Common Drug Review
Clinical Review Report

November 2016

Drug	Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (EVG/COBI/FTC/TAF) (Genvoya) fixed-dose combination, oral tablet)
Indication	As a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and pediatric patients 12 years of age and older (and weighing ≥ 35 kg) and with no known mutations associated with resistance to the individual components of Genvoya
Reimbursement request	For treatment-naive and virologically suppressed HIV-1 infected adult and pediatric patients 12 years of age and older with no known mutations associated with resistance to the individual components of EVG/COBI/FTC/TAF
Dosage form(s)	EVG 150 mg/COBI 150 mg/FTC 200 mg/TAF 10 mg
NOC date	November 27, 2015
Manufacturer	Gilead Sciences Canada, Inc.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in the treatment of HIV infection who provided input on the conduct of the review and the interpretation of findings.

Through the CADTH Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary reimbursement recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

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ABBREVIATIONS

3TC	lamivudine
ABC	abacavir
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ANOVA	analysis of variance
ART	antiretroviral therapy
ARV	antiretroviral
ATV/r	ritonavir-boosted atazanavir
BMI	body mass index
BMD	bone mineral density
CD4	cluster of differentiation 4
CI	confidence interval
CrCl	creatinine clearance
COBI	cobicistat
CTAC	Canadian Treatment Action Council
DB	double-blind
DHHS	Department of Health and Human Services
DTG	dolutegravir
DXA	dual-energy X-ray absorptiometry
EFV	efavirenz
EVG	elvitegravir
eGFR	estimated glomerular filtration rate
$eGFR_{CG}$	estimated glomerular filtration rate according to the Cockcroft-Gault formula
EVG	elvitegravir
FAS	full analysis set
FDC	fixed-dose combination
FTC	emtricitabine
HAART	highly active antiretroviral therapy
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
HBV	hepatitis B virus
HCV	hepatitis C virus
HRQoL	health-related quality of life
LSM	least squares mean
NI	non-inferiority
PP	per-protocol
RCT	randomized controlled trial
RNA	ribonucleic acid
RPV	rilpivirine
SAE	serious adverse event

STR	single-tablet regimen
TAF	tenofovir alafenamide fumarate
TBLH	total body less head
TFV	tenofovir
TDF	tenofovir disoproxil fumarate
URTI	upper respiratory tract infection
VL	viral load
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

The current standard of care for human immunodeficiency virus (HIV) management is to treat patients with a combination of antiretroviral (ARV) drugs with the primary goal of achieving and maintaining maximal suppression of viral load (VL), leading to restoration and preservation of immunologic function, improvement of quality of life, and reduction of HIV-related morbidity and mortality. Genvoya (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fumarate) (EVG/COBI/FTC/TAF) is a single-tablet regimen (STR) with a Health Canada indication for the treatment of HIV type 1 (HIV-1) infection in adults and pediatric patients 12 years of age and older (weighing ≥ 35 kg) with no known mutations associated with resistance to the individual components of EVG/COBI/FTC/TAF. It includes the components of Stribild (EVG/COBI/FTC/tenofovir disoproxil fumarate [TDF]), except that the prodrug TDF has been replaced with the prodrug TAF.

Indication under review
For the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and pediatric patients 12 years of age and older (weighing ≥ 35 kg) with no known mutations associated with resistance to the individual components of EVG/COBI/FTC/TAF.
Listing criteria requested by sponsor
For treatment-naive and virologically suppressed HIV-1 infected adult and pediatric patients 12 years of age and older with no known mutations associated with resistance to the individual components of EVG/COBI/FTC/TAF.

The objective of this systematic review is to evaluate of the beneficial and harmful effects of the fixed-dose combination (FDC) of EVG/COBI/FTC/TAF for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older with no known mutations associated with resistance to the individual components of EVG/COBI/FTC/TAF.

Results and Interpretation

Included Studies

The evidence for this review was drawn from two phase 3 multi-centre, double-blind (DB), double-dummy, active-controlled, non-inferiority trials (Study 104, n = 872; Study 111, n = 872), one phase 3 multi-centre, open-label, active-controlled, non-inferiority trial (Study 109, n = 1,443), and two multi-centre, open-label, single-group cohort studies (Study 112, n = 252; Study 106, n = 48). The primary efficacy outcome for all studies was the percentage of patients with HIV-1 ribonucleic acid (RNA) < 50 copies/mL at week 48 (Studies 104, 111, and 109) or week 24 (Studies 112 and 106) using the FDA-defined snapshot algorithm. The non-inferiority margin in Studies 104, 111, and 109 was 12%, which is accepted by the FDA.

Studies 104 and 111 exclusively enrolled treatment-naive adults, whereas Study 109 enrolled only virologically suppressed adults who had been on an ARV regimen consisting of FTC/TDF + a third drug. No major methodological limitations with these studies were identified. There were no direct comparative data available against dolutegravir/abacavir/lamivudine (DTG/ABC/3TC), which is another US Department of Health and Human Services (DHHS)-preferred initial regimen available in Canada. Studies 112 and 106 evaluated the efficacy and safety of EVG/COBI/FTC/TAF in HIV-infected adults with

mild to moderate renal impairment and treatment-naive adolescents, respectively. Due to the lack of a comparator group, however, the results could not demonstrate the relative efficacy and safety of EVG/COBI/FTC/TAF in the study populations. In addition, given the small sample sizes, the results were insufficient to draw robust conclusions about the efficacy and safety of EVG/COBI/FTC/TAF in these populations.

Efficacy

In Studies 104 and 111, EVG/COBI/FTC/TAF was statistically non-inferior to EVG/COBI/FTC/TDF with respect to the primary efficacy outcome (Table 1). In Study 109, results from the primary analyses demonstrated that significantly more patients who switched to EVG/COBI/FTC/TAF versus those who stayed on their pre-existing FTC/TDF + a third drug regimen achieved VL < 50 copies/mL at week 48. In Study 112, the primary analysis demonstrated that the virologic success rates at 24 weeks were 95.0% and 83.3% among adults who switched to EVG/COBI/FTC/TAF from their existing ARV regimen and treatment-naive adults who received EVG/COBI/FTC/TAF, respectively (Table 2). In Study 106, the virologic success rate at 24 weeks was 91.3% for 23 antiretroviral therapy (ART)-naive adolescents receiving EVG/COBI/FTC/TAF.

Across the three randomized controlled trials (RCTs), there were very few patients who developed primary genotypic resistance through week 48. In Studies 112 and 106, through week 48, no patients receiving EVG/COBI/FTC/TAF developed new resistance or mutations that were not already present at baseline. Further, there were no differences in health-related quality of life (HRQoL) among patients receiving EVG/COBI/FTC/TAF or a comparator.

Harms

Across all five studies, at least 80% of patients in each trial experienced at least one treatment-emergent adverse event (AE). Diarrhea, nausea, upper respiratory tract infections (URTIs), and headache appeared to be the most common AEs reported by patients receiving EVG/COBI/FTC/TAF. The percentage of patients who experienced a serious adverse event (SAE) while receiving EVG/COBI/FTC/TAF varied. Across the three RCTs, fewer patients receiving EVG/COBI/FTC/TAF withdrew due to AEs than those receiving a comparator. There were two deaths reported in Study 104 (one in the EVG/COBI/FTC/TAF group) and three in Study 111 (one in the EVG/COBI/FTC/TAF group). In Study 109, four patients who switched to EVG/COBI/FTC/TAF from a pre-existing regimen of FTC/TDF + a third drug died, although none of those deaths were considered treatment-related; no patients died in the comparator group. There were no deaths in Studies 112 and 106.

Exposure to TDF as part of a combination ART regimen has been shown to increase kidney damage and reduce kidney function in patients with HIV, although these changes rarely warrant discontinuation of therapy according to the clinical expert consulted for this review. EVG/COBI/FTC/TAF decreased the effect on kidney function (median estimated glomerular filtration rate [eGFR]) from baseline to week 48 in treatment-naive patients relative to EVG/COBI/FTC/TDF in Studies 104 and 111. In Study 109, median eGFR increased slightly from baseline among patients who switched to EVG/COBI/FTC/TAF from a pre-existing regimen of FTC/TDF + a third drug but decreased among those who stayed on their pre-existing regimen, resulting in a significant difference between groups. In Study 112, among virologically suppressed adults, overall kidney function appeared to decrease at 24 weeks, although the effect seemed to differ by severity of kidney impairment at baseline. Among treatment-naive patients in the same study, there was minimal change in median eGFR from baseline. In Study 106, there appeared to be a larger decrease compared with the adult studies in overall median eGFR from baseline to week 24 among treatment-naive adolescents receiving EVG/COBI/FTC/TAF. In all, the consulting clinical expert

highlighted that the magnitude of the changes and differences between treatments across studies were not likely to be clinically meaningful in clinical practice, but may be important to track in the long term.

HIV-infected individuals experience accelerated bone loss compared with the general population, especially with TDF exposure, although the risk of fracture is low according to the consulting clinical expert. In the three RCTs, treatment with EVG/COBI/FTC/TAF appeared to decrease harmful effects on the bone system, as measured by changes in mean bone mineral density (BMD) at the hip and spine from baseline to week 48. In Study 112, the overall mean BMD at the hip and spine increased in the patients who switched to EVG/COBI/FTC/TAF from their existing ARV regimen, but decreased among treatment-naive patients at week 24. In Study 106, the overall mean spine and total body less head (TBLH) BMD increased among treatment-naive adolescents from baseline to week 24. The consulting clinical expert highlighted that the magnitude of the changes (across all studies) in BMD were not likely to be clinically meaningful in clinical practice, but may be important to track in the long term.

Conclusions

In two RCTs, EVG/COBI/FTC/TAF was shown to achieve statistically similar rates of VL suppression compared with EVG/COBI/FTC/TDF among treatment-naive adults with HIV infection after 48 weeks of treatment. In a third RCT, switch to EVG/COBI/FTC/TAF from another FTC/TDF-containing regimen among virologically suppressed patients was associated with significantly higher rates of virologic suppression at 48 weeks compared with continued therapy with the existing regimen.
EVG/COBI/FTC/TAF was associated with relatively similar rates of AEs as the comparator in these trials, among which diarrhea, nausea, URTIs, and headache appeared to be the most common. While EVG/COBI/FTC/TAF had smaller effects on kidney function (eGFR) and BMD compared with EVG/COBI/FTC/TDF, the observed changes are unlikely to be clinically significant in the short term and are of uncertain importance with respect to the risks for kidney failure or fracture in the long term.
EVG/COBI/FTC/TAF also demonstrated high rates of virologic suppression in a single-group study of patients with mild to moderate kidney impairment, with minimal changes in median eGFR. High rates of virologic suppression were also observed in a small, single-group trial of treatment-naive adolescents; however, in the absence of a comparative trial against EVG/COBI/FTC/TDF or another STR, there is greater uncertainty regarding relative efficacy and safety in this population compared with adults.

TABLE 1: SUMMARY OF RESULTS — TREATMENT-NAIVE OR VIROLOGICALLY SUPPRESSED ADULTS

		Study 104		Study 111		Study 109	
		EVG/COBI/FTC/TAF (N = 435)	Stribild (N = 432)	EVG/COBI/FTC/TAF (N = 431)	Stribild (N = 435)	EVG/COBI/FTC/TAF (N = 959)	FTC/TDF + third drug (N = 477)
Virologic success[a]							
N	FAS	435	432	431	435	959	477
	PP	[redacted]	[redacted]	[redacted]	[redacted]	921	440
HIV-1 RNA < 50 copies/mL, n (%)	FAS	405 (93.1)	399 (92.4)	395 (91.6)	385 (88.5)	932 (97.2)	444 (93.1)
	PP	[redacted]	[redacted]	[redacted]	[redacted]	913 (99.1)	435 (98.9)
Difference in % (95% CI)[b]; *P* value	FAS	1.0 (–2.6 to 4.5); *P* = 0.58		3.1 (–1.0 to 7.1); *P* = 0.13		4.1 (1.6 to 6.7); *P* = 0.0002	
	PP	[redacted]		[redacted]		0.3 (NR); *P* = NR	

	Study 104		Study 111		Study 109	
	EVG/COBI/FTC/TAF (N = 435)	Stribild (N = 432)	EVG/COBI/FTC/TAF (N = 431)	Stribild (N = 435)	EVG/COBI/FTC/TAF (N = 959)	FTC/TDF + third drug (N = 477)
AEs						
Participants with > 0 AEs, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	828 (86.3)	399 (83.7)
SAEs						
Participants with > 0 SAEs, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	65 (6.8)	35 (7.3)
WDAEs						
WDAEs, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	9 (0.9)	12 (2.5)
Deaths						
Number of deaths, N (%)	1 (0.2)	1 (0.2)	1 (0.2)	2 (0.5)	4 (0.4)	0

AEs = adverse events; CI = confidence interval; COBI = cobicistat; EVG = elvitegravir; FAS = full analysis set; FTC = emtricitabine; HIV-1 = human immunodeficiency virus type 1; NR = not reported; PP = per-protocol; RNA = ribonucleic acid; SAE = serious adverse event; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate; VL = viral load; WDAE = withdrawal due to adverse event.

[a] Non-inferiority margin is 12%.

[b] CI for Studies 104 and 111 is 95.002% and for Study 109 is 95.01%.

TABLE 2: SUMMARY OF RESULTS — SPECIAL POPULATIONS

	Study 112* (Reduced Kidney Function)				Study 106* (Adolescents)
Virologic Success (Snapshot Analysis)	Switch to EVG/COBI/FTC/TAF			ART-naive EVG/COBI/FTC/TAF (N = 6)	EVG/COBI/FTC/TAF (N = 48)
	Baseline $eGFR_{CG}$ < 50 mL/min (N = 80)	Baseline $eGFR_{CG}$ ≥ 50 mL/min (n = 162)	Total (N = 242)		
Virologic Success					
N	80	162	242	6	23
HIV-1 RNA < 50 copies/mL, n (%)	76 (95.0)	154 (95.1)	230 (95.0)	5 (83.3)	21 (91.3)
AEs					
Participants with > 0 AEs, N (%)	67 (83.8)	142 (87.7)	209 (86.4)	5 (83.3)	39 (81.3)
SAEs					
Participants with > 0 SAEs, N (%)	[redacted]	[redacted]	[redacted]	0	4 (8.3)
WDAEs					
WDAEs, N (%)	6 (7.5)	2 (1.2)	8 (3.3)	0	0
Deaths					
Number of deaths, N (%)	0	0	0	0	0

AE = adverse event; ART = antiretroviral therapy; COBI = cobicistat; $eGFR_{CG}$ = estimated glomerular filtration rate according to the Cockcroft-Gault formula; EVG = elvitegravir; FTC = emtricitabine; HIV-1 = human immunodeficiency virus type 1; RNA = ribonucleic acid; SAE = serious adverse event; TAF = tenofovir alafenamide fumarate; WDAE = withdrawal due to adverse event.

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Human immunodeficiency virus (HIV) attacks cluster of differentiation 4 (CD4)+ T-cells, components of the immune system necessary for defending the body against infection.[1] HIV progressively impairs immune response and, if left untreated, may lead to acquired immunodeficiency syndrome (AIDS), the final stage of HIV where a patient can no longer fight off infections and certain malignancies. HIV is transmitted through bodily fluids, and can be passed from an infected individual to a healthy individual through unprotected sex and sharing of drug needles.[2] An infected mother can also pass the virus to her baby during pregnancy or birth (vertical transmission), or breastfeeding. HIV can be divided into two major types: HIV type 1 (HIV-1) and HIV type 2 (HIV-2), between which HIV-1 is the predominant virus worldwide.[3]

At the end of 2011, Health Canada estimated that 71,300 people (range 58,600 to 84,000) were living with HIV infection in Canada,[4] an increase of 11.4% from the 2008 estimate of 64,000. Men who have sex with men (MSM) accounted for 46.7% of the total, injection drugs users 16.9%, heterosexuals 32.5%, and MSM who also inject drugs 3.0%.

In 2011, approximately 95% of reported HIV/AIDS cases were from Ontario (42.6%), Quebec (21.5%), British Columbia (13.4%), Alberta (9.7%), and Saskatchewan (7.7%).[5] The incidence in Canada of HIV infection was estimated at 3,175 (range 2,250 to 4,100) cases in 2011, which was comparable to data from 2008.[5]

1.2 Standards of Therapy

The current standard of care for HIV management is to treat with highly active antiretroviral therapy (HAART) with the primary goal of achieving and maintaining maximal suppression of viral load (VL), which leads to restoration and preservation of immunologic function, improvement of quality of life, and reduction of HIV-related morbidity and mortality.[6]

The choice of the optimal antiretroviral treatment (ART) 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.

