

# Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate versus ritonavir-boosted atazanavir plus co-formulated emtricitabine and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3, non-inferiority trial

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## Summary

**Background** The HIV integrase strand transfer inhibitor elvitegravir (EVG) has been co-formulated with the CYP3A4 inhibitor cobicistat (COBI), emtricitabine (FTC), and tenofovir disoproxil fumarate (TDF) into a once-daily, single tablet. We compared EVG/COBI/FTC/TDF with a ritonavir-boosted (RTV) protease inhibitor regimen of atazanavir (ATV)/RTV+FTC/TDF as initial therapy for HIV-1 infection.

**Methods** This phase 3, non-inferiority study enrolled treatment-naïve patients with an HIV-1 RNA concentration of 5000 copies per mL or more and susceptibility to atazanavir, emtricitabine, and tenofovir. Patients were randomly assigned (1:1) to receive EVG/COBI/FTC/TDF or ATV/RTV+FTC/TDF plus matching placebos, administered once daily. Randomisation was by a computer-generated random sequence, accessed via an interactive telephone and web response system. Patients, and investigators and study staff who gave treatments, assessed outcomes, or analysed data were masked to the assignment. The primary endpoint was HIV RNA concentration of 50 copies per mL or less after 48 weeks (according to the US FDA snapshot algorithm), with a 12% non-inferiority margin. This trial is registered with ClinicalTrials.gov, number NCT01106586.

**Findings** 1017 patients were screened, 715 were enrolled, and 708 were treated (353 with EVG/COBI/FTC/TDF and 355 with ATV/RTV+FTC/TDF). EVG/COBI/FTC/TDF was non-inferior to ATV/RTV+FTC/TDF for the primary outcome (316 patients [89·5%] vs 308 patients [86·8%], adjusted difference 3·0%, 95% CI -1·9% to 7·8%). Both regimens had favourable safety and tolerability; 13 (3·7%) versus 18 (5·1%) patients discontinued treatment because of adverse events. Fewer patients receiving EVG/COBI/FTC/TDF had abnormal results in liver function tests than did those receiving ATV/RTV+FTC/TDF and had smaller median increases in fasting triglyceride concentration (90 µmol/L vs 260 µmol/L,  $p=0\cdot006$ ). Small median increases in serum creatinine concentration with accompanying decreases in estimated glomerular filtration rate occurred in both study groups by week 2; they generally stabilised by week 8 and did not change up to week 48 (median change 11 µmol/L vs 7 µmol/L).

**Interpretation** If regulatory approval is given, EVG/COBI/FTC/TDF would be the first integrase-inhibitor-based regimen given once daily and the only one formulated as a single tablet for initial HIV treatment.

**Funding** Gilead Sciences.

## Introduction

International treatment guidelines<sup>1-4</sup> recommend that initial therapy for treatment-naïve patients with HIV-1 infection consists of two nucleoside/nucleotide reverse transcriptase inhibitors plus a non-nucleoside reverse transcriptase inhibitor (generally efavirenz; EFV), a ritonavir-boosted (RTV) protease inhibitor (generally darunavir or atazanavir; ATV), or the integrase strand transfer inhibitor raltegravir. Guidelines also include a fixed-dose combination tablet of emtricitabine (FTC) plus tenofovir disoproxil fumarate (TDF), as a preferred backbone for initial therapy. Ritonavir-boosted protease inhibitor regimens have antiviral potency and a high barrier for development of drug resistance, and are

an alternative to non-nucleoside reverse transcriptase inhibitors for some patients, including those with transmitted resistance to non-nucleoside reverse transcriptase inhibitors, those unlikely to adhere to therapy, and women of childbearing potential, or to avoid the neuro-psychiatric disorders associated with efavirenz.<sup>1-6</sup> Regimens including ritonavir are generally well tolerated but are associated with metabolic complications such as dyslipidaemia, lipodystrophy, insulin resistance, and multiple drug interactions.<sup>1</sup> The main limitation of ritonavir-based therapy is the additional pill and prescription burdens and tolerability profiles of the protease inhibitors and ritonavir.

Clinical studies show better adherence and treatment satisfaction, and persistent suppression of viral load with

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simple, once-daily highly active antiretroviral therapy regimens than with complex multi-pill ones.<sup>7–10</sup> Only two single-tablet regimens are available, both based on non-nucleoside reverse transcriptase inhibitors: EFV/FTC/TDF and FTC/rilpivirine/TDF. Alternative single-tablet regimens are needed, especially those with new drug classes or mechanisms of action that provide sustained efficacy with favourable tolerability and safety profiles for patients with HIV infection.

Elvitegravir (EVG) is a once-daily investigational HIV integrase strand transfer inhibitor with potent antiretroviral activity that has been co-formulated with cobicistat (COBI), an investigational cytochrome P450 3A inhibitor (a pharmacoenhancer that has no anti-HIV activity), plus the nucleoside/nucleotide reverse transcriptase inhibitor backbone FTC/TDF (elvitegravir 150 mg, cobicistat 150 mg, emtricitabine 200 mg, and tenofovir disoproxil fumarate 300 mg). This formulation had potent and durable antiretroviral efficacy and favourable safety in a phase 2 trial.<sup>11</sup> Here, we report the results of GS-236-0103, an ongoing study to assess the safety and

