SAILING study[13] was documentation of HIV infection with HIV RNA exceeding 400 copies/mL at screening and at least one consecutive HIV RNA higher than 400 copies/mL within the four months prior to screening. Where screening HIV RNA was greater than 1,000 copies/mL, no additional plasma HIV RNA assessment was needed (Table 5). Participants were also required to be ART-experienced with documented resistance to two or more different classes of antiretroviral drugs, but INSTI-naive. Patients were excluded if: they had developed resistance to ART

to the extent that no fully active antiviral drugs were available for an effective background regimen; they were pregnant; had hepatic impairment; or showed any evidence of an active CDC Category C disease (exceptions: patients with cutaneous Kaposi's sarcoma not requiring systemic therapy or current CD4+ cell levels lower than 200 cells/mm^3).

Key inclusion criteria in the VIKING-3 study[15] were documented HIV infection with plasma HIV RNA ≥ 500 copies/mL at screening, being ART-experienced (including INSTI-experienced) but DTG-naive, and on stable ART for at least one month prior to screening and through day 1 of study. In addition, participants either had to be experiencing virological failure to RAL or EVG, or had previously experienced virological failure while on therapy containing RAL or EVG. Evidence of genotypic and/or phenotypic resistance to RAL and/or EVG was also required (Table 5). Patients were excluded from the VIKING-3 study[15] if there was any evidence of an active CDC Category C disease, (except cutaneous Kaposi's sarcoma or current CD4+ cell levels below 200 cells/mm^3). Patients were excluded if they had moderate-to-severe hepatic impairment, were expected to require treatment for Hepatitis C virus during the 24 weeks of the study, or if they had experienced an upper or lower gastrointestinal bleed (with the exception of anal or rectal bleeding) within the last three months. Table 5 provides further details on key inclusion and exclusion criteria for the SAILING and VIKING-3 studies.[13,15]

b) Baseline Characteristics

Studies in ART-Naive Patients

In the SPRING-2 and SINGLE studies,[1-4] the baseline demographic and clinical disease characteristics were generally well balanced across treatment groups. The majority of patients were white (85% in SPRING-2 and 69% in SINGLE)[1-4] and predominantly male (86% SPRING-2 and 85% in SINGLE)[1-4] (Table 6). Mean age was similar across treatment groups in both SPRING-2 and SINGLE (overall mean of approximately 37 years). Baseline viral load and CD4+ cell count were well balanced between the DTG and RAL groups in the SPRING-2 study,[1,2] and between the DTG plus ABC/3TC and EFV/TDF/FTC groups in the SINGLE study[3,4] (Table 6). Most patients (> 68%) had baseline viral loads of ≤ 100,000 copies/mL across treatment groups and both studies. Overall baseline mean CD4+ counts ranged from 349 to 379 cells/mm^3 across the studies. The proportion of patients with hepatitis B (HBV) or hepatitis C (HCV) was generally low, though the rates were relatively higher for HCV in the SPRING-2 and the SINGLE (Table 6). Not more than 2% of patients had HBV at baseline in both studies. In the SPRING-2 study, 10% of patients in the DTG arm had HVC compared with 9% in the RAL group. In the SINGLE study, the rate of HVC was 7% in both treatment groups at baseline. The majority of patients (over 83%) in both studies were classified as asymptomatic (CDC disease category A). In the SPRING-2 study[1,2] approximately 60% of patients in both treatment groups received TDF/FTC as their NRTI backbone treatment; approximately 40% in both treatment groups received ABC/3TC (Table 6).

TABLE 6: SUMMARY OF BASELINE CHARACTERISTICS — STUDIES IN ART-NAIVE PATIENTS

Characteristics	SPRING-2[1,2]	SINGLE[3,4]	Characteristic	SPRING-2[1,2]
	DTG 50 mg q.d. N = 411	RAL 400 mg b.i.d. N = 411		DTG 50 mg q.d. N = 411
Demographics				
Age (Years)				
Mean ± SD	37.3 ± 9.19	36.6 ± 10.02	36.5 ± 10.74	36.4 ± 10.43
Median (range)	37 (18, 68)	35 (18, 75)	36.0 (18, 68)	35.0 (18, 85)
Sex, n (%)				
Male	348 (85)	355 (86)	347 (84)	356 (85)
Race, n (%)				
African American/African heritage	49 (12)	39 (9)	98 (24)	99 (24)
White	346 (84)	352 (86)	284 (69)	285 (68)
Other	16 (4)	20 (5)	32(8)	34 (8)
Disease Characteristics				
Baseline HIV RNA (log_{10} copies/mL)				
Mean ± SD	4.54 ± 0.73	4.60 ± 0.71	4.67 ± 0.68	4.66 ± 0.71
Median (IQR)	4.52 (4.08, 5.06)	4.58 (4.12, 5.07)	4.67 (3.06, 6.46)	4.70 (2.48, 6.35)
Baseline HIV RNA category (copies/mL, n (%)				
≤ 100,000	297 (72)	295 (72)	280 (68)	288 (69)
> 100,000	114 (28)	116 (28)	134 (32)	131 (31)
Baseline CD4+ cell count (cells/mm^3)				
Mean ± SD	379.2 ± 178.3	374.3 ± 163.4	349.1 ± 158.2	350.6 ± 157.5
Baseline CD4+ Cell Count (Cells/mm^3), n (%)				
Mean ± SD	379.2 ± 178.32	374.3 ± 163.37	349.1 ± 158.17	350.6 ± 157.50
Median (IQR)	359.0 (276, 470)	362.0 (267, 469)	334.5 (248, 434)	339.0 (243, 439)
Hepatitis B (HBV) and C (HCV)				
HBV n (%)	7 (2)	8 (2)	1 (< 1)	1 (< 1)
HCV n (%)	41 (10)	35 (9)	27 (7)	29 (7)
HIV Disease Status (CDC Disease Category), n (%)				
A: Asymptomatic	359 (87)	347 (84)	342 (83)	350 (84)
B: Symptomatic	43 (10)	55 (13)	54 (13)	52 (12)
C: AIDS	9 (2)	9 (2)	18 (4)	17 (4)
Backbone NRTI Therapy, n (%)				
ABC/3TC	169 (41)	164 (40)	NR	NR
TDF/FTC	242 (59)	247 (60)	NR	NR
Lipid and Glucose Parameters				
HDL Cholesterol (mmol/L)				
Mean ± SD	1.14 ± 0.31	1.14 ± 0.34	1.12 ± 0.34	1.13 ± 0.33
Median (IQR)	1.10 (0.94, 1.33)	1.13 (0.93, 1.31)	1.10 (0.90, 1.30)	1.10 (0.90, 1.29)
LDL Cholesterol (mmol/L)				
Mean ± SD	2.50 ± 0.78	2.39 ± 0.84	2.41 ± 0.74	2.40 ± 0.82
Median (IQR)	2.46 (1.98, 2.98)	2.36 (1.80, 2.92)	2.33 (1.87, 2.87)	2.35 (1.82, 2.86)
Total Cholesterol/HDL (Ratio)				
Mean ± SD	3.86 ± 1.01	3.83 ± 1.26	3.93 ± 1.27	3.88 ± 1.23
Median (IQR)	3.70 (3.15, 4.47)	3.63 (3.04, 4.42)	3.65 (3.05, 4.61)	3.70 (3.05, 4.54)
Triglycerides (mmol/L)				
Mean ± SD	1.28 ± 0.73	1.30 ± 0.93	1.30 ± 0.89	1.26 ± 0.75

Characteristics	SPRING-2[1,2]	SINGLE[3,4]	Characteristic	SPRING-2[1,2]
	DTG 50 mg q.d. N = 411	RAL 400 mg b.i.d. N = 411		DTG 50 mg q.d. N = 411
Median (IQR)	1.10 (0.82, 1.53)	1.06 (0.79, 1.56)	1.07 (0.82, 1.56)	1.07 (0.77, 1.52)
Blood glucose(mmol/L)				
Mean ± SD	4.89 ± 0.76	5.00 1.04	5.12 ± 1.43	5.10 ± 1.51
Median (IQR)	4.80 (4.50, 5.20)	4.85 (4.60, 5.30)	4.90 (4.60, 5.30)	4.80 (4.50, 5.20)

3TC = lamivudine; ABC = abacavir; AE = adverse event; ARV = antiretroviral; b.i.d. = twice daily; CD4+ = Helper-inducer T-lymphocyte surface antigen; CI = confidence interval; DTG = dolutegravir; EFV = efavirenz; TDF = tenofovir; FTC = emtricitabine; FDC = fixed-dose combination; ITT = intention-to-treat; OR = odds ratio; PP = per protocol; NNH = number needed to harm; NNT = number needed to treat; q.d. = once daily; RNA = Ribonucleic acid; RR = relative risk; SAE = serious adverse event; SD = standard deviation; WDAE = withdrawal due to adverse events;
Source: SPRING-2 weeks 48 and 96 CSRs;[1,2] SINGLE weeks 48 and 96 CSRs.[3,4]

Studies in ART-Experienced Patients

The baseline demographic and clinical disease characteristics were generally well balanced between treatment groups in the SAILING study[13] (see Table 7). One half (50%) of patients were white and 68% were male. The median age of patients in the DTG group was 42.0 years (range: 21 to 69 years) and 43 years (range: 18 to 73 years) in the RAL group. Baseline viral load and CD4+ cell count were also well balanced between the DTG and RAL. Over half of patients in both treatment groups had viral loads of 1,000 to more than 10,000 (DTG: 31% and RAL: 29%) or 10,000 to more than 50,000 copies/mL (DTG: 26% and RAL: 28%). The mean (SD) of baseline CD4+ counts was 254.0 (207.77) cells/mm^3 in the SPRING-2 study and 246.4 (199.02) cells/mm^3 in the SINGLE study. The most frequently used OBT was DRV/r plus TDF, with 18% of DTG-treated patients and 20% of RAL-treated patients receiving this regimen.

Five per cent (5%) of patients in the DTG group had HBV at baseline compared with 4% in the RAL group, while 9% in the DTG group had HVC compared with 13% in the RAL group. The proportion of patients was generally balanced across both treatment groups in terms of HIV-associated diseases, with more patients in both groups having CDC Category C disease (Table 7).

Participants in the VIKING-3 study[15] were predominantly male (77%) and white (71%). The median age of patients was 48 years (range: 19 to 67 years). The mean (SD) HIV RNA (log_{10} copies/mL) was 4.34 (0.95) with a means (SD) baseline CD4+ count of 199.9 ± (192.43). Table 7 provides additional information on patients in the VIKING-3 study.[15] Additional patient characteristics not reported in Table 7 include 56% of the participants with CDC Category C disease, indicating advanced HIV disease; and genotypic and/or phenotypic resistance to integrase transfer inhibitor discovered in 73% of patients at screening while the remaining (27%) had prior history of detection. Less than 1% of patients in the VIKING-3 study had HBV, while 14% had HVC. The majority (56%) of patients had CDC Category C disease (Table 7).

TABLE 7: SUMMARY OF BASELINE CHARACTERISTICS — STUDIES IN ART-EXPERIENCED PATIENTS

Characteristic	SAILING[13]		VIKING-3[15]
	DTG 50 mg N = 354	RAL 400 mg N = 361	DTG 50 mg N = 183
Demographics			
Age (Years)			
Mean ± SD	42.6 ± 10.45	42.5 ± 9.81	47.0 ± 9.26
Median (range)	42.0 (21, 69)	43.0 (18, 73)	48 (19, 67)
Sex			

Characteristic	SAILING[13]		VIKING-3[15]
	DTG 50 mg N = 354	RAL 400 mg N = 361	DTG 50 mg N = 183
Male, n (%)	247 (70)	238 (66)	141 (77)
Race, n (%)			
African American/African heritage	143 (40)	160 (44)	49 (27)
White	178 (50)	175 (49)	130 (71)
Other	22 (6)	8 (2)	5 (3)
Disease Characteristics			
Baseline HIV RNA (log_{10} copies/mL), median (IQR)			
Mean ± SD	4.12 ± 0.95	4.14 ± 0.99	4.34 ± 0.95
Median (IQR)	4.17 (3.461, 4.825)	4.21 (3.428, 4.852)	4.38 (3.592, 5.018)
HIV RNA Copies/mL, n (%)			
< 1,000	45 (13)	50 (14)	21 (11)
1,000 to < 10,000	111 (31)	103 (29)	49 (27)
10,000 to < 50,000	93 (26)	101 (28)	52 (28)
50,000 to < 100,000	38 (11)	34 (9)	20 (11)
> 100,000	67 (19)	73 (20)	41 (22)
Baseline CD4 (Cells/mm^3)			
Mean ± SD	254.0 ± 207.77	246.4 ± 199.02	199.9 ± 192.43
Median (IQR)	204.5 (88.0, 368.0)	193.0 (96.0, 365.0)	140.0 (40.0, 330.0)
Hepatitis B (HBV) and Hepatitis C (HCV)			
HBV n (%)	17 (5)	16 (4)	1 (< 1)
HCV n (%)	31 (9)	48 (13)	26 (14)
HIV Disease Status (CDC Disease Category), n (%)			
A: Asymptomatic	111 (31)	114 (32)	44 (24)
B: Symptomatic	70 (20)	89 (25)	37 (20)
C: AIDS	173 (49)	158 (44)	102 (56)
ART History			
Previous ART Received, n (%)			
NRTI	354 (100)	360 (> 99)	182 (> 99)
NNRTI	295 (83)	309 (86)	156 (85)
PI	204 (58)	223 (62)	178 (97)
FI	17 (5)	12 (3)	89 (49)
CCR5	4 (1)	10 (3)	59 (32)
INSTI	0	1 (< 1)	183 (100)
Other	4 (1)	5 (1)	8 (4)
Drug Class Resistance (Including INSTI), n (%)			
NRTI + NNRTI + INSTI	1 (< 1)	1 (< 1)	NR
NRTI + PI +CCR5 + INSTI	1 (< 1)	0	
NRTI + NNRTI + PI + INSTI	1 (< 1)	0	
NRTI + NNRTI + PI + CCR5 + INSTI	0	1 (< 1)	

Characteristic	SAILING[13]		VIKING-3[15]	
	DTG 50 mg N = 354	RAL 400 mg N = 361	DTG 50 mg N = 183	
INSTI Resistance,[a] n (%)				
Detected	3(< 1)	2(< 1)	60 (33)	
Not detected	NR		123 (67)	
Optimized Background Therapy,[b] n (%)			**Day 1 to Day 7**	**From Day 8**
DRV/r, TDF	62 (18)	73 (20)	0	0
LPV/r, TDF	40 (11)	40 (11)	0	0
DRV/r, ETR	33 (9)	40 (11)	6 (3)	9 (5)
LPV/r	36 (10)	35 (10)	0	0
ATV/r, TDF	37 (10)	33 (9)	0	0
DRV/r, MVC	23 (6)	19 (5)	4 (2)	10 (5)
FTC/TDF	0	0	26 (14)	8 (4)
DRV/r, TDF/FTC	0	0	26 (14)	8 (4)
DRV/r, TDF/FTC, ETR	0	0	11 (6)	11 (6)
DRV/r, TDF/FTC, ENF	0	0	1 (< 1)	11 (6)
DRV/r, TDF/FTC, ETR, ENF	0	0	1 (< 1)	11 (6)

ATV/r = atazanavir/ritonavir; CCR5 =; chemokine receptor type 5; DRV/r = darunavir/ritonavir; ENF = enfuvirtide; ETR = etravirine; FI = fusion/entry inhibitor; LPV/r = lopinavir/ritonavir; INSTI = integrase strand transfer inhibitor; IQR = interquartile range; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NR = not reported; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; TDF = tenofovir.

[a] Genotypic and/or phenotypic resistance.

[b] More than 5% of patients.

Source: SAILING 48-week clinical study report;[13] VIKING-3 48-week clinical study report.[15]

3.2.3 Interventions

a) Studies in ART-Naive Patients

In the SPRING-2 study,[1,2] patients were randomized to DTG 50 mg once daily or to RAL 400 mg twice daily for 96 weeks. Blinding was achieved through a double-dummy design that used matching placebos for both DTG and RAL treatments. The backbone NRTI therapy selected by investigators for each group was either ABC/3TC or TDF/FTC administered once a day in the morning or evening as a fixed-dose combination tablet. In the SINGLE study,[3,4] patients were randomized to DTG + ADC/3TC once daily or to EFV/TDF/FTC once daily for 96 weeks. Blinding was achieved through a double-dummy design that used matching placebos for drugs in each treatment group.

b) Studies in ART-Experienced Patients

In the SAILING study,[13] patients received DTG 50 mg once daily or RAL 400 mg twice daily for 48 weeks. Both DTG and RAL were administered in combination with an investigator-selected OBT regimen consisting of one fully active single drug plus no more than one second single drug, which may or may not have been active. Blinding was achieved through a double-dummy design that used matching placebos for both DTG and RAL treatments.

In the single-arm VIKING-3 study,[15] DTG 50 mg was administered orally twice daily. Only DTG was considered an investigational drug. All background ART was treated as concomitant ART, including those therapies that were failing before, as well as those optimized background regimens introduced in the

course of the study. Though patients had to have documented evidence of resistance to at least one drug in two or more classes of ART, at least one active drug that could be included in the OBT had to have been found before treatment commenced on day 8.

3.2.4 Outcomes

a) Studies in ART-Naive Patients

In both the SPRING-2 and SINGLE studies,[3,4] the primary efficacy outcome was the proportion of patients with a plasma HIV RNA of less than 50 copies/mL through week 48 using the FDA-defined Snapshot analysis. In this algorithm, participants whose last available HIV RNA value in the week 48 analysis window (i.e., from week 42 through week 54) was less than 50 copies/mL were considered as having had a response; participants whose HIV RNA level was ≥ 50 copies/mL in the analysis window, or who did not have available data in the analysis window, were considered as not having had a response.

Secondary outcomes in both SPRING-2 and SINGLE included health-related quality of life, HIV-associated conditions/disease progression (morbidity), and changes from baseline in CD4+ counts. Patients' health status and health-related quality of life (HRQoL) were evaluated using the EQ-5D tool. The EQ-5D is a generic, non-disease-specific; preference-based utility instrument that includes a descriptive system used to rate five dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D also includes a visual analogue scale (VAS) that has a range of 0 (worst imaginable health) to 100 (best imaginable health). The EQ-5D was administered at baseline and at weeks 24, 48, and 96.

In both the SPRING-2 and SINGLE studies, morbidity (HIV-associated conditions/disease progression) was recorded and assessed according to the CDC's 1993 Revised Classification System for HIV Infection and Expanded Surveillance Case Definition for AIDS Among Adolescents and Adults.[20] CD4+ cell counts in both studies were determined using flow cytometry; and immunologic activity over time was compared using summaries of CD4+ values and changes from baseline at each visit.

Safety assessments for both the SPRING-2 and SINGLE studies included monitoring and recording all adverse events (AEs) and serious adverse events (SAEs), as well as laboratory parameters, including hematology, fasting lipid profile, blood chemistry, and urinalysis (including urine microalbumin/creatinine [Cr] ratio). The incidence of AEs, SAEs, and graded laboratory toxicities, as well as summaries of laboratory tests and vital signs, were used to assess the tolerability and long-term safety of DTG compared with RAL.

b) Studies in ART-Experienced Patients

The primary efficacy outcome in the SAILING study[13] was the proportion of patients with HIV RNA < 50copies/mL through week 48. Assessment of this outcome was done using the FDA-defined Snapshot algorithm described in the SPRING-2 and SINGLE studies.

A key secondary outcome was the proportion of patients with detectable virus who had genotypic or phenotypic evidence of INSTI resistance by week 48. Immunologic activity over time was determined by using changes from baseline CD4+ values at each visit. Morbidity (HIV-associated conditions, disease progression) were recorded and assessed according to the CDC's 1993 revised classification system for HIV infection.[20] CD4+ cell counts were determined using flow cytometry; and immunologic activity over time was compared using summaries of CD4+ values and changes from baseline at each visit.

In the VIKING-3 study,[15] the primary efficacy end point at week 24 was the proportion of responders with plasma HIV RNA of less than 50 copies/mL using an MSDF dataset. The secondary efficacy outcomes were proportion of responders with plasma HIV RNA of less than 50 copies/mL and the change from baseline CD4+ cell count at week 48. Other secondary analyses examined continuous measures of virologic activity and the proportion of responders with less than 50 copies/mL and less than 400 copies/mL of plasma HIV RNA over time.

Safety assessments included monitoring and recording all adverse events (AEs) and SAEs, as well as laboratory parameters including hematology, fasting lipid profile, blood chemistry and urinalysis (including urine microalbumin/creatinine [Cr] ratio). The incidence of AEs, SAEs, and graded laboratory toxicities, as well as summaries of laboratory tests and vital signs, were used to assess the tolerability and long-term safety of DTG compared with RAL.

3.2.5 Statistical Analysis

a) Studies in ART-Naive Patients

Primary Outcomes

The adjusted difference in the proportion of participants (intervention group minus the comparator group) with plasma HIV RNA of less than 50 copies/mL through week 48 was based on a stratified analysis using Cochran-Mantel-Haenszel (CMH) weights.

In the SPRING-2 study, stratification was based on screening HIV RNA (≤ 100,000 copies/mL or > 100,000 copies/mL), and backbone NRTI selection (ABC/3TC or TDF/FTC). In the SINGLE study, the adjusted estimates of the difference in the rate of responders with a plasma HIV RNA of less than 50 copies/mL between the two treatment groups was based on a stratified analysis using CMH weights. Stratification was based on baseline HIV RNA (≤ 100,000 copies/mL or > 100,000 copies/mL), and baseline CD4+ cell count (< 200 versus > 200 cells/mm^3).

For both the SPRING-2 and the SINGLE studies, a non-inferiority margin was set as 10%, which is within the 10% to 12% range recommended by the FDA for HIV studies.[21]The analysis was repeated for consistency using a per-protocol (PP) population. Non-inferiority was concluded if the lower bound of a two-sided 95% confidence interval (CI) on the difference in proportions (intervention, comparator) was greater than –10% in both the ITT-E and PP analyses. Superiority of DTG was concluded if both analyses showed non-inferiority and the lower end of the 95% CI from the primary analysis was above 0%. Investigations of heterogeneity were confined to the primary end point at week 48 using the weighted least squares chi-squared Fleiss statistic.

For both studies, sample size and power calculations were based on an estimated 75% response rate at week 48 in the comparator groups (RAL or EFV/TDF/FTC), a non-inferiority margin of 10%, and a one-sided significance level of 0.025. Both studies, therefore, required 394 evaluable patients per treatment group to have 90% power. The estimated response rate in the RAL group was based the lower of two response rates from RAL studies in treatment-naive HIV-infected patients (response rates of approximately 80% at week 48 and 75% at week 96).[1,2] Likewise, the assumption of 75% response rate in the EFV/TDF/FTC group was derived as the mid-range of response rates observed in the EFV groups in recent large clinical studies (response range: 71% to 82%).[3,4]

In both the SPRING-2 and SINGLE studies, multiplicity was adjusted for according to a pre-specified sequence of testing. As well, there was only one key secondary analysis comparison (superiority), which was tested only if non-inferiority for the primary comparison was concluded. This pre-specified

sequence of testing controls the overall type I error among the tests. In the SINGLE study, three categories of superiority tests were pre-specified:

- 1% for superiority of DTG plus ABC/3TC FDC versus EFV/TDF/FTC with respect to time to viral suppression (< 50 copies/mL) (P1);
- 3% for superiority of DTG plus ABC/3TC FDC versus EFV/TDF/FTC with respect to change from baseline in CD4 at week 48 (P2);
- 1% for superiority of DTG plus ABC/3TC FDC versus EFV/TDF/FTC with respect to change from baseline in overall symptom bother count at week 4 (P3).

The fall-back method — where the alpha used for the test of an end point is equal to its a priori alpha plus the accumulated alpha from previously rejected hypotheses — was used to control for overall type I error rate. Any test that is not rejected "burns" alpha: the alpha accumulated up to that point is lost and cannot be used in subsequent tests.[3]

Secondary Outcomes

Changes from baseline in HRQoL as measured by the EQ-5D index and VAS scores at weeks 24 and 48 were analyzed in a similar fashion using an ANCOVA model adjusting for the same covariates. Adjusted mean change from baseline (± 1.96 standard errors) for each treatment group across visits in EQ-5D Index and VAS were measured.

To assess the development of viral resistance in patients experiencing virologic failure, the proportions of patients with both failure and treatment-emergent genotypic or phenotypic evidence of INSTI resistance were compared using a CMH analysis, as previously described.

b) Studies in ART-Experienced Patients

The primary end point for the SAILING study,[13] was the proportion of patients with plasma HIV RNA < 50 copies/mL at week 48 using the MSDF algorithm. The adjusted estimates of the difference in the rate of responders between the two groups (DTG – RAL) were presented along with 95% CIs based on a stratified analysis using CMH weights based on baseline HIV RNA and DRV/r use. With regard to stratification by DRV/r treatment, investigators compared patients with DRV/r in their background regimen and whose screening genotype showed no primary PI mutations with patients without DRV/r or whose screening genotype showed primary PI mutations. All CIs were two-sided. A non-inferiority margin of 12% was chosen based on the observed benefit of RAL versus placebo in INSTI-naive patients in the BENCHMRK studies[14] within the population of patients with Phenotypic Susceptibility Score (PSS) = 1 to 2. The BENCHMRK trials were phase III studies which evaluated the efficacy and safety of RAL in HIV patients with triple-class resistant virus. According to the investigators, benefit with RAL for pooled PSS 1 to 2 population was 32% (95% CI, 22% to 42%) with confidence intervals and observed treatment differences far enough from zero to justify a non-inferiority margin of 12% in patients with PSS = 1, PSS = 2 or PSS 1 to 2.[13] The 12% margin is within the range (10 to 12%) recommended by the FDA for HIV studies.[21]

Non-inferiority in the SAILING study was concluded when both the mITT-E and PP analysis demonstrated that the lower bound of a two-sided 95% CI for the difference in proportions (intervention – comparator) was greater than –12%. Testing for superiority was done once non-inferiority was established, and superiority was concluded when the lower end of the 95% CI from the primary analysis was above 0%.