As viral mutations conferring resistance to ART can occur only during viral replication, the goal of ART is the complete suppression of viral replication, as determined by repeated VL measurements below assay limit.[7] Virologic failure occurs when viral suppression is not achieved or maintained. A number of published guidelines are available to assist clinicians in choosing an appropriate first-line therapy. According to the consulting clinical expert for this review, the guidelines published by the US Department of Health and Human Services (DHHS) are the ones most commonly used in Canada.[6]

Treatment-naive adults

The DHHS recommends five regimens for ART-naive patients — four integrase strand transfer inhibitor (INSTI)-based regimens and one ritonavir-boosted protease inhibitor (PI/r)-based regimen, as follows:

INSTI-based regimens:

- Dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) — only for patients who are human leukocyte antigen (HLA)-B 5701 negative

- DTG plus tenofovir disoproxil fumarate/emtricitabine (TDF/FTC)
- Elvitegravir (EVG)/cobicistat (COBI)/TDF/FTC – only for patients with pre-ART creatinine clearance (CrCl) > 70 mL/min
- Raltegravir (RAL) plus TDF/FTC

PI/r-based regimen:

- Ritonavir-boosted darunavir (DRV/r) plus TDF/FTC

In Canada, two of these preferred regimens are available as single-tablet regimens (STRs): Stribild (EVG/COBI/TDF/FTC) and Triumeq (DTG/ABC/3TC). There are two additional STRs available, although they are listed as "alternative" by the DHHS, as follows: Atripla (efavirenz [EFV]/TDF/FTC) and Complera (rilpivirine [RPV]/TDF/FTC). Key characteristics of these regimens are presented in Table 3.

TABLE 3: KEY CHARACTERISTICS OF DEPARTMENT OF HEALTH AND HUMAN SERVICES-RECOMMENDED HIV REGIMENS FOR ANTIRETROVIRAL THERAPY-NAIVE PATIENTS AVAILABLE IN CANADA

	Stribild	Triumeq	Atripla	Complera
DHHS Listing	Recommended	Recommended	Alternative	Alternative
Base	INSTI	INSTI	NNRTI	NNRTI
Regimen	EVG/COBI/FTC/TDF	DTG/ABC/3TC	EFV/TDF/FTC	FTC/RPV/TDF
Mechanism of Action	**N(t)RTI** (e.g., TDF, FTC), **NNRTI** (e.g., EFV): inhibits HIV reverse transcriptase to prevent early-cycle viral replication **INSTI** (e.g., RAL): inhibits HIV integrase to prevent entry of viral DNA into host cell genome			
Indication[a]	As a complete regimen for the treatment of adults aged 18 years and older infected with HIV-1 with no known mutations to the integrase inhibitor class, tenofovir, or emtricitabine.	For the treatment of HIV infection in adults.	For the treatment of HIV-1 infection in adults.	For the treatment of HIV-1 infection in antiretroviral treatment-naive adults.
Route of Administration	Oral			
Recommended Dose	EVG 150 mg/COBI 150 mg/FTC 200 mg/TDF 300 mg once daily	DTG 50 mg/ABC 600 mg/3TC 300 mg once daily	EFV 600 mg/TDF 300 mg/FTC 200 mg once daily	FTC 200 mg/RPV 25 mg/TDF 300 mg once daily
Serious Side Effects/Safety Issues	Contraindications: Patients with previously demonstrated hypersensitivity to any of the components of product; multiple drugs Warnings and precautions: Lactic acidosis and severe hepatomegaly with	Contraindications: Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container; patients who are positive for the HLA-B 5701 allele and patients with a prior history of a hypersensitivity	Contraindications: Patients with previously demonstrated hypersensitivity to any of the components of product; multiple drugs Warnings and precautions: Lactic acidosis; severe	Contraindications: Patients with previously demonstrated hypersensitivity to FTC, RPV, TDF or to any of the excipients; multiple drugs Warnings and precautions: Lactic acidosis; severe

	Stribild	Triumeq	Atripla	Complera
	steatosis; post-treatment exacerbations of HBV; nephrotoxicity	reaction to ABC, or products containing ABC, regardless of HLA-B 5701 status; patients who are prescribed dofetilide Warnings and precautions: fatal hypersensitivity reactions; lactic acidosis and severe hepatomegaly with steatosis; post-treatment exacerbations of hepatitis B	hepatomegaly with steatosis; safety and efficacy not established in patients co-infected with HBV and HIV; kidney failure, renal insufficiency, elevated creatinine, hypophosphatemia, and Fanconi syndrome have been reported with the use of TDF	hepatomegaly with steatosis; safety and efficacy not established in patients co-infected with HBV and HIV; renal insufficiency, elevated creatinine, hypophosphatemia, and Fanconi syndrome have been reported with the use of TDF

3TC = lamivudine; ABC = abacavir; COBI = cobicistat; DHHS = US Department of Health and Human Services; DNA = deoxyribonucleic acid; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; HBV = hepatitis B virus; HIV = human immunodeficiency virus; HIV-1 = human immunodeficiency virus type 1; INSTI = integrase strand transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; N(t)RTI = nucleoside/nucleotide analogue reverse transcriptase inhibitor; RAL = raltegravir; RPV = rilpivirine; TDF = tenofovir disoproxil fumarate.
[a] Health Canada indication.

Treatment-experienced adults

Apart from virologic failure, changes to ART may be necessary due to adverse events (AEs). Because of the large number of drug options available, careful single or multiple substitutions of the components of an antiretroviral (ARV) regimen can continue to offer optimal virologic suppression with improved tolerability or adherence.

The DHHS does not make specific recommendations for the treatment of ART-experienced patients. Rather, it recommends that a new regimen should include at least two, and preferably three, fully active drugs, which it defines as those that are expected to have "uncompromised activity on the basis of the patient's treatment history and drug-resistance testing results and/or the drug's novel mechanism of action."[6]

Before modifying a regimen, however, the DHHS notes it is critical to carefully evaluate the cause(s) of virologic failure, including incomplete adherence, poor tolerability, and drug and food interactions, as well as review HIV ribonucleic acid (RNA) and CD4 cell count changes over time, treatment history, and drug-resistance test results. If HIV RNA suppression is not possible with currently approved drugs, it suggests use of investigational drugs; failing that, the choice of regimens should focus on minimizing toxicity and preserving treatment options while maintaining CD4 cell counts to delay clinical progression.

Adolescents

The DHHS recommends that the dosage of medications for HIV infection should be prescribed according to the Tanner staging of puberty and not exclusively by age.[8] In particular, it suggests that adolescents in early puberty, i.e., Tanner Stages I and II, should be administered doses on pediatric schedules, whereas those in late puberty, i.e., Tanner Stage V, should follow adult schedules. Nevertheless, the DHHS

emphasizes that selection of an initial regimen should be based on the characteristics of the proposed regimen, patient characteristics, and viral resistance test results.

For treatment-naive children aged six years or older, the DHHS recommends treatment initiation with one of three preferred drugs — ritonavir-boosted atazanavir (ATV/r), EFV, or ritonavir-boosted lopinavir (LPV/r) — plus a dual nucleoside/nucleotide analogue reverse transcriptase inhibitor (N[t]RTI) backbone combination. Among children aged 12 years and older, it recommends ABC + 3TC or ABC + FTC as the N(t)RTI backbone. A list of DHHS-recommended alternative and acceptable regimens most relevant to the population under consideration for this review is presented in Table 4.

TABLE 4: DEPARTMENT OF HEALTH AND HUMAN SERVICES-RECOMMENDED REGIMENS FOR INITIAL THERAPY OF INFECTION IN CHILDREN AND ADOLESCENTS

Preferred regimen	
Children aged ≥ 6 years	2 NRTIs + ATV/r
	2 NRTIs + EFV
	2 NRTIs + LPV/r
Alternative regimen	
Children aged ≥ 12 years	2 NRTIs + once-daily DRV + low-dose RTV
Children aged ≥ 12 years and weighing ≥ 40 kg	2 NRTIs + DTG
Regimens for use in special circumstances	
Treatment-naive adolescents aged ≥ 13 years and weighing > 39 kg	2 NRTIs + ATV unboosted
Preferred 2-NRTI backbone options for use in combination with additional drugs	
Adolescents aged ≥ 13 years at Tanner Stage III	ABC + (3TC or FTC)
Adolescents at Tanner Stage IV or V	ABC + (3TC or FTC)
	TDF + (3TC or FTC)
Alternative 2-NRTI backbone options for use in combination with additional drugs	
Children and adolescents at Tanner Stage III	TDF + (3TC or FTC)
Adolescents ≥ 13 years	ZDV + (3TC or FTC)

3TC = lamivudine; ABC = abacavir; ATV = atazanavir; ATV/r = ritonavir-boosted atazanavir; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; FTC = emtricitabine; HIV = human immunodeficiency virus; LPV/r = fixed-dose formulation lopinavir/ritonavir; NRTI = nucleoside reverse transcriptase inhibitor; RTV = ritonavir; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine.

1.2.1 Drug

Genvoya (EVG/COBI/FTC/tenofovir alafenamide fumarate [TAF]) has a Health Canada indication for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older (weighing ≥ 35 kg) with no known mutations associated with resistance to the individual components of EVG/COBI/FTC/TAF. It is a single-tablet, fixed-dose co-formulation that consists of: EVG 150 mg, COBI 150 mg, FTC 200 mg, and TAF 10 mg. EVG/COBI/FTC/TAF includes the components of Stribild, except that TDF in Stribild has been replaced with TAF. Stribild was recommended for reimbursement by the CADTH Canadian Drug Expert Committee (CDEC) in May 2013 as a complete regimen for ARV treatment-naive HIV-1-infected patients, except those in whom EFV is indicated.[9]

TAF is a prodrug of tenofovir (TFV) that undergoes intracellular activation by cathepsin A. Due to its increased plasma stability, TAF is proposed to be more efficient than TDF in loading TFV into peripheral

blood mononuclear cells. The lower plasma concentrations of TFV with TAF at therapeutic doses minimize the unwanted "off-target" effects typically associated with TDF administration.

At the time of this review, EVG/COBI/FTC/TAF was under review by Health Canada, although it has been approved by the FDA[10] and the European Commission[11] for similar indications.

Per the DHHS, EVG/COBI/FTC/TAF will also be added as one of the recommended initial regimens for ART-naive adults and adolescents with estimated CrCl ≥ 30 mL/min.[12]

Indication under review
For the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and pediatric patients 12 years of age and older (weighing ≥ 35 kg) with no known mutations associated with resistance to the individual components of EVG/COBI/FTC/TAF.
Listing criteria requested by sponsor
For treatment-naive and virologically suppressed HIV-1 infected adult and pediatric patients 12 years of age and older with no known mutations associated with resistance to the individual components of EVG/COBI/FTC/TAF.

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of the fixed-dose combination (FDC) of EVG/COBI/FTC/TAF for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older with no known mutations associated with resistance to the individual components of EVG/COBI/FTC/TAF.

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Studies were selected for inclusion based on the selection criteria presented in Table 5.

TABLE 5: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Patients with HIV-1 infection aged ≥ 12 years with no known mutations associated with resistance to the individual components of EVG/COBI/FTC/TAF Subgroups: • Baseline VL (> 100,000 vs. ≤ 100,000 copies/mL) • Age (12 to 17 years vs. ≥ 18 years) • eGFR (author-specified cut-off)
Intervention	EVG 150 mg/COBI 150 mg/FTC 200 mg/TAF 10 mg in fixed-dose co-formulation taken orally once daily or co-administered individually at the recommended doses
Comparators	Standard of care, i.e., any of the following regimens in co-formulation or co-administered individually at the recommended doses: • DTG/ABC/3TC • DTG + TDF/FTC • EVG/COBI/FTC/TDF • RAL + TDF/FTC • DRV/r + TDF/FTC
Outcomes	**Key efficacy outcome:** • Virologic success: percentage of patients with VL < 50 copies/mL (FDA-defined snapshot algorithm) (author-specified primary time point and longest time point) **Other efficacy outcomes:** • Resistance • Quality of life **Harms outcomes:** • SAEs • AEs • WDAEs • Notable harms (renal and bone systems)
Study Design	Published and unpublished phase 3 RCTs

3TC = lamivudine; ABC = abacavir; AE = adverse event; COBI = cobicistat; DTG = dolutegravir; DRV/r = ritonavir-boosted darunavir; eGFR = estimated glomerular filtration rate; EVG = elvitegravir; FTC = emtricitabine; HIV-1 = human immunodeficiency virus type 1; RAL = raltegravir; RCT = randomized controlled trial; SAE = serious adverse event; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate; VL = viral load; vs. = versus; WDAE = withdrawal due to adverse event.

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 concepts were Genvoya (elvitegravir/cobicistat/emtricitabine/tenofovir).

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 by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on October 23, 2015. Regular alerts were established to update the search until the CADTH CDEC meeting on February 17, 2016. 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 CADTH Grey Matters checklist (https://www.cadth.ca/resources/finding-evidence/grey-matters-practical-search-tool-evidence-based-medicine): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Databases (free), Internet Search. 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 CADTH Common Drug Review (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 6; excluded studies (with reasons) are presented in APPENDIX 3: EXCLUDED STUDIES.

3. RESULTS

3.1 Findings From the Literature

A total of 100 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: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

