Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus co-formulated efavirenz, emtricitabine, and tenofovir for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3 trial, analysis of results after 48 weeks

Paul E Sax, Edwin DeJesus, Anthony Mills, Andrew Zolopa, Calvin Cohen, David Wohl, Joel E Gallant, Hui C Liu, Lijie Zhong, Kitty Yale, Kirsten White, Brian P Kearney, Javier Szwarcberg, Erin Quirk, Andrew K Cheng, for the GS-US-236-0102 study team

Summary

Background The integrase inhibitor elvitegravir (EVG) has been co-formulated with the CYP3A4 inhibitor cobicistat (COBI), emtricitabine (FTC), and tenofovir disoproxil fumarate (TDF) in a single tablet given once daily. We compared the efficacy and safety of EVG/COBI/FTC/TDF with standard of care—co-formulated efavirenz (EFV)/FTC/TDF—as initial treatment for HIV infection.

Methods In this phase 3 trial, treatment-naive patients from outpatient clinics in North America were randomly assigned by computer-generated allocation sequence with a block size of four in a 1:1 ratio to receive EVG/COBI/FTC/TDF or EFV/FTC/TDF, once daily, plus matching placebo. Patients and study staff involved in giving study treatment, assessing outcomes, and collecting and analysing data were masked to treatment allocation. Eligibility criteria included screening HIV RNA concentration of 5000 copies per mL or more, and susceptibility to efavirenz, emtricitabine, and tenofovir. The primary endpoint was HIV RNA concentration of fewer than 50 copies per mL at week 48. The study is registered with ClinicalTrials.gov, number NCT01095796.

Findings 700 patients were randomly assigned and treated (348 with EVG/COBI/FTC/TDF, 352 with EFV/FTC/TDF). EVG/COBI/FTC/TDF was non-inferior to EFV/FTC/TDF; 305/348 (87·6%) versus 296/352 (84·1%) of patients had HIV RNA concentrations of fewer than 50 copies per mL at week 48 (difference 3·6%, 95% CI –1·6% to 8·8%). Proportions of patients discontinuing drugs for adverse events did not differ substantially (13/348 in the EVG/COBI/FTC/TDF group *vs* 18/352 in the EFV/FTC/TDF group). Nausea was more common with EVG/COBI/FTC/TDF than with EFV/FTC/TDF (72/348 *vs* 48/352) and dizziness (23/348 *vs* 86/352), abnormal dreams (53/348 *vs* 95/352), insomnia (30/348 *vs* 49/352), and rash (22/348 *vs* 43/352) were less common. Serum creatinine concentration increased more by week 48 in the EVG/COBI/FTC/TDF group than in the EFV/FTC/TDF group (median 13 µmol/L, IQR 5 to 20 *vs* 1 µmol/L, –6 to 8; p<0·001).

Interpretation If regulatory approval is given, EVG/COBI/FTC/TDF would be the only single-tablet, once-daily, integrase-inhibitor-based regimen for initial treatment of HIV infection.

Funding Gilead Sciences.

Lancet 2012; 379: 2439–48

This online publication has been corrected. The corrected version first appeared at thelancet.com on August 24, 2012

See Comment page 2403

Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA (P E Sax MD); **Orlando Immunology Center, Orlando, FL, USA** (E DeJesus MD); **Anthony Mills MD, Los Angeles, CA, USA** (A Mills MD); **Stanford University, Palo Alto, CA, USA** (Prof A Zolopa MD); **Community Research Initiative of New England, Boston, MA, USA** (C Cohen MD); **University of North Carolina, Chapel Hill, NC, USA** (D Wohl MD, Prof J E Gallant MD); **Johns Hopkins University School of Medicine, Baltimore, MD, USA** (H C Liu PhD); **and Gilead Sciences, Foster City, CA, USA** (L Zhong PhD, K Yale BA, K White PhD, B P Kearney Pharm D, J Szwarcberg MD, E Quirk MD, A K Cheng MD)

Correspondence to:
Dr Paul E Sax, Division of Infectious Diseases, Brigham and Women's Hospital, Boston, MA 02115, USA
psax@partners.org

Introduction

Since the mid-1990s, standard of care for initial treatment of HIV infection has been a combination of at least three active agents from two or more classes of antiretroviral drugs. In the treatment guidelines[1] of the US Department of Health and Human Services and the International Antiviral Society–USA, preferred initial therapy consists of the nucleoside reverse transcriptase inhibitors emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF) combined with a third agent: the non-nucleoside reverse transcriptase inhibitor efavirenz (EFV), one of the ritonavir-boosted protease inhibitors atazanavir and darunavir, or the integrase inhibitor raltegravir.[1,2] Of these preferred regimens, only emtricitabine, tenofovir, and efavirenz are co-formulated as a single tablet (EFV/FTC/TDF). On the basis of high virological efficacy and safety in prospective clinical trials,[3–6] and ease of administration, this regimen is widely used and considered a gold standard for initial treatment in clinical trials and practice.[7,8]

Despite these advantages, EFV/FTC/TDF is not suitable for all patients because it is associated with more CNS side-effects, rash, and hyperlipidaemia than are some comparators,[5,6,9] and it increases the risk of teratogenicity when used during pregnancy.[10] Additionally, among newly diagnosed patients resistance is more common to non-nucleoside reverse transcriptase inhibitors (including efavirenz) than to any other drug class.[11,12] A second single-tablet regimen combining emtricitabine, tenofovir, and rilpivirine is available for initial treatment of HIV-1 infection but is not indicated for patients with high plasma concentrations of HIV-1 RNA in some countries.[13,14]

Elvitegravir (EVG) is an investigational HIV integrase inhibitor with potent antiretroviral activity that can be given once daily when administered with pharmacokinetic boosting.[15,16] In previously treated patients, once daily elvitegravir was non-inferior to raltegravir when combined with regimens that included a boosted protease inhibitor.[17] A single-tablet regimen of elvitegravir, emtricitabine, tenofovir, and the investigational CYP3A4 inhibitor cobicistat (COBI) has been developed; in a phase 2 study, this combination had much the same antiretroviral activity as EFV/FTC/TDF.[18] This phase 3 study was designed to assess safety and efficacy of EVG/COBI/FTC/TDF versus EFV/FTC/TDF for treatment-naive patients; it is the first adequately powered, double-blind study comparing different single-tablet regimens for treatment of HIV infection.

See Online for appendix

Methods

Study design and patients

This study (GS–US–236–0102) is a phase 3 study being done in outpatient clinics in North America and was approved by institutional review boards or ethics committees at all investigation centres. All patients gave written informed consent.

Participants were adults infected with HIV-1 aged at least 18 years with plasma HIV-1 RNA concentrations of 5000 copies per mL or more and no previous use of antiretroviral drugs. Participants had to have an estimated glomerular filtration rate of at least 70 mL/min and be susceptible to efavirenz, emtricitabine, and tenofovir by HIV-1 genotype (GeneSeq assay; Monogram Biosciences, South San Francisco, CA, USA) at screening. Additional inclusion criteria included (for a full list, see appendix) aspartate and alanine aminotransferase concentrations of no more than five times the upper limit of normal; total bilirubin of no more than 25·65 µmol/L or a normal direct bilirubin, absolute neutrophil count of at least 1000 cells per µL; at least 50 000 platelets per µL; haemoglobin concentration of at least 85 g/L; and a negative serum pregnancy test (if applicable). Positive HBsAg or hepatitis C serology was allowed. There was no screening CD4 cell count