Assuming a 65% response rate in the raltegravir group, it was first determined by investigators that a sample size of 333 patients per treatment group provided 90% power given a 12% non-inferiority margin and a one-sided 2.5% significance level. It was further determined that a group-sequential analysis would require 344 patients per group to guarantee a 90% power and this sample size was implemented and maintained based on this latter consideration. The investigators stated that the derived sample size also provided at least 80% power to detect non-inferiority in the key subpopulation who received DRV/r as a component of the background regimen that excluded patients who harbour virus which was fully susceptible to PIs.[13]

According to the CSR for SAILING, adjustments for multiplicity were handled according to the pre-specified fixed sequence testing procedure. For example, testing for superiority proceeded at the 5% two-sided alpha level only if the primary comparison was significant for non-inferiority at the 5% two-sided alpha level; otherwise testing of superiority was not performed.

For the primary end point (HIV RNA < 50 copies/mL) at week 24 in the VIKING-3 study was determined based on MSDF algorithm,[15] though this review focused on data at week 48. The investigators determined that 100 patients would provide a precision (i.e., standard error) of four percentage points, which translates to a 95% CI of 72% to 88% for an assumed response rate of 80%. VIKING-3 was a single-arm study and no adjustment for multiplicity was performed.

Reported secondary end points of interest to this review in both the SAILING and VIKING-3 studies were diseases progression, death, and changes from baseline in CD4+ cell counts.

Missing data for both the SAILING and VIKING-3 studies were handled according to the MSDF algorithm as described earlier in the Studies in ART-naive patients section under Statistical Analysis. The LOCF and OC datasets were used for analysis of health outcomes end points and the OC dataset was used for change from baseline in CD4+ cell counts.

c) Analysis Populations

Studies in ART-Naive Patients

In the both the SPRING-2 and SINGLE studies,[1-4] efficacy analyses were conducted based on the ITT-Exposed (ITT-E) population, which consisted of all randomized patients who received at least one dose of study medication, instead of the ITT population. This was because not all patients who were randomized into the treatment groups were treated with investigational drugs. However, the difference between the ITT and the ITT-E populations was small (< 5%) in both study and is not expected to impact the validity of outcomes. Patients were assessed according to their randomized treatment, regardless of the treatment they received. Non-inferiority and superiority tests were based on analysis of both the ITT-E and the PP populations. The per-protocol (PP) populations consisted of patients in the ITT-E Population with the exception of those with pre-specified criteria of protocol deviation before a specified analysis time point.

Safety analyses in both studies were conducted based on the Safety Population, defined as all patients who received at least one dose of any of the investigational drugs (i.e., DTG or RAL in SPRING-2 and DTG or RAL or DTG 50 mg plus ABC/3TC, or EFV/TDF/FTC as fixed-dose combination tablet in SINGLE).[1-4] Patients were assessed according to the actual treatment they received for the majority of time on the study.

Studies in ART-Experienced Patients

In the SAILING study,[13] efficacy analyses were based on the modified ITT-E (mITT-E) population, which consisted of all randomized patients who received at least one dose of the investigational drug (i.e., DTG or RAL). Modification came about as a result of removing four patients from a study site following protocol non-compliance. Patients were analyzed according to their randomized treatment, regardless of the treatment they actually received. The PP population in the SAILING study[13] consisted of patients in the mITT-E population with the exception of those with a protocol deviation. The Safety population consisted of all patients who received at least one dose of study drug. Patients were analyzed for safety according to the treatment they actually received, regardless of randomization.

The ITT-E population was used for assessment of efficacy in the VIKING-3 study at weeks 24 and 48. The population was defined as all patients who received at least one dose of DTG.

3.3 Patient Disposition

3.3.1 Studies in ART-Naive Patients

In both the SPRING-2 (n = 5) and SINGLE (n = 11) studies, not all randomized patients received study drugs: in SPRING-2, four patients withdrew consent and one patient was randomized in; in SINGLE, seven patients withdrew consent, three were randomized in error and one patient was lost to follow-up (Table 8).

In the SPRING-2 study, the proportion of patients in the DTG group who discontinued prematurely was 11% and 15% at weeks 48 and 96, respectively, compared with 14% and 19% in the RAL group, respectively (Table 8). Lack of efficacy was the most common cause of premature discontinuation of treatment in SPRING-2 (DTG 4%; RAL 6%) at week 48; the proportions were the same at week 96. In SINGLE study, the proportion of patients in the DTG group who discontinued prematurely was 12% and 17% at weeks 48 and 96, respectively, compared with 20% and 26% in the EFV/TDF/TFC group, respectively (Table 8). Lack of efficacy was the most common reason for discontinuation in the DTG plus ABC/3TC group (3% by week 48; 4% by week 96), while the most common reason for discontinuation in the EFV/TDF/TFC was adverse events (10% by week 48; 11% by week 96).[3,4]

TABLE 8: PATIENT DISPOSITION — ART-NAIVE PATIENTS

	SPRING-2[1,2]				SINGLE[3,4]			
			Week 96		Week 48		Week 96	
	DTG 50 mg q.d. + OBT N = 411	RAL 400 mg b.i.d. + OBT N = 411	DTG 50 mg q.d. + OBT N = 411	RAL 400 mg b.i.d. + OBT N = 411	DTG 50 mg q.d. + OBT N = 414	EFV/TDF/FTC N = 419	DTG 50 mg q.d. + OBT q.d. N = 414	EFV/TDF/FTC N = 419
Screened	1,035				1,090			
Randomized,	413(100)	414 (100)	413(100)	414 (100)	422	422		
Discontinued treatment, n (%)	47 (11)	56 (14)	62 (15)	79 (19)	51 (12)	84 (20)	72 (17)	109 (26)
Adverse event n (%)	8 (2)	6 (1)	8 (2)	7 (2)	10 (2)	42 (10)	13 (3)	48 (11)
Had lack of efficacy n (%)	16 (4)	24 (6)	17 (4)	25 (6)	14 (3)	13 (3)	18 (4)	14 (3)

	SPRING-2[1,2]				SINGLE[3,4]			
			Week 96		Week 48		Week 96	
Had protocol deviation n (%)	13 (3)	11 (3)	13 (3)	16 (4)	7 (2)	7 (2)	14 (3)	12 (3)
Lost to follow-up n (%)	4 (< 1)	7 (2)	6 (1)	10 (2)	14 (3)	9 (2)	17 (4)	18 (4)
Withdrew consent n (%)	4 (< 1)	7 (2)	10 (2)	14 (3)	5 (1)	11 (3)	9 (2)	15 (4)
Other n (%)	2 (< 1)	1 (< 1)			1 (< 1)	2 (< 1)	1 (< 1)	2 (< 1)
ITT, N	411	411	411	411	414	419	414	419
PP, N	387	384	393	387	403	412	403	412
Safety, N	411	411	411	411	414	419	414	419

3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; b.i.d. = twice daily; CSR = clinical study report; DTG = dolutegravir; EFV = efavirenz; TDF = tenofovir; FTC = emtricitabine; FDC = fixed-dose combination; ITT = intention-to-treat; OBT = optimized background therapy; PP = per protocol; q.d. = once daily.
Source: SPRING-2 weeks 48 and 96 CSRs;[1,2] SINGLE weeks 48 and 96 CSRs.[3,4]

3.3.2 Studies in ART-Experienced Patients

In SAILING, three randomized patients from the DTG group and two from the RAL group did not receive treatment with study drugs. Of these five patients, one withdrew consent, three were non-compliant with protocol procedures and one received a prohibited medication (Table 10). Fewer patients in the DTG group (16%) than in the RAL group (23%) discontinued treatment prematurely compared. Lack of efficacy was the most common cause of premature discontinuation accounting for 6% in the DTG group compared with 12% in the RAL group by week 48. Proportions of patients who discontinued treatment prematurely due to AEs were low in both arms of the study (DTG, < 1%; RAL, 3%).

In the VIKING-3 study,[15] the primary reason for withdrawal at week 24 was lack of efficacy (13%). No new patients were withdrawn for lack of efficacy after this time point. Withdrawal due to adverse events (WDAEs) occurred in 4% of the ITT-E population (Table 9).

TABLE 9: PATIENT DISPOSITION — ART-EXPERIENCED PATIENTS

	SAILING[13] Week 48		VIKING-3[15] Week 48
	DTG 50 mg + OBT	**RAL 400 mg + OBT**	**DTG 50 mg + OBT**
Screened, N	**1,441**		**323**
Randomized, N	360	364	183
Discontinued, N (%)	68 (19)	82 (23)	46 (25)
Adverse event	4 (1)	11 (3)	7 (4)
Lack of efficacy	20 (6)	42 (12)	24 (13)
Protocol deviation	9 (3)	6 (2)	5 (3)
Met liver chemistry stopping criteria	5 (1)	3 (< 1)	0
Lost to follow-up	5 (1)	10 (3)	5 (3)
Investigator discretion	1 (< 1)	1 (< 1)	1 (< 1)
Withdrew consent	11 (3)	5 (1)	4 (2)
Ongoing, N (%)[a]	282 (80)	43 (12)	137 (75)
mITT-E, N[c]	354	361	NA
ITT-E, N	357	362	183
PP, N	325[d]	340[d]	164[e]

	SAILING[13] Week 48		VIKING-3[15] Week 48
Safety, N	357	362	183

DTG = dolutegravir; ITT-E = intention-to-treat exposed; mITT-E = modified intention-to-treat exposed; OBT = optimized background therapy; PP = per protocol; RAL = raltegravir.
[a] Based on patients completing study: defined as (1) completing the randomized phase and not enrolling in the open-label phase or (2) completing the randomized phase, continuing into and completing the open-label phase.
[b] Includes patients participating in the DTG open-label phase or receiving RAL bridging supplies.
[c] Four patients (DTG: 3; RAL: 1) from one site in Russia were removed from the ITT population following site closure due to non-compliance with good clinical practice on another manufacturer-sponsored study.
[d] Per protocol (PP) at week 48.
[e] PP at week 24.
Source: SAILING 48-week clinical study report;[13] VIKING-3 48-week clinical study report.[15]

3.4 Exposure to Study Treatments

3.4.1 Studies in ART-Naive Patients

Patients in the DTG and RAL arms of the SPRING-2 study[1,2] had similar extent of exposure to their respective study drugs (Table 11). At week 48, the median time of exposure to DTG was 347 days compared with a median time of exposure of 340 days in the RAL group. At the end of the double-blind phase (week 96), the median time of exposure to study drug was the same (672 days) for patients in both the DTG and the RAL groups.

In the SINGLE study,[3,4] patients in the DTG plus ABC/3TC and the EFV/TDF/TFC groups had similar median time of exposure to their respective study drugs by week 48 (DTG plus ABC/3TC, 347 days; EFV/TDF/TFC, 339 days) (Table 10). However by the end of the double-blind phase (week 96), the DTG plus ABC/3TC group had a median time of exposure or 606 days compared with 554 days in the EFV/TDF/TFC group. According to the manufacturer, the difference between treatment groups was driven by the fact that more patients discontinued study drug early in the EFV/TDF/TFC group.

TABLE 10: SUMMARY OF EXTENT OF DRUG EXPOSURE — ART-NAIVE (SAFETY POPULATION)

Exposure (Weeks[a]), n (%)	SPRING-2[1,2]		SINGLE[3,4]	
	DTG 50 mg q.d. N = 411	RAL 400 mg b.i.d. N = 411	DTG 50 mg q.d. N = 411	RAL 400 mg b.i.d. N = 411
< 2	[redacted]	[redacted]	[redacted]	[redacted]
2 to < 4	[redacted]	[redacted]	[redacted]	[redacted]
4 to < 8	[redacted]	[redacted]	[redacted]	[redacted]
8 to < 12	[redacted]	[redacted]	[redacted]	[redacted]
12 to < 16	[redacted]	[redacted]	[redacted]	[redacted]
16 to < 20	[redacted]	[redacted]	[redacted]	[redacted]
20 to < 24	[redacted]	[redacted]	[redacted]	[redacted]
24 to < 32	[redacted]	[redacted]	[redacted]	[redacted]
32 to < 40	[redacted]	[redacted]	[redacted]	[redacted]
40 to < 48	[redacted]	[redacted]	[redacted]	[redacted]
48 to < 60	[redacted]	[redacted]	[redacted]	[redacted]
60 to < 72	[redacted]	[redacted]	[redacted]	[redacted]
72 to > 84	[redacted]	[redacted]	[redacted]	[redacted]
84 to > 96	[redacted]	[redacted]	[redacted]	[redacted]
96 to > 108	[redacted]	[redacted]	[redacted]	[redacted]
≥ 108	[redacted]	[redacted]	[redacted]	[redacted]

Exposure (Weeks[a]), n (%)	SPRING-2[1,2]				SINGLE[3,4]			
	DTG 50 mg q.d. N = 411		RAL 400 mg b.i.d. N = 411		DTG 50 mg q.d. N = 411		RAL 400 mg b.i.d. N = 411	
Exposure (Days[a])	Week 48	Week 96	Week 48	Week 96	Week 48	Week 96	Week 48	Week 96
Mean ± SD	[redacted]							
Median (IQR)	[redacted]							

b.i.d. = twice daily; DTG = dolutegravir; IQR = interquartile range; q.d. = once daily; RAL = raltegravir; SD = standard deviation.
[a] When the stop date of the investigational drug was missing, duration was calculated up to the date of last visit or the recorded date of withdrawal or completion, whichever was earlier.
Source: SPRING-2 weeks 48 and 96 CSRs;[1,2] SINGLE weeks 48 and 96 CSRs.[3,4]

3.4.2 Studies in ART-Experienced Patients

Patients in the DTG and RAL treatment groups of SAILING had similar median time of exposure during the randomization phase (Table 12): 336 days in both treatment groups, with 237 (66%) patients in the DTG group and 233 (64%) in the RAL group receiving therapy for at least 48 weeks.

In the VIKING-3 study,[15] the overall median (range) duration of exposure to DTG was 507 days (range of 14 to 757 days) (Table 12). A total of 147 patients (80%) had at least 48 weeks of exposure to DTG.

TABLE 11: NUMBER AND DURATION OF PRIOR ART (ITT-E POPULATION) — VIKING-3

	DTG 50 mg b.i.d. (N = 183)
Median number of prior ART (range)	14 (3, 22)
Median duration (years) of prior ART (range)	14 (4 months, 27 years)
Median duration (months) of prior RAL (range)	29 (1, 132)
Median duration (months) of prior EVG with/without boost (range)	20 (11, 70)

ART = antiretroviral therapy; b.i.d. = twice daily; DTG = dolutegravir; EVG = elvitegravir; RAL = raltegravir.

TABLE 12: SUMMARY OF EXTENT OF DRUG EXPOSURE — ART-EXPERIENCED

Exposure (Weeks[a]), n (%)	SAILING[13]		VIKING-3[15]
	DTG 50 mg + OBT N = 354	RAL 400 mg+ OBT N = 361	DTG 50 mg + OBT N = 183
< 2	2 (< 1)	2 (< 1)	0
2 to < 4	8 (2)	1 (< 1)	2 (1)
4 to < 8	1 (< 1)	8 (2)	3 (2
8 to < 12	7 (2)	1 (< 1)	2 (1)
12 to < 16	3 (< 1)	6 (2)	6 (3)
16 to < 20	5 (1)	10 (3)	3 (2)
20 to < 24	2 (< 1)	5 (1)	6 (3)
24 to < 32	12 (3)	16 (4)	10 (5)
32 to < 40	7 (2)	14 (4)	1 (< 1)
40 to < 48	73 (20)	66 (18)	3 (2)
48 to < 60	237 (66)	233 (64)	8 (4)
60 to < 72	0	0	30 (16)
72 to > 84	0	0	40 (22)

Exposure (Weeks[a]), n (%)	SAILING[13]		VIKING-3[15]
	DTG 50 mg + OBT N = 354	RAL 400 mg+ OBT N = 361	DTG 50 mg + OBT N = 183
84 to > 96	0	0	35 (19)
96 to > 108	0	0	32 (17)
≥ 108	0	0	2 (1)
Exposure (days[b])			
Mean ± SD	308.0 ± 77.87	303.0 ± 78.04	476 (193)
Median (IQR)	336.0 (333, 337)	336.0 (331, 337)	507 (14, 757)[b]

DTG = dolutegravir; EVG = elvitegravir; IQR = interquartile range; OBT = optimized background therapy; RAL = raltegravir; SD = standard deviation.
[a] When the stop date of the investigational drug was missing, duration was calculated up to the date of last visit or the recorded date of withdrawal or completion, whichever was earlier.
[b] For the VIKING-3 study, median exposure in days was reported with range, not interquartile range.
Source: SAILING 48-week clinical study report;[13] VIKING-3 48-week clinical study report.[15]

3.5 Critical Appraisal

3.5.1 Internal Validity

a) Studies in ART-Naive Patients

Patients in the SPRING-2 study were randomized to receive either DTG or RAL in combination with either ABC/3TC or TDF/FTC as backbone NRTI. Thus, in each treatment group (DTG or RAL) there were patients who took ABC/3TC and others who took TDF/FTC as backbone NRTI. Randomization was stratified by screening HIV RNA and backbone NRTI selection to achieve balance across the two treatment groups. The presence of patients who were treated with either backbone (i.e., ABC/3TC or TDF/FTC) in each treatment group, and an analysis that included the backbones strata helped to assess if the difference in outcome between the two treatment groups could be due to the distinct NRTI backbones. The analysis did not show a difference in outcomes regardless of which backbone was used.

Similarly, in the SINGLE study, the backbone NRTI of the DTG treatment group was solely ABC/3TC, and the backbone NRTI in the EFV group was TDF/FTC (in a fixed-dose combination with EFV). Hence, the investigators assumed the efficacy and safety of the NRTI backbones of the two groups were similar. According to the DHHS guidelines for antiretroviral therapy, ABC/3TC achieved inferior virologic responses in patients with baseline HIV RNA ≥ 100,000 copies/mL when given with EFV or ATV/r, as compared with TDF/FTC in ACTG 5202 study, but no difference was seen when ABC/3TC was used in combination with DTG.[7] Therefore it is not expected that the difference in backbone NRTI would affect the reported differences in the two treatment groups.

Both SPRING-2 and SINGLE were non-inferiority studies. All the drugs, (DTG, RAL, EFV, and NRTIs) were given at the recommended doses for ART-naive HIV patients according to clinical guidelines,[7] and confirmed by the clinical expert to be appropriate. Efficacy analysis was based on ITT-E, not the ITT population, because not all randomized patients received treatment with the study drugs. Of the randomized patients in the SPRING-2 study, two in the DTG group and three in the RAL group did not receive treatment with an investigational drug. For the SPRING study, 7 patients in the DTG plus ABC/3TC group, and 3 patients in the EFV/TDF/FTC group did not receive treatment with an investigational drug. Thus, the differences between the actual ITT and the ITT-E populations for both studies were small (< 1% in SPRING-2 and < 2% in SINGLE) and unlikely to affect the validity of the outcomes. The chosen non-inferiority margin of 10% for each study was within the FDA-recommended limit of 10% to 12% for HIV intervention studies.[21]

The primary outcome analysis was done at 48 weeks for both studies, but the trial remained double-blinded to investigators and patients until the last patient completed 96 weeks on study. The trials were unblinded to an independent data-monitoring committee for periodic review of efficacy and analysis of the primary outcome at week 48; however, this is not believed to have affected the study quality and findings.

In the SPRING-2 study, a possible protocol violation occurred at one study site, which had a total of 14 participants (DTG: n = 8; and RAL: n = 6); however, a sensitivity analysis of the primary outcome as well as analyses within the strata related to randomization, which excluded these 14 patients, did not change any conclusions with respect to non-inferiority of DTG to RAL at week 48 or week 96, with the magnitude of changes between the original and sensitivity analyses limited to less than a percentage point.

In the SINGLE study, more patients in the EFV/TDF/FTC treatment group withdrew from the double-blind phase compared with the DTG+ABC/3TC treatment group (26% versus 17%, respectively). The most common reason for withdrawal was due to AEs, with more patients in the EFV/TDF/FTC treatment group withdrawing compared with the DTG+ABC/3TC treatment group (11% versus 3%, respectively). Because of the MSDF algorithm used to assess outcomes, the difference in withdrawals between treatment groups (especially due to AEs) may be an important contributor to the overall statistical difference between the treatment groups.

b) Studies in ART-Experienced Patients

The SAILING study was a non-inferiority comparison between DTG and RAL. RAL has a Health Canada indication for ART-experienced patients based on its demonstrated efficacy and safety in this patient population, as shown in the BENCHMRK studies.[14] However, the patient population enrolled in the SAILING study was different from the population enrolled in the BENCHMRK-1 and -2 studies in several ways. For example, the BENCHMRK studies required patients to have resistance to three classes of ART drugs and an HIV RNA of more than 1,000 copies/mL. It also did not limit the number of background ART drugs patients were receiving when enrolled into the studies. Conversely, SAILING required resistance to at least two classes of ART drugs, plus two HIV RNA values higher than 400 copies/mL, or one HIV RNA exceeding 1,000 copies/mL. It also limited the number of background ART drugs to two, one of which had to be fully active. These differences make cross-study comparison of the SAILING and BENCHMRK studies complicated.

Baseline demographic and disease characteristics were well balanced across treatment groups in SAILING, with small differences not expected to affect the reported findings of the study. The primary efficacy outcomes were analyzed using a modified ITT-E population and repeated for consistency using the PP population. The mITT-E population came about as a result of five patients (DTG = 3; RAL = 2) who did not receive treatment with a study drug, and an additional four patients (DTG = 3; RAL = 1) who were excluded due to issues with non-compliance at a site. However, the difference between the actual ITT and the mITT-E population for both studies was small (less than 2%) and unlikely to impact on the validity of the outcomes. The non-inferiority and/or superiority of DTG to RAL could be declared using the mITT-E and PP analyses explained under the statistical analysis section. Investigators and patients in the trial remained blinded through the 48-week double-blind phase.

Study enrolment of patients into SAILING who were being treated with ritonavir-boosted darunavir (DRV/r) was capped at 170 people. According to the investigators, this was necessary because if many patients were enrolled who had resistance to NRTIs and NNRTIs, but not PIs, there was a risk that

additional ART drugs would not make a successful virologic response more likely. Under such conditions, according to the investigators, a placebo and a potent drug would appear identical because neither could produce appreciable improvements in response beyond that generated by a potent PI background regimen alone. Thus a non-inferiority assessment could be complicated. Without including the 170 patients in the capped group, the study had at least 80% power with a 12% non-inferiority margin and a one-sided 2.5% level of significance, according to the investigator.

VIKING-3 is subject to the potential biases inherent in an open-label study with no comparison group. Hence, there is no evidence on the comparative efficacy and safety for DTG in treatment-experienced HIV patients that harbour ART-resistance mutations, including resistance to INSTIs. However, these seeming shortcomings ought to be viewed against the fact that effective treatment options may be limited for patients, such as those enrolled in VIKING presenting the ethical dilemma of randomizing patients to ineffective treatment in a clinical trial.

3.5.2 External Validity

a) Studies in ART-Naive Patients

According to the clinical expert involved in the review, the SPRING-2 and SINGLE study populations appeared largely representative of HIV-infected patient populations in Canadian clinical practice. Both the SPRING-2 and SINGLE studies were multi-centre trials that included patients from several countries, including Canada.

The primary outcome in both the SPRING-2 and SINGLE studies was the proportion of patients with plasma HIV RNA of less than 50 copies/mL at week 48. According to the clinical expert involved in the review, virological suppression below detectable limits is a well-established surrogate outcome for prognosis of HIV infection and disease progression. Furthermore, the 48-week outcome to assess efficacy is consistent with the standards described in the FDA guideline for this therapeutic category.[21] Other efficacy outcomes described included virologic failure, protocol-defined virological failure at week 48, time to viral suppression, HRQoL, change from baseline in the CD4+ T-cell count, and incidence of the development of genotypic and phenotypic resistance.

b) Studies in ART-Experienced Patients

Following discussion with the clinical expert involved in the review, the baseline characteristics of patients enrolled in SAILING were similar to ART-experienced patients in Canadian clinical practice except that the proportion of patients who were PI-experienced was much lower in the study. However, this was not surprizing since the investigators had indicated the need to cap patients who received highly active PIs in order not to complicate the ability to assess non-inferiority.

The clinical expert involved in the review indicated that baseline demographic and clinical characteristics of those enrolled in VIKING were representative of treatment-experienced patients in Canadian clinical practice. The primary efficacy outcome of the study was the proportion of patients with HIV RNA < 50 copies/mL, as with the other studies included in the review, was appropriate. However, unlike the other three studies which assessed the primary outcome at 48 weeks, in VIKING the primary outcome was assessed at 24weeks. Though a majority of patients (63%) achieved HIV RNA < 50 copies/mL at week 48 in VIKING, there was no direct or indirect comparator to assess the merit of this response in relation to other options.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported here (see section 2.2, Table 3). For detailed efficacy data, see APPENDIX 4: OTHER EFFICACY OUTCOME DATA.