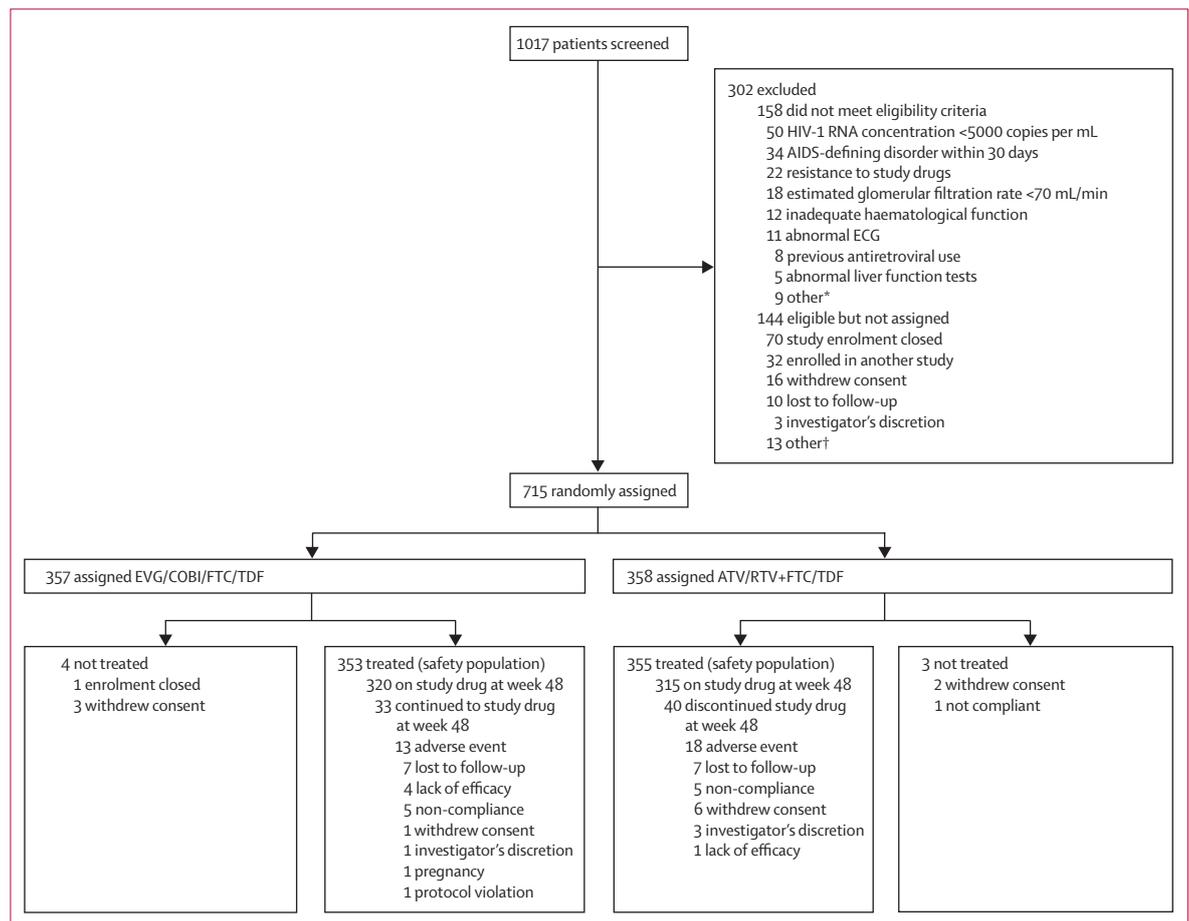
efficacy of EVG/COBI/FTC/TDF versus ATV/RTV+FTC/TDF for first treatment of HIV infection.

## Methods

### Study design and patients

GS-236-0103 is a phase 3, randomised, double-blind study done at 146 sites in Australia, Europe, North America, and Thailand, in accordance with the Declaration of Helsinki. The study was reviewed and approved by central or site-specific review boards or ethics committees. Each patient gave written informed consent.

Adults (aged  $\geq 18$  years) were enrolled if they had HIV-1 and had had no previous antiretroviral treatment, with a plasma HIV RNA concentration of 5000 copies per mL or higher and an estimated glomerular filtration rate of at least 70 mL per min. Eligible patients were susceptible to emtricitabine, tenofovir, and atazanavir. No CD4 cell count criteria were used. Additional inclusion criteria were aspartate and alanine aminotransferase concentrations at or below five times the upper limit of normal, total bilirubin 25.65  $\mu\text{mol/L}$  or less or a normal direct



**Figure 1: Trial profile**

Patients could have been excluded after screening for more than one reason. EVG=elvitegravir. COBI=cobicistat. FTC=emtricitabine. TDF=tenofovir disoproxil fumarate. ATV=atazanavir. RTV=ritonavir. \*Including cardiac abnormalities, alcohol or drug misuse, pregnancy, clinical laboratory test abnormality. †Including adverse events, laboratory errors, non-compliance with protocol.

bilirubin, adequate haematological function (absolute neutrophil count  $\geq 1 \times 10^9$  cells per L,  $\geq 50 \times 10^9$  platelets per L, haemoglobin  $\geq 85$  g/L), and a negative serum pregnancy test for women. Patients with hepatitis B or C coinfection were allowed to enrol. Patients with a new AIDS-defining disorder or other serious infection within 30 days before screening were excluded. Sex and ethnic origin were not restricted.

### Randomisation and masking

Enrolled patients were randomly assigned in a ratio of 1:1, stratified by screening HIV RNA concentration ( $\leq 100\,000$  copies per mL or  $>100\,000$  copies per mL) to receive treatment with either EVG/COBI/FTC/TDF or atazanavir (300 mg), ritonavir (100 mg), emtricitabine (200 mg), and tenofovir disoproxil fumarate (300 mg), once daily with food. The random sequence was generated by computer and patients assigned to treatment by an interactive system accessed via a website or telephone. Patients were assigned with block size of four. Patients, and investigators and study staff who gave treatments, assessed outcomes, and analysed data were masked to the assignment. To conceal allocation, every patient received four tablets per day that looked like the single-tablet regimen of EVG/COBI/FTC/TDF (active or placebo), ATV (active or placebo), RTV (active or placebo), and FTC/TDF (active or placebo).

### Procedures

Laboratory samples were obtained with laboratory kits for each patient and visit. Clinical case report form data were recorded electronically for each patient and visit. Study visits occurred at weeks 2, 4, 8, 12, 16, 24, 32, 40, and 48 and then every 12 weeks until week 96. After the primary endpoint had been reached, masked treatment with study drug was extended to week 192.