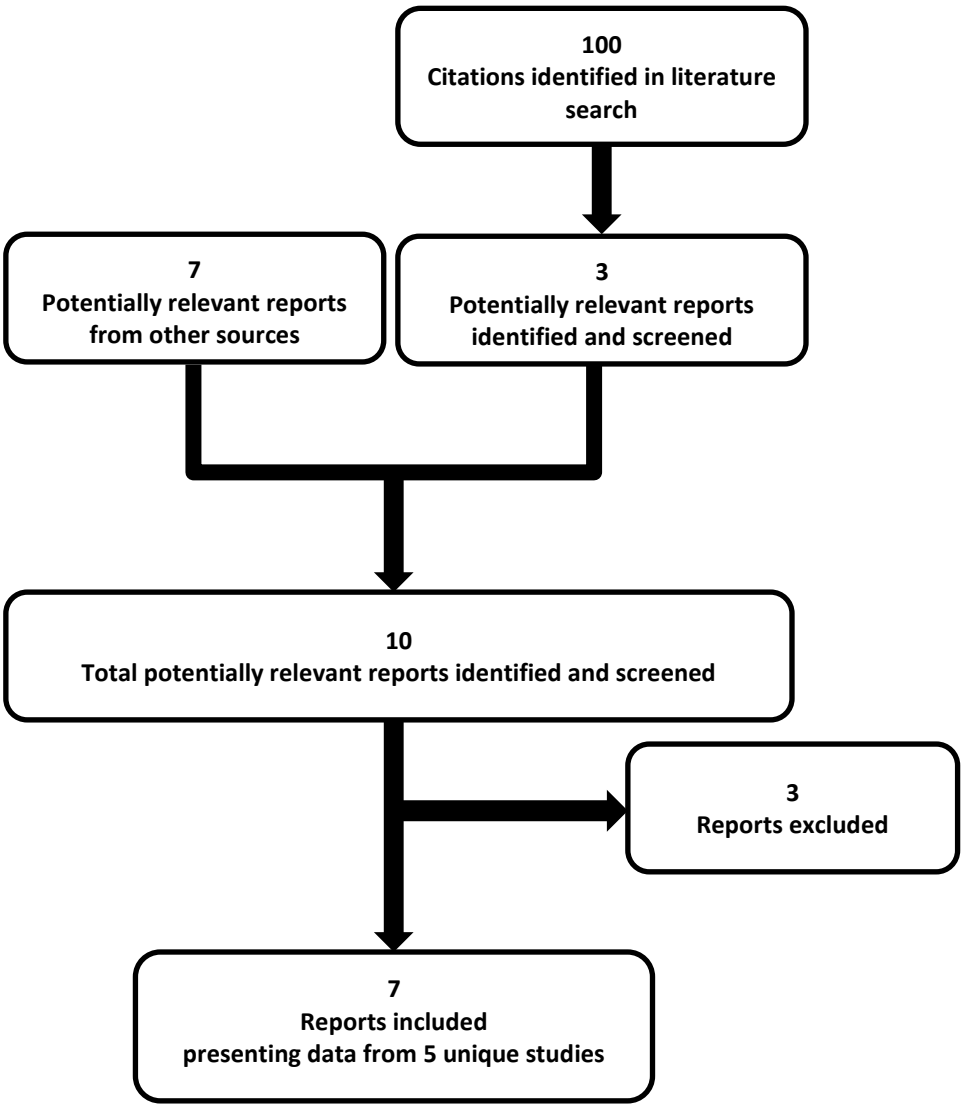

TABLE 6: DETAILS OF INCLUDED STUDIES — TREATMENT-NAIVE OR VIROLOGICALLY SUPPRESSED ADULTS

		Study 104	Study 111	Study 109
DESIGNS & POPULATIONS	**Study Design**	Multi-centre, double-blind, double-dummy, active-controlled, phase 3 non-inferiority RCT stratified by HIV-1 RNA VL, CD4 count, and region at screening		Multi-centre, OL, active-controlled, phase 3 non-inferiority RCT stratified by prior treatment regimen at screening
	Locations	United States, Spain, Canada, Thailand, Australia, Switzerland, Austria, Belgium, Italy, Japan, United Kingdom	United States, United Kingdom, France, Canada, Italy, Portugal, Mexico, Netherlands, Sweden, Dominican Republic	Australia, Austria, Belgium, Brazil, Canada, Denmark, Dominican Republic, France, Germany, Italy, Mexico, Netherlands, Portugal, Spain, Sweden, Switzerland, Thailand, United Kingdom, Puerto Rico, United States
	Randomized (N)	872	872	1,443
	Inclusion Criteria	Age ≥ 18 years; normal ECG; $eGFR_{CG}$ ≥ 50 mL/min; ALT and AST < 5 x ULN; total bilirubin ≤ 1.5 mg/dL or normal direct bilirubin; ANC ≥ 1,000/mm^3, platelets ≥ 50,000/mm^3, Hb ≥ 8.5 g/L; serum amylase ≤ 5 x ULN (or > 5 x ULN with serum lipase ≤ 5 x ULN); using highly effective contraception methods if sexually active		
		HIV-1 RNA VL ≥ 1,000 copies/mL; ART-naive excluding use for PrEP or PEP up to 6 months prior to screening; screening HIV-1 genotype sensitive to EVG, FTC, TDF		On an ARV regimen consisting of FTC/TDF + a third drug for 6 consecutive months preceding the final visit in their earlier study; plasma HIV-1 RNA concentrations at undetectable levels for ≥ 6 consecutive months prior to screening and HIV RNA < 50 copies/mL at screening
	Exclusion Criteria	New AIDS-defining condition < 30 days prior to screening; hepatitis B surface antigen positive; hepatitis C antibody positive; decompensated cirrhosis; pregnancy or breastfeeding; implanted defibrillator or pacemaker; current alcohol or substance use; malignancy (current or within past 5 years) other than KS, BCC, or resected, non-invasive CSC; active, serious (non-HIV) infection requiring parenteral AB or AF treatment; taking interacting drugs (according to list) or allergic to excipients of study drugs		
DRUGS	**Intervention**	FDC tablet of EVG/COBI/FTC/TAF (150/150/200/10 mg) + placebo-to-match EVG/COBI/FTC/TDF once daily		Switch to EVG/COBI/FTC/TAF (150/150/200/10 mg)
	Comparator(s)	FDC tablet of EVG/COBI/FTC/TDF (150/150/200/300 mg) + placebo-to-match EVG/COBI/FTC/TAF once daily		Stay on pre-existing FTC/TDF + a third drug regimen
DURATION	**Phase**			
	Double-blind	96 weeks		
	Follow-up	Every 12 weeks following week 96 until treatment assignments were unblinded, at which point participants were given the option to participate in an OL rollover study to receive EVG/COBI/FTC/TAF		Every 12 weeks following week 96, at which point participants were given the option to receive OL EVG/COBI/FTC/TAF

		Study 104	Study 111	Study 109
OUTCOME	**Primary End Point**	Virologic success (percentage of patients with HIV-1 RNA < 50 copies/mL) at week 48 (snapshot analysis)		
	Other End Points	Virologic success (percentage of patients with HIV-1 RNA < 50 copies/mL) at week 96 (snapshot analysis); resistance; EQ-5D-3L		Resistance; EQ-5D-3L; SF-36
NOTES	**Publications**	None[a]		Mills et al. 2015[13]

AB = antibiotic; AF = antifungal; ALT = alanine aminotransferase; ANC = absolute neutrophil count; ART = antiretroviral therapy; ARV = antiretroviral; AST = aspartate aminotransferase; BCC = basal cell carcinoma; CD4 = cluster of differentiation 4; COBI = cobicistat; CSC = cutaneous squamous carcinoma; ECG = electrocardiogram; EQ-5D-3L = EuroQol 5-Dimensions Questionnaire 3 level; EVG = elvitegravir; $eGFR_{CG}$ = estimated glomerular filtration rate according to the Cockcroft-Gault formula; FDC = fixed-dose combination; FTC = emtricitabine; Hb = hemoglobin; HIV-1 = human immunodeficiency virus type 1; KS = Kaposi sarcoma; OL = open-label; PEP = post-exposure prophylaxis; PrEP = pre-exposure prophylaxis; RCT = randomized controlled trial; RNA = ribonucleic acid; SF-36 = Short Form (36) Health Survey; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate; ULN = upper limit of normal; VL = viral load.

[a] A combined analysis of Studies 104 and 111 was published by Sax et al.[17]

Source: Study 104 Clinical Study Report,[14] Study 111 Clinical Study Report,[15] Study 109 Clinical Study Report.[16]

TABLE 7: DETAILS OF INCLUDED STUDIES — SPECIAL POPULATIONS

		Study 112 (Reduced Kidney Function)	Study 106 (Adolescents)
DESIGNS & POPULATIONS	**Study Design**	Multi-centre, open-label, phase 3, single-group interventional study	Multi-centre, open-label, phase 2/3, multi-part, single-group interventional study
	Locations	United States, Thailand, United Kingdom, Australia, Spain, France, Dominican Republic, Mexico, Netherlands	Thailand, United States, South Africa, Uganda
	Enrolled (N)	252	48 (24 in Part A, 24 in Part B)
	Inclusion Criteria	All cohorts: Age ≥ 18 years; CD4+ count ≥ 50 cells/mcL; stable kidney function; cause of underlying chronic kidney disease stable; normal ECG; ALT and AST < 5 x ULN; total bilirubin ≤ 1.5 mg/dL or normal direct bilirubin; ANC ≥ 1,000/mm^3, platelets ≥ 50,000/mm^3, Hb ≥ 8.5 g/L; serum amylase ≤ 5 x ULN (or > 5 x ULN with serum lipase ≤ 5 x ULN); using highly effective contraception methods if sexually active	Age 12-18 years; weight ≥ 35 kg; HIV-1 RNA VL ≥ 1,000 copies/mL; CD4+ count > 100 cells/mcL; screening genotype sensitive to EVG, FTC, and TFV; adequate renal function: eGFR (using Schwartz Formula) ≥ 90 mL/min/1.73 m^2; normal ECG; documented screening for active pulmonary tuberculosis within 6 months screening; ALT and AST < 5 x ULN; total bilirubin ≤ 1.5 mg/dL or normal direct bilirubin; ANC ≥ 1,000/mm^3, platelets ≥ 50,000/mm^3, Hb ≥ 8.5 g/L; no prior use of any approved or experimental anti-HIV-1 drug for any length of time; using highly effective contraception methods if sexually active; life expectancy > 1 year

		Study 112 (Reduced Kidney Function)	Study 106 (Adolescents)
		Cohort 1: no known resistance to EVG, TDF, or FTC; plasma HIV-1 RNA undetectable for ≥ 6 consecutive months prior to screening and HIV-1 RNA VL < 50 copies/mL at screening; $eGFR_{CG}$ 30 mL/min to 69 mL/min using actual weight Cohort 2: HIV-1 RNA VL ≥ 1,000 copies/mL; screening HIV-1 genotype sensitive to EVG, FTC, TDF; ART-naive excluding use for PrEP or PEP up to 6 months prior to screening; $eGFR_{CG}$ 30 mL/min to 69 mL/min using actual weight	
	Exclusion Criteria	New AIDS-defining condition < 30 days prior to screening; hepatitis B surface antigen positive; hepatitis C antibody positive; receiving or anticipated to receive drug treatment for hepatitis C; decompensated cirrhosis; pregnancy or breastfeeding; implanted defibrillator or pacemaker; current alcohol or substance use; malignancy (current or within past 5 years) other than KS, BCC, or resected, non-invasive CSC; active, serious (non-HIV) infection requiring parenteral AB or AF treatment; participants on hemodialysis, other forms of renal replacement therapy, or on treatment for underlying kidney diseases; taking interacting drugs (according to list) or allergic to excipients of study drugs	New AIDS-defining condition < 30 days prior to screening; hepatitis B surface antigen positive; hepatitis C antibody positive; prior treatment with any approved or investigational or experimental anti-HIV-1 drug for any length of time (other than that given for prevention of mother-to-child transmission); evidence of active pulmonary or extrapulmonary tuberculosis disease within 3 months of screening; anticipated to require rifamycin treatment for mycobacterial infection while participating in study; decompensated cirrhosis; pregnancy or breastfeeding; implanted defibrillator or pacemaker; active or serious medical or psychiatric illness that, per the investigator's opinion, would interfere with treatment assessment or compliance; current alcohol or substance use; history of significant drug sensitivity or drug allergy; known hypersensitivity to study drugs, metabolites, or formulation excipients; treatment with immunosuppressant therapies or chemotherapeutic drugs within 3 months of screening or excepted to receive these drugs during study; malignancy (current or within past 5 years) other than KS, BCC, or resected, non-invasive CSC; active, serious (non-HIV) infection requiring parenteral AB or AF treatment; taking interacting drugs (according to list) or allergic to excipients of study drugs; taking interacting drugs (according to list) or allergic to excipients of study drugs
DRUGS	**Intervention**	EVG/COBI/FTC/TAF (150/150/200/10 mg)	

		Study 112 (Reduced Kidney Function)	Study 106 (Adolescents)
DURATION	**Phase**		
	Open-label	96 weeks	Part A: 48 weeks (to evaluate steady-state PK and confirm the dose of EVG/COBI/FTC/TAF) Part B: 48 weeks (to evaluate the safety, tolerability, and antiviral activity of EVG/COBI/FTC/TAF)
	Follow-up	After week 96, participants continued to take their study drug and receive the EVG/COBI/FTC/TAF until it became commercially available, or until manufacturer terminates the development of EVG/COBI/FTC/TAF with the exception of sites in Sweden. Participants who completed the study through week 96 and did not wish to continue to receive study drug were required to return to the clinic 30 days after the completion of study drug for the 30-day follow-up visit.	Participants who completed 48 weeks on study treatment were given the option to participate in an extension phase of the study until: (a) the participant turned 18 and EVG/COBI/FTC/TAF was commercially available for adults in the country in which the participant is enrolled; (b) EVG/COBI/FTC/TAF became commercially available for adolescents in the country in which the participant was enrolled; or (c) manufacturer elected to terminate development of EVG/COBI/FTC/TAF in that country. Participants who completed the study through week 48 and did not wish to participate in the extension study were required to return to the clinic 30 days after completion of the week 48 visit for a follow-up visit.
OUTCOMES	**Primary End Point**	Virologic success (percentage of patients with HIV-1 RNA < 50 copies/mL) at week 24 (snapshot analysis)	
	Other End Points	Resistance	Resistance
NOTES	**Publications**	Pozniak et al. 2015[18]	None

AB = antibiotic; AF = antifungal; AIDS = acquired immunodeficiency syndrome; ALT = alanine aminotransferase; ANC = absolute neutrophil count; ART = antiretroviral therapy; AST = aspartate aminotransferase; BCC = basal cell carcinoma; CD4 = cluster of differentiation 4; COBI = cobicistat; CSC = cutaneous squamous carcinoma; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; $eGFR_{CG}$ = estimated glomerular filtration rate according to the Cockcroft-Gault formula; EVG = elvitegravir; FTC = emtricitabine; Hb = hemoglobin; HIV-1 = human immunodeficiency virus type 1; KS = Kaposi sarcoma; PEP = post-exposure prophylaxis; PK = pharmacokinetics; PrEP = pre-exposure prophylaxis; RNA = ribonucleic acid; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate; TFV = tenofovir; ULN = upper limit of normal; VL = viral load.
Source: Study 112 Clinical Study Report,[19] Study 106 Clinical Study Report.[20]

3.2 Included Studies

3.2.1 Description of studies

Studies 104[14] (n = 872) and 111[15] (n = 872) were similarly designed multi-centre, double-blind (DB), double-dummy, active-controlled, phase 3 non-inferiority trials. Randomization was stratified by VL (≤ 100,000; > 100,000 to ≤ 400,000; or > 400,000), CD4 count (< 50 cells, 50 to 199, or ≥ 200), and region (US versus ex-US) at screening. Both studies enrolled ART-naive patients from North America and Europe; Study 104 also enrolled patients from Australia and Asia, while Study 111 additionally enrolled patients from Latin America. In both studies, EVG/COBI/FTC/TAF was compared (1:1) against once-daily, single-tablet co-formulation of EVG/COBI/FTC/TDF. Originally planned for 96 weeks, Studies 104 and 111 were extended to 144 weeks; data from the studies presented in this systematic review are primarily from the interim 48-week analyses.

Study 109 (n = 1,443) was a multi-centre, open-label, active-controlled, phase 3 non-inferiority trial.[16] Randomization was stratified by prior treatment regimen at screening. The study enrolled patients from North America, Europe, Australia, Asia, and Latin America. Patients on an ARV regimen consisting of FTC/TDF + a third drug were randomized (2:1) to be switched to EVG/COBI/FTC/TAF or remain on their pre-existing regimen. Data for Study 109 (originally planned for 96 weeks) presented in the systematic review are from the interim and final 48-week analyses. In this and the studies mentioned earlier, the primary efficacy outcome was the percentage of patients with HIV RNA viral load < 50 copies/mL at week 48.

Studies 112[19] (n = 252) and 106[20] (n = 48) were multi-centre, open-label cohort studies that tested the efficacy and safety of EVG/COBI/FTC/TAF in patients with reduced kidney function and pediatric patients, respectively. Total duration of Study 112 was 96 weeks, whereas Study 106 comprised two parts, each of which was 48 weeks in duration: in Part A, steady-state pharmacokinetics (PK) were evaluated and dose of EVG/COBI/FTC/TAF was confirmed, while in Part B, the safety, tolerability, and antiviral activity of EVG/COBI/FTC/TAF were evaluated. In both studies, the primary efficacy outcome was the percentage of patients with HIV RNA viral load < 50 copies/mL at week 24.

3.2.2 Populations

a) Inclusion and exclusion criteria

Studies 104 and 111 were identical with respect to the inclusion and exclusion criteria. Both studies, however, differed from Study 109 in that they exclusively enrolled treatment-naive adults, i.e., ≥ 18 years, whereas Study 109 exclusively enrolled virologically suppressed adults who had been on one of four ARV regimens consisting of FTC/TDF + a third drug — EVG/COBI/FTC/TDF, EFV/FTC/TDF, cobicistat-boosted atazanavir (ATV/co) + FTC/TDF, and ATV/r + FTC/TDF. Study 112 largely enrolled virologically suppressed adults who switched to EVG/COBI/FTC/TAF from their existing ARV regimen ("switch" cohort in this report) and some treatment-naive adults ("ART-naive" cohort in this report), all of whom had mild to moderate kidney impairment, i.e., estimated glomerular filtration rate according to the Cockcroft-Gault formula ($eGFR_{CG}$) of 30 mL/min to 69 mL/min. Study 106 exclusively enrolled treatment-naive adolescents, i.e., 12 years to 18 years of age.

b) Baseline characteristics

Across the four studies that exclusively enrolled adults, i.e., Studies 104, 111, 109, 112, patients were predominantly male and Caucasian. The mean age of patients enrolled in Studies 104, 111, and 109 ranged from 35 to 41 years; in Study 112, the mean age was more than 50 years. Patient body mass index (BMI) appeared be similar across all five studies, and most patients were considered to have asymptomatic HIV. Across the four adult-only studies, the most common HIV risk factor category was

homosexual sex, whereas it was vertical transmission in Study 106, which exclusively enrolled adolescents. Apart from Study 112, which enrolled patients with reduced kidney function, patients in all studies generally appeared to have estimated glomerular filtration rates (eGFRs) of more than 100 units, either calculated by the Cockcroft-Gault formula for those 18 years of age or older (mL/min) or the Schwartz Formula (original) for those younger than 18 years of age (mL/min/1.73m^2).