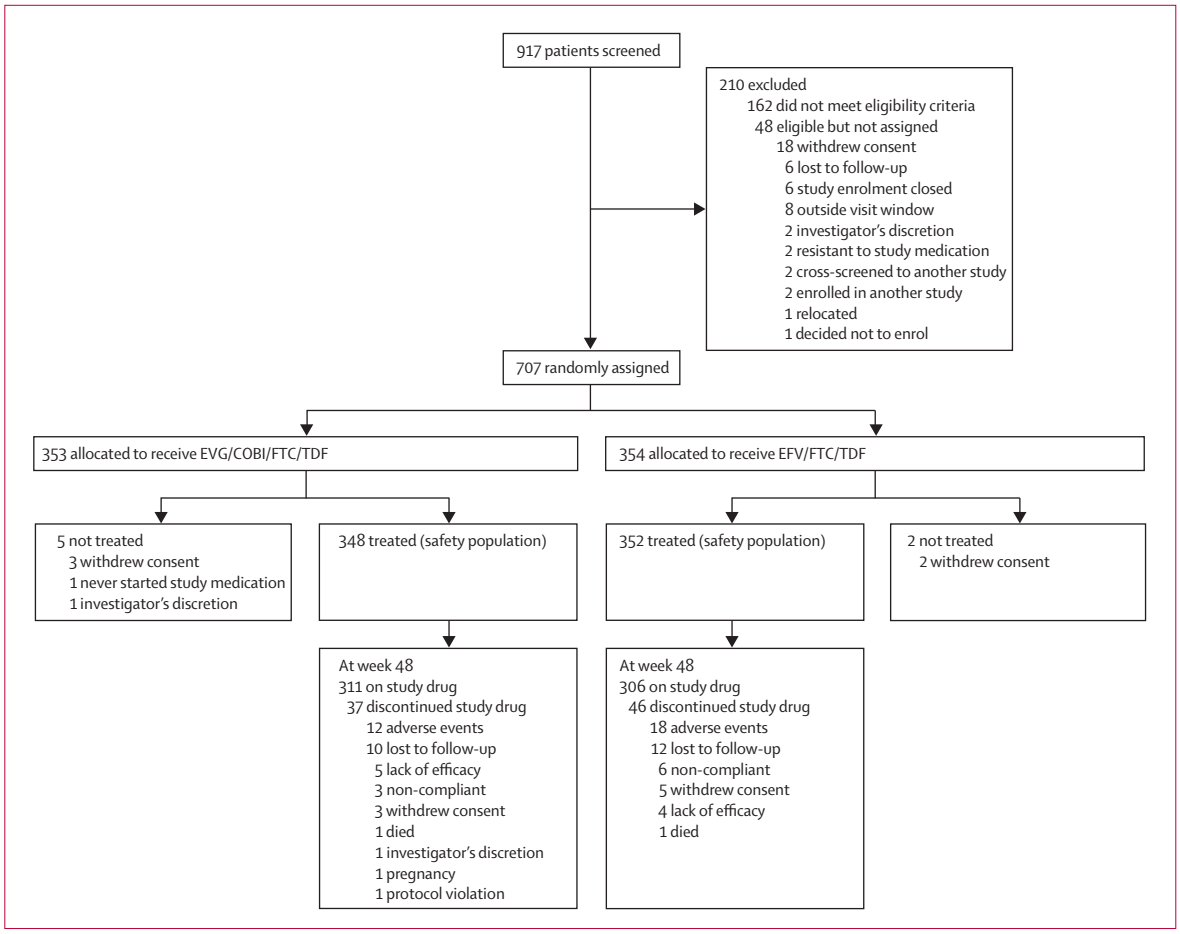

Figure 1: **Trial profile**
For patients for whom investigator's discretion was the reason for discontinuation other details regarding reason for discontinuation were not recorded. EVG=elvitegravir. COBI=cobicistat. FTC=emtricitabine. TDF=tenofovir disoproxil fumarate. EFV=efavirenz.

requirement, but patients with new AIDS-defining disorders or serious infections within 30 days of screening were excluded.

Randomisation and masking

Eligible patients were randomised in a 1:1 ratio to receive either co-formulated elvitegravir 150 mg, cobicistat 150 mg, emtricitabine 200 mg, and tenofovir 300 mg, once daily with food, or co-formulated efavirenz 600 mg, emtricitabine 200 mg, and tenofovir 300 mg at bedtime on an empty stomach. Patients also received placebo tablets matching the alternative treatment; thus, investigators, patients, and study staff giving study treatment, assessing outcomes, collecting data, and analysing data were masked to treatment group. A computer-generated allocation sequence with a block size of four was created by Bracket (San Francisco, CA, USA), and randomisation was stratified by HIV RNA concentration at screening (≤100 000 copies per mL and >100 000 copies per mL). Investigators randomly assigned participants to one of the treatment groups by phone or internet with an interactive system (provided and managed by Bracket).

Procedures

Study visits occurred at weeks 2, 4, 8, 12, 16, 24, 32, 40, and 48, after which patients continued treatment with visits every 12 weeks until week 96. After the primary endpoint was reached, treatment was extended to week 192. Safety was assessed by laboratory tests, 12-lead electrocardiogram (ECG), physical examinations (including height and weight), and adverse events, including prespecified adverse events of interest (fractures and renal events) and importance (rash and neurological and psychiatric events). Laboratory analyses included haematological analysis, serum chemistry tests, and urinalysis (Covance Laboratories, Indianapolis, IN, USA) and measurement of HIV RNA concentration (Amplicor HIV-1 Monitor Test [version 1.5], Roche Diagnostics, Rotkreuz, Switzerland). In patients taking study drugs with confirmed virological rebound of more than 400 HIV RNA copies per mL, or who did not achieve a plasma HIV RNA concentration of fewer than 400 copies per mL at or after week 8, protease, reverse transcriptase, and integrase genotyping and phenotyping assays were done with PhenoSense GT, PhenoSense Integrase, and GeneSeq Integrase (Monogram Biosciences). 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. Adherence was assessed by pill count.

The primary endpoint was the proportion of patients in the intention-to-treat population with viral suppression (HIV RNA <50 copies per mL) at week 48 according to snapshot analysis as defined by the US Food and Drug Administration (FDA). Other endpoints were treatment differences by subgroup, achievement and maintenance of HIV RNA concentration of fewer than 50 copies per mL (based on the FDA-defined time to loss of virological response algorithm),[19] proportion of patients with HIV RNA concentrations of fewer than 50 copies per mL when classing missing as failure and missing as excluded, change in HIV RNA concentration (log_{10} copies per mL) from baseline, and change in CD4 cell count from baseline.

	EVG/COBI/FTC/TDF group (n=348)	EFV/FTC/TDF group (n=352)
Median age (IQR; years)	37 (29–45)	38 (30–45)
Mean age (SD; years)	38 (10·4)	38 (10·6)
Women	41 (12%)	36 (10%)
Ethnic origin		
Native American or native Alaskan	2 (1%)	4 (1%)
Asian	6 (2%)	10 (3%)
Black or African heritage	106 (30%)	91 (26%)
Native Hawaiian or Pacific Islander	4 (1%)	1 (<1%)
White	214 (61%)	227 (64%)
Hispanic or Latino	82 (24%)	85 (24%)
Other	16 (5%)	19 (5%)
Median weight (IQR; kg)	79 (70–88)	78 (70–91)
Mean weight (SD; kg)	81·6 (18·5)	81·0 (17·0)
Median height (IQR; cm)	176 (170–180)	178 (170–183)
Mean height (SD; kg)	174·9 (9·5)	176·1 (9·1)
Median body-mass index (IQR kg/m²)	25·5 (22·7–28·7)	25·1 (22·7–28·5)
Mean body mass index (SD; kg/m²)	26·7 (5·9)	26·1 (5·2)
Median HIV-1 RNA concentration (IQR; log_{10} copies per mL)	4·75 (4·32–5·15)	4·78 (4·37–5·15)
Mean HIV-1 RNA concentration (SD; log_{10} copies per mL)	4·73 (0·6)	4·78 (0·6)
HIV-1 RNA concentration >100 000 copies per mL	118 (34%)	116 (33%)
Median CD4 cell count (IQR; cells per μL)	376 (276–487)	383 (268–479)
Mean CD4 cell count (SD; cells per μL)	391 (188·6)	382 (170·2)
CD4 cell count (cells per μL)		
≤50	7 (2%)	6 (2%)
51 to ≤200	36 (10%)	45 (13%)
201 to ≤350	112 (32%)	96 (27%)
351 to ≤500	113 (32%)	136 (39%)
>500	80 (23%)	69 (20%)
Median estimated glomerular filtration rate (IQR; mL/min)	114·6 (98·7–137·5)	114·1 (98·2–135·0)
HIV risk factors		
Heterosexual sex	68 (20%)	58 (16%)
Homosexual sex	278 (80%)	281 (80%)
Intravenous drug use	11 (3%)	11 (3%)
Transfusion	2 (1%)	2 (1%)
Vertical transmission	0	0
Other	0	4 (1%)
Unknown	7 (2%)	11 (3%)
AIDS diagnosis	28 (8%)	24 (7%)
Positive HBsAg	5 (1%)	9 (3%)
Positive hepatitis C virus antibody	17 (5%)	15 (4%)

Data n (%), unless otherwise specified. EVG=elvitegravir. COBI=cobicistat. FTC=emtricitabine. TDF=tenofovir disoproxil fumarate. EFV=efavirenz.