Safety was assessed by physical examinations, clinical laboratory tests, and documentation of adverse events. Concomitant medications were also assessed throughout the study. Pharmacokinetics ( $C_{max}$ , AUC $_{0-\infty}$ , and  $C_{tr}$ ) were studied for elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate between visits at weeks 2 and 8 for a subset of patients (those willing to participate at a site able to collect samples; target 24 patients) in the EVG/COBI/FTC/TDF group at some study sites. Additionally, all patients had one blood sample obtained at each study visit until week 48 for pharmacokinetic and pharmacodynamic analysis of the relation between elvitegravir trough concentration and pure virological failure (HIV RNA concentration cutoff at 50 copies per mL). Bio-analytical analyses of drug concentrations of elvitegravir, cobicistat, emtricitabine, and tenofovir in plasma were done by QPS (Newark, DE, USA).

In a subset of patients (those willing to participate at centres able to do the test), dual energy x-ray absorptiometry scans of the spine and hip were done at baseline, week 24, and week 48 to measure percent changes in

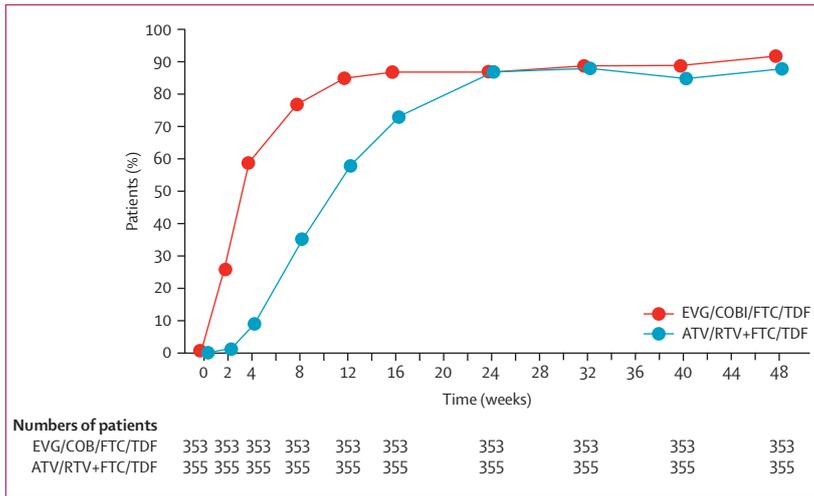
bone mineral density. The scans were processed by BioClinica (Newton, PA, USA).

Laboratory analyses included haematology, serum chemistry, urinalysis (Covance Laboratories, Indianapolis, IN, USA), and measurement of HIV RNA concentration (Amplicor HIV-1 Monitor Test, version 1.5; Roche Diagnostics, Rotkreuz, Switzerland). HIV-1 genotype (reverse transcriptase and protease) was analysed at screening with the GeneSeq assay (Monogram Biosciences, South San Francisco, CA, USA). Analyses of resistance after baseline of patients with virological failure or HIV RNA concentration of more than 400 copies per mL at study discontinuation (at or after week 8 and taking study drug), were done for reverse transcriptase, protease, and integrase with the PhenoSense GT, PhenoSense IN, and GeneSeq IN assays (Monogram Biosciences, South San Francisco, CA, USA). Virological failure was defined as suboptimal virologic response (two consecutive visits with HIV RNA  $\geq 50$  copies per mL and  $<1 \log_{10}$  below baseline at or after week 8), virologic rebound (two consecutive visits

	EVG/COBI/FTC/TDF group (n=353)	ATV/RTV+FTC/TDF group (n=355)
Mean age (SD; years)	38 (10.5)	39 (9.8)
Female	29 (8%)	39 (11%)
Ethnic origin		
White	250 (71%)	277 (78%)
Asian	17 (5%)	17 (5%)
Black or African heritage	72 (20%)	47 (13%)
Hispanic or Latino	64 (18%)	47 (13%)
Mean weight (SD; kg)	79.2 (17.5)	79.7 (16.0)
Mean height (SD; cm)	176.4 (8.2)	175.7 (8.6)
Mean body-mass index (SD; kg/m <sup>2</sup> )	25.4 (5.3)	25.8 (4.8)
Mean HIV RNA concentration (SD; log <sub>10</sub> copies per mL)	4.8 (0.61)	4.8 (0.62)
HIV RNA concentration $>100\,000$ copies per mL	150 (42%)	141 (40%)
Median CD4 cell count (IQR; cells per $\mu$ L)	351 (262–454)	366 (274–466)
Number with CD4 cell count (cells per $\mu$ L)		
$\leq 50$	12 (3%)	5 (1%)
51 to $\leq 200$	42 (12%)	34 (10%)
201 to $\leq 350$	122 (35%)	124 (35%)
351 to $\leq 500$	122 (35%)	122 (34%)
$>500$	55 (16%)	70 (20%)
Median estimated glomerular filtration rate (IQR; mL/min)	113 (99–133)	115 (99–135)
HIV risk factors		
Heterosexual sex	78 (22%)	80 (23%)
Homosexual sex	274 (78%)	274 (77%)
Intravenous drug misuse	5 (1%)	7 (2%)
Transfusion	0 (0%)	3 (1%)
AIDS	32 (9%)	24 (7%)
Positive HBsAg	5 (1%)	7 (2%)
Positive HCV antibody	18 (5%)	10 (3%)

Data are n (%), unless otherwise stated. EVG=elvitegravir. COBI=cobicistat. FTC=emtricitabine. TDF=tenofovir disoproxil fumarate. ATV=atazanavir. RTV=ritonavir. HCV=hepatitis C virus.