TABLE 8: SUMMARY OF BASELINE CHARACTERISTICS — TREATMENT-NAIVE OR VIROLOGICALLY SUPPRESSED ADULTS

Characteristic	Study 104		Study 111		Study 109	
	EVG/COBI /FTC/TAF (N = 435)	EVG/COBI /FTC/TDF (N = 432)	EVG/COBI /FTC/TAF (N = 431)	EVG/COBI /FTC/TDF (N = 435)	EVG/COBI /FTC/TAF (N = 959)	FTC/TDF + third drug (N = 477)
Age (years)						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	41 (10.1)	41 (10.1)
Median	33	35	33	34	41	40
Min, max	18, 74	18, 76	18, 66	18, 71	21, 77	22, 69
Sex, n (%)						
Male	364 (83.7)	376 (87.0)	369 (85.6)	364 (83.7)	856 (89.3)	427 (89.5)
Race, n (%)						
Caucasian	250 (57.5)	255 (59.0)	235 (54.5)	243 (55.9)	651 (67.9)	314 (65.8)
Black	94 (21.6)	81 (18.8)	129 (29.9)	132 (30.3)	169 (17.6)	102 (21.4)
Asian	76 (17.5)	77 (17.8)	15 (3.5)	12 (2.8)	59 (6.2)	35 (7.3)
Other	15 (3.5)	19 (4.4)	52 (12.1)	48 (11.0)	80 (8.3)	26 (5.5)
BMI (kg/m^2)						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	26.6 (5.3)	26.9 (5.3)
HIV-1 RNA (log_{10} copies/mL) at baseline						
Mean (SD)	4.55 (0.68)	4.55 (0.67)	4.53 (0.65)	4.50 (0.69)	NR	NR
HIV-1 RNA category (copies/mL), n (%)						
< 50	NR	NR	NR	NR	943 (98.3)	466 (97.7)
≥ 50	NR	NR	NR	NR	16 (1.7)	11 (2.3)
≤ 100,000	331 (76.1)	336 (77.8)	339 (78.7)	336 (77.2)	NR	NR
> 100,000 to ≤ 400,000	79 (18.2)	72 (16.7)	68 (15.8)	82 (18.9)	NR	NR
> 400,000	25 (5.7)	24 (5.6)	24 (5.6)	17 (3.9)	NR	NR
CD4 cell count (/µL)						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	701 (261.8)	689 (248.0)
CD4 cell count category (/µL), n (%)						
< 50	10 (2.3)	12 (2.8)	14 (3.3)	15 (3.4)	0	0
≥ 50 to < 200	48 (11.0)	41 (9.5)	40 (9.3)	49 (11.3)	5 (0.5)	4 (0.8)
≥ 200 to < 350	103 (23.7)	111 (25.7)	115 (26.7)	89 (20.5)	54 (5.6)	25 (5.2)
≥ 350 to < 500	122 (28.0)	135 (31.3)	134 (31.2)	149 (34.3)	151 (15.7)	70 (14.7)
≥ 500	152 (34.9)	133 (30.8)	127 (29.5)	133 (30.6)	749 (78.1)	378 (79.2)
HIV risk factors,[a] n (%)						
Heterosexual sex	104 (23.9)	103 (23.8)	106 (24.6)	116 (26.7)	216 (22.5)	101 (21.2)
Homosexual sex	321 (73.8)	327 (75.7)	331 (76.8)	318 (73.1)	753 (78.5)	375 (78.6)
IV drug use	[redacted]	[redacted]	[redacted]	[redacted]	9 (0.9)	5 (1.0)

Characteristic	Study 104		Study 111		Study 109	
	EVG/COBI /FTC/TAF (N = 435)	EVG/COBI /FTC/TDF (N = 432)	EVG/COBI /FTC/TAF (N = 431)	EVG/COBI /FTC/TDF (N = 435)	EVG/COBI /FTC/TAF (N = 959)	FTC/TDF + third drug (N = 477)
Transfusion	[redacted]	[redacted]	[redacted]	[redacted]	2 (0.2)	2 (0.4)
Vertical transmission	[redacted]	[redacted]	[redacted]	[redacted]	0	0
Unknown	[redacted]	[redacted]	[redacted]	[redacted]	17 (1.8)	12 (2.5)
Other	[redacted]	[redacted]	[redacted]	[redacted]	8 (0.8)	7 (1.5)
HIV disease status, n (%)						
Asymptomatic	402 (92.6)	406 (94.2)	378 (88.1)	396 (91.7)	NR	NR
Symptomatic	23 (5.3)	15 (3.5)	30 (7.0)	20 (4.6)	NR	NR
AIDS	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Unknown	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
$eGFR_{CG}$ (mL/min)						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	111.9 (33.4)	112.1 (32.7)
Min, max	[redacted]	[redacted]	[redacted]	[redacted]	48, 344.1	53.7, 304.8

AIDS = acquired immunodeficiency syndrome; BMI = body mass index; CD4 = cluster of differentiation 4; COBI = cobicistat; EVG = elvitegravir; FTC = emtricitabine; HIV = human immunodeficiency virus; HIV-1 = human immunodeficiency virus type 1; IV = intravenous; max = maximum; min = minimum; RNA = ribonucleic acid; SD = standard deviation; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate.

[a] A patient may fit more than one category of HIV risk factors; therefore, percentages may add to > 100.

Note: Safety analysis set unless otherwise specified.

Source: Study 104 Clinical Study Report,[14] Study 111 Clinical Study Report,[15] Study 109 Clinical Study Report.[16]

TABLE 9: SUMMARY OF BASELINE CHARACTERISTICS — SPECIAL POPULATIONS

Characteristic	Study 112 (Reduced Kidney Function)		Study 106 (Adolescents)
	Switch (N = 242)	ART-naive (N = 6)	EVG/COBI/FTC/TAF (n = 48)
Age (years)			
Mean (SD)	58 (9.9)	[redacted]	[redacted]
Median	58	[redacted]	15
Min, max	24, 82	[redacted]	12, 17
Sex, n (%)			
Male	192 (79.3)	6 (100)	20 (41.7)
Race, n (%)			
Caucasian	152 (62.8)	2 (33.3)	0
Black	44 (18.2)	3 (50.0)	42 (87.5)
Asian	34 (14.0)	1 (16.7)	6 (12.5)
Other	12 (5.0)	0	0
BMI (kg/m^2)			
Mean (SD)	[redacted]	[redacted]	[redacted]
HIV-1 RNA (log_{10} copies/mL) at baseline			
Mean (SD)	[redacted]	[redacted]	[redacted]
HIV-1 RNA category (copies/mL), n (%)			
< 50	236 (97.5)	[redacted]	NR
≥ 50 to ≤ 100,000	6 (2.5)	[redacted]	NR
≤ 100,000	NR	NR	38 (79.2)

Characteristic	Study 112 (Reduced Kidney Function)		Study 106 (Adolescents)
	Switch (N = 242)	ART-naive (N = 6)	EVG/COBI/FTC/TAF (n = 48)
> 100,000	NR	NR	10 (20.8)
> 100,000 to ≤ 400,000	[redacted]	[redacted]	NR
> 400,000	[redacted]	[redacted]	NR
CD4 cell count (/µL)			
Mean (SD)	[redacted]	[redacted]	[redacted]
CD4 cell count category (/µL), n (%)			
< 50	[redacted]	[redacted]	NR
≤ 199	[redacted]	[redacted]	4 (8.3)
≥ 50 to < 200	[redacted]	[redacted]	NR
≥ 200 to ≤ 349	[redacted]	[redacted]	9 (18.8)
≥ 200 to < 350	[redacted]	[redacted]	NR
≥ 350 to ≤ 499	[redacted]	[redacted]	18 (37.5)
≥ 350 to < 500	[redacted]	[redacted]	NR
≥ 500	[redacted]	[redacted]	17 (35.4)
HIV risk factors,[a] n (%)			
Heterosexual sex	[redacted]	[redacted]	[redacted]
Homosexual sex	[redacted]	[redacted]	[redacted]
IV drug use	[redacted]	[redacted]	[redacted]
Transfusion	[redacted]	[redacted]	[redacted]
Vertical transmission	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
HIV disease status, n (%)			
Asymptomatic	180 (74.4)	[redacted]	40 (83.3)
Symptomatic	28 (11.6)	[redacted]	8 (16.7)
AIDS	34 (14.0)	[redacted]	0
Unknown	0	[redacted]	0
eGFR[b]			
Mean (SD)	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]

AIDS = acquired immunodeficiency syndrome; ART = antiretroviral therapy; BMI = body mass index; CD4 = cluster of differentiation 4; COBI = cobicistat; eGFR = estimated glomerular filtration rate; EVG = elvitegravir; FTC = emtricitabine; HIV = human immunodeficiency virus; HIV-1 = human immunodeficiency virus type 1; IV = intravenous; max = maximum; min = minimum; NR = not reported; RNA = ribonucleic acid; SD = standard deviation; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate.

[a] A patient may fit more than one category of HIV risk factors; therefore, percentages may add to > 100.

[b] For Study 112, eGFR is by Cockcroft-Gault formula (mL/min); for Study 106, eGFR is by original Schwartz Formula (mL/min/1.73m^2).

Note: Safety analysis set unless otherwise specified.

Source: Study 112 Clinical Study Report,[19] Study 106 Clinical Study Report.[20]

3.2.3 Interventions

In all five studies, the intervention was an FDC tablet of EVG/COBI/FTC/TAF (150/150/200/10 mg) taken orally once daily. In Studies 104 and 111, the comparator was an FDC tablet of EVG/COBI/FTC/TDF (150/150/200/300 mg) taken orally once daily. Blinding was achieved in both trials through a double-dummy design that used matching placebos for both study treatments. In Study 109, patients on an ARV

regimen consisting of FTC/TDF + a third drug switched in an open-label fashion to EVG/COBI/FTC/TAF or remained on their pre-existing regimen. In Studies 112 and 106, patients only received open-label EVG/COBI/FTC/TAF.

3.2.4 Outcomes

a) Efficacy

The primary efficacy outcome for Studies 104, 111, and 109 was the percentage of patients with HIV-1 RNA VL suppression to < 50 copies/mL in the week 48 analysis window (days 294 to 377, inclusive) using the FDA-defined snapshot analysis. In this analysis, patients whose last available HIV-1 RNA value in the week 48 analysis window was < 50 copies/mL were considered as having had a response, whereas patients whose last available HIV-1 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. In Studies 112 and 106, the primary efficacy outcome was the percentage of patients with HIV-1 RNA VL suppression to < 50 copies/mL in the week 24 analysis window using the FDA-defined snapshot analysis. In Study 112, the window was defined from days 140 to 209 (inclusive), whereas in Study 106, it was from days 140 to 195 (inclusive). Another efficacy outcome of interest evaluated in all five studies was resistance. Studies 104, 111, and 109 also measured health-related quality of life (HRQoL) using the EuroQol 5-Dimensions Questionnaire 3 level (EQ-5D-3L), and Study 109 evaluated effects on HRQoL using the Short Form (36) Health Survey (SF-36). When available, data from the primary efficacy outcome at the longest study time point, i.e., 96 weeks for Studies 104, 111, and 109 and 48 weeks for Studies 112 and 106, are presented in APPENDIX 4: ADDITIONAL EFFICACY OUTCOME DATA.

b) Harms

Safety data (serious adverse events [SAEs], AEs, withdrawals due to adverse events [WDAEs], and notable harms) were presented through week 48 for Studies 104, 111, and 109, and week 24 for Studies 112 and 106.

3.2.5 Statistical analysis

For Studies 104 and 111, sample sizes were based on an estimated response (HIV-1 < 50 copies/mL at week 48) of 0.85 for each treatment group, a non-inferiority (NI) margin of 12%, power of at least 95%, and a one-sided significance level of 0.025. Both studies estimated requiring a sample size of 840 participants, i.e., 420 in each treatment group. NI was evaluated using a conventional 95% confidence interval (CI) approach against the 12% NI margin, which was previously accepted by the FDA.[21] Two interim data analyses were performed at weeks 12 and 24, each of which spent an alpha of 0.00001. Therefore, the significance level for the two-sided test in the primary analysis at week 48 was set at 0.04998, which corresponded to a 95.002% CI. If NI of EVG/COBI/FTC/TAF versus EVG/COBI/FTC/TDF was established, the same 95.002% CI was used to evaluate superiority; if the lower bound of the 95.002% CI was greater than 0, superiority of EVG/COBI/FTC/TAF over EVG/COBI/FTC/TDF was established. The full analysis set (FAS) was used for the primary efficacy end point analysis and the superiority evaluation, and a secondary analysis based on the per-protocol (PP) analysis set was conducted to evaluate the robustness of the primary analysis results. A similar approach was followed to analyze the primary efficacy outcome in Study 109, except that only one interim data analysis was performed at week 24, which set the significance level for the two-sided test in the primary analysis at 0.0499, thus corresponding to a 95.01% CI.

In Studies 104 and 111, the changes from baseline in $eGFR_{CG}$ between the treatment groups were compared using a two-sided Wilcoxon rank sum test. Both studies featured four key alpha-protected safety end points, of which two (percentage changes from baseline in bone mineral density [BMD] at the

hip or spine at week 48) were of interest. The safety analyses featured a fall-back procedure that confirmed significance using adjusted alphas: 0.02 for hip BMD and 0.01 for spine BMD. Percentage change from baseline in hip and spine BMD were compared between the treatment groups using an analysis of variance (ANOVA) model, which included treatment as a fixed effect. The analyses of percentage change from baseline in hip and spine BMD were performed in two ways: using observed data, and using imputed data, for which the last post-baseline observation was carried forward. Study 109 featured a similar approach to evaluate changes from baseline in $eGFR_{CG}$ between the treatment groups, except that participants who received EFV/TDF/FTC (an unboosted regimen) were excluded from the analysis. It featured a similar fall-back procedure to evaluate BMD at the hip or spine, except that the ANOVA model included prior treatment regimen and study treatment as fixed effects. In Studies 112 and 106, notable kidney and bone system harms were summarized descriptively.

c) Analysis populations

All five studies used the FAS as the primary analysis set for efficacy analyses; the FAS included all participants who were randomized into the study and received at least one dose of study drug. In the FAS, participants were grouped according to the treatment to which they were randomized. The PP analysis set included all randomized patients who received at least one dose of study drug and did not have any major protocol violations. In this set, participants were grouped according to the treatment they actually received. The safety analysis set included all randomized participants who received at least one dose of study drug, but it grouped participants according to the treatment they actually received. This was the primary analysis set for most of the safety analyses.

Studies 104, 111, and 109 included a hip dual-energy X-ray absorptiometry (DXA) analysis set and a spine DXA analysis set, both of which included all participants who were randomized, received at least one dose of study drug, and had non-missing baseline BMD values; participants were grouped according to the treatment they actually received. Study 106 included a total body less head (TBLH) DXA analysis set rather than a hip DXA analysis set.