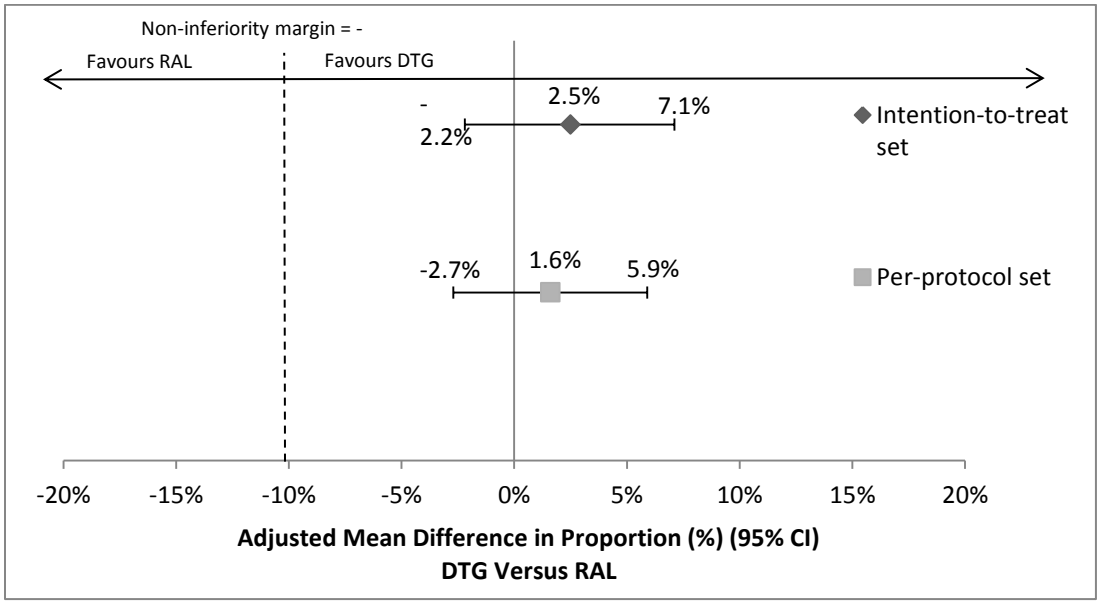
3.6.1 Studies in Art-Naive Patients

a) Percentage of Patients With Plasma HIV RNA (Viral Load) of Less Than 50 Copies/mL

In the SPRING-2 study,[1,2] both treatment groups demonstrated sustained plasma HIV RNA suppression, with 88% of patients in the DTG group and 85% of patients in the RAL group achieving the primary end point of less than 50 copies/mL plasma HIV RNA at week 48 (see Table 13). The adjusted difference (95% CI) was 2.5 (–2.2, 7.1). In the PP analysis, 90% and 88% of DTG and RAL patients, respectively, achieved plasma HIV RNA of less than 50 copies/mL at week 48, with an adjusted difference (95% CI) of 1.6 (–2.7, 5.9). The lower end of the 95% CIs for the treatment difference in the ITT-E and PP analyses (–2.2% and –2.7, respectively) was greater than –10% but not above 0% (Figure 2); therefore, in accordance with the pre-specified criteria, DTG demonstrated non-inferiority without superiority to RAL at week 48.

In the ITT-E analysis at week 96 (Table 13), sustained plasma HIV RNA suppression of less than 50 copies/mL was observed in 81% of patients in the DTG group and 76% of patients in the RAL group. The lower end of the 95% CI for the treatment difference (–1.1%) was greater than –10%. In the PP analysis at the same time point, 83% and 80% of DTG and RAL patients, respectively, achieved plasma HIV RNA of less than 50 copies/mL, and the lower end of the 95% CI for the treatment difference was –2.1%. Thus, the non-inferiority of DTG to RAL was maintained through the entire double-blind phase of the study, but superiority was not concluded.

FIGURE 2: A NON-INFERIORITY PLOT FOR THE SPRING-2 STUDY, WEEK 48



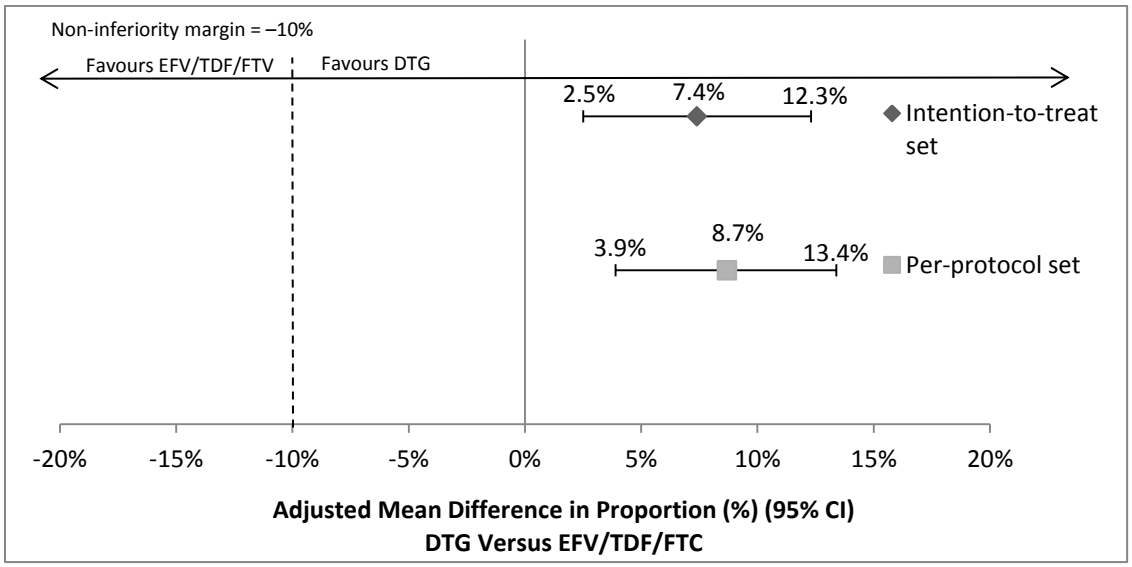
CI = confidence interval; DTG = dolutegravir; RAL = raltegravir.

DTG plus ABC/3TC demonstrated non-inferiority to EFV/TDF/FTC in the SINGLE study with respect to the proportion of patients with plasma HIV RNA of less than 50 copies/mL at week 48 using both the ITT-E and PP analyses (ITT-E: 88% versus 81%; PP: 90% versus 81%, respectively). The adjusted difference (95% CI) in the ITT-E analysis was 7.4 (2.5, 12.3), and 8.7% (3.9%, 13.4%) in the PP analysis. Therefore, the lower limits of the 95% CIs for the treatment differences for both analyses were above 0% and thus

met the criteria for non-inferiority and superiority favouring DTG plus ABC/3TC versus EFV/TDF/FTC at week 48 (Table 13 and Figure 3).

At week 96 of SINGLE (Table 13), HIV RNA suppression of less than 50 copies/mL was observed in 77% of patients in the DTG plus ABC/3TC group, compared with 70% in the EFV/TDF/FTC group, with adjusted treatment difference in favour of the DTG group of 7.3% (95% CI, 1.4 to 13.3). At the same time point, the PP analysis showed 80% of DTG plus ABC/3TC patients and 72% of EFV/TDF/FTC patients achieved the primary end point of less than 50 copies/mL of plasma HIV RNA (Table 13). Both non-inferiority and superiority (test for superiority, *P* = 0.003) of DTG plus ABC/3TC versus EFV/TDF/FTC was also found at 96 weeks in the SINGLE study.[3,4]

FIGURE 3: A NON-INFERIORITY PLOT FOR THE SINGLE STUDY, WEEK 48.



CI = confidence interval; DTG = dolutegravir; EFV = efavirenz; FTC = emtricitabine; TDF = tenofovir.

b) Percentage of Patients with Plasma HIV RNA (Viral Load) ≥ 50 Copies/mL

In SPRING-2,[1,2] there was a low rate of virologic failure in both treatment groups at week 48 and week 96 with (Table 13). Five per cent (5%) of patients in the DTG group had HIV RNA ≥ 50 copies/mL compared with 8% of patients in the RAL group at week 48. At week 96, the reported rate (5%) of patients with HIV RNA ≥ 50 copies/mL was maintained for the DTG group, while the proportion in the RAL group increased to 10%.

In the SINGLE study,[3,4] the proportions of patients with HIV RNA ≥ 50 copies/mL at week 48 were 5% and 6% respectively, for the DTG plus ABC/3TC and the EFV/TDF/FTC groups. Both groups had 7% of patients with HIV RNA ≥ 50 copies/mL at week 96 (Table 13).

c) Health-Related Quality of Life (EQ-5D)

The EQ-5D was one of the instruments used to assess patients' HRQoL in both the SPRING-2 and SINGLE studies.[1-4] In the SPRING-2 study,[1,2] changes from baseline in the EQ-5D index score at both week 48 and week 96 were similar for the two arms of the study (Table 13). The differences (95% CI) in the adjusted mean (standard error) between the DTG and RAL groups were not statistically significant at week 48, nor at week 96 ([redacted], respectively).

The EQ-5D index score in the SINGLE study also did not a show statistically significant difference between the DTG plus ABC/3TC and the EFV/TDF/FTC groups.[3,4] The differences (95% CI) in the adjusted mean (standard error) between the two treatment groups at week 48 and week 96 [redacted], respectively.

d) Morbidity

Morbidity was defined in terms of US Centers for Disease Control and Prevention (CDC) Categories B and C in both the SPRING-2 and SINGLE studies.[1-4] In the SPRING-2 study, the overall rates of HIV-related conditions were small at both week 48 and week 96, with the highest rate (3%) occurring in the DTG group at week 96 (see Table 13 for details). CDC Category B conditions accounted for less than 1% of patient morbidities in the two treatment groups at both week 48 and week 96. The overall category C HIV-related conditions were less than 1% for both groups at week 48, but the DTG group had a 2% rate at week 96 compared with less than 1% in the RAL group at the same time point. The proportions of patients who experienced specific clinical conditions in both CDC Categories B and C were less than 1% for each condition in both treatment groups at all the time points (Table 13).

The overall rates of HIV-related conditions at both weeks 48 and 96 were small in the SINGLE study[3,4] also (see Table 13 for details). The highest overall proportion (6%) of HIV-related morbidity occurred in the EFV/TDF/FTC group at week 96. With respect to CDC Category B conditions, the DTG plus ABC/3TC group had a rate of 2% at week 48 compared with 3% in the EFV/TDF/FTC group. At week 96, 5% category B conditions occurred in patients in the EFV/TDF/FTC group compared with 3% in the DTG plus ABC/3TC group. CDC Category C HIV conditions occurred at a very low rate in the SINGLE study[3,4] with the overall proportions not exceeding 1% in any of the treatment groups (Table 13).

e) Mortality

Mortality was low (less than 1%) in both the SPRING-2 and SINGLE studies[1-4] (see Table 13 for details). In both studies, none of the reported deaths were associated with the study drugs.

TABLE 13: KEY EFFICACY OUTCOMES — ART-NAIVE PATIENTS

Outcome	SPRING-2[1,2]				SINGLE[3,4]			
	Week 48		Week 96		Week 48		Week 96	
	DTG 50 mg q.d. N = 411	RAL 400 mg b.i.d. N = 411	DTG 50 mg q.d. N = 411	RAL 400 mg b.i.d. N = 411	DTG 50 mg q.d. N = 414	EFV/TDF/ FTC N = 419	DTG 50 mg q.d. N = 414	EFV/TDF/ FTC N = 419
Plasma HIV RNA								
ITT-E < 50 copies/mL n (%)	361 (88)	351 (85)	332 (81)	314 (76)	364 (88)	338 (81)	319 (77)	293 (70)
Diff (95% CI)	2.4 (–2.2, 7.1)		4.4 (–1.2, 10.0)		7.3 (2.3, 12.2)		7.1 (1.2, 13.1)	
Adjusted diff.[a] (95% CI)	2.5 (–2.2, 7.1)		4.5 (–1.1, 10.0)		7.4 (2.5, 12.3)		7.3 (1.4, 13.3)	
PP < 50 copies/mL n (%)	348/387 (90)	342/387 (88)	328/393 (83)	311/387 (80)	362/403 (90)	335/412 (81)	316/396 (80)	291/402 (72)
Diff. (95% CI)	1.6 (–2.8, 5.9)		3.1 (–2.3, 8.5)		8.5 (3.7, 13.3)		7.4 (1.5, 13.3)	
Adjusted diff.[a] (95% CI)	1.6 (–2.7, 5.9)		3.2 (–2.1, 8.6)		8.7 (3.9, 13.4)		7.6 (1.7, 13.5)	
P value for test of superiority	NR		NR		0.003		0.016	
Plasma HIV RNA ≥ 50 Copies/mL HIV RNA From Week 24 Onwards,[b] n (%)	20 (5)	31 (8)	22 (5)	43 (10)	21 (5)	26 (6)	31 (7)	33 (7)
Health-Related Quality of Life								
Change from baseline in EQ-5D								
Baseline, mean ± SD	[redacted]							
Change from baseline, mean ± SD	[redacted]							
Adjusted mean (SE)	[redacted]							
Difference (95% CI)	[redacted]							
P value	[redacted]							
Morbidity								
Any HIV condition,[c, d] n (%)	7 (2)	7 (2)	12 (3)	8 (2)	12 (3)	16 (4)	19 (5)	25 (6)
Category B (any), n (%)	2 (< 1)	3 (< 1)	3 (< 1)	3 (< 1)	7 (2)	11 (3)	14 (3)	19 (5)
Peripheral neuropathy	NR	NR	NR	NR	3 (< 1)	2 (< 1)	3 (< 1)	5 (1)
Herpes zoster 2	(< 1) 1	(< 1)	3 (< 1)	1 (< 1)	1 (< 1)	2 (< 1)	1 (< 1)	2 (< 1)
Candidiasis, oropharyngeal	0	1 (< 1)	0	1 (< 1)	1 (< 1)	2 (< 1)	1 (< 1)	2 (< 1)
PID	0	1 (< 1)	0	1 (< 1)	NR	NR	NR	NR
Category C (any), n (%)	4 (< 1)	3 (< 1)	8 (2)	4 (< 1)	5 (1)	6 (1)	5 (1)	7 (1)
Herpes simplex	2 (< 1)	1 (< 1)	4 (< 1)	2 (< 1)	0	1 (< 1)	0	1 (< 1)
Kaposi's sarcoma	1 (< 1)	1 (< 1)	2 (< 1)	1 (< 1)	1 (< 1)	1 (< 1)	1 (< 1)	2 (< 1)

Outcome	SPRING-2[1,2]				SINGLE[3,4]			
	Week 48		Week 96		Week 48		Week 96	
	DTG 50 mg q.d. N = 411	RAL 400 mg b.i.d. N = 411	DTG 50 mg q.d. N = 411	RAL 400 mg b.i.d. N = 411	DTG 50 mg q.d. N = 414	EFV/TDF/ FTC N = 419	DTG 50 mg q.d. N = 414	EFV/TDF/ FTC N = 419
Cytomegalovirus disease	0	1 (< 1)	0	1 (< 1)	NR	NR	NR	NR
Cytomegalovirus retinitis	1 (< 1)	0	1 (< 1)	0	NR	NR	NR	NR
Mycobacterium tuberculosis	1 (< 1)	0	1 (< 1)	0	1 (< 1)	0	1 (< 1)	0
Mortality, n (%)								
Any cause	1 (< 1)	1 (< 1)	1 (< 1)	1 (< 1)	0	2 (< 1)	0	2 (< 1)
Suicide	0	1 (< 1)	0	1 (< 1)	0	0	0	0
Homicide	1 (< 1)	0	1 (< 1)	0	0	0	0	0
Renal disorders	0	0	0	0	0	1 (< 1)	0	1 (< 1)
Respiratory disorders	0	0	0	0	0	1 (< 1)	0	1 (< 1)

CI = confidence interval; diff. = difference; DTG = dolutegravir; EFV = efavirenz; EQ-5D = EuroQol 5-dimensions questionnaire; FTC = emtricitabine; ITT-E = intention-to-treat exposed; NR = not reported; NRTI = nucleoside reverse transcriptase inhibitor; PID = pelvic inflammatory disease; PP = per protocol; q.d. = once daily; RAL = raltegravir; RNA = ribonucleic acid; SD = standard deviation; SE = standard error; TDF = tenofovir.

[a] Adjusted difference based on Cochran-Mantel-Haenszel stratified analysis adjusting for the baseline stratification factors: baseline HIV RNA and backbone dual NRTI.

[b] This represents patients who meet protocol-defined virologic failure (defined as two consecutive HIV RNA ≥ 50 copies/mL from week 24 onward). It includes: patients with HIV RNA of not less than 50 copies/mL; those who discontinued for lack of efficacy or other reason while their viral load was not under threshold; and those who changed antiretroviral therapy.

[c] Patients may have more than one HIV-associated condition. Each condition is counted only once per patient, regardless of recurrence.

[d] Two patients randomized to DTG experienced recurrent disease (herpes simplex virus [HSV] recurrence, Kaposi's sarcoma recurrence) and are not included in this table.

[e] At baseline, 12 patients in the DTG group and 19 patients in the RAL group had genotype for resistance, but they did not have NRTI resistance mutations.

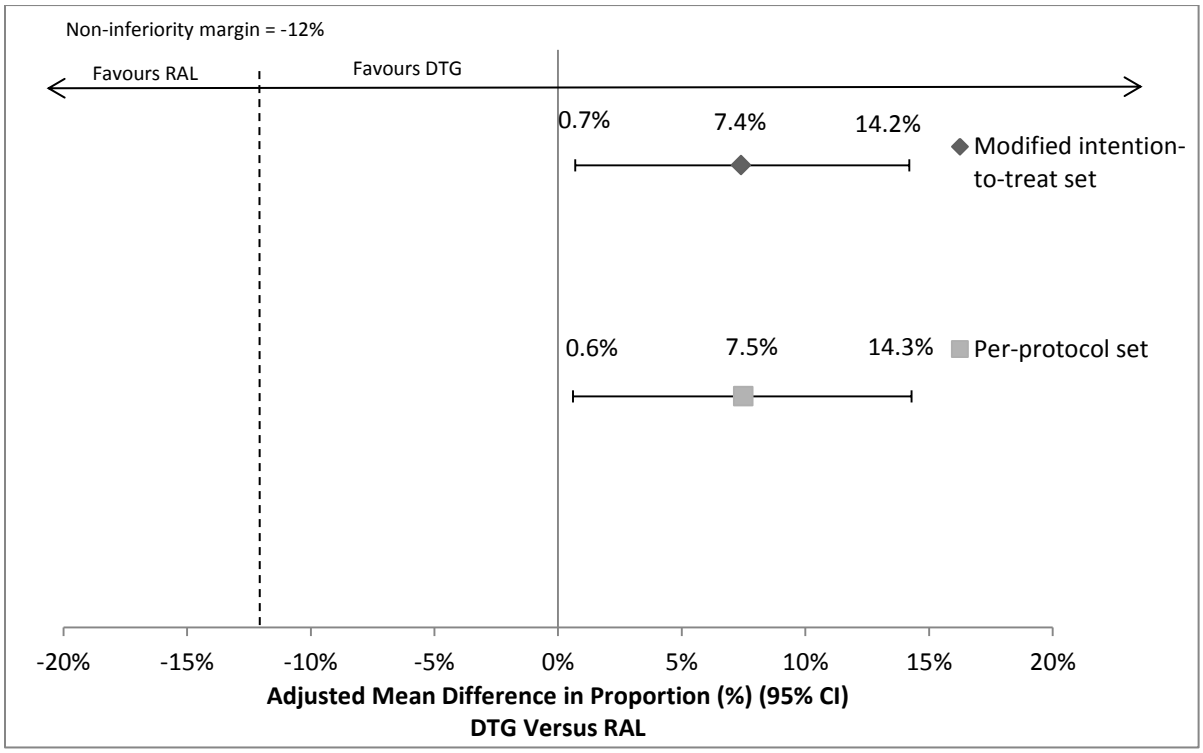
Source: SPRING-2 weeks 48 and 96 CSRs;[1,2] SINGLE weeks 48 and 96 CSRs.[3,4]

3.6.2 Studies in Art-Experienced Patients

a) Percentage of Patients With Plasma HIV RNA (Viral Load) of Less Than 50 Copies/mL

In the SAILING study,[13] 71% of patients in the DTG arm and 64% of patients in the RAL arm in the mITT-E population achieved the primary outcome of < 50 copies/mL plasma HIV RNA at week 48 (see Table 14). The adjusted difference was 7.4% (95% CI, 0.7% to 14.2%). Using the PP analysis, 73% and 66% of DTG and RAL patients, respectively, achieved plasma HIV RNA of less than 50 copies/mL at week 48, with an adjusted difference of 7.5% (95% CI, 0.6% to 14.3%). The lower limits of the mITT-E and PP analyses (0.7% and 0.6%, respectively) of the 95% CIs for the treatment differences were greater than –10% and above 0%. Therefore, non-inferiority and superiority (*P* = 0.03) of DTG to RAL at week 48 were demonstrated in accordance with the previously specified criteria (Figure 4).

FIGURE 4: A NON-INFERIORITY PLOT FOR THE SAILING STUDY, WEEK 48



CI confidence interval; DTG = dolutegravir; RAL = raltegravir

In the VIKING-3 study,[15] 69% of patients harbouring virus with RAL or EVG resistance (historic or current) achieved the primary outcome of plasma HIV RNA of less than 50 copies/mL at week 24 (Table 14). At week 48, 63% of patients achieving plasma HIV RNA < 50 copies/mL (see Table 14).

b) Percentage of Patients With Plasma HIV RNA (Viral Load) ≥ 50 Copies/mL

The DTG arm of the SAILING study[13] had a lower proportion (20%) of patients who did not achieve suppression of HIV RNA < 50 copies/mL, compared with the RAL treatment group (28%) at week 48 (Table 14).

Fifty-eight patients (32%) in the VIKING-3 study[15] did not achieve virological suppression < 50copies/mL at week 48. As in the studies involving ART-naive patients, non-responders in the studies in ART-experienced patients include patients with HIV RNA not < 50 copies/mL, those who discontinued for lack of efficacy or other reason while their viral load was not below threshold, and those who changed antiretroviral therapy.

c) Health-Related Quality of Life (EQ-5D)

In the SAILING study,[13] improvements from baseline in HRQL were marginal for both the DTG and RAL treatment groups as determined by the EQ-5D index score through week 48 (Table 14). The adjusted mean changes from baseline in utility scores for DTG and RAL were [redacted], respectively, with an adjusted difference between the treatment groups of [redacted]. On the VAS of the EQ-5D, the adjusted mean improvements from baseline were [redacted] for the DTG and RAL treatment groups, respectively, with an adjusted difference between the two groups of [redacted]. HRQoL outcomes were not reported in the VIKING study.[15]

d) Morbidity

HIV-associated conditions observed through 48 weeks in the SAILING study[13] were low and similar in both the DTG and RAL treatment groups. Both groups reported overall Category B conditions of 3%, while 3% of the DTG group reported Category C conditions, compared with 2% of the RAL group (Table 14). There was no individual clinical condition in any category that affected more than 1% of patients. HIV-associated conditions observed through 48 weeks in the VIKING-3 study[15] were also low. The most commonly reported CDC Category B clinical conditions in the VIKING-3 study were candidiasis and oropharyngeal constitutional symptoms, which accounted for 4% each. Among the Category C conditions, the most commonly reported clinical condition was herpes simplex, which affected 2% of patients[15] (Table 14).

e) Mortality

There were no deaths reported among patients in the DTG group of the SAILING study[13] (Table 14). Though three patients died in the RAL group through week 48, all the deaths were considered by the investigator to be unrelated to study drug. There were two deaths in the VIKING-3 study through week 48[15] (Table 14). The cause of death was pneumonia in one patient and progressive multifocal leukoencephalopathy in the other.