**Table 1: Baseline characteristics**

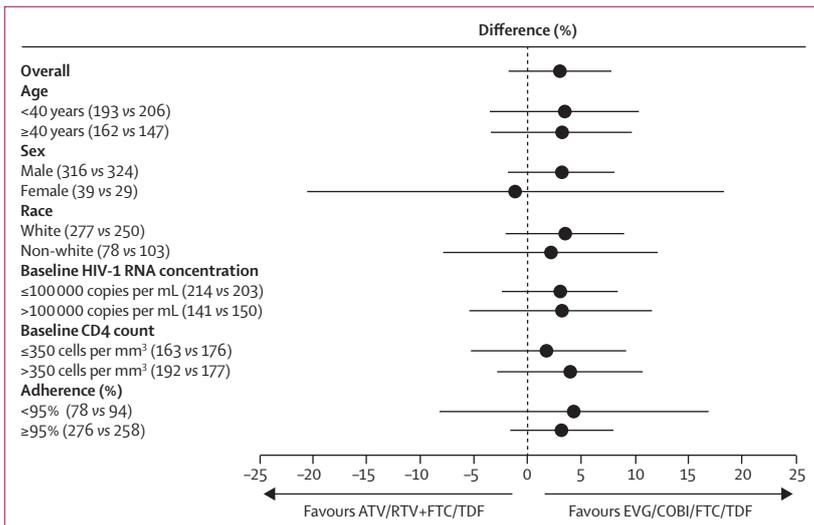


**Figure 2: Proportion of patients with HIV RNA concentrations less than 50 copies per mL**  
 Missing data were classed as failures. Data are for the intention-to-treat population. EVG=elvitegravir. COBI=cobicistat. FTC=emtricitabine. TDF=tenofovir disoproxil fumarate. ATV=atazanavir. RTV=ritonavir.

	EVG/COBI/FTC/TDF	ATV/RTV+FTC/TDF	Adjusted difference (95% CI)
<b>Snapshot analysis</b>			
ITT	316/353 (89.5%)	308/355 (86.8%)	3.0% (-1.9 to 7.8)
PP	310/318 (97.5%)	303/310 (97.7%)	-0.1% (-2.6 to 2.4)
TLOVR analysis (ITT)	304/353 (86.1%)	301/355 (84.8%)	1.6% (-3.6 to 6.8)
Missing classed as failure (ITT)	323/353 (91.5%)	313/355 (88.2%)	3.5% (-1.0 to 8.0)
Missing classed as excluded (ITT)	323/334 (96.7%)	313/323 (96.9%)	0% (-2.8 to 2.8)
Pure virological failure (ITT)	317/353 (89.8%)	316/355 (89.0%)	1.0% (-3.6 to 5.5)

Pure virological failure is HIV RNA concentration cutoff at 50 copies per mL. ITT=intention-to-treat population. PP=per-protocol population. TLOVR=time to loss of virological response. EVG=elvitegravir. COBI=cobicistat. FTC=emtricitabine. TDF=tenofovir disoproxil fumarate. ATV=atazanavir. RTV=ritonavir.

**Table 2: Patients with HIV RNA concentration of 50 copies per mL or less at week 48**



**Figure 3: Differences in response (HIV-1 RNA less than 50 copies per mL) by subgroup at week 48**  
 Data are for the intention-to-treat population. Numbers in parenthesis are the number of patients in the ATV/RTV+FTC/TDF versus EVG/COBI/FTC/TDF groups. EVG=elvitegravir. COBI=cobicistat. FTC=emtricitabine. TDF=tenofovir disoproxil fumarate. ATV=atazanavir. RTV=ritonavir.

with HIV RNA either  $\geq 400$  copies per mL after achieving HIV RNA  $< 50$  copies per mL, or  $> 1 \log_{10}$  increase from nadir, or had HIV RNA  $\geq 400$  copies per mL at their last visit (at or after week 8). Changes in bone mineral density were summarised by treatment at weeks 24 and 48.

Preliminary results were reviewed by an independent data monitoring committee when half of patients had completed week 12 and when all patients had completed weeks 24 and 48 of follow-up. The primary endpoint analysis was done after all enrolled patients had completed their week 48 study visit or had prematurely discontinued study drug.

The primary endpoint was the difference in the proportion of patients in the intention-to-treat population receiving EVG/COBI/FTC/TDF versus ATV/RTV+FTC/TDF achieving viral suppression, defined as an HIV RNA concentration of less than 50 copies per mL at week 48. Secondary and tertiary efficacy endpoints assessed achievement and maintenance of viral suppression (based on the US Food and Drug Administration [FDA] time to loss of virological response algorithm),<sup>12</sup> pure virological failure, proportion of patients with viral suppression when missing data were classed as failure and missing data were classed as excluded, change of HIV RNA concentration ( $\log_{10}$  copies per mL), per-protocol snapshot analysis of viral suppression, change of CD4 cell count, and change of CD4% result.

**Statistical analysis**

For each interim analysis an  $\alpha$  of 0.001 was spent. Therefore, the significance for two-sided test for virological response was 0.048, corresponding to a 95.2% CI. We did the primary analysis by FDA snapshot analysis and calculated 95% CI with stratum-adjusted Mantel-Haenszel proportions.<sup>13</sup> Assessment of non-inferiority of EVG/COBI/FTC/TDF compared with ATV/RTV+FTC/TDF was done with a two-sided 95% CI, with a prespecified non-inferiority margin of 12%. In the snapshot analysis, participants with viral suppression between days 309 and 378 (the week 48 window) while receiving study treatment were classified as successes. Participants missing HIV RNA data in the week 48 analysis window, who discontinued study drug, or who changed treatment before week 48 were classified as failures. A sample size of 700 patients provides at least 95% power to establish non-inferiority between the two treatment groups with an overall response rate of 79.5% for viral suppression at week 48.<sup>14</sup> Sample sizes were calculated with nQuery Advisor (version 6.0).