3.3 Patient Disposition

a) Study 104

In Study 104, a total of 872 patients were randomized, with [redacted] patients ([redacted] in the EVG/COBI/FTC/TAF group and [redacted] in the EVG/COBI/FTC/TDF group) never receiving treatment. A total of 21 (4.8%) and 27 (6.3%) patients discontinued from the EVG/COBI/FTC/TAF and EVG/COBI/FTC/TDF groups, respectively. Reasons for premature discontinuation across the groups varied, with loss to follow-up ([redacted] [redacted%] versus [redacted] [redacted%]), consent withdrawal ([redacted] [redacted%] versus [redacted] [redacted%]), and AEs ([redacted] [redacted%] versus [redacted] [redacted%])] being the most common in the EVG/COBI/FTC/TAF and EVG/COBI/FTC/TDF groups, respectively (Table 10).

b) Study 111

In Study 111, a total of 872 patients were randomized, with six patients (four in the EVG/COBI/FTC/TAF group and two in the EVG/COBI/FTC/TDF group) never receiving treatment. A total of 18 (4.2%) and 28 (6.4%) patients discontinued from the EVG/COBI/FTC/TAF and EVG/COBI/FTC/TDF groups, respectively. Reasons for premature discontinuation across the groups varied, with loss to follow-up ([redacted] [redacted%] versus [redacted] [redacted%]), consent withdrawal ([redacted] [redacted%] versus [redacted] [redacted%]), and investigator's discretion ([redacted] versus [redacted] [redacted%]) being the most common in the EVG/COBI/FTC/TAF and EVG/COBI/FTC/TDF groups, respectively (Table 10).

c) Study 109

In Study 109, a total of 1,443 were randomized, with seven patients (four in the EVG/COBI/FTC/TAF group and three in the FTC/TDF + a third drug group) never receiving treatment. A total of 32 (3.3%) and 40 (8.3%) patients discontinued from the EVG/COBI/FTC/TAF and FTC/TDF + a third drug groups, respectively. Reasons for premature discontinuation across the groups varied, with consent withdrawal (eight [0.8%] versus 16 [3.4%]), AEs (nine [0.9%] versus 12 [12.5%]), and loss to follow-up (six [0.6%] versus seven [1.4%]) being the most common in the EVG/COBI/FTC/TAF and FTC/TDF + a third drug groups, respectively (Table 10).

TABLE 10: PATIENT DISPOSITION — TREATMENT-NAIVE OR VIROLOGICALLY SUPPRESSED ADULTS

	Study 104		Study 111		Study 109	
	EVG/COBI/FTC/TAF	EVG/COBI/FTC/ TDF	EVG/COBI/FTC/ TAF	EVG/COBI/FTC/ TDF	EVG/COBI/FTC/ TAF	FTC/TDF + third drug
Screened, n	1,105		1,070		1,559	
Randomized, n	[redacted]		[redacted]		963	480
Randomized and never treated, n	[redacted]		[redacted]		4	3
Discontinued,[a] n (%)	21 (4.8)	27 (6.3)	18 (4.2)	28 (6.4)	32 (3.3)	40 (8.3)
Adverse event	[redacted]		[redacted]		9 (0.9)	12 (2.5)
Death	[redacted]		[redacted]		4 (0.4)	0
Pregnancy	[redacted]		[redacted]		0	0
Lack of efficacy	[redacted]		[redacted]		1 (0.1)	0
Investigator's discretion	[redacted]		[redacted]		2 (0.2)	3 (0.6)
Non-compliance with study drug	[redacted]		[redacted]		2 (0.2)	2 (0.4)
Protocol violation	[redacted]		[redacted]		0	0
Withdrew consent	[redacted]		[redacted]		8 (0.8)	16 (3.4)
Lost to follow-up	[redacted]		[redacted]		6 (0.6)	7 (1.4)
Safety analysis set, n (%)	[redacted]		[redacted]		959 (99.6)	477 (99.4)
Full analysis set, n (%)	[redacted]		[redacted]		959 (99.6)	477 (99.4)
Week 48 PP analysis set, n (%)	[redacted]		[redacted]		921 (95.6)	440 (91.7)
Hip DXA analysis set, n (%)	[redacted]		[redacted]		NR	NR
Spine DXA analysis set, n (%)	[redacted]		[redacted]		NR	NR

COBI = cobicistat; DXA = dual-energy X-ray absorptiometry; EVG = elvitegravir; FTC = emtricitabine; PP = per-protocol; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate.

[a] Discontinuing from study prior to data cut-off date.

Note: The denominator for percentages was based on the number of participants randomized.

Source: Study 104 Clinical Study Report,[14] Study 111 Clinical Study Report,[15] Mills et al.[13]

d) Study 112

In Study 112, a total of 252 patients were enrolled, with four patients (all in the switch group) never receiving treatment (Table 11). Among patients in the switch group, 10 (4.1%) discontinued, of whom four (1.7%) discontinued due to an AE, one (0.4%) due to protocol violation, two (0.8%) due to loss to follow-up, and three (1.2) due to consent withdrawal. None of the treatment-naive patients discontinued.

e) Study 106

In Study 106, a total of 48 patients were enrolled, of whom none prematurely discontinued from the study (Table 11).

TABLE 11: PATIENT DISPOSITION — SPECIAL POPULATIONS

	Study 112 (Reduced Kidney Function)				Study 106 (Adolescents)
	Switch			ART-naive	EVG/COBI/FTC/TAF
	Baseline $eGFR_{CG}$ < 50 mL/min	Baseline $eGFR_{CG}$ ≥ 50 mL/min	Total		
Screened, n	[redacted]	[redacted]	[redacted]	[redacted]	63
Enrolled, n	[redacted]	[redacted]	[redacted]	[redacted]	48
Enrolled and never dosed, n	[redacted]	[redacted]	[redacted]	[redacted]	0
Discontinued,[a] n (%)	[redacted]	[redacted]	[redacted]	[redacted]	0
Adverse event	[redacted]	[redacted]	[redacted]	[redacted]	0
Protocol violation	[redacted]	[redacted]	[redacted]	[redacted]	0
Lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]	0
Withdrew consent	[redacted]	[redacted]	[redacted]	[redacted]	0
Safety analysis set, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	48 (100)
Full analysis set,[b] n (%)	[redacted]	[redacted]	[redacted]	[redacted]	23 (47.9)
Hip DXA analysis set, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	NA
Spine DXA analysis set, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TBLH DXA analysis set, n (%)	[redacted]				[redacted]

ART = antiretroviral; COBI = cobicistat; DXA = dual-energy X-ray absorptiometry; EVG = elvitegravir; $eGFR_{CG}$ = estimated glomerular filtration rate according to the Cockcroft-Gault formula; FTC = emtricitabine; NA = not applicable; TAF = tenofovir alafenamide fumarate; TBLH = total body less head.

[a] Discontinuing from study prior to data cut-off date.

[b] Week 24 full analysis set for Study 106.

Note: The denominator for percentages was based on the number of participants enrolled.

Source: Study 112 Clinical Study Report,[19] Study 106 Clinical Study Report.[20]

3.4 Exposure to Study Treatments

Adherence to study drug regimen was computed based on pill counts for the active drug only. Across all studies, at least 90% of patients in each treatment group achieved adherence rates of ≥ 90%.

3.5 Critical Appraisal

3.5.1 Internal validity

Studies 104 and 111 were DB, double-dummy, randomized, active-controlled, parallel-group trials with appropriate randomization and allocation concealment processes. Baseline characteristics were similar across treatment groups in both trials. Both studies surpassed the required sample size of 840 participants, i.e., 420 in each treatment group. Even though both trials were designed to test the NI of EVG/COBI/FTC/TAF versus EVG/COBI/FTC/TDF, the primary efficacy outcome was tested using the FAS, which was inherently a modified intention-to-treat analysis that could potentially bias the results in favour of a finding of NI. Nevertheless, secondary analyses using the PP analysis set were conducted to corroborate the primary findings, hence providing reassurance of the results. Further, both studies appropriately tested for superiority of EVG/COBI/FTC/TAF after NI was established. In addition, the significance level for the two-sided test in the primary analysis appropriately accounted for two interim data analyses. The number of premature discontinuations in both trials was low. In both studies, a two-sided Wilcoxon rank sum test was used to evaluate changes from baseline in $eGFR_{CG}$ between the treatment groups. While the use of a non-parametric test was appropriate given the presentation of medians and interquartile ranges, an explicit rationale for why a parametric test (evaluating means and standard deviations [SDs]) was not used would have increased transparency of the analyses. Both studies featured an appropriate approach to analyze safety data, including adjusting for multiplicity by using a fall-back procedure. The studies used an ANOVA model, which included treatment as a fixed effect, to compare percentage change from baseline in hip BMD and spine BMD between the treatment groups. The analyses of percentage change from baseline in hip BMD and spine BMD were performed using observed data and imputed data, for which the last post-baseline observation was carried forward. The number of patients for whom data were imputed was unclear, but appeared to range from four patients to 29 patients across the treatment groups in the two studies. Carrying the last observation forward may inappropriately ignore deterioration and artificial stabilization of bone loss among patients who dropped out. On the other hand, observed data could also be biased if the probability of withdrawal is correlated with the risk or extent of bone loss.

Study 109 was similarly designed to the studies mentioned earlier, except that patients were not blinded to treatment assignments during the trial. Lack of blinding, however, is not a concern for the primary efficacy outcome and relevant safety outcomes were not subjective measures, although it should be considered when interpreting the HRQoL data. Apart from this difference, Study 109 features similar strengths and limitations as the studies previously described. One important point is that although the Study 109 Clinical Study Report presented results from the analyses of the observed and imputed data, it was uncertain which analysis was presented in the published manuscript, from which data were abstracted for this review. Further, the ANOVA in this study included current and prior treatment regimen as fixed effects.

Studies 112 and 106 were single-group interventional studies, which leaves uncertain the comparative efficacy of EVG/COBI/FTC/TAF in HIV-infected adults with mild to moderate reduced kidney function, as well as treatment-naive adolescents.

3.5.2 External validity

The choice of primary efficacy outcome and NI margin, i.e., 12%, were consistent with FDA guidance for efficacy evaluations of HIV therapies; likewise, the presentation of 48-week data for all studies was consistent with the standards described in the FDA guidance for this therapeutic category, although the 48-week time point was secondary (to the 24-week time point) in Studies 112 and 106. HRQoL was only reported in the three randomized controlled trials (RCTs), and not in the two cohort studies. Both the patient input and the consulting clinical expert, however, did not expect a change in quality of life with EVG/COBI/FTC/TAF versus existing therapies, i.e., between treatment groups.

In Studies 104 and 111, EVG/COBI/FTC/TAF was compared against EVG/COBI/FTC/TDF, which is a DHHS-preferred initial regimen. In Study 109, patients were randomized to be switched to EVG/COBI/FTC/TAF from one of four FTC/TDF + a third drug regimens — EVG/COBI/FTC/TDF, EFV/FTC/TDF, ATV/co + FTC/TDF, and ATV/r + TVD — or to remain on their existing regimen. There were no direct comparative data available against DTG/ABC/3TC, which is another DHHS-preferred initial regimen available in Canada.

Discussions with the consulting clinical expert suggested that patients in Studies 104 and 111 might be in worse health than HIV-infected adults in general. More than a third of the participants in each study had a CD4 cell count < 200/μL, which the expert mentioned is uncommon in clinical practice. Most of the trial participants were recruited from US centres, although Study 104 included eight Canadian sites, Study 111 included five Canadian sites, and Study 109 included 10 Canadian sites. No patients were enrolled from Canadian centres in Studies 112 and 106. Additionally, patients with hepatitis B virus (HBV) or hepatitis C virus (HCV) were excluded from the studies, which leaves uncertain the relative efficacy and safety in these subgroups.

Given the small number of treatment-naive patients enrolled in Study 112, the results are insufficient to draw robust conclusions about efficacy and safety in this subgroup of patients. The patients in Study 112 were older than the other studies of adults, although the clinical expert hypothesized that this may be because younger patients with HIV are less likely to experience reduced kidney function.

Study 106 mostly enrolled female patients, which, according to the consulting clinical expert, was most likely due to the fact that most of the population was from HIV-endemic countries or was infected through vertical transmission. The expert, however, did highlight that the most common (66.7% in Study 106) risk factor for HIV infection among adolescents is vertical transmission. The expert also indicated that children infected with HIV through vertical transmission are likely to be treated before reaching adolescence; therefore, most adolescents with HIV infection encountered in clinical practice in Canada are likely to be ART-experienced.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported here (Section 2.2, Table 5). See APPENDIX 4: ADDITIONAL EFFICACY OUTCOME DATA *for long-term efficacy outcome data.*

3.6.1 Virologic success (snapshot analysis)

In Studies 104 and 111, results from the primary (FAS) analyses demonstrated that a similar percentage of patients taking EVG/COBI/FTC/TAF compared with EVG/COBI/FTC/TDF achieved VL of < 50 copies/mL at week 48 (Study 104 difference: 1.0% [95.002% CI, –2.6 to 4.5]; Study 111 difference: 3.1% [95.002% CI, –1.0 to 7.1]) (Table 12). Results from the secondary (PP) analysis were consistent with the primary analyses. Further, there were no significant differences in rates of virologic success by VL subgroups in

these studies. In Study 109, results from the primary (FAS) analyses demonstrated that significantly more patients who switched to EVG/COBI/FTC/TAF (97.2%) versus those who stayed on their pre-existing FTC/TDF + a third drug regimen (93.1%) achieved VL < 50 copies/mL at week 48 (difference: 4.1% [95.01% CI, 1.6 to 6.7]). Whether the PP analyses corroborated these findings was, however, uncertain as no associated measures of precision, e.g., CI, were reported. The efficacy profile of EVG/COBI/FTC/TAF versus EVG/COBI/FTC/TDF at 96 weeks (pooled data from Studies 104 and 111) was similar to the 48-week results (APPENDIX 4: ADDITIONAL EFFICACY OUTCOME DATA).

In Study 112, the primary analysis (FAS) demonstrated that the virologic success rates at 24 weeks (snapshot algorithm) were 95.0% and 83.3% among adults who switched to EVG/COBI/FTC/TAF from their existing ARV regimen and treatment-naive adults who received EVG/COBI/FTC/TAF, respectively (Table 13). The efficacy profile of EVG/COBI/FTC/TAF at 48 weeks was [redacted] to the 24-week results (APPENDIX 4: ADDITIONAL EFFICACY OUTCOME DATA). In Study 106, the virologic success rate at 24 weeks (snapshot algorithm) was 91.3% for 23 ART-naive adolescents receiving EVG/COBI/FTC/TAF (week 24 FAS).

TABLE 12: KEY EFFICACY OUTCOMES — TREATMENT-NAIVE OR VIROLOGICALLY SUPPRESSED ADULTS

	Study 104		Study 111		Study 109	
Virologic success (snapshot analysis), week 48	**EVG/COBI/FTC/TAF**	**EVG/COBI/FTC/TDF**	**EVG/COBI/FTC/TAF**	**EVG/COBI/FTC/TDF**	**EVG/COBI/FTC/TAF**	**FTC/TDF + third drug**
Overall population						
N	FAS	435	432	431	435	959	477
	[redacted]					921	440
HIV-1 RNA < 50 copies/mL, n (%)	FAS	405 (93.1)	399 (92.4)	395 (91.6)	385 (88.5)	932 (97.2)	444 (93.1)
	[redacted]					913 (99.1)	435 (98.9)
Difference in % (95% CI);[a] *P* value	FAS	1.0 (–2.6 to 4.5); 2.0 *P* = 0.58		3.1 (–1.0 to 7.1); *P* = 0.13		4.1 (1.6 to 6.7); *P* = 0.0002	
	[redacted]					0.3 (NR); *P* = NR	
By VL subgroup							
≤ 100,000 copies/mL	[redacted]					NR	
Difference in % (95% CI); *P* value	[redacted]						
> 100,000 copies/mL	[redacted]						
Difference in % (95% CI); *P* value	[redacted]						

CI = confidence interval; COBI = cobicistat; EVG = elvitegravir; FAS = full analysis set; FTC = emtricitabine; HIV-1 = human immunodeficiency virus type 1; NR = not reported; PP = per-protocol; RNA = ribonucleic acid; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate; VL = viral load.

[a] CI for Studies 104 and 111 is 95.002% and for Study 109 is 95.01%.

Note: FAS unless otherwise specified.