Table 1: **Baseline characteristics**

	EVG/COBI/FTC/TDF group	EFV/FTC/TDF group	Difference (95% CI)
Snapshot analysis (intention to treat)			
Virological success	305/348 (87·6%)	296/352 (84·1%)	3·6% (–1·6% to 8·8%)
Snapshot analysis (per protocol)			
Virological success	296/312 (94·9%)	288/300 (96·0%)	–1·0% (–4·4% to 2·4%)
Time to loss of virological response analysis (intention to treat)			
Responder	299/348 (85·9%)	293/352 (83·2%)	2·7% (–2·6% to 8·1%)
Missing=failure	309/348 (89%)	301/352 (86%)	3·3% (–1·6% to 8·3%)
Missing=excluded	309/325(95%)	301/316 (95%)	–0·1% (–3·5% to 3·3%)

EVG=elvitegravir. COBI=cobicistat. FTC=emtricitabine. TDF=tenofovir disoproxil fumarate. EFV=efavirenz.

Table 2: **Patients with HIV-1 RNA concentrations of fewer than 50 copies per mL at week 48**

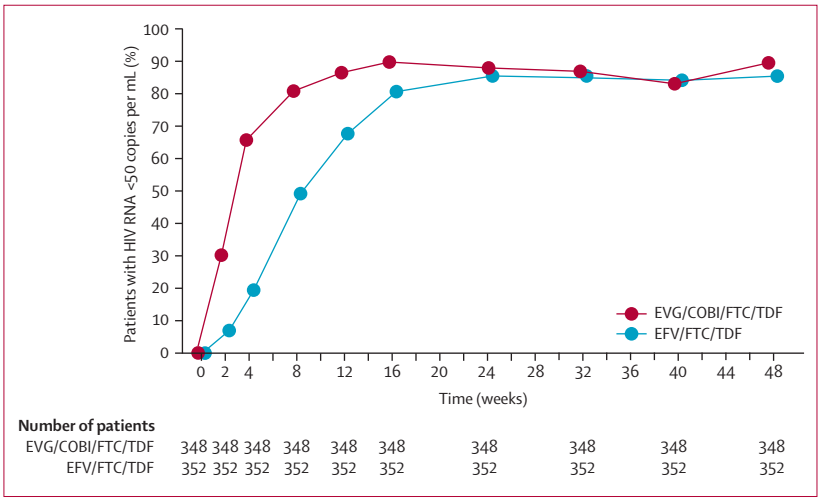

Figure 2: **Proportions of patients with HIV-1 RNA concentrations of fewer than 50 copies per mL**
Patients with missing data were classed as failures. Data are for the intention-to-treat population. EVG=elvitegravir. COBI=cobicistat. FTC=emtricitabine. TDF=tenofovir disoproxil fumarate. EFV=efavirenz.

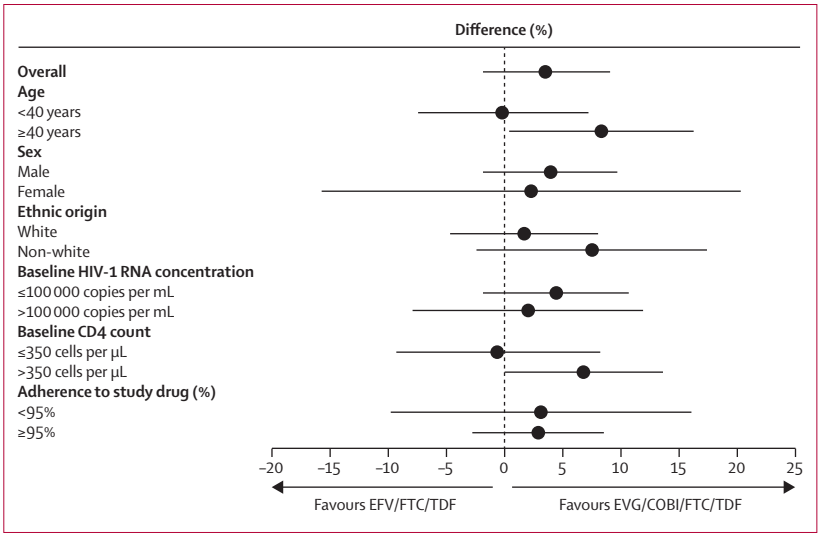

Figure 3: **Differences in response by subgroup at week 48**
For HIV-1 RNA concentration of fewer than 50 copies per mL. Data are for the intention-to-treat population.

Statistical analysis

Analyses included all clinical, laboratory, and virological data available after the last enrolled patient had completed the week 48 study visit or prematurely discontinued study drug. The primary endpoint was assessed by treatment non-inferiority of EVG/COBI/FTC/TDF compared with EFV/FTC/TDF with 95% CI and with a prespecified non-inferiority margin of 12%. In the snapshot analysis, participants with less than 50 copies per mL of HIV RNA between days 309 and 378 (week 48 window) were classified as successes. Participants with missing HIV RNA data for the week 48 analysis window, who discontinued study drug, or who changed therapy before week 48 were classed as failures. The difference, weighted by baseline HIV RNA stratum, for response rate and its 95% CI were calculated on the basis of stratum-adjusted Mantel-Haenszel proportions.[20] For each interim analysis an α of 0·001 was spent. Therefore, the significance for the two-sided test for virological response at week 48 according to the snapshot algorithm, for intention-to-treat and per-protocol populations, was 0·048, corresponding to a 95·2% CI. A sample size of 700 patients provided at least 95% power to establish non-inferiority for the percentage of patients achieving virological suppression at week 48, with assumed response rates of 79·5% in both groups,[21] a non-inferiority margin of 12%, and a one-sided significance of 0·025. Calculations were done with nQuery Advisor (version 6.0).

We did a per-protocol snapshot analysis, which included all participants who were randomly assigned treatment, 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 results missing in the week 48 analysis window, and adherence in the bottom 2·5th percentile. We did prespecified subgroup analyses of treatment differences on the basis of age, sex, ethnic origin, baseline HIV RNA concentration, baseline CD4 cell count, and study drug adherence.

The safety population included all randomly assigned patients who received at least one dose of study drug. We descriptively summarised all safety data collected on or after the date study drug was first administered and up to 30 days after the last dose of study drug (if participants discontinued treatment). Adverse events were coded with the Medical Dictionary for Regulatory Activities (version 14). Glomerular filtration rate was estimated by the Cockcroft-Gault method.[22] We used Fisher's exact test to compare treatment differences for adverse events and Wilcoxon rank sum test to compare treatment differences for continuous laboratory test results (SAS; version 9.2).

This study is registered with ClinicalTrials.gov, number NCT01095796.

Role of the funding source

The sponsor designed the study, collected and analysed data, interpreted the results, and helped write the report. All authors had access to the data used in the analyses and the lead author reviewed the full data report. The full

study data were available to all authors on request. The decision to submit the paper for publication was made by PES, EQ, and AC.