We did a prespecified, per-protocol snapshot analysis, which included all participants who were enrolled, received at least one dose of study drug, and did not meet any of the following prespecified criteria: discontinuation of study drug before week 48 or HIV RNA data missing in week 48 analysis window (accounting for 80% of excluded patients), and adherence in the

	EVG/COBI/FTC/ TDF (n=353)	ATV/RTV+FTC/ TDF (N=355)
Total	13 (3.7%)	18 (5.1%)
Eye disorders	0	4 (1.1%)
Ocular icterus	0	4 (1.1%)
Gastrointestinal disorders	4 (1.1%)	5 (1.4%)
Nausea	1 (0.3%)	4 (1.1%)
Diarrhoea	2 (0.6%)	1 (0.3%)
Vomiting	1 (0.3%)	2 (0.6%)
Abdominal discomfort	1 (0.3%)	0
Flatulence	0	1 (0.3%)
Hypoesthesia oral	1 (0.3%)	0
General disorders and administration site conditions	3 (0.8%)	2 (0.6%)
Fatigue	1 (0.3%)	2 (0.6%)
Pyrexia	2 (0.6%)	0
Hepatobiliary disorders	0	2 (0.6%)
Jaundice	0	2 (0.6%)
Immune system disorders	1 (0.3%)	0
Drug hypersensitivity	1 (0.3%)	0
Infections	1 (0.3%)	2 (0.6%)
Hepatitis C	1 (0.3%)	0
<i>Pneumocystis jiroveci</i> pneumonia	0	1 (0.3%)
Tuberculous pleurisy	0	1 (0.3%)
Injury, poisoning, and procedural complications	0	1 (0.3%)
Overdose	0	1 (0.3%)
Investigations	2 (0.6%)	0
Alanine aminotransferase increased	1 (0.3%)	0
Aspartate aminotransferase increased	1 (0.3%)	0
Blood creatinine increased	1 (0.3%)	0
Musculoskeletal and connective tissue disorders	2 (0.6%)	0
Limb discomfort	1 (0.3%)	0
Rhabdomyolysis	1 (0.3%)	0
Benign, malignant, and unspecified neoplasms*	1 (0.3%)	1 (0.3%)
Burkitt's lymphoma	1 (0.3%)	0
Hodgkin's disease	0	1 (0.3%)

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	EVG/COBI/FTC/ TDF (n=353)	ATV/RTV+FTC/ TDF (N=355)
(Continued from previous column)		
Nervous system disorders	2 (0.6%)	2 (0.6%)
Dizziness	0	2 (0.6%)
Cervicobrachial syndrome	1 (0.3%)	0
Dysgeusia	1 (0.3%)	0
Psychiatric disorders	2 (0.6%)	1 (0.3%)
Loss of libido	0	1 (0.3%)
Schizophrenia	1 (0.3%)	0
Self-esteem decreased	1 (0.3%)	0
Renal and urinary disorders	0	1 (0.3%)
Nephropathy toxic	0	1 (0.3%)
Respiratory, thoracic and mediastinal disorders	1 (0.3%)	0
Pneumonia aspiration	1 (0.3%)	0
Skin and subcutaneous tissue disorders	3 (0.8%)	4 (1.1%)
Drug eruption	0	2 (0.6%)
Dermatitis exfoliative	1 (0.3%)	0
Rash	1 (0.3%)	0
Rash generalised	0	1 (0.3%)
Rash maculo-papular	0	1 (0.3%)
Skin odour abnormal	1 (0.3%)	0
Vascular disorders	1 (0.3%)	0
Ischaemia	1 (0.3%)	0

Multiple adverse events were counted once per patient. \*Including cysts and polyps.

**Table 3: Treatment-emergent adverse events leading to premature discontinuation of study drug**

	EVG/COBI/FTC/TDF (n=353)	ATV/RTV+FTC/TDF (n=355)	p value
Diarrhoea	77 (22%)	97 (27%)	0.097
Nausea	70 (20%)	69 (19%)	0.92
Upper respiratory tract infection	54 (15%)	58 (16%)	0.76
Headache	53 (15%)	44 (12%)	0.33
Fatigue	50 (14%)	45 (13%)	0.58
Ocular icterus	2 (1%)	51 (14%)	<0.001

EVG=elvitegravir. COBI=cobicistat. FTC=emtricitabine. TDF=tenofovir disoproxil fumarate. ATV=atazanavir. RTV=ritonavir.

**Table 4: Treatment-emergent adverse events occurring in at least 10% of patients in either group**

bottom 2.5th percentile (accounting for 20% of the excluded patients). We did prespecified sensitivity and subgroup analyses to assess treatment differences between populations of patients (based on age, sex, ethnic origin, baseline HIV-1 RNA concentration, baseline CD4 cell count, and adherence).

We summarised all safety data collected from first dose of study drug to 30 days after the last dose with descriptive statistics. We coded adverse events with MedDRA (version 14). We calculated estimated glomerular filtration rate by the Cockcroft-Gault and Modification of Diet in Renal Disease methods.<sup>15</sup> Fisher's exact test was used

to compare treatment differences for adverse events and the Wilcoxon rank sum test was used for continuous laboratory results (SAS; version 9.2). Differences between the two treatment groups for change in bone mineral density were estimated by ANOVA.

This trial is registered with ClinicalTrials.gov, number NCT01106586.

#### Role of the funding source

The sponsor designed the study, analysed the data, interpreted the data, and helped to write the report. All authors had access to the analysed data and could assess

the results and conclusions. They could ask for additional information or analyses. EDJ, BPK, JS, and AKC made the decision to submit the report.

**Results**

1017 patients were screened, of whom 715 were randomly assigned treatment. 708 received at least one dose of study drug: 353 in the EVG/COBI/FTC/TDF group and 355 in the ATV/RTV+FTC/TDF group (figure 1). Baseline characteristics were similar between groups (table 1).

EVG/COBI/FTC/TDF was non-inferior to ATV/RTV+FTC/TDF: 316 (89.5%) patients in the EVG/COBI/FTC/TDF group and 308 (86.8%) patients in the ATV/RTV+FTC/TDF group had viral suppression (adjusted treatment difference 3.0%, 95% CI -1.9% to 7.8%). EVG/COBI/FTC/TDF treatment produced more rapid viral suppression than did ATV/RTV+FTC/TDF treatment (figure 2) with greater mean decreases in HIV RNA concentration from baseline (data not shown). Response rates differed between the two groups for the first 12–16 weeks and were much the same for weeks 24–48.

Viral suppression was high in both treatment groups for the secondary endpoints (table 2) and for various subgroups (figure 3), including patients with HIV RNA concentrations higher than 100000 copies per mL at baseline. CD4 cell counts increased in both groups; at week 48 the mean count was 207 cells per  $\mu\text{L}$  (SD 164) in the EVG/COBI/FTC/TDF group and 211 cells per  $\mu\text{L}$  (160) in the ATV/RTV+FTC/TDF group.