Source: Study 104 Clinical Study Report,[14] Study 111 Clinical Study Report,[15] Mills et al.[13]

TABLE 13: KEY EFFICACY OUTCOMES — SPECIAL POPULATIONS

	Study 112* (Reduced Kidney Function)				Study 106* (Adolescents)
Virologic success (snapshot analysis)	Switch to EVG/COBI/FTC/TAF			ART-naive EVG/COBI/ FTC/TAF	EVG/COBI/FTC/TAF
	Baseline $eGFR_{CG}$ < 50 mL/min	Baseline $eGFR_{CG}$ ≥ 50 mL/min	Total		
Week 24					
N	80	162	242	6	23
HIV-1 RNA < 50 copies/mL, n (%)	76 (95.0)	154 (95.1)	230 (95.0)	5 (83.3)	21 (91.3)

ART = antiretroviral therapy; COBI = cobicistat; $eGFR_{CG}$ = estimated glomerular filtration rate according to the Cockcroft-Gault formula; EVG = elvitegravir; FAS = full analysis set; FTC = emtricitabine; HIV-1 = human immunodeficiency virus type 1; RNA = ribonucleic acid; TAF = tenofovir alafenamide fumarate.
Note: FAS.
Source: Study 112 Clinical Study Report,[19] Study 106 Clinical Study Report.[20]

3.6.2 Other efficacy outcomes

a) Resistance development

Across Studies 104 and 111, a total of seven (0.8%) and five (0.6%) patients on EVG/COBI/FTC/TAF and EVG/COBI/FTC/TDF, respectively, who experienced virologic failure developed any primary genotypic resistance through week 48 (Table 20). In Study 109, one patient who switched to the EVG/COBI/FTC/TAF group developed resistance to FTC (M184M/I) through week 48. In Studies 112 and 106, through week 48, no patients receiving EVG/COBI/FTC/TAF developed new resistance or mutations that were not already present at baseline.

b) Health-related quality of life

Across Studies 104, 111, and 109, there were [redacted] differences in change from baseline in the EQ-5D-3L index score and the associated visual analogue scale from baseline through week 48 between patients receiving EVG/COBI/FTC/TAF and EVG/COBI/FTC/TDF. In Study 109, there were [redacted] differences in change from baseline in each sub-component of the SF-36 physical and mental function domains through week 48 between patients who switched to EVG/COBI/FTC/TAF from a pre-existing regimen of FTC/TDF + a third drug and those who remained on the regimen.

3.7 Harms

Only those harms identified in the review protocol are reported in the following section (see 2.2.1, Protocol).

3.7.1 Adverse events

Across all five studies, at least 80% of patients in each trial experienced at least one treatment-emergent AE. In Studies 104, 111, and 109, specifically, the number of AEs appeared similar between patients randomized to EVG/COBI/FTC/TAF or a comparator (Study 104: [redacted]% versus [redacted]%; Study 111: [redacted]% versus [redacted]%; Study 109: 86.3% versus 83.7%) (Table 14). The most common AE across these three studies was diarrhea, which occurred more frequently in patients not receiving EVG/COBI/FTC/TAF. The next most common AEs were nausea, upper respiratory tract infections (URTIs), and headache.

In Study 112, at least one AE was reported in 209 (86.4%) patients who switched to EVG/COBI/FTC/TAF from their existing ARV regimen (Table 16). The most common AEs reported by these patients were diarrhea (8.7%), arthralgia (8.3%), osteopenia (7.9%), and bronchitis (7.9%). In this study, [redacted] of [redacted]

([redacted]%) patients among the treatment-naive cohort experienced an AE. In Study 106, 39 (81.3%) ART-naive adolescents receiving EVG/COBI/FTC/TAF reported an AE, the most common of which was nausea (22.9%), followed by URTI (20.8%), diarrhea (16.7%), headache (14.6%), and abdominal pain (14.6%).

3.7.2 Serious adverse events

In Studies 104 and 111, the percentage of patients receiving EVG/COBI/FTC/TAF who experienced an SAE was slightly higher than among those receiving EVG/COBI/FTC/TDF (Study 104: [redacted]% versus [redacted]%; Study 111: [redacted]% versus [redacted]%). In Study 109, 6.8% of patients who switched to EVG/COBI/FTC/TAF from a pre-existing regimen of FTC/TDF + a third drug reported an SAE compared with 7.3% of those who remained on the pre-existing regimen (7.3%).

In Study 112, [redacted]([redacted]%) patients who switched to EVG/COBI/FTC/TAF from their existing ARV regimen reported an SAE, whereas [redacted] treatment-naive patients experienced an SAE. In Study 106, four (8.3%) patients reported an SAE.

SAEs were varied in nature in all studies, with no individual event appearing to occur more frequently in one treatment group versus another.

3.7.3 Withdrawals due to adverse events

In Studies 104, 111, and 109, fewer patients receiving EVG/COBI/FTC/TAF withdrew due to AEs than those receiving a comparator (Study 104: 0.9% versus 1.4%; Study 111: 0.9% versus 1.6%; Study 109: 0.9% versus 2.5%). In Study 112, eight (3.3%) of patients who switched to EVG/COBI/FTC/TAF from their existing ARV regimen withdrew due to AEs, whereas no treatment-naive patients did so. In Study 106, no ART-naive adolescents receiving EVG/COBI/FTC/TAF withdrew due to AEs.

WDAEs were varied in nature in all studies, with no individual event appearing to occur more frequently in one treatment group versus another.

3.7.4 Mortality

In Study 104, one patient in each group died, whereas in Study 111, one patient receiving EVG/COBI/FTC/TAF and two patients receiving EVG/COBI/FTC/TDF died. In Study 109, four patients who switched to EVG/COBI/FTC/TAF from a pre-existing regimen of FTC/TDF + a third drug died, whereas no patient died in the comparator group. In Studies 112 and 106, no patients died. Of the deaths that occurred, none were considered to be study-drug-related or HIV-related.

3.7.5 Notable harms

a) Kidney function

Across Studies 104 and 111, there were significantly greater decreases in median $eGFR_{CG}$ from baseline to week 48 in patients receiving EVG/COBI/FTC/TDF compared with EVG/COBI/FTC/TAF (Table 15). In Study 109, at week 48, median $eGFR_{CG}$ increased from baseline among patients who switched to EVG/COBI/FTC/TAF from a pre-existing regimen of FTC/TDF + a third drug (except those who switched from EFV/FTC/TDF), but decreased among those who stayed on their pre-existing regimen. The difference between groups was statistically significant.

In Study 112, the overall median (first quartile [Q1], third quartile [Q3]) change from baseline in $eGFR_{CG}$ at week 24 was –0.4 (–4.7, 4.5) mL/min for $eGFR_{CG}$ among patients who switched to EVG/COBI/FTC/TAF from their existing ARV regimen (Table 17). The subgroup with baseline $eGFR_{CG} < 50$ mL/min had a median increase from baseline in $eGFR_{CG}$ at week 24, while the $eGFR_{CG} \geq 50$ mL/min subgroup had a

median decrease at the same time point. Among treatment-naive patients, the overall median (Q1, Q3) change from baseline in $eGFR_{CG}$ at week 24 was –0.3 (–3.6, 1.3) mL/min. In Study 106, the overall median (Q1, Q3) change from baseline in eGFR (according to the Schwartz Formula) at week 24 was –20.0 (–32.0, –12.0) mL/min among treatment-naive adolescents receiving EVG/COBI/FTC/TAF.

b) Bone system

In Studies 104 and 111, there were significantly lower decreases in mean BMD at the hip and spine from baseline to week 48 in in patients receiving EVG/COBI/FTC/TAF compared with EVG/COBI/FTC/TDF ($P < 0.0001$) (Table 15). Analyses of the observed data corroborated the findings of the imputed data.

In Study 109, the overall mean BMD at the hip and spine increased in the patients who switched to EVG/COBI/FTC/TAF from a pre-existing regimen of FTC/TDF + a third drug (except those who switched from EFV/TDF/FTC), but decreased among those who stayed on their pre-existing regimen (difference in least squares mean [LSM] [95% CI] of per cent change in hip BMD at week 48: 1.81 [1.49 to 2.13]; difference in LSM [95% CI] of per cent change in spine BMD at week 48: 2.00 [1.55 to 2.45]). It was unclear whether these results reflected analyses of the observed or imputed data.

In Study 112, the overall mean BMD at the hip and spine increased in the patients who switched to EVG/COBI/FTC/TAF from their existing ARV regimen, but decreased among treatment-naive patients at week 24 (Table 17). In Study 106, the overall mean spine and TBLH BMD increased among treatment-naive adolescents (difference in LSM [95% CI] of per cent change in spine BMD at week 24: [redacted]; difference in LSM [95% CI] of per cent change in TBLH BMD at week 24: [redacted]).

TABLE 14: HARMS — TREATMENT-NAIVE OR VIROLOGICALLY SUPPRESSED ADULTS

	Study 104		Study 111		Study 109	
	EVG/COBI/ FTC/TAF (N = 435)	EVG/COBI/ FTC/TDF (N = 432)	EVG/COBI/ FTC/TAF (N = 431)	EVG/COBI/ FTC/TDF (N = 435)	EVG/COBI/ FTC/TAF (N = 959)	FTC/TDF + third drug (N = 477)
AEs						
Participants with > 0 AEs, N (%)	396 (91.0)	392 (90.7)	382 (88.6)	390 (89.7)	828 (86.3)	399 (83.7)
Most common AEs,[a] N (%)						
Diarrhea	78 (17.9)	81 (18.8)	69 (16.0)	83 (19.1)	96 (10.0)	42 (8.8)
Nausea	62 (14.3)	75 (17.4)	70 (16.2)	76 (17.5)	50 (5.2)	16 (3.4)
Vomiting	23 (5.3)	20 (4.6)	39 (9.0)	34 (7.8)		
Fatigue	33 (7.6)	37 (8.6)	38 (8.8)	34 (7.8)		
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]		
URTI	50 (11.5)	64 (14.8)	49 (11.4)	45 (10.3)	151 (15.7)	54 (11.3)
Nasopharyngitis	35 (8.0)	31 (7.2)	43 (10.0)	49 (11.3)	88 (9.1)	39 (8.2)
Syphilis	[redacted]	[redacted]	[redacted]	[redacted]	46 (4.8)	30 (6.3)
Bronchitis	[redacted]	[redacted]			58 (6.0)	26 (5.5)
Back pain	27 (6.2)	25 (5.8)	33 (7.7)	32 (7.4)	52 (5.4)	25 (5.2)
Arthralgia	26 (6.0)	17 (3.9)	35 (8.1)	22 (5.1)	59 (6.2)	24 (5.0)
Osteopenia	[redacted]	[redacted]			56 (5.8)	22 (4.6)
Headache	50 (11.5)	51 (11.8)	74 (17.2)	57 (13.1)	69 (7.2)	20 (4.2)

	Study 104		Study 111		Study 109	
	EVG/COBI/ FTC/TAF (N = 435)	EVG/COBI/ FTC/TDF (N = 432)	EVG/COBI/ FTC/TAF (N = 431)	EVG/COBI/ FTC/TDF (N = 435)	EVG/COBI/ FTC/TAF (N = 959)	FTC/TDF + third drug (N = 477)
Insomnia	27 (6.2)	23 (5.3)	30 (7.0)	25 (5.7)	50 (5.2)	30 (6.3)
Cough	37 (8.5)	31 (7.2)	30 (7.0)	29 (6.7)	64 (6.7)	25 (5.2)
Rash	25 (5.7)	18 (4.2)	30 (7.0)	28 (6.4)		
Lymphadenopathy			[redacted]	[redacted]		
Constipation			[redacted]	[redacted]		
Dizziness			[redacted]	[redacted]		
Anxiety			[redacted]	[redacted]		
Oropharyngeal pain			[redacted]	[redacted]		
Depression					42 (4.4)	30 (6.3)
Sinusitis					48 (5.0)	25 (5.2)
SAEs						
Participants with > 0 SAEs, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	65 (6.8)	35 (7.3)
WDAEs						
WDAEs, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	9 (0.9)	12 (2.5)
Deaths						
Number of deaths, N (%)	1 (0.2)	1 (0.2)	1 (0.2)	2 (0.5)	4 (0.4)	0

AE = adverse event; COBI = cobicistat; EVG = elvitegravir; FTC = emtricitabine; SAE = serious adverse event; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate; URTI = upper respiratory tract infection; WDAE = withdrawal due to adverse events.

[a] Frequency > 5% in any treatment group. Cells were left blank if the frequency < 5%.

Source: Study 104 Clinical Study Report,[14] Study 111 Clinical Study Report,[15] Mills et al.[13]

TABLE 15: NOTABLE HARMS (BONE AND RENAL SYSTEMS) — TREATMENT-NAIVE OR VIROLOGICALLY SUPPRESSED ADULTS

		Study 104		Study 111		Study 109	
		EVG/COBI/ FTC/TAF	EVG/COBI/ FTC/TDF	EVG/COBI/ FTC/TAF	EVG/COBI/ FTC/TDF	EVG/COBI/ FTC/TAF	FTC/TDF + third drug
$eGFR_{CG}$ (mL/min)[a]							
Baseline (mL/min)	**N**	[redacted]				708	352
	Median (Q1, Q3)					103.8 (87.7, 120.9)	102.4 (84.4, 121.5)
P value						0.55	
Change at week 48	**N**	[redacted]				545	265
	Median (Q1, Q3)					1.8 (–6.6, 9.7)	–3.7 (–11.1, 3.6)
P value						< 0.001	
Hip BMD[b]							
Baseline (g/cm^2)	**N**	[redacted]				NR	NR
	Mean (SD)					NR	NR

		Study 104		Study 111		Study 109	
		EVG/COBI/ FTC/TAF	EVG/COBI/ FTC/TDF	EVG/COBI/ FTC/TAF	EVG/COBI/ FTC/TDF	EVG/COBI/ FTC/TAF	FTC/TDF + third drug
Difference in LSM (95% CI), *P* value		[redacted]		[redacted]		NR	
% Change at week 48	**N**	[redacted]		[redacted]		869	428
	Mean (SD)	[redacted]		[redacted]		1.47 (2.71)	–0.34 (2.83)
Difference in LSM (95% CI), *P* value		[redacted]		[redacted]		1.81 (1.49 to 2.13); *P* < 0.0001	
Spine BMD[b]							
Baseline (g/cm^2)	**N**	[redacted]		[redacted]		NR	NR
	Mean (SD)	[redacted]		[redacted]		NR	NR
Difference in LSM (95% CI), *P* value		[redacted]		[redacted]		NR	
% Change at week 48	**N**	[redacted]		[redacted]		881	436
	Mean (SD)	[redacted]		[redacted]		1.56 (3.84)	–0.44 (4.14)
Difference in LSM (95% CI), *P* value		[redacted]		[redacted]		2.00 (1.55 to 2.45); *P* < 0.0001	

BMD = bone mineral density; CI = confidence interval; COBI = cobicistat; DXA = dual-energy X-ray absorptiometry; $eGFR_{CG}$ = estimated glomerular filtration rate according to the Cockcroft-Gault formula; EVG = elvitegravir; FTC = emtricitabine; LSM = least squares mean; NR = not reported; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate.

[a] Safety analysis set. Study 109 excludes participants who were previously receiving EFV/TDF/FTC.

[b] Observed data and hip and spine DXA analysis sets, except for Study 109, for which it was uncertain which data and analysis sets were used in Lancet publication of Study 109.[13]

Source: Study 104 Clinical Study Report,[14] Study 111 Clinical Study Report,[15] Study 109 Clinical Study Report [16] ($eGFR_{CG}$ data), Mills et al.[13] (hip BMD and spine BMD data).