Results

Screening began in March, 2010, and by August, 2010, 917 patients had been screened, and 707 of them were randomly assigned treatment (figure 1). 700 received study medication; 348 in the EVG/COBI/FTC/TDF group and 352 in the EFV/FTC/TDF group. Baseline characteristics were much the same in the two treatment groups (table 1). 34% of patients had a baseline HIV RNA concentration of more than 100 000 copies per mL. Study drug discontinuation rates and reasons for discontinuation were similar between treatment groups (figure 1). The last patient's week 48 visit was completed in July, 2011. At interim reviews, the data monitoring committee recommended that the study continue as planned and at week 48 endorsed an extension of the masked, comparative phase to week 192.

In the EVG/COBI/FTC/TDF group, 305 of 348 (87·6%) patients had an HIV RNA concentration of fewer than 50 copies per mL at week 48 compared with 296 of 352 (84·1%) patients in the EFV/FTC/TDF group (difference 3·6%, 95% CI −1·6% to 8·8%). Virological responses to EVG/COBI/FTC/TDF and EFV/FTC/TDF did not differ significantly for other efficacy endpoints (table 2). The proportion of patients with HIV RNA concentrations of fewer than 50 copies per mL (missing classed as failure) was higher in the EVG/COBI/FTC/TDF group than in the EFV/FTC/TDF group at all visits up to week 16, after which response rates between the two groups did not differ substantially (figure 2).

Responses to EVG/COBI/FTC/TDF were much the same as to EFV/FTC/TDF for subgroups of patients (figure 3), including those with HIV RNA concentrations of more than 100 000 copies per mL at baseline. Mean increases of CD4 cell count at most timepoints were similar in the two groups (figure 4); however, at week 48 mean increase in CD4 cell count was significantly higher in the EVG/COBI/FTC/TDF group than in the EFV/FTC/TDF group (239 cells per µL *vs* 206 cells per µL; p=0·009).

Of patients who received treatment, 31 (4%) met the criteria for resistance testing, 14 (4%) in the EVG/COBI/FTC/TDF group and 17 (5%) in the EFV/FTC/TDF group. Of the 14 patients in the EVG/COBI/FTC/TDF group, eight had resistance mutations (table 3). These eight patients had nucleoside reverse transcriptase inhibitor resistance mutations (five had Met184Val/Ile [M184V/I] only, three had Met184Val/Ile and Lys65Arg [K65R]). Seven of the eight patients also had integrase resistance mutations (mainly Glu92Gln [E92Q]). Of the 17 patients in the EFV/FTC/TDF group analysed for resistance, eight developed resistance to one or more components of EFV/FTC/TDF; the most common resistance profile was the Lys103Asn (K103N) mutation (seven patients, five with Lys103Asn, two with Lys103Asn, Met184Val, and Lys65Arg).

Tables 4 and 5 show reported adverse events. Most adverse events in each group were mild or moderate. Three patients died during the study, one in the EVG/COBI/FTC/TDF group (suicide) and two in the EFV/FTC/TDF group (one suicide and one metastatic carcinoma). Similar numbers of patients discontinued treatment because of an adverse event in each group (table 5). Nausea was significantly more common in the EVG/COBI/FTC/TDF group than in the EFV/FTC/TDF group (table 4); however, proportions of moderate and severe nausea did not differ between the two groups (ten of 348 patients [3%] in the EVG/COBI/FTC/TDF group

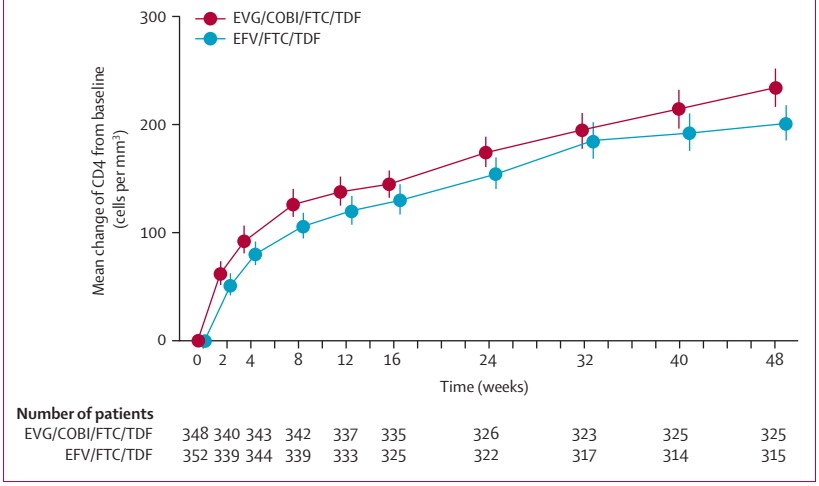

Figure 4: **Mean change of CD4 cell count from baseline**

	EVG/COBI/FTC/TDF group (n=348)	EFV/FTC/TDF group (n=352)
Resistance analysis population	14 (4%)	17 (5%)
Developed resistance to antiretroviral regimen	8 (2%)	8 (2%)
Any primary integrase resistance	7 (2%)	0
Glu92Gln (E92Q)	7 (2%)	0
Thr66Ile (T66I)	1 (<1%)	0
Gln148Arg (Q148R)	1 (<1%)	0
Asn155His (N155H)	1 (<1%)	0
Any primary non-nucleoside reverse transcriptase inhibitor resistance*	0	8 (2%)
Lys103Asn (K103N)	0	7 (2%)
Lys101Glu (K101E)	0	3 (1%)
Val108Ile (V108I)	0	2 (1%)
Tyr188Phe/His/Lys (Y188F/H/K)	0	1 (<1%)
Gly190Ala (G190A)	0	1 (<1%)
Any primary nucleoside reverse transcriptase inhibitor resistance*	8 (2%)	2 (1%)
Met184Val/Ile (M184V/I)	8 (2%)	2 (1%)
Lys65Arg (K65R)	3 (1%)	2 (1%)

Data are n (%). EVG=elvitegravir. COBI=cobicistat. FTC=emtricitabine. TDF=tenofovir disoproxil fumarate. EFV=efavirenz. *Primary resistance mutations to EFV, FTC, or TDF, according to International Antiviral Society–USA.

Table 3: **Primary integrase and reverse transcriptase resistance at week 48**

	EVG/COBI/FTC/TDF group (n=348)	EFV/FTC/TDF group (n=352)
Diarrhoea	80 (23%)	66 (19%)
Nausea*	72 (21%)	48 (14%)
Fatigue	40 (11%)	45 (13%)
Upper respiratory infection	48 (14%)	38 (11%)
Dizziness†	23 (7%)	86 (24%)
Headache	49 (14%)	34 (10%)
Abnormal dreams†	53 (15%)	95 (27%)
Insomnia‡	30 (9%)	49 (14%)
Depression	33 (9%)	39 (11%)
Rash§	22 (6%)	43 (12%)

Data are n (%). p>0·05 unless otherwise stated. Groups compared with Fisher's exact test. EVG=elvitegravir. COBI=cobicistat. FTC=emtricitabine. TDF=tenofovir disoproxil fumarate. EFV=efavirenz. *p=0·016. †p<0·001. ‡p=0·031. §p=0·009.