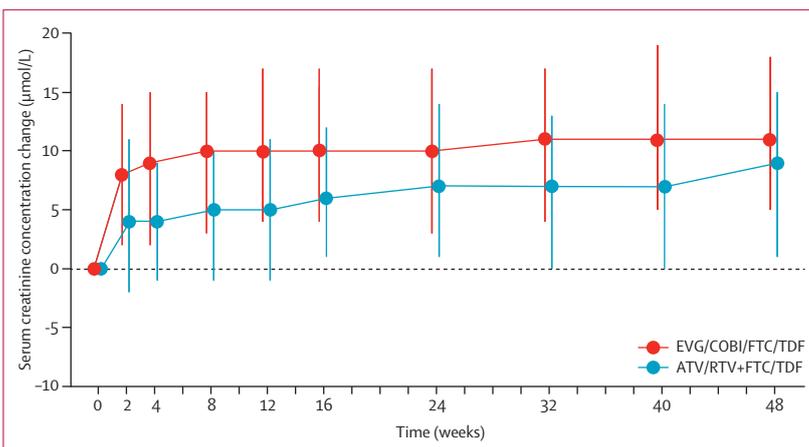
27 patients were included in the pharmacokinetic analysis. Pharmacokinetics of emtricitabine, tenofovir, and cobicistat were consistent with previous data.<sup>16,17</sup> Elvitegravir (n=350 samples) pharmacokinetic parameters had low variability between and within patients and all patients had plasma concentrations at the end of the dosing interval ( $C_{\tau}$ ) above the protein-binding-adjusted IC95 with a mean  $C_{\tau}$  to protein-binding adjusted IC95 ratio of 10:1 over the 48-week period. Virological success rates were high (82–98%) for the EVG/COBI/FTC/TDF regimen over the range of elvitegravir  $C_{\tau}$  concentrations.

Development of resistance to one or more component of the EVG/COBI/FTC/TDF regimen was infrequent. Of 708 treated patients, 20 (3%) were analysed for the development of resistance: 12 (3%) in the EVG/COBI/FTC/TDF group and eight (2%) in the ATV/RTV+FTC/TDF group. Five in the EVG/COBI/FTC/TDF group developed a resistance mutation versus no patients in the ATV/RTV+FTC/TDF group. Four patients had emergent primary integrase mutations; two had Gln148Arg (Q148R), one had Asn155His (N155H), and one had Thr66Ile (T66I), Glu92Gln (E92Q), and Asn155His; all had phenotypic resistance to elvitegravir and cross-resistance to raltegravir. Three of these patients also developed reverse transcriptase resistance mutations (Met184Val [M184V]) and phenotypic resistance to emtricitabine, and one also developed Lys65Arg (K65R). The assay for reverse transcriptase resistance failed for the fourth patient with elvitegravir resistance. One patient developed Met184Val with no integrase resistance.

	EVG/COBI/FTC/TDF (n=353)	ATV/RTV+FTC/TDF (n=355)	p value
Median change in fasting lipid concentration (IQR; mmol/L)			
Total cholesterol	0.26 (-0.15 to 0.75)	0.21 (-0.31 to 0.77)	0.30
LDL cholesterol	0.28 (-0.11 to 0.65)	0.27 (-0.20 to 0.70)	0.92
HDL cholesterol	0.15 (0.00 to 0.31)	0.13 (-0.05 to 0.28)	0.23
Triglycerides (mg/dL)	0.09 (-0.22 to 0.42)	0.26 (-0.13 to 0.67)	0.006
Mean change in renal measurements (SD)			
Serum creatinine concentration ( $\mu\text{mol/L}$ )	12 (11.7)	8 (11.7)	..
eGFR* (mL/min)	-13.3 (14)	-9.3 (16)	..
eGFR† (mL/min per $1.73\text{m}^2$ )	-14.6 (13)	-9.9 (14)	..
Median change in renal measurements (IQR)			
Serum creatinine concentration ( $\mu\text{mol/L}$ )	11 (5 to 18)	7 (1 to 15)	<0.001
eGFR* (mL/min)	-12.7 (-21.8 to -4.3)	-9.5 (-17.9 to 0.2)	<0.001
eGFR† (mL/min per $1.73\text{m}^2$ )	-14.1 (-21.0 to -7.1)	-9.6 (-17.0 to -1.7)	<0.001
Graded abnormalities in liver function tests‡			
Alanine aminotransferase concentration	54 (15.3%)	76 (21.6%)	0.041
Aspartate aminotransferase concentration	62 (17.6%)	77 (21.9%)	0.18
$\gamma$ glutamyl transferase concentration	37 (10.5%)	36 (10.2%)	1.00
Total bilirubin abnormalities‡			
Any	11 (3.1%)	339 (96.3%)	<0.001
Mild	5 (1.4%)	26 (7.4%)	..
Moderate	4 (1.1%)	108 (30.7%)	..
Severe	2 (0.6%)	169 (48.0%)	..
Life threatening	0	36 (10.2%)	..
Alkaline phosphatase concentration abnormality	14 (4.0%)	17 (4.8%)	0.71

**Table 5: Laboratory test results at week 28**

EVG=elvitegravir. COBI=cobicistat. FTC=emtricitabine. TDF=tenofovir disoproxil fumarate. ATV=atazanavir. RTV=ritonavir. eGFR=estimated glomerular filtration rate. \*Calculated by the Cockcroft-Gault method. †Calculated by the Modification of Diet in Renal Disease method.<sup>18</sup> ‡Denominators for graded abnormalities are the number of patients with at least one laboratory assessment after baseline (352 in the EVG/COBI/FTC/TDF group, 352 in the ATV/RTV/FTC/TDF group).



**Figure 4: Median change in serum creatinine concentration from baseline**

Data are for the safety population. Bars are IQRs. EVG=elvitegravir. COBI=cobicistat. FTC=emtricitabine. TDF=tenofovir disoproxil fumarate. ATV=atazanavir. RTV=ritonavir.