TABLE 14: KEY EFFICACY OUTCOMES — ART-EXPERIENCED PATIENTS

Outcome	SAILING[13]		VIKING-3[15]
	Week 48		Week 48
	DTG 50 mg + OBT N = 354	RAL 400 mg+ OBT N = 361	DTG 50 mg + OBT N = 183
Plasma HIV RNA			
mITT-E/ITT < 50 copies/mL, n (%)	251 (71)	230 (64)	116 (63)
RD (95% CI)	7.2 (0.3, 14.0)		NA
Adjusted RD[a] (95% CI)	7.4 (0.7, 14.2)		
P value[b]	0.030		
VL < 50 Copies/mL at Week 48 (PP Population) (MSDF Analysis)			
n/N (%)	238/325 (73)	225/340 (66)	
RD (95% CI)	7.1 (0.1, 14.0)		NA
Adjusted RD[a] (95% CI)	7.5 (0.6, 14.3)		
P value	NR		
VL ≥ 50 copies/mL at Week 48 (MSDF Analysis)			
N (%)	35 (10)	48 (13)	58 (32)
EQ-5D Utility Score at Week 48			
Baseline mean (SD), N	[redacted]	[redacted]	NA
Adjusted mean change (SE)[c]	[redacted]	[redacted]	
Adjusted difference (95% CI)[c] *P* value	[redacted]		
EQ-5D VAS Score at Week 48			
Baseline mean (SD), N	[redacted]	[redacted]	NA
Adjusted mean change (SE)[d]	[redacted]	[redacted]	
Adjusted difference (95% CI)[d]	[redacted]		
P value	[redacted]		
Morbidity (HIV-Associated Conditions) N (%)[c]			
CDC Category B	11 (3)	11 (3)	

Outcome	SAILING[13]		VIKING-3[15]
	Week 48		Week 48
	DTG 50 mg + OBT N = 354	RAL 400 mg+ OBT N = 361	DTG 50 mg + OBT N = 183
Candidiasis, oropharyngeal	4 (1)	2 (< 1)	7 (4)
Constitutional symptoms > 1 month	4 (1)	2 (< 1)	7 (4)
Peripheral neuropathy	1 (< 1)	4 (1)	3 (2)
Herpes zoster	1 (< 1)	3 (< 1)	3 (2)
Pelvic inflammatory disease	1 (< 1)	0	0
CDC Category C	10 (3)	6 (2)	
Mycobacterium tuberculosis, any site	3 (< 1)	3 (< 1)	
Herpes simplex	4 (1)	0	4 (2)
Cervical cancer, invasive	0	1 (< 1)	0
Kaposi's sarcoma	1 (< 1)	0	0
Lymphoma, immunoblastic	0	1 (< 1)	0
Pneumocystis carinii pneumonia	1 (< 1)	0	0
Pneumonia, recurrent	1 (< 1)	0	2 (1)
Progressive multifocal leukoencephalopathy	0	0 1 (< 1)	1 (< 1)
Toxoplasmosis of brain	1 (< 1)	0	1 (< 1)
Candidiasis, esophageal	0	0	2 (1)
Cryptosporidiosis, chronic intestinal	0	0	1 (< 1)
Cytomegalovirus disease	0	0	1 (< 1)
Encephalopathy, HIV-related	0	0	1 (< 1)
Mycobacterium avium complex or kansasii	0	0	1 (< 1)
Mortality[d]			
N (%)	0	3 (< 1)	2 (1)
Acute hepatic failure	0	1 (< 1)	0
Adenocarcinoma	0	1 (< 1)	0
Cervix carcinoma	0	1 (< 1)	0
Renal failure acute	0	1 (< 1)	0
Pneumonia	0	0	1 (< 1)
Progressive multifocal leukoencephalopathy	0	0	1 (< 1)

ART = antiretroviral therapy; CDC = Centers for Disease Control and Prevention; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EQ-5D = EuroQol 5-dimensions questionnaire; ITT = intention-to-treat population; LOCF = last observation carried forward; mITT-E = modified intention-to-treat exposed; MSDF = missing, switch, or discontinuation equals failure analysis; OBT = optimized background therapy; PI = protease inhibitor; RAL = raltegravir; RD = risk difference; RNA = ribonucleic acid; SD = standard deviation; VAS = visual analogue scale; VL = viral load.

Note: m-ITT was the primary population analyzed for SAILING, while ITT was the primary population analyzed for VIKING-3.

[a] Adjusted difference based on Cochran-Mantel-Haenszel stratified analysis adjusting for baseline HIV RNA (≤ 50 000 copies/mL versus > 50 000 copies/mL), darunavir plus ritonavir use without primary protease inhibitor mutations (yes vs. no), and baseline phenotypic susceptibility score (2 vs. < 2) to background regimen.

[b] *P* value for test of superiority.

[c] Using LOCF and based on ANCOVA and adjusted for: gender, race, age, baseline score, baseline HIV RNA, baseline Phenotypic Susceptibility Score (PSS) (< 2 vs. 2) to background regimen, and DRV/r use in background ART without primary PI mutations at baseline.

[d] Patient may have had more than one HIV-associated condition. Each condition was counted only once per patient, regardless of recurrence.

Source: SAILING 48-week clinical study report;[13] VIKING-3 48-week clinical study report.[15]

3.6.3 Subgroup Analysis of Primary Outcome

a) Studies in ART-Naive Patients

Of the subgroups pre-specified in the review protocol for treatment-naive patients (Table 3), only those based on the baseline viral load (≤ or > 100,000 copies/mL) could be assessed from SPRING-2 and SINGLE. The age subgroups (12 to < 18 years, and ≥ 18 years) could not be assessed because all patients in the reviewed clinical trials were 18 years or older.

Consistency of the treatment difference in the SPRING-2 study was explored separately in baseline HIV RNA (≤ 100,000 and > 100,000 copies/mL) in pre-specified analyses. At week 48, similar proportions (DTG: 90%; RAL: 89%) of patients with baseline HIV RNA ≤ 100,000 copies/mL achieved viral suppression of less than 50 copies/mL, with a difference in proportion between the DTG and RAL treatment groups of 0.4 (95% CI, –4.5 to 5.3) (Table 17). Among patients with a baseline viral load greater than 100,000 copies/mL, 82% in the DTG group and 75% in the RAL group achieved HIV RNA suppression of less than 50 copies/mL at week 48, with a treatment difference of 7.5 (95% CI, –3.1 to 18.0). The test for homogeneity of the treatment difference across high- and low-baseline HIV RNA subgroups was not statistically significant (*P* = 0.236), suggesting the outcome will be consistent regardless of the baseline HIV RNA.

At week 96 of the SPRING-2 study,[2] an almost identical rate (approximately 82%) of HIV RNA suppression to less than 50 copies/mL was reported among patients with baseline HIV RNA ≤ 100,000 copies/mL in both the DTG and RAL treatment groups. A treatment difference in proportions of 0.1% (95% CI, –6.1 to 6.3) was reported (Table 15). Among patients with a baseline viral load of more than 100,000 copies/mL, 78% and 63% in the DTG and RAL groups, respectively, achieved HIV RNA suppression to less than 50 copies/mL at week 96, with a treatment difference in proportions of 15.1% (95% CI, 3.5 to 26.8). The *P* value (0.026) for test of homogeneity indicated the treatment difference seen in the subgroup of patients with HIV RNA ≤ 100,000 copies/mL was different than that seen in the subgroup of patients with HIV RNA greater than 100,000 copies/mL at week 96.

In the SINGLE study,[3,4] response rates for DTG plus ABC/3TC were comparable to EFV/TDF/FTC across subgroups, including baseline HIV RNA (≤ 100,000 and > 100,000 copies/mL). Among patients with baseline HIV RNA ≤ 100,000 copies/mL, 90% in the DTG plus ABC/3TC group, and 83% of the DTG plus and EFV/TDF/FTC group, achieved HIV RNA below 50 copies/mL at week 48 (see Table 15 for details). Of patients with baseline HIV RNA greater than 100,000 copies/mL, 83% in the DTG plus ABC/3TC group, and 76% of the DTG plus EFV/TDF/FTC group achieved suppression to less than 50 copies/mL at week 48 (Table 15). The test for homogeneity of the treatment difference across high- and low-baseline HIV RNA subgroups was not statistically significant (*P* = 0.831), suggesting the outcome will be consistent regardless of the baseline HIV RNA.

At week 96 of the SINGLE study,[4] patients with baseline plasma HIV RNA ≤ 100,000 copies/mL 85% and 73% achieved HIV RNA of less than 50 copies/mL in the DTG plus ABC/3TC and EFV/TDF/FTC groups, respectively (see Table 15). The treatment difference was 12.1% (95% CI, 5.4 to 18.7). Seventy-one per cent (71%) of patients with baseline HIV RNA higher than 100,000 copies/mL in the DTG plus ABC/3TC group achieved HIV RNA suppression to less than 50 copies/mL, compared with 72% in the EFV/TDF/FTC group (Table 15). The treatment difference was –0.9% (95% CI, –11.7 to 10.0) and the test for evidence against homogeneity of the treatment difference between baseline plasma HIV RNA levels was statistically significant (*P* = 0.048) at week 96.

TABLE 15: PROPORTION OF PATIENTS WITH PLASMA HIV RNA OF LESS THAN 50 COPIES/ML BY BASELINE HIV RNA SUBGROUPS (ITT-E) — ART-NAIVE PATIENTS

SPRING-2[1,2]						
	Week 48			Week 96		
Baseline Plasma HIV RNA	DTG 50 mg q.d. N = 411	RAL 400 mg b.i.d. N = 411	Difference in Proportion (95% CI)	DTG 50 mg q.d. N = 411	RAL 400 mg b.i.d. N = 411	Difference in Proportion (95% CI)
≤ 100,000, n/N (%)	267/297 (90)	264/295 (89)	0.4 (–4.5 to 5.3)	243/ 297 (82)	241/ 295 (82)	0.1 (–6.1 to 6.3)
> 100,000, n/N (%)	94/114 (82)	87/116 (75)	7.5 (–3.1 to 18.0)	89/114 (78)	73/116 (63)	15.1 (3.5 to 26.8)
P value for homogeneity			0.236			0.026
SINGLE[3,4]						
	Week 48			Week 96		
Baseline Plasma HIV RNA	DTG 50 mg q.d. N = 414	EFV/TDF/FTC N = 419	Difference in Proportion (95% CI)	DTG 50 mg q.d. N = 414	EFV/TDF/FTC N = 419	Difference in Proportion (95% CI)
≤ 100,000, n/N (%)	253/ 280 (90)	238/288 (83)	7.7 (2.1 to 13.3)	237/280 (85)	209/288 (73)	12.1 (5.4 to 18.7)
> 100,000, n/N (%)	111/134 (83)	100/131 (76)	6.5 (–3.2 to 16.2)	95/134 (71)	94/131 (72)	–0.9 (–11.7 to 10.0
P value for homogeneity			0.831			0.048

b.i.d. = twice daily; CI = confidence interval; EFV = efavirenz; FTC = emtricitabine; DTG = dolutegravir; q.d. = once daily; RAL = raltegravir; RNA = Ribonucleic acid; TDF = tenofovir.
Source: SPRING-2 48-week and 96-week CSRs[1,2]; SINGLE 48-week and 96-week CSRs.[3,4]

b) Studies in ART-Experienced Patients

The subgroups pre-specified in the review protocol for treatment-experienced patients are summarized in Table 3. The multi-viral load cut-offs presented in the CSR for SAILING were adapted to coincide with the review protocol subgroups and corresponding risk differences (95% CIs) were calculated by CDR; no tests for interaction were performed on these subgroup analyses.

At week 48, a greater proportion (74%) of patients in the DTG group with baseline plasma HIV RNA ≤ 100,000 copies/mL achieved viral suppression to < 50 copies/mL compared with RAL (69%). The between-group treatment difference (DTG-RAL) was 5.1% (95% CI, –2.3 to 12.5) (Table 18). Among patients with baseline viral load > 100,000 copies/mL, 58% and 44% in the DTG and RAL groups, respectively, achieved HIV RNA suppression < 50 copies/mL at week 48, with a treatment difference of 6.3% (95% CI, –0.7 to 13.2). A similar trend was observed in patients with baseline plasma HIV RNA levels ≤ or > 500,000 copies/mL with non-statistically significant numerically larger proportions of patients achieving viral suppression to < 50 copies/mL by week 48 in favour of DTG.

The VIKING-3 study showed a similar response trend to the SAILING study based on base line HIV RNA; with progressively fewer proportions of patients achieving viral suppression to < 50 copies/mL as the baseline viral load increased from ≤ 100,000 copies/mL to > 500,000 copies/mL (Table 18).

In terms of baseline ART drug resistance, more patients in the DTG group who had either 2-drug or ≥ 3-drug resistance at baseline achieved HIV RNA < 50 copies/mL at week 48 compared with similar patients in the RAL (see Table 16 for details). The risk difference (5.8% [95% CI, –3.7 to 15.2]) was numerically

smaller in patients with 2-drug resistance compared with those who had 3-drug resistance at baseline (8.4% [95% CI:–1.5 to 18.3]). See Table 16.

TABLE 16: PROPORTION OF PATIENTS WITH PLASMA HIV RNA OF < 50 COPIES/ML BY BASELINE HIV RNA AND DRUG RESISTANCE MUTATION SUBGROUPS — ART-EXPERIENCED PATIENTS

Subgroups	SAILING		VIKING-3
	DTG 50 mg + OBT N = 354	RAL 400 mg+ OBT N = 361	DTG 50 mg + OBT N = 183
Plasma HIV RNA < 50 Copies/mL at Week 48			
Plasma HIV RNA copies/mL at baseline, n (%)			
≤ 100,000	[redacted][a]	[redacted][a]	[redacted]
RD (95% CI)	[redacted][a]		NA
> 100,000	[redacted][a]	[redacted][a]	[redacted]
RD (95% CI)	[redacted][a]		NA
≤ 500,000	[redacted][a]	[redacted][a]	[redacted][a]
RD (95% CI)	[redacted][a]		NA
> 500,000	[redacted]	[redacted]	[redacted]
RD (95% CI)	[redacted]		NA
Evidence of genotypic ART resistance at baseline			
Primary INSTI mutation not detected	NR	38/60 (63)	
Primary INSTI mutation detected	NR		73/123 (63)
Resistance to two drug classes at baseline	125/189 (66)	115/186 (62)	NR
RD (95% CI)	5.8 (–3.7 to 15.2)		NR
Resistance to ≥ 3 drug classes at baseline	126/165 (76)	115/175 (66)	NR
RD (95% CI)	8.4 (–1.5 to 18.3)		NR

CI = confidence interval; DTG = dolutegravir; INSTI = integrase strand transfer inhibitor; NR = not reported; OBT = optimized background therapy; RAL = raltegravir; RD = risk difference; RNA = ribonucleic acid; VL = viral load.
Note difference: Proportion on DTG vs. proportion on RAL (unadjusted).
[a] Calculated by CADTH review team from data available in clinical study report for the SAILING study.
Source: SAILING 48-week clinical study report;[13] VIKING-3 48-week clinical study report.[15]

3.6.4 Other Efficacy Outcomes

a) Studies in ART-Naive Patients

Change in CD4+ Count

In the SPRING-2 study,[1,2] changes from baseline in the CD4+ cell counts were similar across the treatment groups. The mean (SD) increase from baseline in CD4+ cells in the DTG group was 292.2 (195.7) cells/mm^3 compared with 286.2 (192.5) cells/mm^3 in the RAL group at week 96 (Table 19). The between-group difference was not reported. In the SINGLE study, the DTG plus ABC/3TC treatment group demonstrated a greater increase from baseline in CD4+ cell counts compared with that seen in the EFV/TDF/FTC treatment group at week 48 and week 96 (Table 19). The adjusted mean differences (95% CI) were statistically significant in favour of the DTG plus ABC/FTC group at both week 48 and week 96 (58.90 [95% CI, 33.41 to 84.40] cells/mm^3; $P < 0.001$); and 43.95 [95% CI to 14.34, 73.55] cells/mm^3; $P = 0.004$, respectively).

Development of Resistance

Treatment-emergent INSTI resistance was very low (less than 1%) in the two treatment groups in the SPRING-2 study (Table 19).[1,2] Four patients in the RAL group and none in the DTG group experienced resistance to the backbone nucleoside reverse transcriptase inhibitor (NRTI) at week 48 through week 96. In the SINGLE study,[3,4] there was no report of treatment-emergent resistance to INSTI or NRTI backbone in the DTG group. Through week 96, treatment-emergent resistance mutation to NRTI occurred in one patient, and six patients developed resistance to NNRTI. All the patients who developed resistance were in the EFV/TDF/FTC treatment group (Table 19).

b) Studies in ART-Experienced Patients

Change in CD4+ Count

Both the DTG and RAL groups of the SAILING study[13] demonstrated increased mean and median CD4+ cell counts from baseline to week 48. The mean (SD) increase at 48 weeks in CD4+ cell count from baseline was 162.4 (151.4) cells/mm^3 in the DTG group, compared with 153.2 (143.9) cells/mm^3 in the RAL group (see Table 20 for details). In the VIKING-3 study,[15] the median (IQR) increase from baseline in CD4+ cell count was 110 (40, 190) cells/mm^3 at week 48 (Table 20).

Development of Resistance

Evidence of treatment-emergent genotypic or phenotypic INSTI resistance was observed in 1% and 5% of patients receiving DTG and RAL, respectively, at the time of protocol-defined virologic failure by week 48 in the SAILING study[13] (Table 20). The treatment difference was statistically significant in favour of DTG (–3.7%; 95% CI, –6.1 to –1.2; *P* = 0.003). Nineteen (19) patients in the VIKING-3 study[15] developed resistance to ART through week 48 (Table 20).

In the SAILING study,[13] DTG demonstrated a higher barrier to resistance than RAL, as shown by the adjusted risk difference of –3.6 (95% CI, –6.0 to –1.1; *P* = 0.003) in favour of DTG in the proportion of patients harbouring treatment-emergent resistant virus by week 48.

3.7 Harms

Only those harms identified in the review protocol are reported here (See section 2).

3.7.1 Studies in ART-Naive Patients

TABLE 17: HARMS IN ART-NAIVE PATIENTS

	SPRING-2[1,2]				SINGLE[3,4]			
	Week 48		Week 96		Week 48		Week 96	
	DTG 50 mg q.d. N = 411	RAL 400 mg b.i.d. N = 411	DTG 50 mg q.d. N = 411	RAL 400 mg b.i.d. N = 411	DTG 50 mg q.d. N = 414	EFV/TDF/ FTC N = 419	DTG 50 mg q.d. N = 414	EFV/TDF/ FTC N = 419
Adverse Events, n (%)								
Any event	339 (82)	340 (83)	349 (85)	349 (85)	369 (89)	387 (92)	376 (91)	394 (94)
Most common AEs[a]								
Infections and infestations	213 (52)	222 (54)	245 (60)	250 (61)	232 (56)	211 (50)	257 (62)	240 (57)
Nasopharyngitis	46 (11)	48 (12)	55 (13)	58 (14)	62 (15)	60 (14)	74 (18)	66 (16)
URTI	26 (6)	26 (6)	34 (8)	30 (7)	36 (9)	43 (10)	50 (12)	53 (13)
GI disorders	169 (41)	160 (39)	182 (44)	169 (41)	180 (43)	184 (44)	199 (48)	199 (47)
Diarrhea	47 (11)	47 (11)	57 (14)	55 (13)	72 (17)	75 (18)	84 (20)	83 (20)
Nausea	59 (14)	53 (13)	60 (15)	56 (14)	59 (14)	57 (14)	65 (16)	61 (15)
Vomiting	16 (4)	16 (4)	16 (4)	19 (5)	20 (5)	19 (5)	26 (6)	24 (6)
Nervous system disorders	81 (20)	90 (22)	93 (23)	103 (25)	111 (27)	212 (51)	121 (29)	225 (54)
Dizziness	23 (6)	23 (6)	24 (6)	25 (6)	37 (9)	148 (35)	40 (10)	153 (37)
Headache	51 (12)	48 (12)	56 (14)	55 (13)	55 (13)	56 (13)	63 (15)	63 (15)
Psychiatric disorders	81 (20)	73 (18)	94 (23)	86 (21)	125 (30)	168 (40)	144 (35)	178 (42)
Insomnia	21 (5)	17 (4)	25 (6)	19 (5)	64 (15)	43 (10)	69 (17)	46 (11)
Depression	21 (5)	14 (3)	26 (6)	19 (5)	23 (6)	26 (6)	31 (7)	34 (8)
Anxiety	14 (3)	20 (5)	17 (4)	22 (5)	14 (3)	27 (6)	26 (6)	30 (7)
Serious Adverse Events, n (%)								
Any SAE	29 (7)	31 (8)	41 (10)	48 (12)	37 (9)	35 (8)	44 (11)	51 (12)
Most common SAEs								
Infections and infestations	8 (2)	12 (3)	15 (4)	18 (4)	13 (3)	12 (3)	17 (4)	18 (4)
Immune system disorders	4 (< 1)	1 (< 1)	4 (< 1)	1 (< 1)	1 (< 1)	2 (< 1)	1 (< 1)	2 (< 1)
Psychiatric disorders	2 (< 1%)	4 (< 1%)	2 (< 1)	6 (1)	3 (< 1)	8 (2)	3 (< 1)	12 (3)
Nervous system disorders	0	4 (< 1)	2 (< 1)	4 (< 1)	3 (< 1)	3 (< 1)	3 (< 1)	8 (2)
Withdrawal Due to AEs, N (%)								
Any WDAE	10 (2)	7 (2)	10 (2)	10 (2)	10 (2)	42 (10)	14 (3)	52 (12)
Most common reasons								

	SPRING-2[1,2]				SINGLE[3,4]			
	Week 48		Week 96		Week 48		Week 96	
	DTG 50 mg q.d. N = 411	RAL 400 mg b.i.d. N = 411	DTG 50 mg q.d. N = 411	RAL 400 mg b.i.d. N = 411	DTG 50 mg q.d. N = 414	EFV/TDF/ FTC N = 419	DTG 50 mg q.d. N = 414	EFV/TDF/ FTC N = 419
Infections and infestations	2 (< 1)	2 (< 1)	2 (< 1)	3 (< 1)	1 (< 1)	2 (< 1)	2 (< 1)	2 (< 1)
Psychiatric disorder	1 (< 1)	1 (< 1)	1 (< 1)	2 (< 1)	2 (< 1)	15 (4)	4 (< 1)	23 (5)
Nervous system disorder	1 (< 1)	1 (< 1)	1 (< 1)	1 (< 1)	0	13 (3)	1 (< 1)	17 (4)
Skin and subcutaneous-tissue disorder	1 (< 1)	1 (< 1)	1 (< 1)	1 (< 1)	2 (< 1)	8 (2)	2 (< 1)	9 (2)
GI disorder	1 (< 1)	2 (< 1)	1 (< 1)	2 (< 1)	0	8 (2)	2 (< 1)	3 (< 1)
General disorder or administration-site condition	1 (< 1)	0	1 (< 1)	0	0	7 (2)	0	10 (2)
Notable Harms, n (%)								
Metabolic disorders	18 (4)	21 (5)	21 (5)	25 (6)	22 (5)	37 (9)	40 (10)	42 (10)
% Change From Baseline in Lipid Parameters								
HDL cholesterol (mmol/L) mean ± SD	8.87 ± 24.80	8.88 ± 25.17	7.57 ± 26.16	8.11 ± 24.81	15.01 ± 22.35	22.84 ± 34.99	15.42 ± 24.52	22.85 ± 37.17
Median (IQR)	5.79 (–5.56, 19.58)	4.32 (–8.42, 21.60)	2.94 (–8.81, 20.00)	3.20 (–7.14, 21.43)	13.21 (0.00, 25.09)	15.74 (2.94, 36.84	12.50 (0.00, 29.41)	18.182 (2.33, 37.96)
LDL cholesterol (mmol/L) mean ± SD	6.18 ± 31.44	7.41 ± 30.94	8.48 ± 28.56	10.07 ± 29.71	11.06 ± 27.82	17.714 ± 37.37	19.25 ± 31.72	23.96 ± 39.26
Median (IQR)	1.85 (– 10.74, 13.33)	2.86 (–10.59, 16.42)	3.40 (–9.21, 19.62)	5.63 (–8.33, 22.82)	7.90 (–5.14, 23.67)	11.33 (–2.72, 27.81)	14.27 (0.00, 31.41)	15.80 (1.08, 35.89)
Total cholesterol/HDL (ratio) mean ± SD	0.03 ± 21.94	0.82 ± 20.03	1.76 ± 20.54	3.13 ± 28.60	–0.65 ± 18.95	–1.70 ± 19.60	5.23 ± 29.55	2.43 ± 26.38
Median (IQR)	2.29 (– 13.31, 8.70)	–2.251 (–10.92, 10.44)	–0.25 (–9.95, 12.56)	–0.98 (–9.91, 12.78)	-2.81 (–12.47, 8.28)	–3.40 (–14.66, 9.10)	1.83 (–9.03, 13.61)	0.04 (–12.77, 15.97)
Triglycerides (mmol/L) mean ± SD	14.02 ± 56.91	20.01 ± 60.78)	12.87 ± 57.86)	14.10 ± 56.66	24.02 ± 58.02	21.81 ± 52.24	25.56 ± 61.96	19.12 ± 59.75
Median (IQR)	0.97 (– 21.33, 31.03)	6.72 (–17.42, 43.6)	1.16 (–24.17, 30.52)	3.08 (–20.76, 36.28)	13.71 (–11.57, 42.43)	13.39 (–13.86, 46.03)	11.91 (–13.51, 50.40)	8.57 (–15.82, 36.84)

	SPRING-2[1,2]				SINGLE[3,4]			
	Week 48		Week 96		Week 48		Week 96	
	DTG 50 mg q.d. N = 411	RAL 400 mg b.i.d. N = 411	DTG 50 mg q.d. N = 411	RAL 400 mg b.i.d. N = 411	DTG 50 mg q.d. N = 414	EFV/TDF/ FTC N = 419	DTG 50 mg q.d. N = 414	EFV/TDF/ FTC N = 419
Change in glucose (mmol/L) mean ± SD	0.21 ± 0.82	0.28 ± 1.14	0.19 ± 1.15	0.30 ± 1.54	0.21 ± 1.18	0.20 ± 1.13	0.13± 1.25	0.16 ± 1.66
Median (IQR)	0.20 (–0.20, 0.50)	0.20 (–0.20, 0.60)	0.10 (–0.20, 0.50)	0.20 (–0.20, 0.50)	0.20 (–0.20, 0.60)	0.30 (–0.10, 0.70)	0.20 (–0.30, 0.50)	0.30 (–0.10 0.60)
Cardiac disorders	5 (1)	6 (1)	5 (1)	9 (2)	9 (2)	6 (1)	11 (3)	8 (2)
CNS/cognitive effect (see most common AEs)								

AE = adverse event; b.i.d. = twice daily; CI = confidence interval; CNS = central nervous system; DTG = dolutegravir; EFV = efavirenz; TDF = tenofovir; FTC = emtricitabine; IQR=interquartile range; q.d. = once daily; RAL = raltegravir; RNA = ribonucleic acid; SD = standard deviation; SAE = serious adverse event; URTI = Upper respiratory tract infection.
[a] Frequency ≥ 5% incidence in either treatment group.
Source: SPRING-2 48-week and 96-week CSRs;[1,2] SINGLE 48-week and 96-week CSRs.[3,4]

a) Adverse Events

There was no appreciable difference in overall frequency of adverse events (AEs) between the DTG and RAL groups in the SPRING-2 study at week 48 (82% versus 83%, respectively) or at week 96 (85% in both groups) (Table 17). The most commonly reported AEs among patients receiving DTG and RAL were nausea, nasopharyngitis, diarrhea, and headache, with similar percentages reported for the two treatment groups.