Table 4: **Adverse events in ≥10% of patients in either group**

	EVG/COBI/FTC/TDF group (n=348)	EFV/FTC/TDF group (n=352)
Patients with any treatment-emergent adverse event leading to premature discontinuation of study drug*	13 (4%)	18 (5%)
Gastrointestinal disorders	1 (<1%)	0
Nausea	1 (<1%)	0
General disorders and administration site conditions	1 (<1%)	3 (1%)
Fatigue	1 (<1%)	1 (<1%)
Pyrexia	0	1 (<1%)
Sluggishness	0	1 (<1%)
Hepatobiliary disorders	1 (<1%)	0
Liver injury	1 (<1%)	0
Immune system disorders	0	1 (<1%)
Drug hypersensitivity	0	1 (<1%)
Infections	1 (<1%)	0
Hepatitis C	1 (<1%)	0
Injury, poisoning, and procedural complications	0	1 (<1%)
Contusion	0	1 (<1%)
Investigations	2 (1%)	0
Blood creatinine concentration increased	2 (1%)	0
Benign, malignant, and unspecified neoplasms (including cysts and polyps)	1 (<1%)	1 (<1%)
Lymphoma	1 (<1%)	0
Metastatic neoplasm	0	1 (<1%)
Nervous system disorders	1 (<1%)	3 (1%)
Amnesia	0	1 (<1%)
Grand mal convulsion	0	1 (<1%)
Headache	1 (<1%)	0
Presyncope	0	1 (<1%)

(Continues on next page)

vs nine of 352 [3%] in the EFV/FTC/TDF group). One patient discontinued EVG/COBI/FTC/TDF because of nausea. The proportions of patients who had abnormal dreams, insomnia, dizziness, and rash were significantly lower in the EVG/COBI/FTC/TDF group than in the EFV/FTC/TDF group (table 4). Although most of these events were mild, moderate and severe abnormal dreams and moderate and severe dizziness were less common in the EVG/COBI/FTC/TDF group (two patients [1%]) than in the EFV/FTC/TDF group (13 patients [4%]; p=0·007 for both types of event).

Fractures occurred in six patients (2%) in each treatment group; all were related to trauma, and none were considered pathological or osteoporotic. Five patients (1%) had renal adverse events leading to treatment discontinuation (two had increased serum creatinine concentration, two had renal failure, and one had Fanconi syndrome); all of them were being treated with EVG/COBI/FTC/TDF. One of these patients had an increase in serum creatinine concentration from baseline, which fully resolved 2 weeks after stopping study drug. The other four patients also developed signs of tubular toxicity (a combination of hypophosphataemia, glycosuria, or proteinuria). Despite having eligible estimated glomerular filtration rates at screening, these four patients had evidence of renal impairment before starting study drug (two had pre-treatment proteinuria and two had glomerular filtration rate <70 mL/min at baseline). Renal laboratory test results either improved or returned to baseline after all four patients stopped study medication. Dialysis or other form of renal replacement therapy were not started for any patient. As expected from previous studies of cobicistat,[18,23,24] serum creatinine concentration increased more by week 48 (median 13 µmol/L, IQR 5 to 20 *vs* 1 µmol/L, –6 to 8; p<0·001) and median estimated glomerular filtration rate decreased more (–14·3 mL/min, –24·2 to –4·3 *vs* –3·0 mL/min, –11·2 to 8·2; p<0·001) in the EVG/COBI/FTC/TDF group than in the EFV/FTC/TDF group. Most of the change in serum creatinine concentration occurred by week 2, with little progression between weeks 2 and 48 (figure 5).

Median fasting total cholesterol concentration increased less from baseline to week 48 in the EVG/COBI/FTC/TDF group than in the EFV/FTC/TDF group (0·25 mmol/L *vs* 0·49 mmol/L; p<0·001). Likewise for LDL concentration (0·26 mmol/L *vs* 0·44 mmol/L; p=0·001), and HDL cholesterol concentration (0·13 mmol/L *vs* 0·20 mmol/L; p=0·001). Changes in the ratio of total to HDL cholesterol from baseline to week 48 were much the same in the two treatment groups (data not shown). Alanine aminotransferase and aspartate aminotransferase increased in fewer patients in the EVG/COBI/FTC/TDF group (53/347 (15%), for alanine aminotranferase and 62/347 (18%), for aspartate aminotransferase) than in the EFV/FTC/TDF group (119/351 (34%), for alanine aminotranferase and 109/351 (31%), for aspartate aminotransferase; p<0·001 for both).

	EVG/COBI/FTC/TDF group (n=348)	EFV/FTC/TDF group (n=352)
(Continued from previous page)		
Psychiatric disorders	3 (1%)	6 (2%)
Depression	1 (<1%)	3 (1%)
Abnormal dreams	0	2 (1%)
Paranoia	1 (<1%)	1 (<1%)
Anxiety	0	1 (<1%)
Claustrophobia	0	1 (<1%)
Completed suicide†	1 (<1%)	0
Hallucination	0	1 (<1%)
Insomnia	0	1 (<1%)
Nightmare	0	1 (<1%)
Suicide attempt	0	1 (<1%)
Renal and urinary disorders	3 (1%)	0
Renal failure	2 (1%)	0
Fanconi syndrome acquired	1 (<1%)	0
Respiratory, thoracic, and mediastinal disorders	0	1 (<1%)
Dyspnoea	0	1 (<1%)
Dyspnoea (exertional)	0	1 (<1%)
Skin and subcutaneous tissue disorders	0	5 (1%)
Rash	0	2 (1%)
Drug eruption	0	1 (<1%)
Hyperhidrosis	0	1 (<1%)
Rash maculo-papular	0	1 (<1%)
Vascular disorders	0	1 (<1%)
Hot flush	0	1 (<1%)

Adverse events were coded using MedDRA (version 14.0). EVG=elvitegravir. COBI=cobicistat. FTC=emtricitabine. TDF=tenofovir disoproxil fumarate. EFV=efavirenz. *Multiple adverse events were counted only once per patient for each system organ class and preferred term. †One patient in the EVG/COBI/FTC/TDF group had an adverse event (suicide) leading to study drug discontinuation and death as the reason for study drug discontinuation. Another patient in the EFV/FTC/TDF group committed suicide, and death was reported as an adverse event leading to discontinuation of study drug.

Table 5: **Adverse events leading to study drug discontinuation by system organ class**

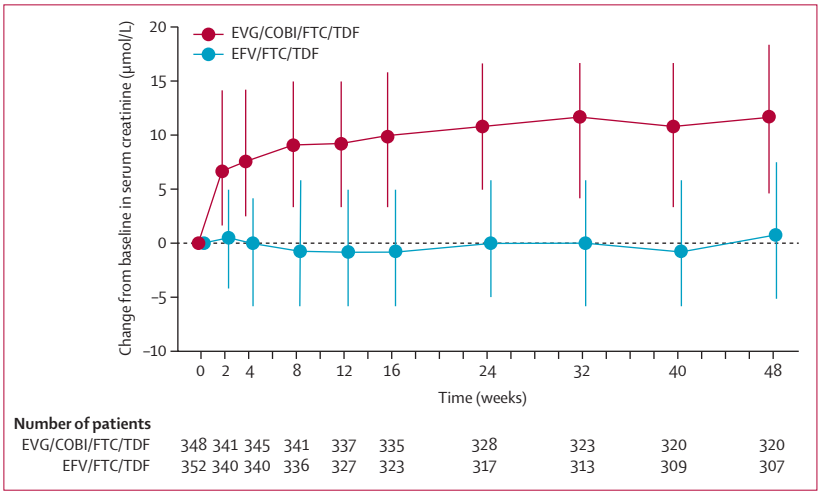

Figure 5: **Change of serum creatinine concentration from baseline**
Bars are IQR. Data are for the safety population.

Discussion

Efficacy of EVG/COBI/FTC/TDF was non-inferior to standard-of-care for a range of endpoints. Additionally, subgroup analyses that included various demographic and clinical characteristics indicate that the response to EVG/COBI/FTC/TDF did not differ substantially from that to EFV/FTC/TDF and that virological success in patients with HIV RNA concentration of more than 100 000 copies per mL was high in both groups. In a parallel study, DeJesus and colleagues[25] report that virological success of EVG/COBI/FTC/TDF treatment is non-inferior to treatment with FTC/TDF and ritonavir-boosted atazanavir, with high response rates across subgroups. These analyses add to the evidence supporting the antiviral efficacy of EVG/COBI/FTC/TDF (panel).