Discontinuation from study drug in either group was infrequent (table 3). Both treatments were well tolerated: most adverse events were mild (grade 1) or moderate (grade 2) in severity. Three patients died (one because of septic shock, one because of *Pneumocystis jirovecii* pneumonia, and one because of cardiopulmonary arrest after overdose of recreational drugs) during the study, all in the ATV/RTV+FTC/TDF group and deemed by the relevant investigators as not related to study drug. Two (1%) patients in the EVG/COBI/FTC/TDF group had ocular icterus versus 51 (14%) in the ATV/RTV+FTC/TDF group. Other treatment-emergent adverse events included diarrhoea, nausea, upper respiratory tract infection, headache, and fatigue; they occurred in much the same proportions (table 4) and severities (data not shown) in each group. Nausea and diarrhoea occurred early during treatment, were self-limiting, mild in severity, and led to study drug discontinuation in few patients (three receiving EVG/COBI/FTC/TDF and five patients receiving ATV/RTV+FTC/TDF). Renal adverse events were infrequent in both groups; two patients, one in each treatment group, discontinued because of a renal adverse event (increased creatinine concentration and toxic nephropathy) with abnormalities that were reversed after discontinuation of study drugs. Fractures were infrequent in both groups (three patients in the EVG/COBI/FTC/TDF group and six in the ATV/RTV+FTC/TDF group); most were caused by traumatic injury.

Most treatment-emergent laboratory abnormalities were mild or moderate in severity in the EVG/COBI/FTC/TDF group and severe in the ATV/RTV+FTC/TDF group. Severe and life-threatening (grade 3 or 4) laboratory abnormalities were less frequent in the EVG/COBI/FTC/TDF group than in the ATV/RTV+FTC/TDF group (47 patients [16.2%] vs 239 patients [67.9%]), caused largely by a difference in the number of patients with total bilirubin abnormalities (table 5). Fewer patients in the EVG/COBI/FTC/TDF group than in the ATV/RTV+FTC/TDF group had increased aspartate aminotransferase concentrations (62 patients [17.6%] vs 77 patients [21.9%]) or alanine aminotransferase concentrations (54 patients [15.3%] vs 76 patients [21.6%]). Patients with clinically significant liver function test abnormalities generally had concurrent underlying hepatic disease such as chronic hepatitis or history of alcoholism. Increases from baseline for metabolic measures did not differ substantially between groups, except for fasting triglyceride concentration (table 5). Significant changes in serum creatinine concentration with accompanying decreases in estimated glomerular filtration rate occurred in both groups (table 5), as early as the first study visit (week 2), they generally stabilised by week 8, and did not progress thereafter (figure 4). Mean decreases in bone mineral density of the lumbar spine (−2.63% vs −3.33%) and hip (−3.06% vs −3.88%) were similar for the EVG/COBI/FTC/TDF group versus the ATV/RTV+FTC/TDF group.

## Discussion

This study is the first assessment of a once-daily single-tablet regimen based on an integrase strand transfer inhibitor compared with ATV/RTV+FTC/TDF for first treatment of HIV infection in patients who have not previously received any antiretroviral treatment. In addition to meeting the primary endpoint of non-inferiority to ATV/RTV+FTC/TDF, EVG/COBI/FTC/TDF had high viral suppression according to secondary and tertiary efficacy analyses and demographic subgroup analyses. Sax and colleagues<sup>18</sup> report that virological success of EVG/COBI/FTC/TDF is non-inferior to the single-tablet regimen of EFV/FTC/TDF, with high response across subgroups. The results of these two, large, active controlled studies provide strong evidence of consistent and robust antiviral efficacy of EVG/COBI/FTC/TDF.

Elvitegravir had high  $C_{75}$  values that exceed the protein-binding-adjusted  $IC_{95}$  in all patients analysed and resulted in uniformly high viral suppression, consistent with near maximal integrase strand transfer inhibitor antiviral activity as defined by elvitegravir dose-ranging phase 1b, 2, and 3 studies.<sup>11,19,20</sup>

The number of patients who received EVG/COBI/FTC/TDF and developed resistance was low and not substantially different from that for other first-line regimens.<sup>21–25</sup> The absence of development of drug resistance in patients with virological failure is characteristic of regimens such as ATV/RTV+FTC/TDF.<sup>1</sup> The most common pattern of resistance in participants whose EVG/COBI/FTC/TDF treatment failed was a primary elvitegravir resistance mutation and Met184Val in reverse transcriptase. A low rate of resistance and frequent link of integrase and reverse transcriptase resistance was also noted in clinical studies of raltegravir in combination with emtricitabine and tenofovir disoproxil fumarate for treatment-naïve patients.<sup>24,25</sup> EVG/COBI/FTC/TDF also had favourable safety and tolerability compared with ATV/RTV+FTC/TDF.

The pharmacoenhancers cobicistat and ritonavir are potent inhibitors of CYP3A. Both can also transiently inhibit the multidrug efflux transporter P-glycoprotein, present in the gastrointestinal tract, and also the cationic renal transport pathway for creatinine, putatively the multidrug and toxin extrusion transporter.<sup>17,26–28</sup> As with regimens based on ritonavir-boosted protease inhibitors, EVG/COBI/FTC/TDF could have clinically significant drug–drug interactions with drugs that depend on CYP3A for clearance and for which high plasma concentrations are associated with serious or life-threatening adverse events (eg, orally administered sedatives and hypnotics, lovastatin, and simvastatin are contraindicated for use). Tenofovir disoproxil fumarate—the orally bioavailable prodrug of tenofovir—is a substrate for P-glycoprotein; coadministration with regimens that include cobicistat or ritonavir modestly increases plasma tenofovir exposures.<sup>17,29</sup> The numbers and types of renal adverse events leading to study drug discontinuation were consistent with previous clinical studies and post-marketing data

**Panel: Research in context****Systematic review**

Current standard-of-care and regimens preferred in guidelines for the treatment of HIV infection share some key characteristics, including high efficacy and favourable safety profiles for patients that tolerate and adhere to their complete regimen. Key differences include the availability of once daily and single-tablet regimens. Raltegravir, the only approved integrase strand transfer inhibitor, is administered twice daily, thus precluding a complete, single-tablet regimen containing an integrase strand transfer inhibitor. Although two once-daily, single-tablet regimens containing a non-nucleoside reverse transcriptase inhibitor are approved for treatment of HIV infection, both have limitations. An unmet need for HIV infection treatment is the absence of an alternative single-tablet regimens based on a non-nucleoside reverse transcriptase inhibitor.