TABLE 16: HARMS — SPECIAL POPULATIONS

	Study 112 (Reduced Kidney Function)				Study 106 (Adolescents)
	Switch to EVG/COBI/FTC/TAF				
	Baseline $eGFR_{CG}$ < 50 mL/min (N = 80)	Baseline $eGFR_{CG}$ ≥ 50 mL/min (N = 162)	Total (N = 242)	ART-naive EVG/COBI/FTC/TAF (N = 6)	EVG/COBI/FTC/TAF (N = 48)
AEs					
Participants with > 0 AEs, N (%)	67 (83.8)	142 (87.7)	209 (86.4)	5 (83.3)	39 (81.3)
Most common AEs,[a] N (%)					
Headache	2 (2.5)	15 (9.3)	17 (7.0)	0	7 (14.6)
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]	7 (14.6)
Abdominal pain upper					3 (6.3)
Respiratory tract infection					7 (14.6)

	Study 112 (Reduced Kidney Function)				Study 106 (Adolescents)
	Switch to EVG/COBI/FTC/TAF				
	Baseline $eGFR_{CG}$ < 50 mL/min (N = 80)	Baseline $eGFR_{CG}$ ≥ 50 mL/min (N = 162)	Total (N = 242)	ART-naive EVG/COBI/FTC/TAF (N = 6)	EVG/COBI/FTC/TAF (N = 48)
Nausea	5 (6.3)	12 (7.4)	17 (7.0)	0	11 (22.9)
Diarrhea	8 (10.0)	13 (8.0)	21 (8.7)	1 (16.7)	8 (16.7)
URTI	1 (1.3)	16 (9.9)	17 (7.0)	1 (16.7)	10 (20.8)
Vomiting					6 (12.5)
Dizziness	7 (8.8)	7 (4.3)	14 (5.8)	0	5 (10.4)
Vitamin D deficiency					5 (10.4)
Renal cyst	5 (6.3)	8 (4.9)	13 (5.4)	0	
Cough	4 (5.0)	8 (4.9)	12 (5.0)	0	
Constipation	[redacted]	[redacted]	[redacted]	[redacted]	
Fatigue	4 (5.0)	10 (6.2)	14 (5.8)	1 (16.7)	
Bronchitis	7 (8.8)	12 (7.4)	19 (7.9)	0	
Arthralgia	6 (7.5)	14 (8.6)	20 (8.3)	1 (16.7)	
Osteopenia	[redacted]	[redacted]	[redacted]	[redacted]	
Pain in extremity	[redacted]	[redacted]	[redacted]	[redacted]	
Back pain	2 (2.5)	13 (8.0)	15 (6.2)	0	
Body tinea					4 (8.3)
Bronchopneumonia					4 (8.3)
Upper tract infection					3 (6.3)
Somnolence					3 (6.3)
Rash popular					3 (6.3)
SAEs					
Participants with > 0 SAEs, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	4 (8.3)
WDAEs					
WDAEs, N (%)	6 (7.5)	2 (1.2)	8 (3.3)	0	0
Deaths					
Number of deaths, N (%)	0	0	0	0	0

AE = adverse event; ART = antiretroviral; COBI = cobicistat; $eGFR_{CG}$ = estimated glomerular filtration rate according to the Cockcroft-Gault formula; EVG = elvitegravir; FTC = emtricitabine; SAE = serious adverse event; TAF = tenofovir alafenamide fumarate; WDAE = withdrawal due to adverse event.

[a] Frequency > 5% in any treatment group. Cells were left blank if the frequency < 5%.

Source: Study 112 Clinical Study Report,[19] Study 106 Clinical Study Report.[20]

TABLE 17: NOTABLE HARMS (BONE AND RENAL SYSTEMS) — SPECIAL POPULATIONS

		Study 112 (Reduced Kidney Function)				Study 106 (Adolescents)
		Switch to EVG/COBI/FTC/TAF			ART-naive EVG/COBI/ FTC/TAF	EVG/COBI/FTC/ TAF
		Baseline $eGFR_{CG}$ < 50 mL/min	Baseline $eGFR_{CG}$ ≥ 50 mL/min	Total		
eGFR[a]						
Baseline (mL/min)	**N**	80	162	242	6	
	Median (Q1, Q3)	43	60	56		
Change at week 24	**N**	76	157	233	6	
	Median (Q1, Q3)	1.2 (–3.9, 5.6)	–0.9 (–4.8, 3.6)	–0.4 (–4.7, 4.5)	–0.3 (–3.6, 1.3)	
Hip BMD						
Baseline (g/cm^2)	**N**	NR		236	6	
	Mean (SD)			0.918 (0.1554)	0.973 (0.2124)	
% Change at week 24	**N**			225	6	
	Mean (SD)			0.733 (2.7674)	–0.022 (1.6853)	
Spine BMD						
Baseline (g/cm^2)	**N**	NR		236	6	
	Mean (SD)			1.076 (0.1879)	1.034 (0.2432)	
	Median (Q1, Q3)					
% Change at week 24	**N**			226	6	
	Mean (SD)			1.643 (3.6250)	–2.686 (4.5755)	
	Median (Q1, Q3)					
TBLH BMD						
Baseline (g/cm^2)	**N**	NR				
	Mean (SD)					
	Median (Q1, Q3)					
% Change at week 24	**N**					
	Mean (SD)					
	Median (Q1, Q3)					

ART = antiretroviral; BMD = bone mineral density; COBI = cobicistat; eGFR = estimated glomerular filtration rate; $eGFR_{CG}$ = estimated glomerular filtration rate according to the Cockcroft-Gault formula; EVG = elvitegravir; FTC = emtricitabine; NR = not reported; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; TAF = tenofovir alafenamide fumarate; TBLH = total body less head.

[a] For Study 112, eGFR is by Cockcroft-Gault formula (mL/min); for Study 106, eGFR is by Schwartz Formula ($mL/min/1.73m^2$).

Source: Study 112 Clinical Study Report,[19] Study 106 Clinical Study Report.[20]

4. DISCUSSION

4.1 Summary of Available Evidence

The evidence for this review was drawn from two phase 3, multi-centre, DB, double-dummy, active-controlled, NI trials (Study 104, n = 872; Study 111, n = 872), one phase 3 multi-centre, open-label, active-controlled, NI trial (Study 109, n = 1,443), and two multi-centre, open-label cohort studies (Study 112, n = 252; Study 106, n = 48). The primary efficacy outcome for all studies was the percentage of patients with HIV-1 RNA < 50 copies/mL at week 48 (Studies 104, 111, and 109) or week 24 (Studies 112 and 106) using the FDA-defined snapshot algorithm.

Studies 104 and 111 exclusively enrolled treatment-naive adults, whereas Study 109 enrolled only virologically suppressed adults who had been on an ARV regimen consisting of FTC/TDF + a third drug. No major methodological issues were identified in these three studies. The consulting clinical expert confirmed that the study populations were generally reflective of Canadian practice. In terms of limitations, only a small proportion of women were studied, and patients with HBV or HCV were excluded from the studies; hence, the data are insufficient or unavailable to determine the relative efficacy and safety of EVG/COBI/FTC/TAF in these subgroups. Patients with HBV or HCV may have been excluded due to uncertainty regarding the safety and efficacy of EVG/COBI/FTC/TAF in patients co-infected with HIV-1 and HBV, or because of interactions with drugs required for treatment of HCV infection, e.g., ledipasvir/sofosbuvir. It is also unknown how EVG/COBI/FTC/TAF directly compares with FTC/RPV/TDF and DTG/ABC/3TC, the other STRs available in Canada.

Studies 112 and 106 evaluated the efficacy and safety of EVG/COBI/FTC/TAF in HIV-infected adults with mild to moderate kidney impairment, and treatment-naive adolescents, respectively. Due to the single-group design of the studies, the results did not demonstrate the relative efficacy and safety of EVG/COBI/FTC/TAF in the study populations. Further, Study 112 exclusively enrolled patients with mild to moderate kidney impairment, which leaves uncertain the generalizability of the results to HIV-infected patients with more severe kidney impairment. In addition, given the small number of treatment-naive patients enrolled in this study (n = 6), the results were insufficient to draw robust conclusions about the efficacy and safety of EVG/COBI/FTC/TAF in this particular subgroup of patients. Study 106 only enrolled treatment-naive adolescents, i.e., 12 years to 18 years of age, who weighed ≥ 35 kg. Given the small number of patients analyzed (n = 23) for the primary efficacy outcome, it is difficult to draw robust conclusions about safety and efficacy in this population. As well, there were no data for treatment-experienced adolescents requiring a switch from existing therapy, which is a limitation since many patients with HIV in this age group would have contracted the infection through vertical transmission and would have been initiated on ART earlier in childhood.

4.2 Interpretation of Results

4.2.1 Efficacy

In Studies 104 and 111, EVG/COBI/FTC/TAF was statistically non-inferior to EVG/COBI/FTC/TDF with respect to the primary efficacy outcome. These results were consistent in a pooled analysis of the data from both studies at 48 weeks[17] and 96 weeks (APPENDIX 4: ADDITIONAL EFFICACY OUTCOME DATA). In Study 109, results from the primary analyses demonstrated that significantly more patients who switched to EVG/COBI/FTC/TAF versus those who stayed on their pre-existing FTC/TDF + a third drug regimen achieved VL < 50 copies/mL at week 48. In Study 112, the primary analysis demonstrated that the virologic success rates at 24 weeks were 95.0% and 83.3% among adults who switched to EVG/COBI/FTC/TAF from their existing ARV regimen and treatment-naive adults who received

EVG/COBI/FTC/TAF, respectively. In Study 106, the virologic success rate at 24 weeks was 91.3% for 23 ART-naive adolescents receiving EVG/COBI/FTC/TAF. In all, the consulting clinical expert highlighted that the rates of virologic success across the studies, although quite good, were lower than what is observed in usual clinical practice. This may be due to the greater flexibility (in choosing regimens) that clinicians have in treating HIV-infected patients in everyday settings.

Across the three RCTs, there were very few patients who developed primary genotypic resistance through week 48. In Studies 112 and 106, through week 48, no patients receiving EVG/COBI/FTC/TAF developed new resistance or resistance-associated mutations that were not already present at baseline. The small number of patients who developed resistance was consistent with the impression of the consulting clinical expert, who noted that it was unusual to see resistance with these drugs.

There were no differences in HRQoL among patients receiving EVG/COBI/FTC/TAF or a comparator, which is consistent with the expectations noted in the patient input submission and by the consulting clinical expert.

The data for adolescents with HIV infection were non-comparative, although the rate of virological suppression in Study 106 was similar to the rates observed in the comparative trials in adults. EVG/COBI/FTC/TAF represents the first STR indicated for the pediatric population in Canada, and as such, may offer benefits in terms of convenience and enhanced adherence that the availability of STRs has conferred for the adult population. According to the clinical expert, STRs are preferred where possible based on resistance patterns, as they have a substantial impact on adherence in the pediatric population. The STRs EFV/TDF/FTC, FTC/RPV/TDF, and DTG/ABC/3TC are prescribed despite the lack of an indication in the pediatric population. The DHHS pediatric guidelines for HIV infection provide weight-based guidance for patients at least 12 years of age, specifically recommending (as an alternative regimen) the use of two nucleoside reverse transcriptase inhibitors (NRTIs) and DTG in children weighing ≥ 40 kg (Table 4).

4.2.2 Harms

Across all five studies, at least 80% of patients in each trial experienced at least one treatment-emergent AE. Diarrhea, nausea, URTIs, and headache appeared to be the most common AEs reported by patients receiving EVG/COBI/FTC/TAF. The types of AEs were consistent with the experience of the consulting clinical expert, although the rates in the studies were thought to be higher than those observed in clinical practice. This discrepancy may be attributable to the highly controlled settings of the clinical trials, which would detect even the most benign of AEs. The percentage of patients who experienced an SAE while receiving EVG/COBI/FTC/TAF varied. Across the three RCTs, fewer patients receiving EVG/COBI/FTC/TAF withdrew due to AEs than those receiving a comparator. There were two deaths reported in Study 104 (one in the EVG/COBI/FTC/TAF group) and three in Study 111 (one in the EVG/COBI/FTC/TAF group). In Study 109, four patients who switched to EVG/COBI/FTC/TAF from a pre-existing regimen of FTC/TDF + a third drug died, whereas no patient died in the comparator group, although none of those deaths were considered treatment-related. Additionally, no patients in Studies 112 and 106 died.

All five studies evaluated the impact of EVG/COBI/FTC/TAF on kidney function. This was important to investigate since evidence suggests that the risk of kidney disease is increased by as much as seven-fold in HIV-infected individuals compared with the general population.[22,23] Moreover, exposure to TDF, as part of a combination ART regimen, has been shown to increase renal toxicity and reduce kidney function in patients with HIV.[24-29] According to the consulting clinical expert, reductions in eGFR are

observed in about 10% to 15% of patients treated with TDF, but these changes rarely warrant discontinuation of therapy. EVG/COBI/FTC/TAF had less of an impact on kidney function (as measured by overall median change in $eGFR_{CG}$ from baseline to week 48) in treatment-naive patients relative to EVG/COBI/FTC/TDF in Studies 104 and 111. In Study 109, median $eGFR_{CG}$ increased slightly from baseline among patients who switched to EVG/COBI/FTC/TAF from a pre-existing regimen of FTC/TDF + a third drug, but decreased among those who stayed on their pre-existing regimen, resulting in a significant difference between groups. In Study 112, among virologically suppressed adults, overall kidney function appeared to decrease at 24 weeks, although the effect seemed to differ by severity of kidney impairment at baseline: specifically, patients with $eGFR_{CG}$ < 50 mL/min at baseline experienced an overall increase in $eGFR_{CG}$ at week 24, whereas those with $eGFR_{CG}$ ≥ 50 mL/min had a median decrease at the same time point. Among treatment-naive patients in the same study, there was minimal change in median $eGFR_{CG}$ from baseline. In Study 106, there appeared to be a larger decrease compared with the adult studies in overall median eGFR (according to the Schwartz Formula) from baseline to week 24 (median [Q1, Q3] change: –20.0 [–32.0, –12.0] mL/min/1.73 m^2) among treatment-naive adolescents receiving EVG/COBI/FTC/TAF. According to the consulting clinical expert, this magnitude of change may have been due to chance, use of the Schwartz Formula which can overestimate the changes, or the benign effects of COBI. In all, however, the consulting clinical expert highlighted that the magnitude of the changes and differences between treatments across studies were not likely to be clinically meaningful in clinical practice, but may be important to track in the long term.

The five included studies also evaluated the impact of EVG/COBI/FTC/TAF on the bone system. HIV-infected individuals experience accelerated bone loss compared with the general population, especially with TDF exposure, although the risk of fracture is low according to the consulting clinical expert.[30] In the three RCTs included in this review, treatment with EVG/COBI/FTC/TAF appeared to decrease harmful effects on the bone system compared with EVG/COBI/FTC/TDF, as measured by changes in mean BMD at the hip and spine from baseline to week 48. In Study 109, the overall mean BMD at the hip and spine increased at week 48 in patients who switched to EVG/COBI/FTC/TAF from a pre-existing regimen of FTC/TDF + a third drug, but decreased among those who stayed on their pre-existing regimen. In Study 112, the overall mean BMD at the hip and spine increased in the patients who switched to EVG/COBI/FTC/TAF from their existing ARV regimen, but decreased among treatment-naive patients at week 24. In Study 106, the overall mean spine and TBLH BMD increased among treatment-naive adolescents from baseline to week 24. The consulting clinical expert highlighted that the magnitude of the changes (across all studies) in BMD were not likely to be clinically meaningful in clinical practice, but may be important to track in the long term. It is noteworthy, however, that Health Canada raised concerns with respect to the harmful effects on the bone system in adolescents, in light of a week 24 interim analysis of Study 106 that identified four participants with worsening in the spine or TBLH height-age-adjusted BMD z score from baseline. The manufacturer highlighted that three of these patients subsequently showed improvements in BMD at week 48. Still, the true effects of EVG/COBI/FTC/TAF on the bone system in adolescents remains somewhat uncertain given the small sample size of Study 106.

4.3 Potential Place in Therapy

The optimal ARV therapy is one that suppresses HIV replication completely, promotes adherence, and has no short-term AEs or long-term toxicities. The ideal treatment for HIV-infected patients is a one tablet once per day formulation, i.e., an STR. In Canada, there are five available STR formulations: EFV/TDF/FTC, FTC/RPV/TDF, EVG/COBI/FTC/TDF, DTG/ABC/3TC, and now EVG/COBI/FTC/TAF. EFV/TDF/FTC is less commonly used, mostly because of its prominent side effects. FTC/RPV/TDF is well tolerated, but must be taken with food, and antacids must be avoided. HLA-B 5701 is a major

histocompatability complex class 1 allele that strongly predicts for the development of a hypersensitivity reaction to the ABC component of DTG/ABC/3TC. Assuming the patient is HLA-B 5701-negative, DTG/ABC/3TC is well tolerated in the short and long term, allows for flexibility in dosing, and is mostly free of drug interactions. EVG/COBI/FTC/TDF is very well tolerated in the short term, and although it may lead to numerous drug interactions, these are mostly well recognized and quite manageable. Its use is hindered by the potential for kidney dysfunction and reduced BMD. EVG/COBI/FTC/TAF addresses these longer term complications, making it akin to DTG/ABC/3TC in short- and long-term tolerability.