In the SINGLE study,[3,4] the overall frequency of AEs was numerically higher in the EFT/TDF/FTC group (48 weeks: 92%; 96 weeks: 94%) versus the DTG plus ABC/3TC group (48 weeks: 89%; 96 weeks: 91%) (Table 17). The proportions of infections and infestation were slightly higher in the DTG plus ABC/3TC group than in the EFT/TDF/FTC group at both weeks 48 and 96; however, the most commonly reported AEs (nasopharyngitis and upper respiratory tract infections) occurred at similar rates across both treatment groups. Similar rates of gastrointestinal disorders were reported across the two treatment groups. Overall, a greater proportion of patients in the EFT/TDF/FTC group experienced nervous system disorders and psychiatric disorders than patients in the DTG plus ABC/3TC group at both weeks 48 and 96. At week 48, the overall proportion of patients in the EFT/TDF/FTC group who experienced nervous system disorders and psychiatric disorders was 51% and 40%, respectively, compared with 27% and 30%, respectively, of patients in DTG plus ABC/3TC group. At week 96, 54% and 42% of patients in the EFT/TDF/FTC group experienced nervous system disorders and psychiatric disorders, respectively, compared with 29% and 35% of patients in the DTG plus ABC/3TC group; however, some particular AEs related to nervous system and psychiatric disorders did not show a similar trend. While headache, depression, and anxiety were reported at similar rates between the two groups, dizziness and insomnia occurred more in the DTG plus ABC/3TC group than in the EFT/TDF/FTC group.

b) Serious Adverse Events

The proportion of patients with at least one serious adverse event (SAE) reported was similar across treatment groups in both the SPRING-2 and SINGLE studies (Table 17).[1-4] The most commonly reported

SAEs (by system organ class) included infections and infestations, immune systems disorders, psychiatric disorders, and nervous system disorders. Rates of individual SAEs were low, with none exceeding 4% in the SPRING-2 study.[1,2] The SINGLE study[3,4] also had low incidence of SAEs(mostly less than 1%), with psychiatric disorders at week 96 having the highest rate (3%).

c) Withdrawals Due to Adverse Events

In the SPRING-2 study,[1,2] WDAEs occurred at similar frequency (2%) across the DTG and the RAL groups at weeks 48 and 96 (Table 17). In the SINGLE study,[3,4] a higher proportion of patients in the EFV/TDF/FTC group withdrew from the study drug due to AEs, compared with the DTG plus ABC/3TC group for the same reason at both weeks 48 and 96 (10% versus 2%; and 12% versus 3%, respectively) (see Table 17).

d) Notable Harms

In the SPRING-2 study,[1,2] the median (IQR) percentage changes from baseline in high-density lipoprotein (HDL) and low-density lipoprotein (LDL) were similar across the DTG and RAL groups (Table 17). At week 48, the RAL group had a much higher median (IQR) percentage change from baseline triglycerides compared with the DTG group (6.72 [–17.42, 43.60] mmol/L versus 0.97 [–21.33, 31.03] mmol/L). The between-group difference in change in triglycerides was lessened by week 96, but still higher in the RAL group. Median (IQR) changes from baseline in plasma glucose were low and similar across both treatment groups. Proportions of patients who experienced cardiac disorders and central nervous system (CNS) or cognitive effects of interest were low and balanced between the DTG and RAL groups.

In the SINGLE study,[3,4] percentage change from baseline in lipid parameters was higher in the EFV/TDF/FTC group than the DTG plus ABC/3TC group, with the differences being larger at week 96 (Table 17). Median changes of plasma glucose and the proportion of patients with cardiac disorders were similar across both groups at both weeks 48 and 96. Trends of changes in CNS or cognitive effects of interest were mostly comparable across the treatment groups, with dizziness occurred at a higher rate among the EFV/TDF/FTC group than in the DTG plus ABC/3TC group (see Table 17).

3.7.2 Studies in ART-Experienced Patients

TABLE 18: HARMS IN ART-EXPERIENCED PATIENTS

	SAILING[13]		VIKING-3[15]
	DTG 50 mg + OBT N = 354	RAL 400 mg+ OBT N = 361	DTG 50 mg + OBT N = 183
Adverse Events, n (%)			
Any AE	280 (78)	286 (79)	166 (91)
Most common AEs[a]			
Diarrhea	71 (20)	64 (18)	39 (21)
Upper respiratory tract infection	38 (11)	29 (8)	18 (10)
Headache	33 (9)	31 (9)	21 (11)
Nausea	29 (8)	29 (8)	23 (13)
Cough	33 (9)	24 (7)	22 (12)
Serious Adverse Events, n (%)			
Any SAE	33 (9)	42 (12)	39 (21)
Most common SAEs[a]			

	SAILING[13]		VIKING-3[15]
	DTG 50 mg + OBT N = 354	RAL 400 mg+ OBT N = 361	DTG 50 mg + OBT N = 183
Infections and infestations	12 (3)	19 (5)	16 (9)
Hepatobiliary disorders	4 (1)	3 (< 1)	7 (4)
Nervous system disorders	1 (< 1)	3 (< 1)	5 (3)
Gastrointestinal disorders	5 (1)	5 (1)	6 (3)
Withdrawal Due to Adverse Events, n (%)			
WDAEs	7 (2)	13 (4)	8 (4)
Most common reasons			
Hepatobiliary disorders	2 (< 1)	3 (< 1)	1 (< 1)
Infections and infestations	1 (< 1)	4 (1)	1 (< 1)
Notable Harms, n(%)			
Dyslipidemia	1 (< 1)	1 (< 1)	1 (< 1)
Hyperglycemia	1 (< 1)	1 (< 1)	NR
Hyperlipidemia	1 (< 1)	1 (< 1)	3 (2)
Cardiac complications	8 (2)	13 (4)	8 (4)
Headache	33 (9)	31 (9)	21 (11)
Fatigue	15 (4)	24 (7)	16 (9)
Nausea	29 (8)	29 (8)	23 (13)
Insomnia	12 (3)	14 (4)	12 (7)
Dizziness	13 (4)	14 (4)	7 (4)
Depression	11 (3)	7 (2)	6 (3)
Anxiety	5 (1)	6 (2)	7 (4)

AE = adverse event; DTG = dolutegravir; OBT = optimized background therapy; RAL = raltegravir; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
[a] AEs occurring in ≥ 5% of patients.
Source: SAILING 48-week clinical study report,[13] VIKING-3 48-week clinical study report.[15]

e) Adverse Events

Reported rates of overall adverse events (AEs) at week 48 between the treatments groups in the SAILING study[13] were similar, with 78% in the DTG arm compared with 79% in the RAL arm (Table 18). Diarrhea, upper respiratory tract infections, headache, nausea, and cough were the most commonly reported clinical AEs, and they occurred at similar rates in the DTG and RAL groups. In the VIKING-3 study,[15] 91% of patients experienced AEs through week 48, with similar most commonly reported AEs as in the SAILING study.[13]

f) Serious Adverse Events

The proportion of patients with at least one SAE reported was similar across treatment groups in the SAILING study[13] (Table 18).The overall proportion of SAEs in the DTG group was 9% compared with 12% in the RAL group. The most commonly reported SAEs included infections and infestations, which occurred in 3% of patients in the DTG group compared with 5% in the RAL group. None of the other reported SAEs had a rate exceeding 1%. The VIKING study[15] recorded SAEs in 21% of patients at week 48, with infections and infestations being the most commonly (9%) reported class of SAE (Table 18).

g) Withdrawals Due to Adverse Events

In the SAILING study,[13] low and similar rates of premature withdrawal from study drug due to adverse were reported in both the DTG and the RAL groups at week 48 (seeTable 18). Two per cent (2%) of patients in the DTG group withdrew prematurely compared with 4% in the RAL group. In the VIKING-3 study,[15] 4% of patients withdrew from study drug due to AEs (see Table 18).

h) Notable Harms

Lipids and glucose related metabolic complications reported in the SAILING study[13] included dyslipidemia, hyperlipidemia, and hyperglycemia. The reported rates were very low and similar (less than 1% in all cases) across the DTG and RAL groups at week 48 (seeTable 18). With the exception of headache and nausea, which occurred in 9% and 8%, respectively, and with identical proportions in both treatment groups in each case, each of the AEs of interest under notable harms occurred in less than 5% of patients (Table 18).

4. DISCUSSION

4.1 Summary of Available Evidence

This review included evidence from four phase III, double-blind, RCTs. Two of the studies, SPRING-2 and SINGLE, enrolled ART-naive participants. A third study, SAILING, involved ART-experienced but INSTI-naive patients, while the fourth study, VIKING-3, was conducted in highly ART-experienced patients with current or historical evidence of INSTI-resistant virus. Suppression of plasma HIV RNA below the assay limit of detection (defined as less than 50 copies/mL) at week 48 was the primary efficacy outcome of the SPRING-2, SINGLE, and SAILING studies. For the VIKING-3 study, plasma HIV RNA of less than 50 copies/mL at week 24 was the primary outcome.

Apart from the VIKING-3 trial which was a single-arm study, the others were active control, non-inferiority studies. The SPRING-2 and SAILING studies were in-class comparisons, whereas DTG was compared with RAL (both belonging to the INSTI class), while the SINGLE study compared DTG to EFV, which belongs to the NNRTI class. There was no direct comparison of DTG with other drugs of the INSTI or the NNRTI classes, or to any drugs from other ART classes such as PIs, fusion, and entry inhibitors, or CCR5 drugs. However, DTG was directly compared with ritonavir-boosted darunavir (DRV/r) in the FLAMINGO study (summarized in Appendix 5: SUMMARY OF OTHER STUDIES and the manufacturer provided an indirect comparison (using network meta-analysis) of DTG to ritonavir-boosted PIs and drugs from NNRTIs and INSTI classes (see APPENDIX 6: SUMMARY OF COMPARATORS).

According to the patient input received for the review, only one respondent in a survey had experience with DTG (Appendix 1 for details). The patient reported undetectable viral levels two months after initiating treatment and had a positive experience with the drug despite nausea and insomnia, which were managed by modifying the patient's diet and time of day the medication was taken. Citing the efficacy, safety, and tolerability of DTG, its once-daily dosing regimen and the flexibility of individualized treatment owing to the possibility of using either Kivexa (ABC/3TC) or Truvada (TDF/FTC) as backbone.

The clinical expert involved in the review indicated the baseline demographic and clinical characteristics of all the studies reflected those of patients with similar disease conditions seen in clinical practice in Canada. The NRTI OBTs in the SPRING-2 study were investigator-selected and there was no detail given about the basis of the selection process. While this has the potential of introducing bias, sensitivity analysis showed the outcomes remained consistent regardless of the OBT in each treatment group. In

the SINGLE study, many more patients withdrew prematurely from the EFV/TDF/FTC group compared with the DTG plus ABC/3TC group, particularly because of AEs. This seems to be a major factor behind the difference in outcomes between the two treatment groups. Thus, a definite conclusion about relative efficacies of DTG versus EFV may not be made at this moment beyond the limits of the FDA-recommended snapshot algorithm for clinical trials in HIV studies.

4.2 Interpretation of Results

4.2.1 Efficacy

The percentage of patients with viral-load suppression less than 50 copies/mL at the end of trial was a primary key efficacy outcome in this review. Other key efficacy outcomes are listed in Table 3.

The primary (ITT-E) analysis of the percentage of patients achieving HIV RNA viral-load suppression to less than 50 copies/mL at 48 weeks using the FDA Snapshot analysis showed non-inferiority between DTG and RAL in SPRING-2 (difference: 2.4%; 95% CI, –2.2 to 7.1) and between DTG plus ABC/3TC and EFV/FTC/TDF in SINGLE (difference: 7.4%; 95% CI, 2.5 to 12.3), based on the previously specified margin of 10%. Moreover, DTG plus ABC/3TC demonstrated superiority versus EFV/TDF/FTC at week 48 (P = 0.003) and week 96 (P = 0.006). The superior efficacy of DTG may have been driven by the higher number of early treatment discontinuations due to AEs observed in the EFV/TDF/FTC group. Non-inferiority, and superiority in the case of SINGLE, was confirmed in both studies based using the PP analysis set. Moreover, the pre-specified subgroup analysis by baseline viral load (i.e., $\leq$ 100,000 or > 100,000 copies/mL) did not reveal any treatment by baseline viral load interactions in SPRING-2 (P = 0.236) or SINGLE (P = 0.831) at week 48, with both subgroups achieving rates of viral-load suppression consistent with those of the primary analysis.

Overall, the results of the NMA showed a statistically significant higher probability of virological suppression with DTG compared with all included NNRTIs (EFV, RPV, and PIs [ATV/r, DRV/r, and LPV/r]) at week 48. In addition, the NMA showed significantly higher CD4+ cell increases from baseline with DTG compared with NNRTI and PIs at the same time point.

Differences in NRTI backbone regimens (ABC/3TC for DTG and TDF/TFC for EFV) for the two SINGLE treatment groups complicates the direct comparison between DTG and EFV and inference of non-inferiority. However, the sponsors made an assumption that the antiviral efficacy of ABC/3TC is not superior to the antiviral efficacy of TDF/FTC, enabling a non-inferiority comparison of DTG to EFV in a regimen-to-regimen comparison. In a previous study, TDF/FTC was shown to be superior to ABC/3TC, which might bias the SINGLE study in favour of the EFV/TDF/FTC group over the DTG +ABC/3TC group.[7]

The snapshot analysis of virological response captures overall success rates, but does not shed light on the reasons for treatment failure.[21] According to the clinical expert involved in the review, failure with initial ART therapy due to virologic failure is clinically a much more serious concern than failure due to intolerable adverse effects. This is because uncontrolled viral replication imparts risk for development of resistance mutations, potentially limiting future treatment options. For this reason, virological failure rates are an important consideration in assessing comparative efficacy. Virologic failure occurred at a similar rate between groups in SPRING-2 and SINGLE at week 48: 5% of DTG patients compared with 8% of RAL patients in SPRING-2, 5% of DTG plus ABC/3TC patients; and 6% of EFV/FTC/TDF patients in SINGLE. Similar results were also noted at week 96 in both studies. While the included trials were not powered to detect differences on virologic failure, the similarity of the point estimates provide a degree of reassurance that DTG is not associated with a higher risk of virologic failure.

Responses in terms of HRQoL at weeks 48 and 96 were comparable across the DTG and comparator groups in SPRING-2 and SINGLE. Incidence of HIV-associated conditions was low and similar across treatment groups in both studies at weeks 48 and 96. Likewise, very few deaths occurred in either SPRING-2 or SINGLE, with a rate of less than 1% per treatment group and study.

In the SAILING study,[13] the primary objective was to demonstrate antiviral activity of DTG 50 mg once daily compared with RAL 400 mg twice daily at week 48 in treatment-experienced, INSTI-naive, HIV-infected patients. DTG 50 mg once daily was found to be noninferior and superior to RAL 400 mg twice daily at week 48, as shown by the statistically significantly higher proportion of patients in the DTG group who achieved HIV RNA of less than 50 copies/mL, and the pre-specified criteria for superiority. The response rate (64%) of RAL 400 mg twice daily in the SAILING study is similar to the overall response rate (63%) in the BENCHMRK-1 and -2 studies,[14] and both are numerically less than the response rate (71%) achieved by DTG 50 mg once daily in the SAILING study. However, a cross-study comparison between SAILING and BENCHMRK is complicated due to the difference in the baseline characteristics of participants enrolled in the studies.

Subgroup analysis in the SPRING-2 and SINGLE studies showed consistent outcomes irrespective of baseline HIV RNA. In the SPRING-2 study, subgroup analysis showed the selection of either ABC/3TC or TDF/FTC as backbone therapy did not change the outcome.

The proportion of patients who experienced virologic non-response in the DTG group in SAILING was similar to that in the RAL group, and similar small improvements from baseline in EQ-5D scores were observed in both treatment groups. As in the treatment-naive studies, the incidence of HIV- and AIDS-related morbidity was low and balanced between DTG and RAL treatment groups. No deaths occurred in the DTG group, while three deaths occurred in the RAL group.

The primary objectives of the VIKING-3 study was to characterize the antiviral activity of DTG at day 8 and week 24 in HIV patients who were harbouring INSTI-resistant virus that was also resistant to drugs from at least two other ART classes. However, week-48 outcomes were also reported for the purpose of this review according to pre-defined protocol (Table 3). The population assessed was predominantly very highly ART-experienced, with advanced HIV infection and with few remaining treatment options due to the development of resistance to several drugs in different ART classes. The low median CD4+ (140 cells/mm^3, range: 19 to 1,100) and the high percentage of patients with CDC Category C disease indicated the severity of their condition. All of the patients (n = 183) had resistance to INSTIs (RAL or EVG). By week 48, 63% of patients achieved HIV RNA levels of less than 50 copies/mL using the MSDF algorithm. Baseline HIV RNA levels were the most important predictors of the proportions of patients who achieved HIV RNA of less than 50 copies/mL at week 48, with the highest proportion (90%) occurring in patients with less than 1,000 copies/mL and the lowest (17%) occurring in patients with > 500,000 copies/mL. VIKING-3 was a single-arm study without a comparator group and there was no comparable phase III study found for this review, which included patients with multiple ART-class experience, including resistance to INSTIs. The population assessed had very few remaining treatment options due to the development of resistance to several drugs in different ART classes; therefore, a randomized controlled study would have been difficult and ethically challenging to conduct.

4.2.2 Harms

In the SPRING-2 study, AEs were similar across the DTG and RAL treatment groups at weeks 48 and 96. Generally, infections and infestations were the most commonly reported AEs and occurred at a similar rate in both treatment groups. Of this class of AEs, nasopharyngitis and upper respiratory tract

infections were the most common and did not appear to be treatment-related. Across the various SOCs of AEs, the most commonly reported clinical AE among patients in both treatment groups were nausea, headache, diarrhea, and nasopharyngitis, with no appreciable difference between the DTG and RAL treatment groups. SAEs occurred rarely, and discontinuation of study drug due to adverse events was low, with no discernible patterns to individual events.

All of the pre-specified AEs under notable harms occurred infrequently in both SPRING-2 study treatment group. There were only small changes in lipid parameters in both the DTG and RAL groups, with none of the reported changes in the lipid profiles for total cholesterol, LDL cholesterol, HDL cholesterol, total HDL cholesterol ratio, or triglycerides indicating clinical impairment. Changes in glucose were small and cardiac disorders were reported rarely by both treatment groups. Unlike the SINGLE study, where the insomnia rate was high (15%) in the DTG +ABC/3TC treatment group, the SPRING-2 study reported lower rates (5% at week 48 and 6% at week 96), which were comparable to the RAL treatment group at these time points (4% at week 48 and 5% at week 96).

At both the 48- and 96-week time points in the SINGLE study, there was a similar rate of system organ class AEs for DTG plus ABC/3TC and EFV/TDF/FTC in all reported cases, except for nervous system disorders and psychiatric disorders. At weeks 48 and 96, 27% and 29%, respectively, of patients receiving DTG plus ABC/3TC experienced nervous system disorders compared with 51% and 54%, respectively, of patients receiving EFV/TDF/FTC. Patients in the EFV/TDF/FTC treatment group were more likely to develop dizziness, which is consistent with the product monograph for EFV/TDF/FTC.[22] With regard to psychiatric disorders, 30% and 40%, respectively, were reported at weeks 48 and 96 in the DTG plus ABC/3TC group, compared with 35% and 42%, respectively, in the EFV/TDF/FTC group at the same time points. However, unlike the other AEs listed under psychiatric disorders, insomnia occurred at a higher frequency in patients in the DTG plus ABC/3TC treatment group compared with patients in the EFV/TDF/FTC treatment group. This higher proportion of reported insomnia in patients receiving DTG in the SINGLE study (15% and 17% at weeks 48 and 96, respectively), was a deviation from all the other studies used for this review, all of which reported a less than 10% incidence at all analysis time points. In fact, the reported rate of insomnia in the VIKING-3 study, where a higher (double) dose was administered to patients, was 7% at week 48.

The incidence of SAEs was low in each treatment group of the SINGLE study. Two deaths were reported, with both occurring in the EFV/TDF/FTC group. Overall, incidences of AEs leading to withdrawal were low (2% at week 48 and 3% at week 96) in the DTG plus ABC/3TC treatment group compared with the EFV/TDF/FTC treatment group (10% at week 48 and 12% at week 96). There was no discernible difference in reported rates of WDAEs in the DTG plus ABC/3TC treatment group, where less than a 1% incidence rate was reported in all cases. The most common WDAEs in the EFV/TDF/FTC treatment group were nervous system disorders and psychiatric disorders.

Increases in mean serum lipid parameters were small across the two treatment groups, suggesting the DTG plus ABC/3TC once-daily regimen does not appear to have an untoward effect on lipids, compared with EFV/TDF/FTC. Metabolic and cardiovascular events were reported rarely in both treatment groups. The manufacturer-provided NMA showed that the difference in AEs between RAL and DTG was not statistically significant, but DTG showed statistically significant lower odds of AEs compared with ATV/r, LPV/r, and EFV (Table 48).

The safety profile for DTG was similar to RAL in the SAILING study, with a similar rate of overall AEs for DTG and RAL. The most commonly reported clinical AEs in both study groups were diarrhea, upper

respiratory infection, headache, and nausea, with no appreciable difference between treatment groups. The incidence of SAEs was low in both the DTG and the RAL groups, with the highest number of infections and infestations reported by the DTG group (3%) compared with 5% of the RAL group. Overall, incidences of AEs leading to withdrawal were infrequent in both treatment groups (2% in DTG versus 4% in RAL). In terms of individual clinical WDAEs, there was no discernible difference, with a reported incidence rate of less than 1% observed across both the DTG and RAL groups.

Of the AEs listed under notable harms, the most commonly reported was headache (9%) followed by nausea (8%) and insomnia. The proportions are numerically lower but not too different from rates of headache and nausea reported from 48-week data of studies in ART-naive HIV-infected patients, (SPRING-2 and SINGLE).[1,2] Changes in lipid parameters were small in both groups, with less than 1% each of dyslipidemia and hyperlipidemia reported across both treatment groups. Reported cardiac complications were also low: 2% in the DTG group compared with 4% in the RAL group.

In the VIKING-3 study, patients received DTG 50 mg twice daily instead of the usual once-daily dose given to patients with less advanced HIV disease. Even at this higher dose, DTG 50 mg twice daily was well tolerated, with a safety profile similar to that described for DTG 50 mg once daily from 48-week data in ART-naive patient participants in the SPRING-2 and SINGLE studies, and the 48-week data in ART-experienced, INI-naive patients participating in the SAILING study; however, the rate of SAEs was approximately double in the VIKING-3 study compared with the SPRING-2, SINGLE, and SAILING studies. It is likely the higher rate of SAEs is related to the more advanced nature of HIV disease in the study population. Nausea and headache had higher reported rates (13% and 11%, respectively) among the notable harms for this review; however, they occurred at a consistent rate. The observations from the 48-week data for both the SPRING-2 and SINGLE studies were not very different from the SAILING data. Changes in blood lipid parameters were small, with a rare incidence (less than 1%) of dyslipidemia. Incidence of cardiac complications was also low (4%).

5. CONCLUSIONS

The included studies demonstrated the efficacy and safety of DTG or DTG-containing regimens to be noninferior or superior to RAL and EFV/TDF/FTC regimens for HIV-infected ART-naive and ART-experienced patients. The SPRING-2 and SAILING studies demonstrated non-inferiority of DTG to RAL in ART-naive patients, and the ART-experienced but INSTI-naive populations, respectively, in achieving sustained viral-load suppression. DTG also demonstrated superiority to RAL in the SAILING study at week 48. In the SINGLE study, DTG plus ABC/3TC was noninferior and superior to EFV/TDF/FTC at week 48 and week 96. The majority (63%) of treatment-experienced and INSTI-resistant HIV-infected patients in the VIKING-3 study who received DTG 50 mg twice daily with optimized background therapy (OBT) achieved HIV RNA of less than 50 copies/mL at week 48. DTG appeared to be well tolerated in the included studies, including the VIKING-3 study where the patients received a 100 mg (50 mg twice daily) dose instead of the usual 50 mg once daily. In the SINGLE study, the safety and tolerability profile of DTG+ABC/3TC was generally better than that of EFV/TDF/FTC over the period of the study, with a higher rate of patients in the EFV/TDF/FTC arm withdrawing from the study drug due to adverse events.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was summarized by CADTH staff based on the input provided by patient groups. This section was summarized by CDR staff based on the input provided by patient groups. It has not been systematically reviewed. It has been reviewed by the submitting patient groups.

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

The Canadian Treatment Action Council (CTAC) is a national non-governmental organization addressing access to holistic treatment, care, and support for people living with HIV and hepatitis C. Its goals are to engage 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 hepatitis C co-infection); and organizations, groups, or projects with a substantial HIV mandate (including hepatitis C co-infection).

CTAC received unrestricted organizational and educational grants from the following in the 2012-2013 fiscal year: Abbott/Abbvie, Boehringer Ingelheim, Gilead Sciences, Janssen, and ViiV Healthcare.

2. Condition and Current Therapy-Related Information

Information for this submission was collected from: a survey in follow-up to a national webinar on the CDR process and key findings from DTG clinical trials (13 respondents: 9 HIV-positive and 4 HIV-negative); a previous HIV-related patient input submission for Stribild, and information from clinical trial results presented at various conferences.