Virological resistance was infrequent. Of patients who received EVG/COBI/FTC/TDF, eight (2% of those enrolled) developed resistance to EVG, FTC, or TDF, all had Met184Val in reverse transcriptase, three developed Lys65Arg, and seven had Glu92Gln in integrase. The integrase gene resistance mutations in seven patients treated with EVG/COBI/FTC/TDF conferred decreased susceptibility to elvitegravir and raltegravir, another licensed integrase inhibitor. The incidences and linkages of integrase and reverse transcriptase resistance mutations in our study are much the same as those in treatment-naive patients receiving raltegravir with emtricitabine and tenofovir.[9,26]

Virological suppression was more rapid with EVG/COBI/FTC/TDF than with EFV/FTC/TDF. This rapid response was also reported when raltegravir was compared with efavirenz.[9] High early response rates to EVG/COBI/FTC/TDF in our study are consistent with an effect of drugs in the integrase strand-transfer inhibitor class. Although both CD4 cell response at week 48 and initial reduction in HIV RNA concentration are significantly greater with treatments based on strand-transfer integrase inhibitors compared with those based on efavirenz, the clinical significance of these differences is unknown.

Both regimens were well tolerated, with infrequent drug discontinuation because of adverse events in both groups. Insomnia, abnormal dreams, dizziness, and rash occurred in a higher proportion of patients receiving EFV/FTC/TDF than those receiving EVG/COBI/FTC/TDF, and led to study drug discontinuations in that group. These side-effects are associated with efavirenz treatment, and were also more common for regimens based on efavirenz in other masked studies with non-efavirenz comparators.[5,6,9] By contrast, a significantly higher proportion of EVG/COBI/FTC/TDF recipients reported nausea than did EFV/FTC/TDF recipients; the nausea was generally mild and led to study drug discontinuation in only one patient.

***Panel:* Research in context**

Systematic review

We searched four databases (Medline, Embase, Biosis, and Current Contents) for randomised controlled clinical trials in treatment-naive, HIV-infected patients with the search terms "elvitegravir", "cobicistat", and "treatment naïve". We included reports published only in English, with no date restrictions. Excluding reviews, we identified only one report, a phase 2b clinical trial of EVG/COBI/FTC/TDF compared with EFV/FTC/TDF as initial treatment of HIV infection (NCT 00869557). In this study, viral suppression was high at weeks 24 and 48 for both single-tablet regimens. Fewer drug-related CNS and psychiatric adverse events occurred with EVG/COBI/FTC/TDF than with EFV/FTC/TDF. In the EVG/COBI/FTC/TDF group, estimated glomerular filtration rates decreased from baseline in the first few weeks of therapy, but did not progress at weeks 24 or 48.[18]

Interpretation

Two independent, fully-powered phase 3 non-inferiority trials have compared the new EVG/COBI/FTC/TDF tablet with two current standard-of-care regimens for initial HIV treatment: one regimen containing a non-nucleoside reverse transcriptase inhibitor and one regimen based on boosted protease inhibitor. In both studies, EVG/COBI/FTC/TDF was well tolerated and caused high viral suppression, which was non-inferior to the standard-of-care. In our study, we compared single-tablet EVG/COBI/FTC/TDF with the current, preferred single-tablet regimen EFV/FTC/TDF. Virologic success rates at week 48 were non-inferior between the two regimens and were similar across subgroups. Although both regimens were well tolerated, their adverse event profiles differed. Nausea was more frequent in the EVG/COBI/FTC/TDF group than in the EFV/FTC/TDF group while insomnia, abnormal dreams, dizziness, and rash were less frequent. Additionally, as in the phase 2 study, serum creatinine concentration increases from baseline were higher for EVG/COBI/FTC/TDF than for EFV/FTC/TDF whereas increases in liver transaminase concentrations were greater with EFV/FTC/TDF than with EVG/COBI/FTC/TDF. The results of the phase 3 trials of EVG/COBI/FTC/TDF suggest that this new integrase inhibitor-containing single tablet might be an important complete regimen that is well tolerated and effective as initial therapy for adult HIV patients, irrespective of viral load.

Efavirenz is associated with a greater rise in plasma lipid concentrations than are other non-nucleoside reverse transcriptase inhibitors.[5,6,27] Treatment groups did not differ for change from baseline of triglyceride concentration or the ratio of total to HDL cholesterol, and HDL cholesterol concentration increased more in the EFV/FTC/TDF group than in the EVG/COBI/FTC/TDF group. Increases in total and LDL cholesterol concentrations were also greater with EFV/FTC/TDF than with EVG/COBI/FTC/TDF. Total and LDL cholesterol concentration changes with a boosted integrase inhibitor were favourable compared with a non-boosted regimen; by contrast, results of other studies have shown increases of concentrations of these lipids after treatment with boosted protease inhibitors compared with non-boosted regimens.[28,29]

In phase 1 and 2 trials,[18,23,24] cobicistat rapidly induced a small increase in serum creatinine concentration, with a consequent reduction of estimated glomerular filtration rate. These changes are caused by inhibition of tubular secretion of creatinine, with no effect on actual glomerular filtration rate as measured by clearance of iohexol.[23] In our study, patients treated with EVG/COBI/FTC/TDF had a greater increase in serum creatinine concentration and decrease in estimated glomerular filtration rate than did those receiving EFV/FTC/TDF. Most of the increase in the EVG/COBI/FTC/TDF group occurred by week 8; serum creatinine concentration and estimated glomerular filtration rate seemed to stabilise thereafter without further change up to week 48. Five patients receiving EVG/COBI/FTC/TDF had renal events necessitating drug discontinuation; for one patient, discontinuation was the investigator's request after a small increase of serum creatinine concentration, and was probably related to treatment with cobicistat. The other four patients had tubular toxicity consistent with a pattern of tenofovir renal injury. These patients had renal impairment at baseline, and all improved after discontinuation of treatment with none needing renal replacement therapy. Patients enrolled in the study will continue to take treatment while masked to their allocation until week 192, which should provide evidence about long-term trends in renal safety and estimated glomerular filtration rate associated with EVG/COB/FTC/TDF.

The simplicity of treatment resulting from combination of several active antiretroviral agents in a single pill has potential advantages.[30] These advantages include improved adherence, reduced risk of selective non-compliance, and reduced risk of prescription error, all of which might decrease the likelihood of treatment failure and drug resistance. Results of surveys show that patients prefer to take fewer daily pills,[31,32] and observational studies indicate that virological and clinical outcomes are better for individuals treated with single versus multiple-pill regimens, even among difficult-to-treat populations.[33–35] In view of the non-inferior virological response to EVG/COBI/FTC/TDF treatment compared with EFV/FTC/TDF, and their similar tolerability, treatment with EVG/COBI/FTC/TDF is likely to have similar benefits.

A limitation of our study is the small number of women, who accounted for only 11% of participants. This under-representation restricts definitive assessment of safety and tolerability of EVG/COBI/FTC/TDF in women. Additionally, an estimated glomerular fitration rate of at least 70 mL/min was required at entry; therefore, our study does not provide data for HIV-infected patients with lower glomerular fitration rates. Other planned or current studies will define the clinical usefulness of EVG/COBI/FTC/TDF for treatment of HIV-infected women and patients with estimated glomerular fitration rates ranging from 50 to 90 mL/min (ClinicalTrials.gov number NCT01363011). Median baseline CD4 cell count for patients in both treatment groups exceeded 350 cells per μL, with a small proportion of patients having advanced immunosuppression when they started therapy. This high cell count at baseline is indicative of a trend towards start of therapy at early stages of HIV infection according to some treatment guidelines,[1] which recommend antiretroviral therapy for all individuals with HIV infection, irrespective of CD4 cell count.

This study is the first fully powered, randomised, double-blind clinical trial to compare two single-tablet HIV treatments. If approved, EVG/COBI/FTC/TDF would be the only single-tablet, once-daily, integrase-inhibitor-based regimen available for initial HIV treatment.

Contributors

PES requested new analyses of data and approved the final report. PES, EDJ, AM, AZ, CC, DW, and JEG enrolled patients and reviewed and interpreted analyses of data. HCL, LZ, KY, KW, and AKC designed the study. Data collection was overseen by HCL, LJ, KY, EQ, and AKC. HCL, LJ, and KW analysed data, which were reviewed and interpreted by HCL, LZ, KY, BPK, JS, EQ and AKC. The first draft of this report was written by PES, EQ and AKC. The draft report was edited by PES, EDJ, AM, AZ, CC, DW, JEG, HCL, LZ, KY, JS, EQ, and AKC.