In a phase 2b clinical trial of the elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) single-tablet regimen and the study of Paul Sax and colleagues,<sup>18</sup> both single-tablet regimens had high rates of viral suppression. Fewer drug-related CNS and psychiatric adverse events occurred with EVG/COBI/FTC/TDF than with the non-nucleoside reverse transcriptase inhibitor regimen of efavirenz (EFV)/FTC/TDF. In the EVG/COBI/FTC/TDF treatment group, estimated glomerular filtration rates decreased from baseline in the first few weeks but did not progress at weeks 24 or 48.

**Interpretation**

In our study, the EVG/COBI/FTC/TDF single tablet was compared to an HIV protease inhibitor-based regimen of ritonavir-boosted atazanavir (ATV/RTV) and the nucleoside/nucleotide reverse transcriptase inhibitor emtricitabine and tenofovir disoproxil fumarate. The proportion of patients with virologic success at week 48 did not differ significantly between regimens and was similar across demographic and disease state subgroups. Both regimens were well tolerated; the EVG/COBI/FTC/TDF group had few virologic failures or treatment discontinuations caused by adverse effects combined with a favourable safety and tolerability profile, including for renal, hepatic, metabolic, and bone parameters. Increases of serum creatinine from baseline occurred with EVG/COBI/FTC/TDF and ATV/RTV+FTC/TDF. The results of the phase 3 trials suggest that the EVG/COBI/FTC/TDF regimen—the first single tablet, once-daily integrase strand transfer inhibitor regimen—is well tolerated and highly effective as initial therapy for treatment of adults with HIV infection and is an alternative to protease inhibitor or integrase strand transfer inhibitor, twice-daily and multi-tablet treatment regimens.

included on labelling for products that contain tenofovir disoproxil fumarate.<sup>30</sup> The small increase in serum creatinine concentration and accompanying decrease of estimated glomerular filtration rate caused by interaction between cobicistat and the multidrug and toxin extrusion transporter 1 supports the need for monitoring of renal function to distinguish between the drug-transporter effect and tenofovir-associated kidney injury, which can present as an increased serum creatinine concentration combined with proximal tubular injury (ie, glycosuria, proteinuria, and hypophosphataemia).<sup>30</sup> Changes in bone mineral density were consistent with previously published data<sup>31</sup> identifying a small decrease in bone mineral density after starting antiretroviral therapy, including regimens containing tenofovir disoproxil fumarate, which plateau over 48 weeks. Patients enrolled in the study will continue treatment until week 192; therefore, data will be available for long-term renal and bone safety associated with EVG/COBI/FTC/TDF.

Viral suppression rates in both groups are among the highest reported in clinical trials of first treatment of adults with HIV infection, especially for regimens based on a protease inhibitor with ritonavir.<sup>5,6,32,33</sup> Patients in this study had higher baseline CD4 cell counts than did patients in previous clinical studies of this population and few had a baseline CD4 cell count of less than 200 cells per  $\mu\text{L}$ , possibly a result of the effect of new healthcare and HIV treatment guidelines, which recommend earlier diagnosis and treatment of HIV infection than previously.<sup>34</sup>

A limitation of our study is the generalisability of the results to all subgroups of patients. Participants were recruited from 146 sites across many countries with broadly representative populations based on study feasibility assessments and the study had no restrictions on the sex of enrolled patients; however, few women were enrolled. Furthermore, because of the requirement for a screening estimated glomerular filtration rate of at least 70 mL/min, our study does not provide data for patients with clinically significant renal impairment, which is a limitation because serum creatinine concentrations increased with administration of cobicistat. Additional studies (either being done or planned) will further define the safety and efficacy of EVG/COBI/FTC/TDF for women with HIV infection and also for patients with estimated glomerular filtration rates of 50–90 mL/min (ClinicalTrials.gov study NCT01363011).

Development of single-tablet regimens is a key strategy to simplify highly active antiretroviral therapy, and should improve adherence and treatment outcomes for patients with HIV infection.<sup>35–38</sup> EVG/COBI/FTC/TDF combines a once-daily integrase strand inhibitor—elvitegravir—boosted by a first-in-class, pharmacoenhancer—cobicistat—plus a preferred backbone of emtricitabine and tenofovir disoproxil fumarate. It is an attractive treatment option for patients who otherwise might choose or be compelled to start therapy with protease inhibitor and ritonavir-based therapy or a non-nucleoside transcriptase inhibitor-based single-tablet regimen; no single-tablet regimens consisting of a protease inhibitor and ritonavir plus a nucleoside reverse transcriptase inhibitor are available (panel). Administration of multiple pills and management of additional prescriptions increases complexity, costs for patients, and the chances of poor or partial adherence. For regimens of the same efficacy, total pill burden and dosing frequency are some of the most significant obstacles to achieving high adherence.<sup>34–37</sup>

The EVG/COBI/FTC/TDF single-tablet regimen is undergoing regulatory review; if approved, it would provide an important new treatment option as the only once-daily, integrase-inhibitor-based, single-tablet regimen for initial treatment of patients with HIV.

**Contributors**

EDJ enrolled patients, and edited and approved the report. JKR, KH, J-MM, and JG enrolled patients, reviewed and interpreted analyses of data, and edited the draft report. SR, KY, KW, AKC, and BPK designed the study. KY, JS, and AKC oversaw data collection. SR, XW, and KW did data

analyses, which were reviewed and interpreted by KY, JS, AKC, and BPK. The first draft was written by BPK, SR, and KW. The manuscript was edited by SR, XW, KY, JS, KW, AKC, and BPK.

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#### Conflicts of interest

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