HIV is a serious, life-threatening illness that threatens the immune system. If left untreated, HIV can compromise a person's immune system to the point that the body may no longer be able to fight off opportunistic infections. At that point, an AIDS diagnosis and death may occur. In most cases, people taking highly active antiretroviral treatment (HAART) achieve an undetectable viral load (or viral suppression) and can live long lives, managing their HIV as a chronic illness.

Many people living with HIV experience negative mental health outcomes, either as side effects from treatment, or from facing stigma and discrimination and related stress. Most of these individuals also experience fatigue, both before and after they initiated treatment, making it difficult to maintain diet and exercise routines, and even to work. A few respondents stated that their quality of life related to these areas has improved as a result of treatment. There have been a few respondents as well as caregivers who have noted the substantial impact that the social determinants of health, particularly living conditions, have had on managing their HIV.

Treatment regimens change often for people living with HIV; thus, there is a significant need for the availability of several HIV treatments. Some of these people do not achieve virological suppression despite numerous attempts on multiple treatment regimens. The majority of respondents were taking raltegravir, atazanavir, and nevirapine-based regimens and mostly did not experience side effects associated with their medications. With respect to quality of life, one respondent cited an overall improvement as a result of treatment initiation; three respondents noted that treatment had not yielded any improvements; and one respondent was not certain due to initiating treatment within three months of diagnosis.

Treatment adherence is necessary for treatment to be effective. Non-adherence can lead to drug class resistance, requiring the adoption of a new regimen selected from fewer available treatment options. Barriers or hardships in obtaining access to treatments, particularly travel, administrative, and cost-related, impede adherence.

Respondents noted a substantial impact on their caregivers, including challenges to establish a social safety net due to respondents hiding their HIV-positive status. The barriers to receiving support identified by respondents were staff time, lack of funding, transportation, and other associated costs.

3. Related Information About the Drug Being Reviewed

One respondent took dolutegravir, the newest integrase inhibitor, and achieved undetectable viral levels two months after initiating treatment, as well as a continuous rise in CD4 count. The respondent experienced nausea and insomnia but was able to manage these by modifying his/her diet and the time of day the medication was taken and reported that, despite these side effects, the experience with the therapy was very positive.

Despite several advantages found for dolutegravir in clinical trials, five of six respondents stated they would not stop current therapy and take dolutegravir, unless advised by their physician or if it were required due to how their HIV evolves. The respondent who would switch from his/her current treatment regimen to dolutegravir because of its improvements over existing therapy, noted its advantages as, “One dosing per day; therefore, increased confidence, decreased need to manage environmental factors (hiding, food intake), increased adherence, and more user-friendly.” Other respondents were unsure about whether dolutegravir would improve their overall quality of life, with one stating that the quality of life would be comparable to what it is currently, and another expressing concerns regarding the adverse events associated with dolutegravir, particularly nausea, dizziness, and insomnia, and the effects of these on daily functioning and overall health state. Some respondents had mixed feelings regarding the severity of adverse events associated with dolutegravir; however, one respondent also indicated that the adverse events associated with dolutegravir seem less severe compared with existing available therapy. Insomnia was reported as a common adverse event in only one of the five dolutegravir clinical trials.

CTAC notes that dolutegravir allows for individualized treatment, as it could be combined with either Kivexa or Truvada, has minimal drug–drug interactions and has a once-daily dosing regimen which makes it a viable treatment option for many. Based on its safety, efficacy, and tolerability profile, dolutegravir has the potential to reduce the burden of HIV, reducing strain on the health care system and supporting people living with HIV as they lead healthy, active lives and fully contribute to society. CTAC strongly recommends that dolutegravir be listed.

4. Additional Information

In the five dolutegravir phase III trials, hepatitis B and C co-infected individuals were included, ranging anywhere from 10 to 23%. The extensive data gathered from dolutegravir clinical trials suggest potential use in co-infected patients, which is particularly important as approximately one-third of people living with HIV are also living with viral hepatitis co-infection. Thus, CTAC strongly recommends that dolutegravir be listed for the reasons outlined in the patient input submission, and that summary and clinical trial safety and efficacy data on dolutegravir and co-infection be comprehensively reviewed to determine its indication in co-infected populations.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	March 13, 2014
Alerts:	Weekly search updates until (date of CDEC meeting)
Study Types:	randomized controlled trials
Limits:	No date or language limits were used Human filter was applied Conference abstracts were excluded
SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a 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
adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
Line #	**Strategy**
1	(Tivicay* or dolutegravir* or GSK-1349572 or GSK 1349572 or GSK1349572 or S349572 or S 349572 or SGSK1349572 or S GSK1349572 or SGSK1349572 or SGSK13 49572 or S GSK13 49572).ti,ab,ot,sh,hw,rn,nm.
2	((integrase strand transfer inhibit* or INSTI*) adj4 DTG).ti,ab.
3	(1051375-19-9 or 1051375 19 9 or "1051375199" or 1051375-16-6 or "1051375166" or 1051375 16 6 or "105137516 6" or 1172581-47-3 or "1172581473" or DKO1W9H7M1 or UNIIDKO1W9H7M1 or UNII-DKO1W9H7M1).rn,nm.
4	1 or 2 or 3
5	4 use pmez
6	exp *dolutegravir/
7	(Tivicay* or dolutegravir* or GSK-1349572 or GSK 1349572 or GSK1349572 or S349572 or S 349572 or SGSK1349572 or S GSK1349572 or SGSK1349572 or SGSK13 49572 or S GSK13 49572).ti,ab.
8	((integrase strand transfer inhibit* or INSTI*) adj4 DTG).ti,ab.
9	6 or 7 or 8
10	9 use oemezd
11	10 not conference abstract.pt
12	5 or 11
13	remove duplicates from 12

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	To March 10, 2014
Keywords:	Tivicay, dolutegravir
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion[a]
Clinical study report: ING114915 (FLAMINGO).	Did not meet inclusion criteria for review
Clinical study report: ING111762 (SAILING); week 24 results	
Clinical study report: ING112574 (VIKING-3); week 24 results	
Eron JJ, Clotet B, Durant J, Katlama C, Kumar P, Lazzarin A, et al. Safety and efficacy of dolutegravir in treatment-experienced patients with raltegravir-resistant HIV type 1 infection: 24-week results of the VIKING Study. J Infect Dis [Internet]. 2013 Mar 1 [cited 2014 Mar 19];207(5):740-8. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3563307/pdf/jis750.pdf	
Castagna A, Maggiolo F, Penco G, Wright D, Mills A, Grossberg R, et al. Dolutegravir in antiretroviral-experienced patients with raltegravir- and/or elvitegravir-resistant HIV: 24-week results of the phase III VIKING-3 study. J Infect Dis. 2014 Feb 23. Epub ahead of print.	
Stellbrink HJ, Reynes J, Lazzarin A, Voronin E, Pulido F, Felizarta F, et al. Dolutegravir in antiretroviral-naive adults with HIV: 96-week results from a randomized dose-ranging study. AIDS [Internet]. 2013 Jul 17 [cited 2014 Mar 19];27(11):1771-8. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3694319/pdf/aids-27-1771.pdf	
van Lunzen J, Maggiolo F, Arribas JR, Rakhmanova A, Yeni P, Young B, et al. Once daily dolutegravir (S/GSK1349572) in combination therapy in antiretroviral-naive adults with HIV: planned interim 48 week results from SPRING-1, a dose-ranging, randomized, phase 2b trial. Lancet Infect Dis. 2012 Feb;12(2):111-8	
Messiaen P, Wensing AMJ, Fun A, Nijhuis M, Brusselaers N, Vandekerckhove L. Clinical Use of HIV Integrase Inhibitors: A Systematic Review and Meta-Analysis. PLoS ONE [Internet]. 2013 [cited 2014 Mar 19];8(1). Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3541389/pdf/pone.0052562.pdf	Review
Rathbun RC, Lockhart SM, Miller MM, Liedtke MD. Dolutegravir, a second-generation integrase inhibitor for the treatment of HIV infection. Ann Pharmacother. 2014 Mar;48(3):395-403.	

[a] Clinical study reports were used as sources for this review.

APPENDIX 4: OTHER EFFICACY OUTCOME DATA

TABLE 19: OTHER EFFICACY OUTCOMES — ART-NAIVE PATIENTS

	SPRING-2[1,2]				SINGLE[3,4]			
	Week 48		Week 96		Week 48		Week 96	
	DTG 50 mg q.d. N = 411	RAL 400 mg b.i.d. N = 411	DTG 50 mg q.d. N = 411	RAL 400 mg b.i.d. N = 411	DTG 50 mg q.d. N = 414	EFV/TDF/FTC N = 419	DTG 50 mg q.d. N = 414	EFV/TDF/FTC N = 419
Change from Baseline in CD4+ (cells/mm^3)								
Mean ± SD	238.90 ± 171.81	257.50 ± 178.69	292.20 ± 195.70	286.20 ± 192.45	267.0 ± 192.19	209.5 ± 164.37	323.5 ± 205.66	286.3 ± 195.97
Adjusted mean difference (95% CI)	NR		NR		58.90 (33.41, 84.40)		43.95 (14.34, 73.55)	
P value	NR		NR		< 0.001		0.004	
Treatment-Emergent Art-Resistance Mutations								
Treatment-emergent INSTI resistance, n	0	1 (<1)	0	1 (< 1)	0	0	0	0
Adjusted difference (95% CI) (DTG – RAL)	–0.2 (–1.1, 0.6)		–0.2 (–1.1, 0.6)		NA		NA	
Treatment-emergent NRTI resistance, n	0	4	0	4	0	1	0	1
Treatment-emergent NNRTI resistance, n	NA	NA	NA	NA	0	4	0	6

b.i.d. = twice daily; CD4+ = Helper-inducer T-lymphocyte surface antigen; CI = confidence interval; DTG = dolutegravir; EFV = efavirenz; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; NA = not applicable; NR = not reported; NRTI = nucleoside reverse transcriptase inhibitor; q.d. = once daily; RAL = raltegravir; SD = standard deviation; TDF = tenofovir.

TABLE 20: OTHER EFFICACY OUTCOMES — ART-EXPERIENCED PATIENTS

	SAILING[13] Week 48		VIKING-3[15] Week 48
	DTG 50 mg q.d. N = 354	RAL 400 mg b.i.d. N = 361	DTG 50 mg q.d. N = 183
Change in CD4+ Cell Count From Baseline at Week 48			
Mean (SD) at baseline	254.0 (207.77) N = 354	246.4 (199.02) N = 361	NR
Median (IQR) at baseline	204.5 (88.0, 368.0) N = 354	193.0 (96.0, 365.0) N = 361	140.0 (40.0, 330.0) N = 183
Mean (SD) change from baseline at 48 weeks	162.4 (151.43) N = 294	153.2 (143.90) N = 283	NR
Median (IQR) change from baseline	144.0 (73.0, 242.0) N = 294	137.0 (67.0, 224.0) N = 283	110.0 (40.0, 190.0) N = 145
Development of INSTI-Resistance Mutations by Week 48			
n (%)	4 (1)	17 (5)	19 (10)
Adjusted RD[a] (95% CI)	–3.7 (–6.1, –1.2)		NA
P value	0.003		
VL < 50 Copies/mL at Week 24 (mITT-E/ITT-E Population)* (MSDF Analysis)			
N (%)	281 (79)	252 (70)	126(69)
RD (95% CI)	9.6 (3.2 to 15.9)		NA
Adjusted RD[a] (95% CI)	9.7 (3.2 to 15.9)		
P value	0.003		
VL < 50 Copies/mL at Week 24 (PP Population)* (MSDF Analysis)			
n/N (%)	263/323 (81)	245/339 (72)	118/164(72)
RD (95% CI)	9.2 (2.8 to 15.5)		NA
Adjusted RD[a] (95% CI)	9.3 (3.0 to 15.7)		

ANCOVA = analysis of covariance; b.i.d. = twice daily; CD4+ = Helper-inducer T-lymphocyte surface antigen; CI = confidence interval; DTG = dolutegravir; INSTI = integrase strand transfer inhibitor; IQR = interquartile range; ITT-E = intention-to-treat exposed; LOCF = last observation carried forward; mITT-E = modified intention-to-treat exposed; MSDF = missing, switch, or discontinuation equals failure analysis; NA = not applicable; NR = not reported; PP = per protocol; PSS = Phenotypic Susceptibility Score; q.d. = once daily; RAL = raltegravir; RD = risk difference; SD = standard deviation; VL = viral load.
Note*: mITT-E was primary population analyzed for SAILING while ITT-E was the primary population analyzed for VIKING-3
[a] = Adjusted difference based on Cochran-Mantel-Haenszel stratified analysis adjusting for baseline HIV RNA (≤ 50 000 copies/mL vs. > 50 000 copies/mL), darunavir-ritonavir use without primary protease inhibitor mutations (yes vs. no), and baseline phenotypic susceptibility score (2 vs. < 2) to background regimen.
[b] = *P* value for test of superiority
[c] = Using LOCF and based on ANCOVA adjusted for: gender, race, age, baseline score, baseline HIV RNA baseline PSS (< 2 vs. 2) to background regimen, DRV/r use in background ART w/o primary PI Mutations at BL.
[d] Patient may have had more than one HIV-associated condition. Each condition was counted only once per patient, regardless of recurrence.
Source: SAILING 48-week clinical study report;[13] VIKING-3 48-week clinical study report.[15]

APPENDIX 5: SUMMARY OF OTHER STUDIES

1. Summary of Findings of the FLAMINGO Study[23]

Objectives

To summarize the clinical efficacy and harms of the FLAMINGO study in which dolutegravir (DTG) 50 mg once daily was compared with darunavir 800 mg plus ritonavir 100 mg (DRV/r) once daily among individuals who are naive to antiretroviral therapy.

Study Characteristics

FLAMINGO was a 96-week, multi-centre, open-label phase III, non-inferiority study. Included patients were aged 18 years or older, with a concentration of plasma HIV RNA of 1,000 copies/mL or higher, no previous treatment with antiretroviral therapy, and no primary resistance to NRTIs or PIs. Patients were excluded if they had active disease of category C from the Centers for Disease Control and Prevention, if they were pregnant, had moderate or severe hepatic impairment, an anticipated need for hepatitis C treatment during the study, estimated creatinine clearance of less than 50 mL/min, recent (within the past five years) or ongoing malignancy, or treatment with an HIV vaccine within 90 days of screening or with any immunomodulator within 28 days.

Patients were randomized to receive either DTG 50 mg once daily, or DRV/r 800 mg/100 mg once daily. Randomization was stratified by HIV RNA (> 100,000 copies/mL or ≤ 100,000 copies/mL) and NRTI backbone. The primary end point was the proportion of patients with HIV RNA lower than 50 copies/mL at week 48 using the FDA snapshot algorithm. Secondary end points of interest at 48 weeks included changes in HRQoL, change in CD4 cell counts from baseline, and treatment-emergent genotypic or phenotypic evidence of resistance. The incidence and severity of adverse events was assessed. Study visits were performed at baseline and weeks 2, 4, 8, 12, 16, 24, and every 12 weeks thereafter.

Adjusted difference in proportions were calculated using stratified analysis with a CMH test with weights for baseline HIV RNA and investigator-selected backbone dual NRTIs. The primary analysis was based on a modified intention-to-treat population that consisted of all patients randomly assigned to treatment groups who received at least one dose of study drug, with the exception of one patient with non-compliance issues at one study site in Russia. Tests for homogeneity were assessed for stratification factors at the one-sided 10% level. A non-inferiority margin of 12% was selected based on response rates of dual-NRTI therapy and dual-NRTI plus third-agent therapy in recent studies, and was also the mid-range of the margins described in a review of non-inferiority trials in HIV conducted between 2000 and 2007.[24] Superiority testing with the general multi-stage gate-keeping procedure was performed if both the PP and modified intention-to-treat exposed analyses showed non-inferiority. For the HRQoL outcome (EQ-5D), ANCOVA models were used to produce means adjusted for the same categorical covariates used in the primary end point analysis. Sex, race, baseline score, and age were also used as continuous variables. As seen in Table 21, the median age was 34 years, and the majority of patients were white males.

TABLE 21: BASELINE DEMOGRAPHICS

	DTG 50 mg + OBT N = 242	DRV/r 800 mg/100 mg+ OBT N = 242
Age in years, median (IQR)	34 (18, 67)	34 (19, 67)
Male, n (%)	211 (87)	201 (83)
African American/African heritage	60 (25)	53 (22)
White	173 (71)	176 (73)
Other	8 (3)	13 (5)
Baseline HIV RNA (log10 copies/mL), median (IQR)	4.49 (4.02, 5.02)	4.48 (4.01, 5.01)
> 100,000	61 (25)	61 (25)
Baseline CD4 (cells/mm^3), median (IQR)	390 (290, 500)	400 (300, 530)

DTG = dolutegravir; DRV/r = darunavir/ritonavir; IQR = interquartile range; OBT = optimized background therapy.

A total of 243 patients and 245 patients were randomized to the dolutegravir and darunavir/ritonavir groups respectively. The disposition of patients through to week 48 is summarized in Table 22. A total of 18 (7%) patients in the DTG group and 29 (12%) patients in the DRV/r group prematurely withdrew from the study before the 48-week time point. The median time of exposure to both DTG and DRV/r groups was 337 days. The proportion of patients receiving therapy for greater than 48 weeks in the DTG group (186, 77%) was similar to the DRV/r group (181, 75%).

TABLE 22: PATIENT DISPOSITION TO WEEK 48

	DTG 50 mg + OBT	DRV/r 800 mg/100 mg + OBT	Total
Randomized, N	243	245	484
Ongoing at the time of analysis, N (%)	224 (93)	213 (88)	437 (90)
Discontinued[a]	18 (7)	29 (12)	47 (10)
Adverse event	3 (1)	9 (4)	12 (2)
Lack of efficacy (virologic failure)	2 (< 1)	2 (< 1)	4 (< 1)
Protocol deviation	3 (1)	3 (1)	6 (1)
Pregnancy	1 (< 1)	1 (< 1)	2 (< 1)
Non-compliance with IP treatment	2 (< 1)	2 (< 1)	4 (< 1)
Non-compliance with protocol	0	2 (< 1)	2 (< 1)
Reached protocol-defined liver-stopping criteria	1 (< 1)	1 (< 1)	2 (< 1)
Lost to follow-up	6 (2)	10 (4)	16 (3)
Patient was incarcerated	1 (< 1)	2 (< 1)	3 (< 1)
Investigator discretion	2 (< 1)	3 (1)	5 (1)
Withdrew consent	1 (< 1)	1 (< 1)	2 (< 1)
Analysis Populations at Week 48			
Modified intention-to-treat, N	242	242	484
Per protocol, N	237	235	472
Modified safety, N	242	242	484

DTG = dolutegravir; IP = intensive phase; mITT-E = modified intention-to-treat exposed; OBT = optimized background therapy; DRV/r = darunavir and ritonavir.

[a] Reasons for withdrawal based upon the mITT-E population. Patients may have only one primary reason for withdrawal.

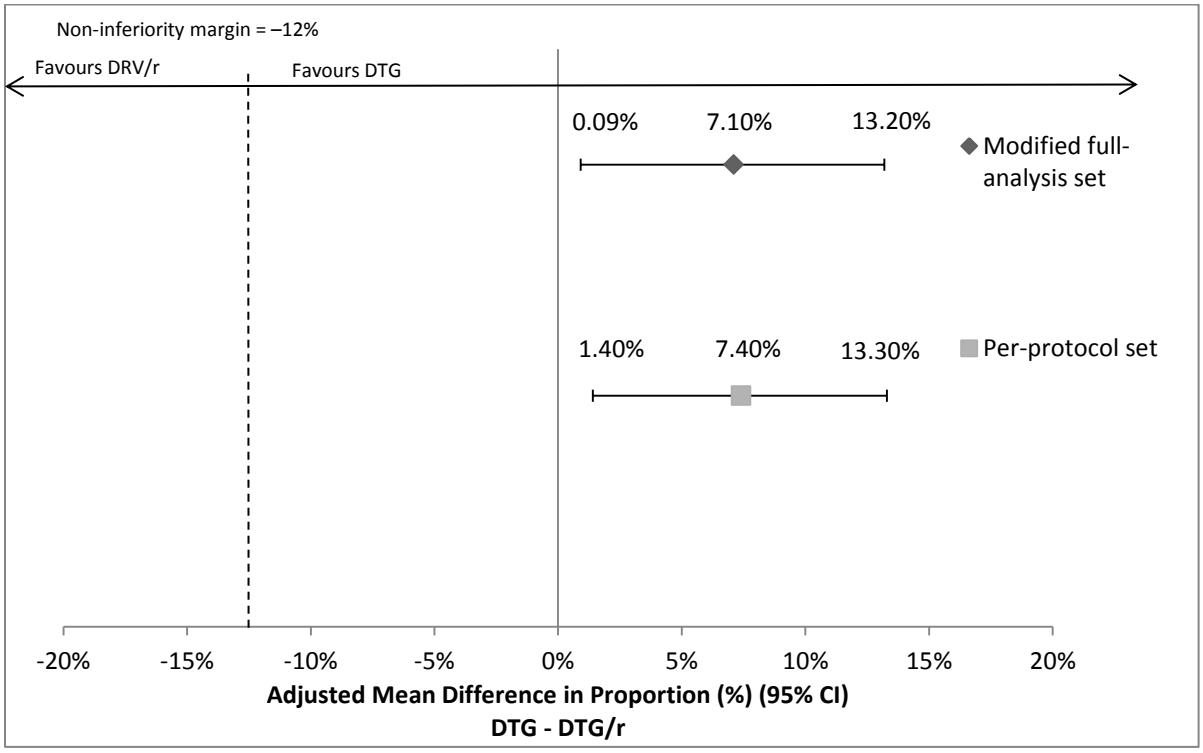
Source: CSR.[23]

Results

Efficacy

As seen in Figure 5, the primary analysis demonstrated that DTG was noninferior to DRV/r for the proportion of patients with plasma HIV RNA < 50 copies/mL at week 48 based on the FDA snapshot algorithm. Results of the modified ITT were consistent with the PP analysis. In both analysis sets, DTG was, in fact, statistically superior to DRV/r. As seen in Table 23, there were similar increases in CD4+ cell counts from baseline at 48 weeks. No patients had HIV disease progression to CDC Class C or death in either treatment group (Table 23). There was a similarly low incidence in the number of patients with HIV-associated conditions (< 1% in both treatment groups) (Table 23). In both treatment groups, there were modest increases in the mean EQ-5D visual analogue scale (VAS) scores compared with pre-treatment scores at week 48. EQ-5D utility scores in both treatment groups had minimal change from baseline at 48 (Table 23). Difference between treatment groups was not statistically significant (Table 23). At 48 weeks, no patients had treatment-emergent resistance mutations (Table 23).

FIGURE 5: PROPORTION OF PATIENTS ACHIEVING VIROLOGIC SUPPRESSION (HIV RNA < 50 COPIES/ML) AT WEEK 48 — SNAPSHOT ANALYSIS



3TC = lamivudine; ABC = abacavir; DTG = dolutegravir; DTG/r = darunavir/ritonavir; FTC = emtricitabine; RNA = ribonucleic acid; TDF = tenofovir disoproxil fumarate.

Note: Adjusted difference based on Cochran-Mantel-Haenszel stratified analysis adjusting for the following baseline stratification factors: baseline plasma HIV RNA (≤ 100,000 copies/mL vs. > 100,000 copies/mL) and baseline background dual-NRTI therapy (ABC/3TC vs. TDF/FTC).

TABLE 23: OTHER EFFICACY OUTCOMES

	DTG 50 mg + OBT N = 242	DRV/r 800 mg/100 mg+ OBT N = 242
VL ≥ 50 copies/mL at Week 48 (MSDF Analysis)		
N (%)	6 (2)	11 (5)
EQ-5D Utility Score at Week 48		
Baseline mean (SD), N	0.86 (0.195) N = 232	0.85 (0.198) N = 234
Adjusted mean change (SE)[a]	0.01 (0.012)	0.01 (0.012)
Adjusted difference (95% CI)[a]	-0.00 (–0.04, 0.03)	
P value	0.860	
EQ-5D VAS Score at Week 48		
Baseline mean (SD), N	77.96 (16.340)) N = 231	78.88 (17.220) N = 237
Adjusted mean change (SE)[a]	5.78 (0.762)	6.95 (0.769)
Adjusted difference (95% CI)[a]	–1.17 (–3.30, 0.96)	
P value	0.281	
Morbidity (HIV-Associated Conditions) N (%)		
CDC Category B		
Candidiasis, oropharyngeal	2 (< 1)	2 (< 1)
Mortality	0	0
Change in CD4+ Cell Count from Baseline at Week 48		
Mean (SD) at Baseline	402 (176.95) N = 242	421 (196.44) N = 242
Median (IQR) at Baseline	390 (290, 500 N = 242	400 (300, 530) N = 242
Mean (SD) change from baseline at 48 weeks	244 (180.68) N = 227	215 (177.26) N = 212
Median (IQR) change from baseline	210 (120.0, 350.0) N = 227	210 (110.0, 290.0) N = 212
Development of Resistance Mutations By Week 48		
N (%)	0	0

ANCOVA = analysis of covariance; CDC = Centers for Disease Control and Prevention; CD4+ = helper-inducer T-lymphocyte surface antigen; DTG = dolutegravir; DRV/r = darunavir/ritonavir; EQ-5D = EuroQol 5-dimensions questionnaire; IQR=interquartile range; LOCF = last observation carried forward; OBT = optimized background therapy; SD = standard deviation; VL = viral load.