GS-US-236-0102 study investigators

USA B Akil, (Chelsea Village Medical), H Albrecht (University of South Carolina), N Bellos (Southwest Infectious Disease Clinical Research), P Benson (Be Well Medial Center), R Bolan (Jeffrey Goodman Clinic), I Brar (Henry Ford Hospital), U Bredeek (Metropolis Medical), J Burack (Alta Bates Summit Medical Center), R Campo (University of Miami), C Cohen (Community Research Initiative), D Condoluci (Garden State Infectious Disease Associates), P Cook (East Carolina University), D Coulston (Spokane Pulmonary and Critical Care), C Creticos (Howard Brown Health Center), J Barrett (Howard Brown Health Center), G Crofoot (Gordon E Crofoot, MD), F Cruickshank (Rosedale Infectious Diseases), E DeJesus (Orlando Immunology Center), R Dretler (Infectious Disease Specialists of Atlanta), H Edelstein (Alameda County Medical Center), R Elion (Whitman Walker Health), T File (Summa CARE Center), J Flamm (Kaiser Hospital Sacramento), S Follansbee (Kaiser Permanente Medical Center), J Gallant (Johns Hopkins Rockland Physicians Practice and Research Group at Greenspring Station), F Garcia (Garcia Family Health Group), J Gathe (Therapeutic Concepts), P Greiger-Zanlungo (Greiger Clinic), R Grossberg (Montefiore Medical Center), W Hardy (Cedars-Sinai Medical Center), T Hawkins (Southwest CARE Center), W Henry (Hennepin County Medical Center), J Horton (Carolinas Medical Center), R Hsu (Ricky K Hsu, MD), G Huhn (Ruth M Rothstein CORE Center), T Jefferson (Health For Life Clinic), H Khanlou (AHF Research Center), C Kinder (The Kinder Medical Group), D Klein (Kaiser Permanente), M Kozal (Yale University School of Medicine), A LaMarca (Therafirst Medical Center), R Landovitz (UCLA Center for Clinical AIDS Research & Education), C Lucasti (South Jersey Infectious Disease), A Leutkemeyer (UCSF Positive Health Program), M Markowitz (The Aaron Diamond AIDS Research Center), C Martorell (The Research Institute), C Mayer (St Joseph's Comprehensive Research Institute), C McDonald (Tarrant County Infectious Disease Associates), J McGowan (North Shore University Hospital), M McKellar (Duke University Health System), G McLeod (Stamford Infectious Diseases), D Mildvan (Beth Israel Medical Center), A Mills (Anthony Mills MD), K Mounzer (Philadelphia FIGHT), R Nahass (ID Care), A Paez (Baystate Infectious Diseases Clinical Research), P Palmieri (Upstate Infectious Diseases Associates), D Parks (Central West Clinical Research), A Petroll (Medical College of Wisconsin Froedtert Hospital), G Pierone (Treasure Coast Infectious Disease Consultants), D Prelutsky (Southampton Healthcare), M Ramgopal (Midway Immunology & Research Center), B Rashbaum (Capital Medical Associates), J Ravishankar (SUNY Downstate Medical Center), M Rawlings (Peabody Health Center/AIDS Arms), G Richmond (Gary Richmond, MD), W Robbins (ValuHealthMD), A Roberts (Medical Faculty Associates), J Rodriguez (Orange Coast Medical Group), P Ruane (Peter J Ruane, MD), M Saag (University of Alabama at Birmingham), P Sax (Brigham & Women's Hospital), S Schneider (Living Hope Clinical Foundation), S Schrader (Research Access Network), A Scribner (DCOL Center for Clinical Research), S Segal-Maurer (New York Hospital Queens), M Sension (Comprehensive Care Center), P Shalit (Peter Shalit, MD), D Shamblaw (La Playa Medical Group and Clinical Research), C Shikuma (Leahi Hospital), J Slim (Saint Michael's Medical Center), D Stein (Jacobi Medical Center), J Stephens (Mercer University School of Medicine), P Tebas (University of Pennsylvania), M Thompson (AIDS Research Consortium of Atlanta), W Towner (Kaiser Permanente Medical Center), T Vanig (Spectrum Medical Group), D Ward (Dupont Circle Physicians Group), D Wheeler (Clinical Alliance for Research & Education, Infectious Diseases, CARE-ID), A Wilkin (Wake Forest University Health Sciences), T Wills (Hillsborough County Health Department), D Wohl (Clinical and Translational Research Center), M Wohlfeiler (Wohlfeiler, Piperato and Associates), K Workowski (Emory University), B Yangco (Infectious Disease Research Institute), B Young (Denver Infectious Disease Consultants), A Zolopa (Stanford University), C Zurawski (Infectious Disease Solutions). *Puerto Rico* J Morales-Ramirez (Clinical Research Puerto Rico), S Saavedra-Sanquirico (VA Caribbean Healthcare System), J Santana-Bagur (University of Puerto Rico School of Medicine), L Santiago (Hope Clinical Research), G Sepulveda-Arzola (Instituto de Investigacion Cientifica del Sur).

Conflicts of interest

PES has received research support from Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck Laboratories, and Tibotec; consulting fees from Abbott Laboratories, Aeliron Scientific, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck Laboratories, and Janssen Therapeutics. EDJ has received research grant support from Abbott Laboratories, Achillion Pharmaceuticals, Avexa, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Hoffmann LaRoche, Idenix, Janssen, Merck, Pfizer, Sangamo, Taimed, Tobira, and Vertex; and consulting fees as a member of advisory boards for Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck, and Vertex. AM has received research support from Boehringer Ingelheim, Gilead Sciences, GlaxoSmithKline, Janssen Therapeutics, Kowa, Merck, Pfizer, Tobira, and ViiV, and consulting fees for speakers bureaux and advisory boards from Bristol-Myers Squibb, Gilead Sciences, Janssen Therapeutics, and Merck. AZ has received research grant support from Gilead Sciences, consulting fees as an advisory board member for Bristol-Myers Squibb, Gilead Sciences, and Janssen Therapeutics. CC has received research grant support from Gilead Sciences, Bristol-Myers Squibb, Merck, Janssen, and Viiv, and receives consulting fees from Gilead Sciences, Bristol-Myers Squibb, Merck, Janssen, Viiv, and Tobira. DW has received research grant support from Merck and GlaxoSmithKline, and receives consulting fees from Janssen Therapeutics and Gilead Sciences. JEG has received research support from Gilead Sciences and consulting fees from Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck, and Janssen Therapeutics. DW has received grant support from Merck & Co, and GlaxoSmithKline, and has been on advisory boards for Janssen Therapeutics and Gilead Sciences. HCL, LZ, KY, KW, BPK, JS, EQ, and AKC are employed by Gilead Sciences.

Acknowledgments

We thank Michael Wulfsohn for his critical review of the report and Peter Royce for assistance with preparation of the final draft. We also thank the GS-US-236-0102 study team, including Steven Chuck, Andrew Plummer, Tom Doan, Jason Carlson, Jay Huang, Caroline Shi, Sandy Chang, Yuhui Sun, Akashdeep Singh, Yu Ning, Gregory Campbell, Nick Wei, and Pei Sern. Parts of this study were presented at the 19th Conference on Retroviruses and Opportunistic Infections, Seattle, WA, USA; March 5–8, 2012.

References

1 US Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. 2011; Department of Health and Human Services. http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf (accessed Feb 22, 2012).

2 Thompson MA, Aberg JA, Cahn P, et al. Antiretroviral treatment of adults with HIV infection; 2010 Recommendations of the International AIDS Society-USA Panel. *JAMA* 2010; **304:** 321–33.

3 Arribas JR, Pozniak AL, Gallant JE, et al. Tenofovir disoproxil fumarate, emtricitabine and efavirenz compared with zidovudine/lamivudine and efavirenz in treatment-naive patients; 144-week analysis. *J Acquir Immune Defic Syndr* 2008; **47:** 74–78.