There are many potential places in therapy for EVG/COBI/FTC/TAF:

- Treatment-naive patients: Among the most important factors considered when initiating therapy is the capacity to adhere to it. As EVG/COBI/FTC/TAF is tolerable in the short term, it is an excellent candidate for first-line ARV therapy, as are FTC/RPV/TDF and DTG/ABC/3TC. In light of the excellent prognosis of HIV-infected persons and the anticipated need for many years of ARV therapy, EVG/COBI/FTC/TAF will likely be heavily used in this role, more so than EVG/COBI/FTC/TDF or FTC/RPV/TDF.
- Substitution for EVG/COBI/FTC/TDF: EVG/COBI/FTC/TAF is as effective at suppressing HIV replication as EVG/COBI/FTC/TDF, and as tolerable in the short term, but with a lesser tendency to cause reductions in BMD or affect kidney function. As such, it is extremely likely that EVG/COBI/FTC/TAF would supplant EVG/COBI/FTC/TDF entirely.
- Substitution for intolerance, inconvenience, or simplification: Assuming an undetectable VL and favourable baseline genotype, physicians quite freely substitute one therapy for another in order to optimize adherence and reduce side effects or inconvenience. EVG/COBI/FTC/TAF would certainly be a good option in substitution for any number of other regimens.
- Use in previous treatment failure: Virologic failure of HIV medications leads to the development of genotypic resistance, and second-line therapies must take into account these in order to re-suppress HIV replication. There are limited situations in which EVG/COBI/FTC/TAF could be used in salvage therapy, such as following virologic failure with a regimen containing non-nucleoside reverse transcriptase inhibitors (NNRTIs), e.g., EFV/TDF/FTC and FTC/RPV/TDF. The use of EVG/COBI/FTC/TAF with darunavir (DRV) would yield a two-pill combination that would likely re-suppress HIV replication, with few side effects. It is anticipated that this would be an unusual and infrequent use of EVG/COBI/FTC/TAF.
- Post-exposure prophylaxis: As there is no clinical trial evidence available to support any single regimen to prevent infection after potential HIV exposure, standards of care differ locally, but most consist of a standard three-drug ARV regimen. Because of its tolerability and safety, EVG/COBI/FTC/TAF would be a reasonable option for post-exposure prophylaxis.

The patient characteristics that would prevent the use of EVG/COBI/FTC/TAF include a CrCl of less than 30 mL/min. The concomitant use of medications with which there is a deleterious or unmanageable drug interaction (such as inhaled corticosteroids, ergotamines, or novel oral anticoagulants) also represents a strong contraindication to the use of EVG/COBI/FTC/TAF.

5. CONCLUSIONS

In two RCTs, EVG/COBI/FTC/TAF was shown to achieve statistically similar rates of VL suppression compared with EVG/COBI/FTC/TDF among treatment-naive adults with HIV infection after 48 weeks of treatment. In a third RCT, the switch to EVG/COBI/FTC/TAF from another FTC/TDF-containing regimen among virologically suppressed patients was associated with significantly higher rates of virologic suppression at 48 weeks compared with continued therapy with the existing regimen.
EVG/COBI/FTC/TAF was associated with relatively similar rates of AEs as the comparator in these trials, among which diarrhea, nausea, URTIs, and headache appeared to be the most common. While EVG/COBI/FTC/TAF had smaller effects on kidney function (eGFR) and BMD compared with EVG/COBI/FTC/TDF, the observed changes are unlikely to be clinically significant in the short term and are of uncertain importance with respect to the risks for kidney failure or fracture in the long term.
EVG/COBI/FTC/TAF also demonstrated high rates of virologic suppression in a single-group study of patients with mild to moderate kidney impairment, with minimal changes in median eGFR. High rates of virologic suppression were also observed in a small, single-group trial of treatment-naive adolescents; however, in the absence of a comparative trial against EVG/COBI/FTC/TDF or another STR, there is greater uncertainty regarding relative efficacy and safety in this population compared with adults.

APPENDIX 1: PATIENT INPUT SUMMARY

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

1. Brief Description of Patient Group 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 human immunodeficiency virus (HIV) and hepatitis C virus (HCV). 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: a) individuals living with HIV (including HCV co-infection); b) organizations, groups, or projects with a substantial HIV mandate (including HCV co-infection).

CTAC received unrestricted organizational and educational grants from the following in the 2014-2015 fiscal year: Abbott/AbbVie, Gilead Sciences, Janssen, and ViiV Healthcare. It was not stated whether these conflicts of interest affected the submission.

2. Condition-Related Information

Information for this submission was primarily collected from a national consultation webinar on the CADTH Common Drug Review (CDR) process and on key findings from the elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fumarate (EVG/COBI/FTC/TAF) clinical trials. The link to the webinar along with a feedback survey was also sent to webinar attendees (two in total) and to principal investigators. Information was compiled from two respondents who identified as being HIV positive. In addition, information was obtained from survey data used in submissions pertaining to Stribild, Tivicay, Triumeq, and Prezcobix.

HIV is a serious, life-threatening disease that compromises a patient's immune system and, if left untreated, predisposes these patients to opportunistic infections. Highly active antiretroviral treatment (HAART) is the mainstay for HIV management. For the most part, patients taking HAART achieve viral suppression (an undetectable viral load [VL]), whereby there are less than 50 copies/mL in a blood sample. Hence, patients with HIV manage their disease as a chronic illness. However, patients with HIV often tend to experience "accelerated aging" and become more susceptible to inflammatory and non-infectious comorbidities such as cardiovascular (CV), kidney, and liver disease, along with bone fractures.

Patients living with HIV often experience negative mental health outcomes. These can be due to the side effects from treatment or from social stigma, discrimination, and related stress. Mental health issues and stigma are noted by the following respondents, whereby one person's biggest challenge was regarding the "ignorance about HIV and healthy living and stigma attached to infection," while the other respondent stated, "I was quite depressed and suicidal early on in my infection, and my caregivers had to deal with this". The most common physical symptom associated with HIV is fatigue, which also happens to be one of the main side effects of HAART treatment.

In addition to both mental and physical side effects, patients with HIV often experience stress, hardship, and access difficulties associated with the disease and treatments. For instance, access to affordable treatment remains difficult for many patients, as are the complications associated with access to treatment when moving between provinces. Additionally, since HIV is treated in a multi-faceted way, most often through collaboration between different specialists, adherence programs, and outreach programs, stress is often compounded when trying to obtain proper care. Flexible work hours are a necessity for

many patients and their caregivers, which compounds the social stigma and stress associated with having and treating HIV.

Caregivers to patients with HIV can be negatively affected in many ways. They are often responsible for or aid in the travel associated with treatment, they often face monetary hardships (either due to treatment costs or required travel, especially when living in remote areas), and they are often the main persons (aside from the patient) ensuring adherence to medication. In addition, the peace of mind of the caregivers can be negatively affected when they see their loved ones experience treatment side effects and constantly have to encourage them to adhere to their treatment regimen.

3. Current Therapy-Related Information

The two respondents reported that they were either on a Tivicay-based regimen (one year) or a Triumeq-based regimen (two months). VLs on these treatments remained undetectable; however, both experienced numerous side effects. In addition to the aforementioned fatigue, side effects included hypercholesterolemia, bone density loss, nausea, diarrhea, insomnia, and depression. One respondent claimed there was no impact on quality of life, while the other noted a positive impact, particularly with regard to "…energy level, work life, home life, relationship with pet, etc."

Both advantages and challenges were reported by the patients that responded to the previous Stribild, Tivicay, Triumeq, and Prezcobix surveys. "Minor" adverse events (AEs) were noted by one patient taking darunavir (DRV), while CV events (including a stroke), gum disease, lipodystrophy, and fatigue were reported by a patient taking a Viramune and Truvada-based regimen. On ritonavir (RTV), one patient reported experiencing gastrointestinal (GI) events such as GI distress, diarrhea, gas, and weight gain. When adding DRV to RTV, another patient also reported high cholesterol and loose stools. One patient taking Complera reported fatigue and a big stomach, while one patient on Isentress for a four-year period reported a feeling of "wasting" as a side effect.

While all of these side effects affect the patient, some also state that, in addition to the low VLs, they have "Less fear of catching opportunistic infections." One patient noted that there were still challenges associated with their rehabilitation from sickness to health and subsequent return to work, but that their quality of life improved. Another patient reported no change in quality of life, while another patient reported a decrease, stating, "…I'm more depressed than I used to be."

Treatment adherence (specifically taking the medication *when* prescribed, *as* prescribed) is particularly important with regard to HIV treatment as non-adherence can lead to drug class resistance. Once this occurs, it is necessary for the patient to embark on a different treatment regimen. Therefore, patients and patient groups note that having many options available is of the utmost clinical importance.

4. Expectations About the Drug Being Reviewed

CTAC feels that having a maximum number of possible treatment options is of great clinical importance, not only to achieve sufficiently low VLs but also in the case of adherence issues.

The two webinar respondents indicated that they had no experience with EVG/COBI/FTC/TAF. One respondent was uninterested in trying the EVG/COBI/FTC/TAF regimen due to the perceived challenges associated with a new treatment, while the other would only do so on the advice of his infectious disease specialist, especially considering "There is no compelling reason to change to another therapy when the one I am on is effective and has a better safety profile than previous therapies." Both suspected that their quality of life would be the same on the EVG/COBI/FTC/TAF regimen as it is on their current therapy.

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:	October 23, 2015
Alerts:	Monthly search updates until February 17, 2016
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as 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
.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

MUTLI-DATABASE STRATEGY	
#	**Searches**
1	("EVG/COBI/FTC/TAF" or "elvitegravir/cobicistat/emtricitabine/tenofovir").ti,ab.
2	697761-98-1.rn,nm. or (elvitegravir* or Vitekta* or JTK303 or "JTK 303" or "GS 9137" or GS9137 or 4GDQ854U53).ti,ab,ot,kw,hw,rn,nm.
3	1004316-88-4.rn,nm. or (cobicistat* or Tybost* or "GS 9350" or GS9350 or "COBI cpd" or LW2E03M5PG).ti,ab,ot,kw,hw,rn,nm.
4	143491-57-0.rn,nm. or (emtricitabin* or emtriva* or coviracil* or racivir* or Hui Er Ding* or Xin Luo Shu* or 524W91 or "BW 1592" or "BW 524 w 91" or "BW 524 W91" or "BW 524W" or BW524W or BW524W91 or "DRG 0208" or DRG0208 or "psi 5004" or psi5004 or "HSDB 7337" or HSDB7337 or G70B4ETF4S or dOTFC).ti,ab,ot,kw,hw,rn,nm.
5	(379270-37-8 or 377091-31-1 or 147127-20-6).rn,nm. or (tenofovir* or "GS 7340" or GS7340 or EL9943AG5J).ti,ab,ot,kw,hw,rn,nm.
6	and/2-5

MUTLI-DATABASE STRATEGY	
#	**Searches**
7	6 use pmez
8	*elvitegravir/ or (elvitegravir* or Vitekta* or JTK303 or "JTK 303" or "GS 9137" or GS9137 or 4GDQ854U53).ti,ab.
9	*cobicistat/ or (cobicistat* or Tybost* or "GS 9350" or GS9350 or "COBI cpd" or LW2E03M5PG).ti,ab.
10	*emtricitabine/ or (emtricitabin* or emtriva* or coviracil* or racivir* or Hui Er Ding* or Xin Luo Shu* or 524W91 or "BW 1592" or "BW 524 w 91" or "BW 524 W91" or "BW 524W" or BW524W or BW524W91 or "DRG 0208" or DRG0208 or "psi 5004" or psi5004 or "HSDB 7337" or HSDB7337 or G70B4ETF4S or dOTFC).ti,ab.
11	tenofovir.hw. or (tenofovir* or "GS 7340" or GS7340 or EL9943AG5J).ti,ab.
12	and/8-11
13	12 use oemezd
14	1 or 7 or 13
15	14 not conference abstract.pt.
16	remove duplicates from 15

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. 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:	October 2015
Keywords:	elvitegravir/cobicistat/emtricitabine/tenofovir, HIV
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" (https://www.cadth.ca/resources/finding-evidence/grey-matters-practical-search-tool-evidence-based-medicine) 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
Sax et al. 2015	Inappropriate design — pooled analysis
Sax et al. 2014	Inappropriate design — phase 2
Mills et al. 2015	Inappropriate design — phase 2

APPENDIX 4: ADDITIONAL EFFICACY OUTCOME DATA

This section was taken from contents of a manufacturer's response to a request for additional information dated November 3, 2015.

TABLE 18: ADDITIONAL EFFICACY OUTCOMES — TREATMENT-NAIVE OR VIROLOGICALLY SUPPRESSED ADULTS

		Study 104 and Study 111	
Virologic Success (Snapshot Analysis), Week 96		**Genvoya (N = 866)**	**Stribild (N = 867)**
Overall population			
HIV-1 RNA < 50 copies/mL, n (%)	FAS	[redacted](87)	[redacted](85)
	PP	[redacted]	[redacted]
Difference in % (95.002% CI); *P* value	FAS	1.5 (–1.8 to 4.8)	
	PP	[redacted]	
By VL subgroup			
≤ 100,000 copies/mL		[redacted]	[redacted]
Difference in % (95% CI), *P* value		[redacted]	
> 100,000 copies/mL		[redacted]	[redacted]
Difference in % (95% CI), *P* value		[redacted]	

CI = confidence interval; FAS = full analysis set; HIV-1 = human immunodeficiency virus type 1; NR = not reported; PP = per-protocol; RNA = ribonucleic acid; VL = viral load.
Note: FAS unless otherwise specified.

This section was taken from the Clinical Study Reports of Studies 112[19] and 106.[20]

TABLE 19: ADDITIONAL EFFICACY OUTCOMES — SPECIAL POPULATIONS

	Study 112				Study 106
Virologic Success (Snapshot Analysis), Week 48	**Switch to EVG/COBI/FTC/TAF**			**ART-naive EVG/COBI/ FTC/TAF**	**EVG/COBI/ FTC/TAF**
	Baseline $eGFR_{CG}$ < 50 mL/min	**Baseline $eGFR_{CG}$ ≥ 50 mL/min**	**Total**		
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HIV-1 RNA < 50 copies/mL, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	

ART = antiretroviral therapy; CI = confidence interval; COBI = cobicistat; $eGFR_{CG}$ = estimated glomerular filtration rate according to the Cockcroft-Gault formula; EVG = elvitegravir; FAS = full analysis set; FTC = emtricitabine; HIV-1 = human immunodeficiency virus type 1; NR = not reported; RNA = ribonucleic acid; TAF = tenofovir alafenamide fumarate; VL = viral load.
Note: Week 48 FAS unless otherwise specified.

APPENDIX 5: RESISTANCE DATA

This section was taken verbatim from contents of a manufacturer's response to a request for additional information dated November 3, 2015.

TABLE 20: RESISTANCE THROUGH WEEK 48 IN STUDIES 104 AND 111 COMBINED

		Genvoya (n = 866)	Stribild (n = 867)
Patients analyzed for resistance		16 (1.8)	19 (2.2)
Primary genotypic resistance	Any, n (%)	7 (0.8)	5 (0.6)
	Study 104, n	3	3
	Study 111, n	4	2
NRTI resistance, n	Any, n	7	5
	M184V/I	6	3
	M184V/I + K65R	1	2
INSTI resistance, n	Any, n	5	3
	T66A	1	0
	E92Q	2	1
	N155H	1	0
	Q148R	0	1
	Q148R + T66I/A	1	0
	Q148R + E92Q	0	1

INSTI = integrase strand transfer inhibitor; NRTI = nucleoside reverse transcriptase inhibitor.

Study 109 — Resistance through week 48: Of a total 959 patients in the Genvoya "switch" group, 10 patients developed virologic failure, with one having resistance to emtricitabine (FTC) (M184M/I). Of a total 477 patients in the tenofovir disoproxil fumarate (TDF)-based group, there were six patients who developed virologic failure with no documented cases (n = 0) of resistance to study drug.

Study 112 — Resistance through week 48: Of a total 242 patients, three patients experienced virologic failure; however, none of the three patients (n = 0) who failed had new resistance or mutations that were not already present at baseline. The first of these three patients had human immunodeficiency type 1 (HIV-1) ribonucleic acid (RNA) [redacted] copies/mL on Genvoya prior to switching to a new regimen, the second patient who had HIV-1 RNA [redacted] copies/mL on Genvoya demonstrated [redacted] and [redacted] resistance mutations which were identical to a pre-study historical genotype, and the third patient took [redacted] through day [redacted] ([redacted]) but was maintained on Genvoya alone with HIV-1 RNA [redacted] copies/mL through week 48 after the [redacted] was discovered.

Study 106 — Resistance through week 24: Of a total 23 patients, two patients experienced virologic failure with no documented cases (n = 0) of resistance to study drug.

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