[a] Using LOCF, and based on ANCOVA, adjusted for: age, sex, race, baseline viral load, background dual-NRTI therapy, and baseline EQ-5D utility or VAS score as appropriate.

Source: CSR.[23]

Harms

The main adverse events, serious adverse events and withdrawals due to adverse events are summarized in Table 24. The overall safety profile of DTG was similar to DRV/r over 48 weeks. The incidence of SAEs was greater among the DTG treatment group, though events appeared to be isolated. Proportions of WDAEs were marginally greater in the DRV/r group.

TABLE 24: SUMMARY OF ADVERSE EVENTS REPORTED THROUGH WEEK 48

	DTG 50 mg + OBT N = 242	DRV/r 800 mg/100 mg+ OBT N = 242
AEs		
Patients with > 0 AEs, N (%)	206 (85)	205 (85)
Most common AEs[a]		
Diarrhea	41 (17)	70 (29)
Upper respiratory tract infection	13 (5)	23 (10)
Headache	37 (15)	24 (10)
Nausea	39 (16)	43 (18)
Nasopharyngitis	22 (9)	19 (8)
SAEs		
Patients with > 0 SAEs, N (%)	26 (11)	13 (5)
Most common SAEs[a]		
Infections and infestations	5 (2)	8 (3)
Nervous system disorders	4 (2)	0
Psychiatric disorders	4 (2)	1 (< 1)
Gastrointestinal disorders	6 (2)	2 (< 1)
WDAEs		
WDAEs, N (%)	3 (1)	9 (4)
Notable Harms, N(%)		
Fatigue	15 (6)	12 (5)
Insomnia	18 (7)	15 (6)
Dizziness	14 (6)	11 (5)
Depression	11 (5)	6 (2)

AE = adverse event; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
[a] Incidence higher than 5%.
Source: CSR.[23]

Critical Appraisal

The open-label design may have biased the safety assessment, as knowledge of the treatment may have biased reporting rates by patients, withdrawals due to AEs (which were slightly greater in the DRV/r group), and drug relatedness of events as determined by the investigator. According to the clinical expert consulted for this review, FLAMINGO is strongly representative of the Canadian population and DTG is compared with a reasonable comparator that is a reasonable choice for first-line therapy for treatment-naive patients. The expert also confirmed that the open-label design likely did not have an impact on the primary efficacy outcome.

Patients were randomized to respective groups using a central randomization schedule. The study was properly conducted as multiplicity adjustments were performed for secondary outcomes using a general multi-stage gate-keeping procedure. An appropriate non-inferiority margin of 12% was employed and is in concordance with the US FDA guidelines.[21] The study appeared to be powered accordingly (90%) with appropriate sample size calculation. The baseline demographics between the two groups were generally well balanced. The primary end point results of virologic success appear to be robust, as analyses were adjusted for background therapy and baseline virologic load. The PP analysis results of the primary end point were in concordance and supported the findings from the modified ITT population. Although results were based on a modified ITT and safety population, differences compared with the original ITT sample are minimal and likely had no impact on the overall findings.

Given the limitations of using an open-label design with self-report measures, this study was not appropriately designed to measure and detect differences in HRQoL. Furthermore, investigators used the last observation carried forward approach to adjust for missing EQ-5D data, which may not be the most conservative approach.

Summary

DTG 50 mg administered once daily was statistically noninferior and superior was compared with darunavir 800 mg plus ritonavir 100 mg (DRV/r) once daily for virological suppression (HIV RNA < 50 copies/mL) at week 48 among individuals who are naive to antiretroviral therapy. At 48 weeks, increases in CD4+ cell counts from baseline were similar between treatment groups and differences in improvements of HRQoL were not statistically significant. In both groups, no patients had treatment-emergent resistance mutations, or encountered disease progression to CDC Class C or death. The overall safety profile of DTG was similar to DRV/r, though these results should be interpreted with caution given the open-label design.

2. Summary of Findings of IMPAACT P1093[25]

Objective

To summarize the preliminary findings of the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) P1093 study[25] that determined the appropriate dose of dolutegravir (DTG) among HIV-infected INSTI-naive adolescents.

Study Characteristics

IMPAACT P1093[25] is an ongoing, multi-centre, open-label, non-comparative, phase I and II, pharmacokinetic study designed to find safe dosages of DTG plus optimized background therapy for five age-defined cohorts (Table 25). Each cohort consists of two sequential stages: Stage 1, performed for dose-finding purposes that included intensive PK and safety evaluations during the first 4 weeks of DTG exposure, and Stage 2, which enrolled additional patients treated at the dose determined in Stage 1 and assessed long-term (e.g., 24 weeks) safety and antiviral activity data. This report summarizes the preliminary results of cohort I. IMPAACT P1093 was submitted to Health Canada to support the currently approved indication for DTG in adolescents 12 years of age and older (cohort I), weighing at least 40 kg.

TABLE 25: IMPAACT P1093 COHORTS

Cohort (status)	Cohort Description	Minimum Accrual	
		Stage 1	Stage II
I (completed week 24)	Adolescents ≥ 12 to < 18 years of age (Tablet formulation)	10 (completed week 24, n = 10 actual)	12 (completed week 24, n = 13 actual)
IIA (ongoing)	Children ≥ 6 to < 12 years of age (Tablet formulation)	10	12
IIB (not enrolled)	Children ≥ 6 to < 12 years of age (Pediatric formulation)	10	0
III (not enrolled)	Children ≥ 2 to < 6 years of age (Pediatric formulation)	10	12
IV (not enrolled)	Children ≥ 6 months to < 2 years (Pediatric formulation)	10	12
V (not enrolled)	Infants > 6 weeks to < 6 months (Pediatric formulation)	10	12

Patients included in IMPAACT P1093 were ART-experienced, with no prior treatment with an INSTI, HIV-infected male and female patients who were ≥ 6 weeks to ≤ 18 years old, with a screening plasma HIV RNA ≥ 1,000 copies/mL, and must have had available at least one fully active drug for the planned OBT regimen. Patients in cohort I were to be between ≥ 12 to < 18 years of age. Patients were excluded if they had known resistance to an INSTI, presence of any active AIDS-defining opportunistic infection, known ≥ Grade 3 and Grade 4 lab toxicities, evidence of pancreatitis, liver toxicity and known exposure to an INSTI.

Patients were given DTG once a day with target dose of approximately 1 mg/kg according to weight and the dosing chart using 10 mg, 25 mg, or 50 mg tablets. The weight-based dose that was administered was DTG 50 once daily if the patient weighed at least 40 kg, or DTG 35 mg once daily if he or she was under that weight. In Stage 1, most patients (n = 9) received 50 mg once daily, while one patient weighing under 40 kg received 35 mg once daily. In Stage 2, after 24 weeks, 19 patients received 50 mg once daily and four patients received DTG 35 mg once daily.

The primary PK end point was the area under the curve at 24 hours (AUC24), with the concentration at the end of the 24-hour dosing interval (C24) as secondary end point. The primary and secondary PK targets were to match the adult AUC24 (46 mcg*h/mL [range: 37–67 mcg*h/mL]) and C24 (0.96 mcg/mL (range: 0.77–2.26 mcg/mL)] observed at the 50 mg once-daily dose. [redacted]

Secondary end points included virologic suppression (HIV RNA < 50 copies/mL) at week 24, calculated using the FDA's snapshot missing, switch, or discontinuation equals failure (MSDF) algorithm, and change from baseline CD4 cell count at week 24. Safety was assessed through to week 48, though preliminary results until week 24 were only available at the time of the report.

The sample size selection of 10 patients in Stage 1 was based on targeting a 95% CI within 60% to 140% of the point estimate for the geometric mean estimates of clearance (CL/F) and volume of distribution (Vd) for DTG with a power of at least 78%. The manufacturer also stated that this selection is also based on the feasibility of their historical pediatric recruitment experience.

As seen in Table 26, the median age among all 23 patients in cohort I was 15 years, the majority of patients were African American (52.2%), [redacted].

TABLE 26: IMPAACT P1093 BASELINE DEMOGRAPHICS

Cohort I, Stage 1	DTG 50 mg + OBT N = 10 Cohort I, Stage 1	DTG 50 mg + OBT N = 23 Cohort I, Stage 1 and 2
Age in years, median (range)	13.5 (12 to 17)	15 (12 to 17)
Weight (kg), median (range)	51.7 (37.7 to 91)	52.2 (33 to 91)
Male, n (%)	3 (30)	5 (21.7)
African American/African heritage	6 (60)	12 (52.2)
White	4 (40)	8 (34.8)
Other	0	3 (13.0)

Cohort I, Stage 1	DTG 50 mg + OBT N = 10 Cohort I, Stage 1	DTG 50 mg + OBT N = 23 Cohort I, Stage 1 and 2
Baseline HIV RNA (copies/mL)		
400 to < 5,000	[redacted]	[redacted]
5,000 to < 10,000	[redacted]	[redacted]
10,000 to < 25,000	[redacted]	[redacted]
25,000 to < 50,000	[redacted]	[redacted]
≥ 50,000	[redacted]	[redacted]
Baseline CD4 cell count (cells/mm^3)		
< 50	[redacted]	[redacted]
≥ 50 to < 200	[redacted]	[redacted]
≥ 200 to < 350	[redacted]	[redacted]
≥ 350 to < 500	[redacted]	[redacted]
≥ 500	[redacted]	[redacted]

CD4 = helper-inducer T-lymphocyte surface antigen; DTG = dolutegravir; OBT = optimized background therapy; RNA = ribonucleic acid
Source: CSR,[25] 60 Safety report.[26]

As seen in Table 27, in Stage 1, a total of 11 patients were screened and 10 patients were enrolled into the study. No patients prematurely withdrew from the study through to week 24. In Stage 2, an additional 13 patients were enrolled (n = 23). [redacted].

TABLE 27: IMPAACT P1093 PATIENT DISPOSITION IN COHORT I AND STAGES 1 AND 2

	DTG 50 mg + OBT N = 10 Cohort I, Stage 1	DTG 50 mg + OBT N = 23 Cohort I, Stage 1 and 2
Screened	[redacted]	[redacted]
Enrolled, N	[redacted]	[redacted]
Safety	[redacted]	[redacted]
Completed week 24	[redacted]	[redacted]
Completed week 48	[redacted]	[redacted]
Discontinued	[redacted]	[redacted]

DTG = dolutegravir; NA = not applicable; NR = not reported; OBT = optimized background therapy.
Source: CSR,[25] 60-day safety report.[26]

Results

Pharmacokinetics

As seen in Table 28, the geometric mean AUC24 for cohort I was 46 mcg hour/mL, and the C24h was 0.90.

TABLE 28: IMPAACT P1093 DOLUTEGRAVIR PHARMACOKINETIC PARAMETERS IN COHORT I, STAGE 1

Age/Weight	Dolutegravir Dose	Dolutegravir Pharmacokinetic Parameter Estimates Geometric Mean (CV%) (n = 10)		
		AUC (0–24) mcg.hr/mL	Cmax mcg/mL	C24 mcg/mL
12 to 18 years and ≥ 40 kg[a]	50 mg once daily[a]	46 (43)	3.49 (38)	0.90 (59)

AUC = area under the curve; Cmax = maximum concentration; C24 = 24-hour dosing interval.
[a] One patient weighing 37 kg received 35 mg once daily.

Efficacy

As seen in Table 29, 69.6% of patients achieved virological suppression (HIV RNA < 50 copies/mL) at week 24. The median change from baseline in CD4 cell count at week 24 was 63 cells/mm^3.

TABLE 29: IMPAACT P1093 OTHER EFFICACY OUTCOMES, COHORT I

	DTG 50 mg + OBT N = 23
VL < 50 copies/mL at Week 24 (MSDF Analysis)	
n/N (%) 95% CI	16/23 (69.6) 47.1, 86.8
Change in CD4+ cell count from baseline (cells/mm^3)	
Median at baseline (min, max)	466 (11, 1025) N = 23
Median (IQR) change from baseline at week 24	63 (–56, 180) N = 23

CD4 = helper-inducer T-lymphocyte surface antigen; CI = confidence interval; DTG = dolutegravir; IQR = interquartile range; OBT = optimized background therapy; VL = viral load; MSDF = missing, switch, or discontinuation equals failure analysis.
Note: 19 patients received 50 mg/day and four patients received 35mg/day.
Source: 60-day safety report.[26]

Harms

The main adverse events, SAEs, and withdrawals due to adverse events are summarized in Table 30. Based on the preliminary data at week 24 from the 60-day safety report, there were no deaths, SAEs, withdrawals due to AEs or Grade 3 or Grade 4 clinical adverse events. Overall, 16 patients (69.6%) experienced a Grade 1 AE, and six patients (26.1%) experienced a Grade 2 AEs. The most common AEs included cough, diarrhea, pyrexia, pain in extremity, and dizziness.

TABLE 30: SUMMARY OF ADVERSE EVENTS (WORST GRADE) REPORTED THROUGH WEEK 48, COHORT I

	DTG 50 mg + OBT N = 23 Cohort I	
AEs	**Grade 1**	**Grade 2**
Patients with > 0 AEs, N (%)	16 (69.6)	6 (26.1)
Most common AEs[a]		
Cough	6 (26.1)	1 (4.3)
Diarrhea	4 (17.4)	2 (8.7)
Pyrexia	4 (17.4)	1 (4.3)
Pain in extremity	4 (17.4)	0
Dizziness	4 (17.4)	0
SAEs		
Patients with > 0 SAEs, N (%)	0	
WDAEs		
WDAEs, N (%)	0	
Notable Harms, N(%)		
Fatigue	0	2 (8.7)
Nausea	3 (13)	0
Headache	3 (13)	2 (8.7)

AE = adverse event; DTG = dolutegravir; OBT = optimized background therapy; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
[a] More than one patient.
Source: 60-day safety report.[26]

Critical Appraisal

In this phase I/II study, matching pediatric and adult (SPRING-1) PK data were used to extrapolate efficacy. Cross-trial comparisons may not always be appropriate; thus, results should be interpreted with caution. The investigators provided a justified sample size calculation indicating sufficient power, yet it was stated there was uncertainty concerning both the number of patients needed to complete the dose-finding procedures in Stage 1, and the number who may be lost to follow-up for reasons other than treatment failure. Although this is an ongoing study, the findings are limited to 24 weeks, thus long-term safety and tolerability remain uncertain. [redacted]. While single-arm trials are a common study design used in HIV pediatric trials and are in line with International Conference on Harmonisation (ICH) E11 guidance,[27] a larger-scale phase III study may provide more robust results.

Summary

DTG 50 mg once daily plus OBT achieved exposures in adolescents within the pre-defined targeted exposure range, as defined by the SPRING-1 data. The geometric mean for AUC24 and C24 were 46 mcg*h/mL and 0.9 mcg/mL, respectively. Overall, DTG 50 mg appeared to be well tolerated among all patients through week 24.

APPENDIX 6: SUMMARY OF COMPARATORS

Issues considered in this section were provided as supporting information. The information has not been systematically reviewed.

Objective

To summarize the methods and results, and to conduct a critical appraisal of, the manufacturer submitted NMA comparing the efficacy and safety of antiretroviral (ARV) third agents and fixed-dose regimens in treatment-naive HIV-infected individuals at 48 weeks.

Rationale

According to the investigators, the NMA was undertaken as the current comparative efficacy between third-agent comparators is limited and often involves comparisons between therapies within a single class, and includes older studies with third agents or NRTI background therapies that are no longer considered standard of care. Comparative data that includes all publicly available RCTs for third-agent HIV treatments for treatment-naive patients was needed to inform the economic analysis.

Methods

TABLE 31: INCLUSION CRITERIA FOR TRIALS ELIGIBILITY IN THE NMA

Population	Treatment-naive HIV-infected patients ≥ 13 years of age who reported on at least one treatment group and outcome of interest.
Interventions	• **Boosted PIs:** ritonavir-boosted atazanavir (ATV/r), ritonavir-boosted darunavir (DRV/r), ritonavir-boosted lopinavir (LPV/r) • **NNRTIs:** efavirenz (EFV), rilpivirine (RPV) • **INSTI:** dolutegravir (DTG), raltegravir (RAL), cobicistat-boosted elvitegravir (EVG/c)
Outcomes	**Primary efficacy end points at 48 weeks** • Virologic suppression [HIV RNA < 50] **Other efficacy end points at 48 weeks** • CD4 change from baseline to time point **Safety at 48 weeks** [redacted] • Adverse events
Study Design	Phase III/IV RCTs

AE = adverse event; CD4 = helper-inducer T-lymphocyte surface antigen; INSTI = integrase strand transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitors; PI = protease inhibitor; RCT = randomized controlled trial; RNA = ribonucleic acid.

Studies were excluded if they were non-randomized observational studies (including crossover studies), single-arm or examined different dosages of the same drug, examined structured treatment interruptions, or studies of maintenance treatments and/or treatment switching when HIV RNA was undetectable.

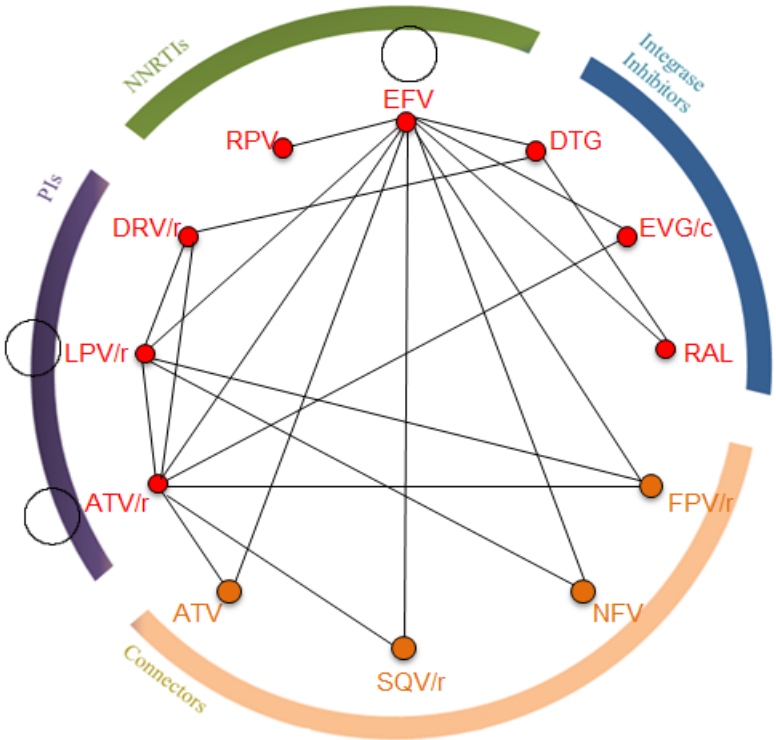
Network Meta-analysis and Systematic Review

A systematic review was carried out to identify all RCTs investigating US Department of Health and Human Services-recommended third agents for HIV treatment for treatment-naive patients.[7] Databases such as PubMed, Embase, and Cochrane Library, as well as grey literature, were included in the systematic literature search. The systematic review included both treatment-naive and treatment-experienced study populations. The authors concluded the body of literature for treatment-experienced patient populations was not as robust as that for treatment-naive patients and an NMA was not feasible.

After the completion of data extraction, initial evaluation of trial comparability was assessed to determine the feasibility of analysis. Outcome definitions and baseline values were examined and plotted to determine potential outliers and data similarity. Efavirenz (EFV) was chosen as the reference base treatment and, where applicable, TDF/FTC was chosen as the base NRTI backbone, as these were the most commonly observed treatments.

Bayesian meta-analytical techniques were used to analyze the efficacy and safety outcomes for the selected third agents seen in Table 31. The NMA models were programmed in WinBUGS software. Model selection was based on model convergence and model-fit statistics. Both fixed-effects and random-effects models were presented, though given the relatively small sample size and lack of two or more studies per comparison, the investigators chose to report the fixed-effects model. In addition, the analysis made adjustments for background therapies, using three categories: tenofovir disoproxil fumarate/emtricitabine (TDF/FTC), abacavir/lamivudine (ABC/3TC), or any other background therapy (other).

FIGURE 6: NETWORK OF INCLUDED RCTS



Source: Manufacturer's NMA technical report.[28]

Efficacy and Safety Outcomes

The primary efficacy outcome of interest was virologic suppression (HIV RNA < 50 copies/mL) at 48 weeks, and the secondary efficacy outcome of interest was CD4 change from baseline at 48 weeks. The NMA made no adjustment for the multiple comparisons that were being made between DTG and each comparator. Results from the systematic review revealed differences in analytical methods such as the snapshot, time to loss of virologic response (TLOVR), and complete virologic response (CVR). The analysis defined virologic suppression as achieving HIV RNA < 50 within the intention-to-treat population. The US FDA guidelines[21] have determined that both the snapshot and TLOVR methods are comparable. Based on these considerations, the four methods presented in Table 32 were considered appropriate to assess virologic suppression and the included studies had to have used at least one of the four methods seen in Table 32. When more than one method was reported, the method of higher preference was selected for the analysis.

TABLE 32: VIROLOGIC SUPPRESSION METHODS AND DEFINITIONS BY ORDER OF PREFERENCE

Method	Definition
Snapshot 50	**FDA snapshot algorithm** utilizes HIV RNA data at the visit of interest only
TLOVR-50	**Time to loss of virologic response (TLOVR)** HIV RNA < 50 copies/mL; treatment failure is defined as (1) discontinuing; (2) not achieving VL suppression below threshold for two consecutive measurements; or (3) any measurement above threshold after previous suppression
CVR-50	**Confirmed virologic response (CVR)** HIV RNA < 50 copies/mL is defined as (1) discontinuing; (2) not achieving VL suppression below threshold for two consecutive measurements; or (3) sustained loss of virologic suppression
HIV RNA < 50 (only if ITT, NC/M = F is explicitly defined)	HIV RNA < 50 copies/mL (**n**on-**c**ompleter/**m**issing = **f**ailure)

Safety outcomes included AEs and lipid (total cholesterol, HDL, LDL, and triglycerides) change from baseline at week 48. Subgroup analyses for baseline viral load were performed when pooled data were sufficient to support the analysis.

Study Characteristics

26 RCTs were included in the meta-analysis for the primary outcome of virologic suppression at 48 weeks (Table 33). All studies were phase III or IV RCTs. The included studies evaluated the following third-agent comparators: dolutegravir (DTG), ritonavir-boosted atazanavir (ATV/r), ritonavir-boosted darunavir (DRV/r), efavirenz (EFV), elvitegravir/cobicistat (EVG/c), ritonavir-boosted lopinavir (LPV/r), raltegravir; (RAL) and rilpivirine (RPV). [redacted] Table 33. The network for virologic suppression at 48 weeks is provided in Figure 6. Baseline CD4 cell count and virologic load were comparable among the included studies, with the exception of studies specifically including study cohorts with comorbidities (e.g., HIV-HBV co-infection, HIV-TB co-infection, etc.) or patients with CD4 cell levels below a specified threshold (Figure 7).

FIGURE 7: BASELINE CD4 (CELLS/MM^3) VERSUS BASELINE HIV RNA (LOG$_{10}$ COPIES/ML)

Figure 7 contained confidential information and was removed at the request of the manufacturer.

TABLE 33: STUDY CHARACTERISTICS OF INCLUDED TRIALS IN THE NMA FOR VIRAL SUPPRESSION

Study Name	Reference	TA1	BT1	n1	Responders	%	TA2	BT2	n2	Responders	%
[redacted]											

ABC/3TC = abacavir/lamivudine; ATV/r = ritonavir-boosted atazanavir; BT = background therapy; CrI = credible interval; DRV/r = ritonavir-boosted darunavir; EFV = efavirenz; EVG/c = elvitegravir/cobicistat; FPV/r = ritonavir-boosted fosamprenavir; LPV/r = ritonavir-boosted lopinavir; RAL = raltegravir; RPV = rilpivirine; SQV/r = ritonavir-boosted saquinavir; TA = treatment arm; TDF/FTC = tenofovir disoproxil fumarate/emtricitabine; ZDV = zidovudine.
Note: Three studies had additional treatment groups not shown in Table 33:

[redacted]

Results of the Network Meta-analysis

Efficacy Outcomes

Virologic Suppression

Data for virologic suppression at 48 weeks was available for 26 studies for the adjusted background therapy analysis, and for 22 studies for the unadjusted analysis. As seen in Table 34, the results for

virological suppression at 48 weeks demonstrated that DTG was numerically superior to all NNRTIs and boosted PIs and INSTIs. All results were statistically significant with the exception of the INSTIs, though statistical significance was not achieved for the INSTIs (EVG/c and RAL) for both the adjusted and unadjusted background therapy analyses, and RPV for the unadjusted analysis. As seen in Table 35, regardless of background therapy, DTG demonstrated the highest absolute proportion of patients achieving virologic suppression at week 48. Results at 96 weeks, which included 13 studies for the adjusted background therapy analysis and 10 studies from the unadjusted analysis, supported the findings from week 48 as the odds ratios (ORs) and risk differences favoured DTG when compared with all other treatments (results not shown). The results of the adjusted background therapy analysis were all statistically significant, while the results of the unadjusted analysis only demonstrated statistical significance for the ATV/r, LPV/r, EFV, and RPV comparisons.

