Simplification to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus continuation of ritonavir-boosted protease inhibitor with emtricitabine and tenofovir in adults with virologically suppressed HIV (STRATEGY-PI): 48 week results of a randomised, open-label, phase 3b, non-inferiority trial

Jose R Arribas, Gilles Pialoux, Joseph Gathe, Giovanni Di Perri, Jacques Reynes, Pablo Tebas, Thai Nguyen, Ramin Ebrahimi, Kirsten White, David Piontkowsky

Summary

Background Patients with HIV on antiretroviral therapy might benefit from regimen simplification to reduce pill burden and dosing frequency. We aimed to assess the safety and efficacy of simplifying the treatment regimen for adults with virologically suppressed HIV infection from a ritonavir-boosted protease inhibitor and emtricitabine plus tenofovir disoproxil fumarate (tenofovir) regimen to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir.

Methods STRATEGY-PI is a 96 week, international, multicentre, randomised, open-label, phase 3b trial in which HIV-infected adults with a plasma HIV-1 RNA viral load of less than 50 copies per mL for at least 6 months who were taking a ritonavir-boosted protease inhibitor with emtricitabine plus tenofovir were randomly assigned (2:1) either to switch to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir or to continue on their existing regimen. Key eligibility criteria included no history of virological failure, no resistance to emtricitabine and tenofovir, and creatinine clearance of 70 mL/min or higher. Neither participants nor investigators were masked to group allocation. The primary endpoint was the proportion of participants with a viral load of less than 50 copies per mL at week 48, based on a US Food and Drug Administration snapshot algorithm for the modified intention-to-treat population, which excluded major protocol violations (prohibited resistance or not receiving a protease inhibitor at baseline). We prespecified non-inferiority with a 12% margin; if non-inferiority was established, superiority was tested as per a prespecified sequential testing procedure. This trial is registered at ClinicalTrials.gov, number NCT01475838.

Findings Between Dec 12, 2011, and Dec 20, 2012, 433 participants were randomly assigned and received at least one dose of study drug. Of these participants, 293 were assigned to switch to the simplified regimen (switch group) and 140 to remain on their existing regimen (no-switch group); after exclusions, 290 and 139 participants, respectively, were analysed in the modified intention-to-treat population. At week 48, 272 (93·8%) of 290 participants in the switch group maintained a viral load of less than 50 copies per mL, compared with 121 (87·1%) of 139 in the no-switch group (difference 6·7%, 95% CI 0·4–13·7; p=0·025). The statistical superiority of the simplified regimen was mainly caused by a higher proportion of participants in the no-switch group than in the switch group discontinuing treatment for non-virological reasons; virological failure was rare in both groups (two [1%] of 290 *vs* two [1%] of 139). We did not detect any treatment-emergent resistance in either group. Adverse events leading to discontinuation were rare in both groups (six [2%] of 293 *vs* four [3%] of 140). Switching to the simplified regimen was associated with a small, non-progressive increase from baseline in serum creatinine concentration. Nausea was more common in the switch group than in the no-switch group, but rates of diarrhoea and bloating decreased compared with baseline from week 4 to week 48 in the switch group, whereas there were generally no changes for these symptoms in the no-switch group.

Interpretation Coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir might be a useful regimen simplification option for virologically supressed adults with HIV taking a multitablet ritonavir-boosted protease inhibitor regimen.

Funding Gilead Sciences.