4 Sax PE, Tierney C, Collier AC, et al. Abacavir-lamivudine versus tenofovir-emtricitabine for initial HIV therapy. *N Engl J Med* 2009; **361:** 2230–40.

5 Cohen CJ, Andrade-Villanueva J, Clotet B, et al. Rilpivirine versus efavirenz with two background nucleoside or nucleotide reverse transcriptase inhibitors in treatment-naive adults infected with HIV-1 (THRIVE): a phase 3, randomised, noninferiority trial. *Lancet* 2011; **378:** 229–37.

6 Molina J-M, Cahn P, Grinsztejn B, et al. Rilpivirine versus efavirenz with tenofovir and emtricitabine in treatment-naive adults infected with HIV-1 (ECHO): a phase 3 randomised double-blind active-controlled trial. *Lancet* 2011; **378:** 238–46.

7 McKinnell JA, Willig JH, Westfall AO, et al. Antiretroviral prescribing patterns in treatment-naive patients in the United States. *AIDS Patient Care STDs* 2010; **24:** 79–85.

8 Gazzard BG, on behalf of the BHIVA Treatment Guidelines Writing Group. British HIV Association guidelines for the treatment of HIV-1-infected adults with antiretroviral therapy 2008. *HIV Med* 2008; **9:** 563–608.

9 Lennox JL, DeJesus E, Lazzarin A, et al. Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naive patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. *Lancet* 2009; **374:** 796–806.

10 ATRIPLA (efavirenz/emtricitabine/tenofovir disoproxil fumarate) tablets. US prescribing information. Gilead Sciences and Bristol-Myers Squibb. September 2011.

11 Ocfemia CB, Kim D, Ziebell R, et al. Prevalence and trends of transmitted drug resistance-associated mutations by duration of infection among persons newly diagnosed with HIV-1 infection: 5 states and 3 municipalities, US, 2006 to 2009. 19th Conference on Retroviruses and Opportunistic Infections; Seattle, USA; March 5–8, 2012. Abstract 730.

12 Kim D, Wheeler W, Ziebell R, et al. Prevalence of transmitted antiretroviral drug resistance among newly-diagnosed HIV-1 infected persons, United States, 2007. 17th Conference on Retroviruses and Opportunistic Infections; San Francisco, USA; Feb 16–19, 2010. Abstract 580.

13 COMPLERA (emtricitabine/rilpivirine/tenofovir disoproxil fumarate) tablets. US prescribing information. Gilead Sciences. August 2011.

14 Eviplera 200 mg/25mg/245mg film-coated tablets: summary of product characteristics. Gilead Sciences. Cambridge, UK. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002312/WC500118802.pdf (accessed June 14, 2012).

15 Shimura K, Kodama E, Sakagami Y, et al. Broad antiretroviral activity and resistance profile of the novel human immunodeficiency virus integrase inhibitor elvitegravir (JTK-303/GS-9137). *J Virol* 2008; **82:** 764–74.

16 DeJesus E, Berger D, Markowitz M, et al. Antiviral activity, pharmacokinetics, and dose response of the HIV–1 integrase inhibitor GS–9137 (JTK–303) in treatment-naive and treatment-experienced patients. *J Acquir Immune Defic Syndr* 2006; **43:** 1–5.

17 Molina JM, LaMarca A, Andrade-Villanueva J, et al. Efficacy and safety of once daily elvitegravir versus twice daily raltegravir in treatment-experienced patients with HIV–1 receiving a ritonavir-boosted protease inhibitor: randomised, double-blind, phase 3, non-inferiority study. *Lancet Infect Dis* 2012; **12:** 27–35.

18 Cohen C, Elion R, Ruane P, et al. Randomized, phase 2 evaluation of two single-tablet regimens elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate versus efavirenz/emtricitabine/tenofovir disoproxil fumarate for the initial treatment of HIV infection. *AIDS* 2011; **25:** F7–12.

19 US Department of Health and Human Services Food and Drug Administration. Guidance for industry: antiretroviral drugs using plasma HIV RNA measurements. 2002. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070968.pdf (accessed April 20, 2012).

20 Koch GG, Carr GJ, Amara IA, Stokes ME, Uryniak TJ. Categorical Data Analysis. In: Berry DA, ed. Statistical Methodology in the Pharmaceutical Sciences. New York: Marcel Dekker, 1989: 414–21.

21 Gallant J, DeJesus E, Arribas JR, et al. Tenofovir DR, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. *N Engl J Med* 2006; **354:** 251–60.

22 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; **16:** 31–41.

23 German P, Lui C, Warren D, et al. Effect of cobicistat on glomerular filtration rate (GFR) in subjects with normal and impaired renal function. 51st Interscience Conference on Antimicrobial Agents and Chemotherapy; Chicago, USA; Sept 17–20, 2011. Abstract H2-804.

24 Elion R, Cohen C, Gathe J, et al. Phase 2 study of cobicistat versus ritonavir each with atazanavir plus fixed-dose emtricitabine/tenofovir DF in the initial treatment of HIV infection. *AIDS* 2011; **25:** 1881–86.

25 DeJesus E, Rockstroh JK, Henry K, et al, for the GS-236-0103 Study Team. 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. *Lancet* 2012; **379:** 2429–38.

26 Lennox JL, DeJesus E, Berger DS, et al. Raltegravir versus efavirenz regimens in treatment-naive HIV-1-infected patients: 96-week efficacy, durability, subgroup, safety, and metabolic analyses. *JAIDS* 2011; **55:** 39–48.

27 Daar ES, Tierney C, Fischl M, et al. ACTG 5202: final results of abacavir/lamivudine (ABC/3TC) or tenofovir DF/emtricitabine (TDF/FTC) with either efavirenz (EFV) or atazanavir/ritonavir (ATV/r) in treatment-naive HIV-infected patients. 17th Conference on Retroviruses and Opportunistic Infections; San Francisco, USA; Feb 16–19, 2010. 59LB.

28 Van Leth F, Phanuphak P, Ruxrungtham K, et al. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. *Lancet* 2004; **363:** 1253–63.

29 Haubrich RH, Riddler SA, Ribaudo H, et al. Initial viral decay to assess the relative antiretroviral potency of protease inhibitor-sparing, nonnucleoside reverse transcriptase inhibitor-sparing, and nucleoside reverse transcriptase inhibitor-sparing regimens for first-line therapy of HIV infection. *AIDS* 2011; **25:** 2269–78.

30 Llibre JM, Arribas JR, Domingo P, et al. Clinical implications of fixed-dose coformulations of antiretrovirals on the outcome of HIV-1 therapy. *AIDS* 2011; **25:** 1683–90.

31 Hodder SL, Mounzer K, Dejesus E, et al. Patient-reported outcomes in virologically suppressed, HIV-1-infected subjects after switching to a simplified, single-tablet regimen of efavirenz, emtricitabine, and tenofovir DF. *AIDS Patient Care STDs* 2010; **24:** 87–96.

32 Airoldi M, Zaccarelli M, Bisi L, et al. One-pill once-a-day HAART: a simplification strategy that improves adherence and quality of life of HIV-infected subjects. *Patient Prefer Adherence* 2010; **4:** 115–25.

33 Bangsberg DR, Ragland K, Monk A, Deeks SG. A single tablet regimen is associated with higher adherence and viral suppression than multiple tablet regimens in HIV+ homeless and marginally housed people. *AIDS* 2010; **24:** 2835–40.

34 Cohen C, Davis KL, Meyers J. Association between daily antiretroviral pill burden and hospitalization risk in a medicaid population with HIV. 51st Interscience Conference on Antimicrobial Agents and Chemotherapy; Chicago, USA; Sept 17–20, 2011. Abstract H2-791.

35 Sax PE, Meyers J, Mugavero M, Davis KL. Adherence to antiretroviral treatment regimens and correlation with risk of hospitalization among commercially insured HIV patients in the United States. *PLoS One* 2012; **7:** e31591.