TABLE 34: ODDS RATIOS AND RISK DIFFERENCES FOR VIROLOGIC SUPPRESSION AT 48 WEEKS (FIXED-EFFECTS MODEL)

	OR (95% CrI)		RD (95% CrI)	
DTG Versus	BT Adjusted [N = 26 Studies]	BT Unadjusted [N = 22 Studies]	BT Adjusted [N = 26 Studies]	BT Unadjusted [N = 22 Studies]
ATV/r	**2.20 (1.46, 3.18)[a]**	**2.08 (1.40 to 2.96)[a]**	[redacted]	[redacted]
DRV/r	**1.96 (1.30, 2.85)[a]**	**1.90 (1.27 to 2.74)[a]**	[redacted]	[redacted]
EFV	**1.85 (1.34, 2.50)[a]**	**1.75 (1.29 to 2.33)[a]**	[redacted]	[redacted]
EVG/c	1.53 (0.95, 2.33)	1.45 (0.90 to 2.19)	[redacted]	[redacted]
LPV/r	**2.61 (1.78, 3.68)[a]**	**2.48 (1.72 to 3.46)[a]**	[redacted]	[redacted]
RAL	1.30 (0.92, 1.79)	1.26 (0.90 to 1.73)	[redacted]	[redacted]
RPV	**1.51 (1.01, 2.17)[a]**	1.42 (0.96 to 2.03)	[redacted]	[redacted]

ATV/r = ritonavir-boosted atazanavir; BT = background therapy; BTA = background therapy adjusted; CrI = credible interval; DRV/r = ritonavir-boosted darunavir; DTG = dolutegravir; EFV = efavirenz; EVG/c = elvitegravir/cobicistat; LPV/r = ritonavir-boosted lopinavir; OR = odds ratio; RAL = raltegravir; RD = risk difference; RPV = rilpivirine.
[a] Statistically significant at 95% CrI.
Note: OR greater than one favours DTG.

TABLE 35: ABSOLUTE PROPORTION OF PATIENTS ACHIEVING VIROLOGIC SUPPRESSION AT 48 WEEKS (FIXED-EFFECTS MODEL)

Pooled Absolute Probabilities of Virologic Suppression (95% CrI)				
Third Agent	TDF/FTC [N = 26 Studies]	ABC/3TC [N = 22 Studies]	Other [N = 26 Studies]	BT Unadjusted [N = 22 Studies]
ATV/r	0.74 (0.68, 0.79)	0.72 (0.66, 0.78)	0.68 (0.62, 0.74)	0.71 (0.66, 0.76)
DRV/r	0.76 (0.68, 0.83)	0.74 (0.66, 0.81)	0.71 (0.62, 0.78)	0.73 (0.65, 0.80)
DTG	**0.86 (0.81, 0.90)**	**0.85 (0.80, 0.88)**	**0.82 (0.77, 0.87)**	**0.84 (0.79, 0.87)**
EFV	0.77 (0.74, 0.79)	0.75 (0.72, 0.78)	0.72 (0.68, 0.75)	0.75 (0.74, 0.76)
EVG/c	0.80 (0.74, 0.85)	0.79 (0.72, 0.84)	0.76 (0.69, 0.82)	0.78 (0.72, 0.83)
LPV/r	0.70 (0.65, 0.76)	0.68 (0.62, 0.74)	0.65 (0.58, 0.71)	0.68 (0.62, 0.73)
RAL	0.83 (0.77, 0.87)	0.81 (0.75, 0.86)	0.78 (0.72, 0.84)	0.80 (0.75, 0.85)
RPV	0.80 (0.76, 0.84)	0.79 (0.74, 0.83)	0.76 (0.71, 0.80)	0.78 (0.75, 0.82)

ABC/3TC = abacavir/lamivudine; ATV/r = ritonavir-boosted atazanavir; BT = background therapy; CrI = credible interval; DRV/r = ritonavir-boosted darunavir; DTG = dolutegravir; EFV = efavirenz; EVG/c = elvitegravir/cobicistat; LPV/r = ritonavir-boosted lopinavir; RAL = raltegravir; RPV = rilpivirine; TDF/FTC = tenofovir disoproxil fumarate/emtricitabine.

Virologic Suppression by Baseline Virologic Load at 48 Weeks

[redacted]As seen in Table 37, [redacted]Table 37.

TABLE 36: RELATIVE ODDS OF VIROLOGIC SUPPRESSION AT WEEK 48 BY BASELINE VIROLOGIC LOAD SUBGROUP

DTG Versus	VL < 100,000 [N = 12 Studies]			VL > 100,000 [N = 14 Studies]			Overall [N = 22 Studies]		
	Mean	SD	95% CrI	Mean	SD	95% CrI	Mean	SD	95% CrI
ATV/r	[redacted]								
DRV/r	[redacted]								
EFV	[redacted]								
EVG/c	[redacted]								
LPV/r	[redacted]								
RAL	[redacted]								
RPV	[redacted]								

ATV/r = ritonavir-boosted atazanavir; BT = background therapy; CrI = credible interval; DRV/r = ritonavir-boosted darunavir; EFV = efavirenz; EVG/c = elvitegravir/cobicistat; LPV/r = ritonavir-boosted lopinavir; RAL = raltegravir; RPV = rilpivirine; SD = standard deviation; VL = viral load.
Note: Odds ratio greater than 1 favours DTG.

TABLE 37: ABSOLUTE PROBABILITIES OF VIROLOGIC SUPPRESSION AT WEEK 48 BY BASELINE VIROLOGIC LOAD SUBGROUP

	VL < 100,000 [N = 11 Studies]			VL > 100,000 [N = 13 Studies]			Overall [N = 19 Studies]		
Third Agent	Mean	SD	95% CrI	Mean	SD	95% CrI	Mean	SD	95% CrI
ATV/r	[redacted]								
DRV/r	[redacted]								
DTG	[redacted]								
EFV	[redacted]								
EVG/c	[redacted]								
LPV/r	[redacted]								
RAL	[redacted]								
RPV	[redacted]								

ATV/r = ritonavir-boosted atazanavir; BT = background therapy; CrI = credible interval; DRV/r = ritonavir-boosted darunavir; EFV = efavirenz; EVG/c = elvitegravir/cobicistat; LPV/r = ritonavir-boosted lopinavir; RAL = raltegravir; RPV = rilpivirine; SD = standard deviation; VL = viral load.

CD4 Cell Change From Baseline

Data for relative differences in CD4 cells from baseline was available for 28 studies for the adjusted background therapy analysis, and for 24 studies for the unadjusted analysis. As seen in Table 38, DTG had higher mean CD4 increases compared with all other treatments at 48 weeks. Statistical significance was achieved for all comparisons, with the exception of EVG/c for the adjusted background therapy analysis, and RAL for both the adjusted and unadjusted background therapy analyses. [redacted]

[redacted] (Table 39).

TABLE 38: RELATIVE DIFFERENCE OF MEAN CD4 CELL CHANGE FROM BASELINE AT 48 WEEKS (FIXED-EFFECTS MODEL)

	Relative CD4 Difference (95% CrI)	
DTG Versus	BT Adjusted [N = 28 Studies]	BT Unadjusted [N = 24 Studies]
ATV/r	[redacted]	[redacted]
DRV/r	[redacted]	[redacted]
EFV	[redacted]	[redacted]
EVG/c	[redacted]	[redacted]
LPV/r	[redacted]	[redacted]
RAL	[redacted]	[redacted]
RPV	[redacted]	[redacted]

ATV/r = ritonavir-boosted atazanavir; BT = background therapy; CrI = credible interval; DRV/r = ritonavir-boosted darunavir; EFV = efavirenz; EVG/c = elvitegravir/cobicistat; LPV/r = ritonavir-boosted lopinavir; RAL = raltegravir; RPV = rilpivirine.
[redacted]

TABLE 39: ABSOLUTE MEAN CD4 CELL CHANGE FROM BASELINE AT 48 WEEKS (FIXED-EFFECTS MODEL)

	Absolute CD4 Change From Baseline to Week 48 (95% CrI)			
Third Agent	TDF/FTC [N = 28 Studies]	ABC/3TC [N = 28 Studies]	Other [N = 28 Studies]	BT Unadjusted [N = 24 Studies]
ATV/r	[redacted]	[redacted]	[redacted]	[redacted]
DRV/r	[redacted]	[redacted]	[redacted]	[redacted]
DTG	[redacted]	[redacted]	[redacted]	[redacted]
EFV	[redacted]	[redacted]	[redacted]	[redacted]
EVG/c	[redacted]	[redacted]	[redacted]	[redacted]
LPV/r	[redacted]	[redacted]	[redacted]	[redacted]
RAL	[redacted]	[redacted]	[redacted]	[redacted]
RPV	[redacted]	[redacted]	[redacted]	[redacted]

ABC/3TC = abacavir/lamivudine; ATV/r = ritonavir-boosted atazanavir; BT = background therapy; CD4+ = helper-inducer T-lymphocyte surface antigen; CrI = credible interval; DRV/r = ritonavir-boosted darunavir; EFV = efavirenz; EVG/c = elvitegravir/cobicistat; LPV/r = ritonavir-boosted lopinavir; RAL = raltegravir; RPV = rilpivirine; TDF/FTC = tenofovir disoproxil fumarate/emtricitabine.

Safety Outcomes

Total Cholesterol

[redacted] As seen in Table 40, [redacted]

[redacted]

Table 41.

TABLE 40: RELATIVE DIFFERENCE OF TOTAL CHOLESTEROL CHANGE FROM BASELINE AT 48 WEEKS (FIXED-EFFECTS MODEL)

	Relative Total Cholesterol Difference (95% CrI)	
DTG Versus	BT Adjusted[a] [N = 20 Studies]	BT Unadjusted [N = 19 Studies]
ATV/r	[redacted]	[redacted]
DRV/r	[redacted]	[redacted]
EFV	[redacted]	[redacted]
EVG/c	[redacted]	[redacted]
LPV/r	[redacted]	[redacted]
RAL	[redacted]	[redacted]
RPV	[redacted]	[redacted]

ATV/r = ritonavir-boosted atazanavir; BT = background therapy; CrI = credible interval; DRV/r = ritonavir-boosted darunavir; EFV = efavirenz; EVG/c = elvitegravir/cobicistat; LPV/r = ritonavir-boosted lopinavir; RAL = raltegravir; RPV = rilpivirine.
[a] Based on reference background therapy TDF/FTC.

[redacted]

TABLE 41: ABSOLUTE TOTAL CHOLESTEROL CHANGE FROM BASELINE AT 48 WEEKS (FIXED-EFFECTS MODEL)

	Absolute Total Cholesterol Change From Baseline To Week 48 (95% CrI)			
Third Agent	TDF/FTC [N = 20 Studies]	ABC/3TC [N = 20 Studies]	Other [N = 20 Studies]	BT Unadjusted [N = 19 Studies]
ATV/r	[redacted]	[redacted]	[redacted]	[redacted]
DRV/r	[redacted]	[redacted]	[redacted]	[redacted]
DTG	[redacted]	[redacted]	[redacted]	[redacted]
EFV	[redacted]	[redacted]	[redacted]	[redacted]
EVG/c	[redacted]	[redacted]	[redacted]	[redacted]
LPV/r	[redacted]	[redacted]	[redacted]	[redacted]
RAL	[redacted]	[redacted]	[redacted]	[redacted]
RPV	[redacted]	[redacted]	[redacted]	[redacted]

ABC/3TC = abacavir/lamivudine; ATV/r = ritonavir-boosted atazanavir; BT = background therapy; CrI = credible interval; DRV/r = ritonavir-boosted darunavir; EFV = efavirenz; EVG/c = elvitegravir/cobicistat; LPV/r = ritonavir-boosted lopinavir; RAL = raltegravir; RPV = rilpivirine; TDF/FTC = tenofovir disoproxil fumarate/emtricitabine.

HDL Change

[redacted] As seen in Table 42, [redacted] in Table 43.

TABLE 42: RELATIVE DIFFERENCE OF MEAN HDL CHANGE FROM BASELINE AT 48 WEEKS (FIXED-EFFECTS MODEL)

	Relative HDL Difference (95% CrI)	
DTG Versus	BT Adjusted[a] [N = 19 Studies]	BT Unadjusted [N = 18 Studies]
ATV/r	[redacted]	[redacted]
DRV/r	[redacted]	[redacted]
EFV	[redacted]	[redacted]
EVG/c	[redacted]	[redacted]
LPV/r	[redacted]	[redacted]
RAL	[redacted]	[redacted]
RPV	[redacted]	[redacted]

ATV/r = ritonavir-boosted atazanavir; BT = background therapy; CrI = credible interval; DRV/r = ritonavir-boosted darunavir; EFV = efavirenz; EVG/c = elvitegravir/cobicistat; LPV/r = ritonavir-boosted lopinavir; RAL = raltegravir; RPV = rilpivirine.
[a] Based on tenofovir disoproxil fumarate/emtricitabine TDF/FTC) reference background therapy.
[redacted]

TABLE 43: ABSOLUTE HDL CHANGE FROM BASELINE AT 48 WEEKS (FIXED-EFFECTS MODEL)

	Absolute HDL Change From Baseline to Week 48 (95% CrI)			
Third Agent	TDF/FTC [N = 19 Studies]	ABC/3TC [N = 19 Studies]	Other [N = 19 Studies]	BT Unadjusted [N = 18 Studies]
ATV/r	[redacted]	[redacted]	[redacted]	[redacted]
DRV/r	[redacted]	[redacted]	[redacted]	[redacted]
DTG	[redacted]	[redacted]	[redacted]	[redacted]
EFV	[redacted]	[redacted]	[redacted]	[redacted]
EVG/c	[redacted]	[redacted]	[redacted]	[redacted]
LPV/r	[redacted]	[redacted]	[redacted]	[redacted]
RAL	[redacted]	[redacted]	[redacted]	[redacted]
RPV	[redacted]	[redacted]	[redacted]	[redacted]

ABC/3TC = abacavir/lamivudine; ATV/r = ritonavir-boosted atazanavir; BT = background therapy; CrI = credible interval; DRV/r = ritonavir-boosted darunavir; EFV = efavirenz; EVG/c = elvitegravir/cobicistat; HDL = high-density lipoprotein; LPV/r = ritonavir-boosted lopinavir; RAL = raltegravir; RPV = rilpivirine; TDF/FTC = tenofovir disoproxil fumarate/emtricitabine.

LDL Change

[redacted] As seen in Table 44, [redacted] in Table 45.

TABLE 44: RELATIVE DIFFERENCE OF MEAN LDL CHANGE FROM BASELINE AT 48 WEEKS (FIXED-EFFECTS MODEL)

	Relative LDL Difference (95% CrI)	
DTG Versus	BT Adjusted[a] [N = 17 Studies]	BT Unadjusted [N = 16 Studies]
ATV/r	[redacted]	[redacted]
DRV/r	[redacted]	[redacted]
EFV	[redacted]	[redacted]
EVG/c	[redacted]	[redacted]
LPV/r	[redacted]	[redacted]
RAL	[redacted]	[redacted]
RPV	[redacted]	[redacted]

ATV/r = ritonavir-boosted atazanavir; BT = background therapy; CrI = credible interval; DRV/r = ritonavir-boosted darunavir; EFV = efavirenz; EVG/c = elvitegravir/cobicistat; LDL = low-density lipoprotein; LPV/r = ritonavir-boosted lopinavir; RAL = raltegravir; RPV = rilpivirine; TDF/FTC = tenofovir disoproxil fumarate/emtricitabine.
[a] Based on TDF/FTC reference background therapy.
[redacted]

TABLE 45: ABSOLUTE HDL CHANGE FROM BASELINE AT 48 WEEKS (FIXED-EFFECTS MODEL)

	Absolute HDL Change From Baseline to Week 48 (95% CrI)			
Third Agent	TDF/FTC [N = 17 Studies]	ABC/3TC [N = 17 Studies]	Other [N = 17 Studies]	BT Unadjusted [N = 16 Studies]
ATV/r	[redacted]	[redacted]	[redacted]	[redacted]
DRV/r	[redacted]	[redacted]	[redacted]	[redacted]
DTG	[redacted]	[redacted]	[redacted]	[redacted]
EFV	[redacted]	[redacted]	[redacted]	[redacted]
EVG/c	[redacted]	[redacted]	[redacted]	[redacted]
LPV/r	[redacted]	[redacted]	[redacted]	[redacted]
RAL	[redacted]	[redacted]	[redacted]	[redacted]
RPV	[redacted]	[redacted]	[redacted]	[redacted]

ABC/3TC = abacavir/lamivudine; ATV/r = ritonavir-boosted atazanavir; BT = background therapy; CrI = credible interval; DRV/r = ritonavir-boosted darunavir; EFV = efavirenz; EVG/c = elvitegravir/cobicistat; HDL = high-density lipoprotein; LPV/r = ritonavir-boosted lopinavir; RAL = raltegravir; RPV = rilpivirine; TDF/FTC = tenofovir disoproxil fumarate/emtricitabine.

Triglycerides

[redacted] As seen in Table 46, [redacted] in Table 47.

TABLE 46: RELATIVE DIFFERENCE OF MEAN TRIGLYCERIDES CHANGE FROM BASELINE AT 48 WEEKS (FIXED-EFFECTS MODEL)

	Relative Triglycerides Difference (95% CrI)	
DTG Versus	BT Adjusted[a] [N = 17 Studies]	BT Unadjusted [N = 16 Studies]
ATV/r	[redacted]	[redacted]
DRV/r	[redacted]	[redacted]
EFV	[redacted]	[redacted]
EVG/c	[redacted]	[redacted]
LPV/r	[redacted]	[redacted]
RAL	[redacted]	[redacted]
RPV	[redacted]	[redacted]

ATV/r = ritonavir-boosted atazanavir; BT = background therapy; CrI = credible interval; DRV/r = ritonavir-boosted darunavir; EFV = efavirenz; EVG/c = elvitegravir/cobicistat; LPV/r = ritonavir-boosted lopinavir; RAL = raltegravir; RPV = rilpivirine.
[a] Based on TDF/FTC reference background therapy.
[redacted]

TABLE 47: ABSOLUTE TRIGLYCERIDE CHANGE FROM BASELINE AT 48 WEEKS (FIXED-EFFECTS MODEL)

	Absolute Triglycerides Change From Baseline to Week 48 (95% CrI)			
Third Agent	TDF/FTC [N = 17 Studies]	ABC/3TC [N = 17 Studies]	Other [N = 17 Studies]	BT Unadjusted [N = 17 Studies]
ATV/r	[redacted]	[redacted]	[redacted]	[redacted]
DRV/r	[redacted]	[redacted]	[redacted]	[redacted]
DTG	[redacted]	[redacted]	[redacted]	[redacted]
EFV	[redacted]	[redacted]	[redacted]	[redacted]
EVG/c	[redacted]	[redacted]	[redacted]	[redacted]
LPV/r	[redacted]	[redacted]	[redacted]	[redacted]
RAL	[redacted]	[redacted]	[redacted]	[redacted]
RPV	[redacted]	[redacted]	[redacted]	[redacted]

ABC/3TC = abacavir/lamivudine; ATV/r = ritonavir-boosted atazanavir; BT = background therapy; CrI = credible interval; DRV/r = ritonavir-boosted darunavir; EFV = efavirenz; EVG/c = elvitegravir/cobicistat; LPV/r = ritonavir-boosted lopinavir; RAL = raltegravir; RPV = rilpivirine; TDF/FTC = tenofovir disoproxil fumarate/emtricitabine.

Adverse Events at Week 48

[redacted] As seen in Table 1, [redacted] in Table 49.

TABLE 48: ODDS OF OVERALL ADVERSE EVENTS AT 48 WEEKS (FIXED-EFFECTS MODEL)

	Odds of Overall Adverse Events		
DTG Versus	Mean	SD	(95% CrI)
ATV/r	[redacted]	[redacted]	[redacted]
DRV/r	[redacted]	[redacted]	[redacted]
EFV	[redacted]	[redacted]	[redacted]
EVG/c	[redacted]	[redacted]	[redacted]
LPV/r	[redacted]	[redacted]	[redacted]
RAL	[redacted]	[redacted]	[redacted]
RPV	[redacted]	[redacted]	[redacted]

ATV/r = ritonavir-boosted atazanavir; BT = background therapy; CrI = credible interval; DRV/r = ritonavir-boosted darunavir; EFV = efavirenz; EVG/c = elvitegravir/cobicistat; LPV/r = ritonavir-boosted lopinavir; RAL = raltegravir; RPV = rilpivirine.
Note: Less than 1 favours DTG.
[redacted]

TABLE 49: ABSOLUTE PROPORTION OF ADVERSE EVENTS AT 48 WEEKS (FIXED-EFFECTS MODEL)

	Overall Adverse Events		
Third Agent	Mean	SD	(95% CrI)
ATV/r	[redacted]	[redacted]	[redacted]
DRV/r	[redacted]	[redacted]	[redacted]
DTG	[redacted]	[redacted]	[redacted]
EFV	[redacted]	[redacted]	[redacted]
EVG/c	[redacted]	[redacted]	[redacted]
LPV/r	[redacted]	[redacted]	[redacted]
RAL	[redacted]	[redacted]	[redacted]
RPV	[redacted]	[redacted]	[redacted]

Critical Appraisal of Network Meta-analysis

The quality of the manufacturer-submitted NMA was assessed according to recommendations provided by the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons. Details and commentary for each of the relevant items identified by ISPOR are provided in Table 50.

Strengths

The NMA appears to satisfy most of the ISPOR criteria. A clearly stated rationale and objectives for the NMA were clearly stated. The inclusion criteria for individual RCTs were clearly stated and the study selection and the data extraction process were provided. A comprehensive search strategy was employed to identify and select relevant RCTs for the third-agent comparators. The methodological quality of the included RCT was assessed using the Effective Public Health Practice Project Quality Assessment (EPHPP).[29]

The NMA was conducted using appropriate methodology (i.e., Bayesian NMA models created with WinBUGS) and a description of the statistical model was provided. The outcome measures assessed in the NMA were appropriate and clearly stated. The use of virological suppression, measured as HIV RNA < 50 copies/mL, was justified, as it is in concordance with the US FDA guidelines[21] for determining virologic success. A fixed-effects model was selected based on the results of model convergence and model-fit statistics. Model fit was determined by the Deviance Information Criterion and residual

deviance. Results according to the random-effects model were provided and were generally comparable. Non-informative prior distributions on model parameters were used. As suggested by the clinical expert consulted on this review, the choice of background therapy may impact outcomes, as background therapy with TDF/FTC tends to be more effective in reducing viral loads. Thus, the adjusted analysis for background treatment may provide more robust results. There was no statistically significant difference between direct evidence and model estimates when consistency testing was performed using one non-EFV arm of each independent loop.

Limitations

The investigators deemed that the included studies were comparable with generally similar inclusion and exclusion criteria, though this specific data were not provided to CDR reviewers; consequently, this conclusion cannot be confirmed. Furthermore, individual study data for the outcomes of interest were not provided. Based on the EPHPP scale, the majority of the included studies (60.8%) had moderate global rating and methodological quality. According to the investigators, the main attribute that contributed to the greater proportion of studies being of moderate methodological quality was the inclusion of open-label designs.

Summary

The NMA methodology was appropriate and provided an up-to-date comparison of treatment efficacy and safety of guideline-recommended and newly approved ART third agents in treatment-naive HIV-infected individuals. Overall, the results of the NMA showed a statistically significant higher probability of virological suppression with DTG compared with all NNRTIs (EFV, RPV) and PIs (ARV/r, DRV/r, LPV/r) at 48 weeks. Patients with high virological loads (HIV RNA > 100,000) favoured DTG over all treatments of interest with the exception of RAL, whereas low virological patients (HIV RNA < 100,000) favoured EFV only. At 96 weeks, DTG had a higher probability of virologic suppression compared with all comparators of interest after backbone adjustment.

At 48 weeks, DTG resulted in significantly higher CD4 cell increases from baseline compared with all NNRTIs (EFV, RPV) and PIs (ARV/r, DRV/r, LPV/r) and [redacted]

TABLE 50: APPRAISAL OF NETWORK META-ANALYSIS USING ISPOR CRITERIA

ISPOR Checklist Item		Details and Comments
1.	Are the rationale for the study and the objectives stated clearly?	• The rationale for conducting a network meta-analysis and the study objectives were clearly stated.
2.	Does the methods section include the following? • Eligibility criteria • Information sources • Search strategy • Study selection process • Data extraction • Validity of individual studies	• The eligibility criteria for individual RCTs was clearly stated. • Search strategy, study selection process, and data extraction were clearly stated for all comparators. • The search strategy was provided. • Study selection and data extraction process were identified. • Methodological quality of the individual study trials was assessed using the Effective Public Health Practice Project Quality Assessment (EPHPP). • Heterogeneity between studies was assessed.
3.	Are the outcome measures described?	• Specific outcomes were clearly stated. • The justification for the efficacy outcomes used was that this

ISPOR Checklist Item		Details and Comments
		was in concordance with the US FDA guidelines[21] for determining virologic success (HIV RNA < 50).
4.	Is there a description of methods for analysis/synthesis of evidence? • Description of analyses methods, and models • Handling of potential bias or inconsistency • Analysis framework	• A description of the statistical model was provided. • Model selection was based on model convergence and model-fit statistics. • A fixed model was selected for the analysis; results for random effects were also provided for reference.
5.	Are sensitivity analyses presented?	• Sensitivity analyses for background treatment adjustment were performed.
6.	Do the results include a summary of the studies included in the network of evidence? • Individual study data? • Network of studies?	• A table with study characteristics was provided, though basic demographic information (i.e., age, sex, race) for each included study was not provided. • A figure showing the network of studies was provided. • Individual study results were not provided.
7.	Does the study describe an assessment of model fit?	• Model fit was determined by the Deviance Information Criterion and residual deviance.
8.	Are the results of the evidence synthesis presented clearly?	• Tables were provided with both absolute and relative results for each outcome.
9.	Sensitivity and scenario analyses	• Sensitivity analyses for background treatment adjustment were performed. Baseline virologic load was also presented for the primary outcome.

FDA = Food and Drug Administration; RCT = randomized controlled trial; RNA = ribonucleic acid.

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