Lancet Infect Dis 2014

Published Online
June 5, 2014
http://dx.doi.org/10.1016/S1473-3099(14)70782-0

See Online/Comment
http://dx.doi.org/10.1016/S1473-3099(14)70743-1

See Online/Articles
http://dx.doi.org/10.1016/S1473-3099(14)70796-0

HIV Unit, Internal Medicine, Hospital La Paz, IdiPAZ, Madrid, Spain (J R Arribas MD); **Infectious Diseases, Pierre and Marie Curie University, Hôpital Tenon, Paris, France** (Prof G Pialoux MD); **Infectious Diseases, Baylor College of Medicine, Houston, TX, USA** (J Gathe MD); **Medical Sciences, University of Turin School of Medicine, Turin, Italy** (Prof G Di Perri MD); **Infectious Diseases, Centre Hospitalier Universitaire Gui de Chauliac, Montpellier, France** (Prof J Reynes MD); **Infectious Diseases, University of Pennsylvania School of Medicine, Philadelphia, PA, USA** (P Tebas MD); **and Gilead Sciences, Foster City, CA, USA** (T Nguyen MD, R Ebrahimi MS, K White PhD, D Piontkowsky MD)

Correspondence to:
Dr Jose R Arribas, HIV Unit, Internal Medicine, Hospital La Paz, IdiPAZ, Madrid 28046, Spain
joser.arribas@salud.madrid.org

Introduction

Patients with HIV on combination antiretroviral therapy consisting of a multitablet regimen could benefit from regimen simplification, defined by the US Department of Health and Human Services and European AIDS Clinical Society HIV treatment guidelines[1–3] as a change in established effective therapy to reduce pill burden and dosing frequency. Simplification of antiretroviral therapy

with the replacement of multitablet protease inhibitor regimens, some of which are associated with a risk of cardiovascular disease[4] and chronic gastrointestinal disturbances,[5] has been widely pursued. Previous non-inferiority studies (SWITCHMRK 1 and 2[6] and SPIRAL[7]) that examined the simplification of a multitablet ritonavir-boosted protease inhibitor regimen to one based on raltegravir, an integrase strand transfer inhibitor taken twice daily, showed inconsistent virological efficacy of the raltegravir-containing regimens compared with continuation of a ritonavir-boosted protease inhibitor regimen in patients with a history of virological failure on previous antiretroviral therapy.[6,7] Similar studies to assess the simplification of a multitablet ritonavir-boosted protease inhibitor regimen to newer integrase inhibitors, which are taken once daily, have not been done.

Coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate (tenofovir), which contains the HIV-1 integrase inhibitor elvitegravir boosted by the CYP3A4 enzyme-based pharmacokinetic enhancer cobicistat, is safe and effective in HIV-infected, antiretroviral-naive adults and is a recommended integrase inhibitor-based regimen in treatment guidelines from the US Department of Health and Human Services and British HIV Association.[1,8–12] Virologically suppressed patients on a multitablet ritonavir-boosted protease inhibitor regimen might benefit from a regimen simplification to this single-tablet regimen. Although the evidence is not definitive, single-tablet regimens can be beneficial with respect to improvement of treatment adherence and persistence.[13,14] We aimed to investigate whether this benefit might be outweighed by an increased risk of virological failure after regimen simplification to the single-tablet elvitegravir, cobicistat, emtricitabine, and tenofovir regimen. Here we report the 48 week results of a clinical trial to assess the safety and efficacy of simplifying the treatment regimen for adults with virologically suppressed HIV infection from a multitablet ritonavir-boosted protease inhibitor and emtricitabine plus tenofovir regimen to the single-tablet coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir regimen.

Methods

Study design and participants

STRATEGY-PI is a phase 3b, randomised, open-label, ongoing study taking place at 86 sites in Europe and North America. At recruitment, eligible participants were HIV-infected adults (aged 18 years or older) on a stable antiretroviral therapy regimen consisting of a ritonavir-boosted protease inhibitor and emtricitabine plus tenofovir, and had a plasma HIV-1 RNA viral load of less than 50 copies per mL for at least 6 consecutive months. Participants were on their first or second regimen at randomisation; if on their second regimen, they must not have had a viral load of 50 or more copies per mL at the time of the change in antiretroviral therapy, or ever have had two consecutive measurements of 50 or more copies per mL after first achieving virological control (<50 copies per mL). Participants must have had genotypic testing, although integrase testing was not required, before starting first antiretroviral therapy, with no known resistance to any of the study drugs, including the reverse transcriptase resistance mutations Met184Val/Ile, Lys65Arg, or at least three thymidine analogue-associated mutations (Met41Leu, Asp67Asn, Lys70Arg, Leu210Trp, Thr215Tyr/Phe, or Lys219Gln/Glu/Asn/Arg) including Met41Leu or Leu210Trp. Additionally, participants had to have an estimated glomerular filtration rate of 70 mL/min or higher and must not have previously used any approved or investigational integrase strand transfer inhibitor.

The study is being done in accordance with the Declaration of Helsinki. The protocol was reviewed and approved by central or site-specific institutional review boards or ethics committees covering all participating sites. All participants provided written informed consent.

Randomisation and masking

Eligible participants were randomly assigned (2:1) to either switch to coformulated elvitegravir 150 mg, cobicistat 150 mg, emtricitabine 200 mg, tenofovir 300 mg once daily with food (switch group), or remain on the regimen being used at screening (no-switch group). A computer-generated randomisation schedule was created, and an interactive voice-response or web-response system was used. The study design was open-label, so participants and investigators were not masked to group allocation. This strategy allowed assessment of patient satisfaction and adherence for the single-tablet and multitablet regimens.

Outcomes

The primary endpoint was the proportion of participants who maintained a viral load of less than 50 copies per mL at week 48. In a secondary efficacy analysis, we assessed the proportion of participants who maintained a viral load of less than 50 copies per mL at week 48 on the basis of the FDA-defined time to loss of virological response (TLOVR) algorithm.[15] We also explored rates of virological success and differences by subgroup divided by age, sex, race, protease inhibitor being used at random assignment, and number of previous antiretroviral regimens. Other secondary endpoints were change in CD4 cell count, safety, and tolerability of the two regimens to week 96.

Procedures

Post-baseline study visits occurred at weeks 4, 8, 12, 24, 36, and 48, after which participants will continue treatment with visits every 12 weeks until week 96. We assessed safety with laboratory tests, physical examinations, and reporting of adverse events. Haematology, serum chemistry, urinalysis, CD4 cell count, and fasting lipid

concentrations were analysed by Covance Laboratories (Indianapolis, IN, USA). Plasma HIV-1 RNA viral load was assessed with the Amplicor HIV-1 Monitor Test (version 1.5; Roche Diagnostics, Rotkreuz, Switzerland). We did HIV-1 genotyping and phenotyping of protease, reverse transcriptase, and integrase in cases of confirmed virological failure in participants on study drugs who had viral loads of 400 copies per mL or higher at the second visit or at week 48, or at early discontinuation for any reason, using the PhenoSense GT, PhenoSense Integrase, and GeneSeq Integrase assays (Monogram Biosciences, South San Francisco, CA, USA). We obtained data for patient-reported outcomes using health-related quality of life questionnaires, some done at all study visits (HIV Symptom Index, Short Form 36, and visual analog scale adherence questionnaires) and one done at baseline and weeks 4 and 24 (HIV Treatment Satisfaction questionnaire).

Statistical analysis

All analyses were prespecified in the protocol and statistical analysis plan and were done with SAS software (version 9.2). Analyses included all data available after the last enrolled participant had completed the week 48 visit or prematurely discontinued the study drug. No interim analysis was done before week 48. The full analysis set was the modified intention-to-treat population, which consisted of participants who were randomly assigned and treated with at least one dose of study drug, excluding those with a documented prohibited resistance mutation on their

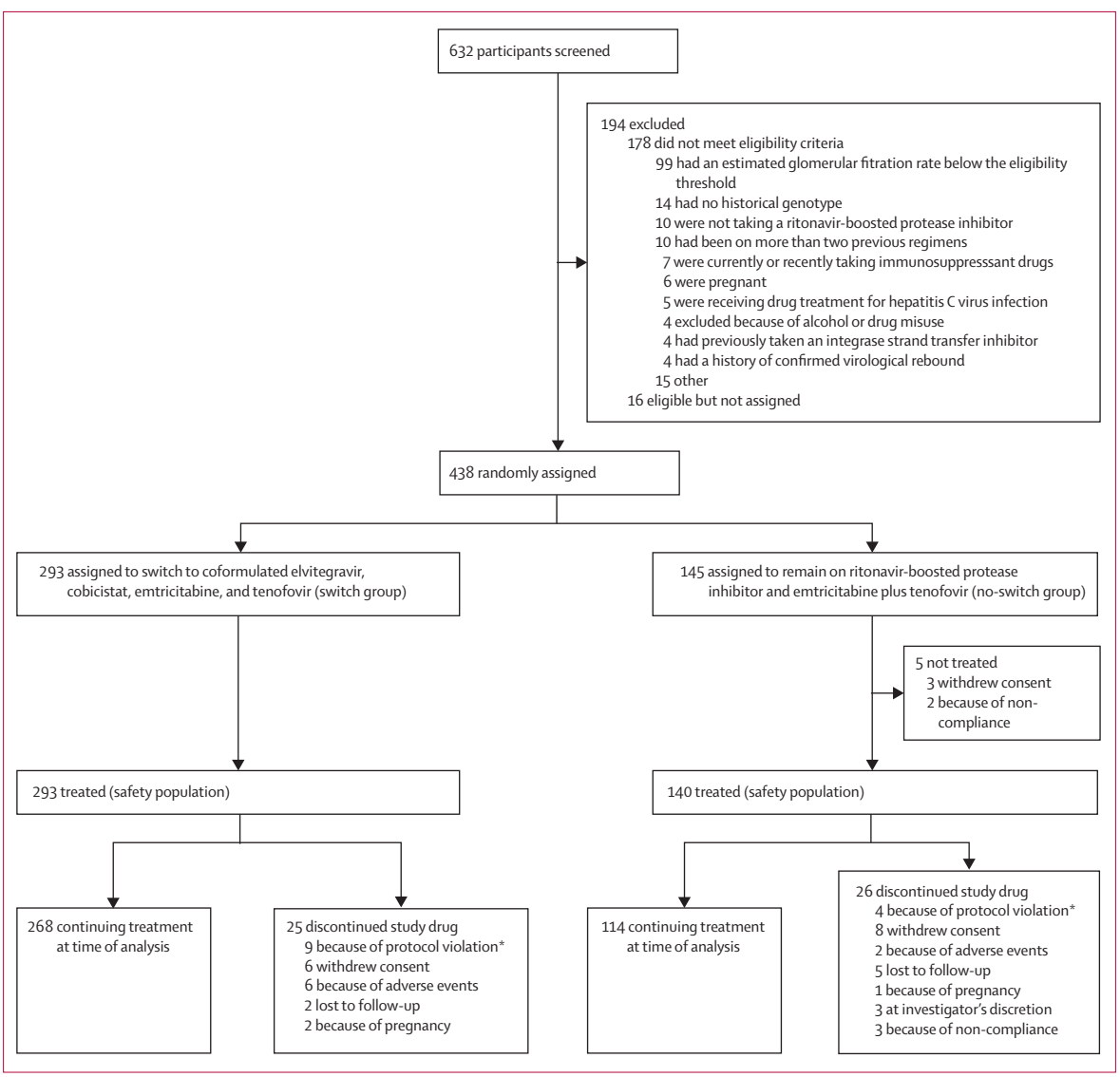

Figure 1: **Trial profile**
Patients could have been excluded after screening for more than one reason. *Participants were excluded from the modified intention-to-treat population if they had a prespecified major eligibility criteria violation.

historical genotypes or not on a protease inhibitor-containing regimen at screening.[16] Participants in both groups were scrutinised equally and excluded for violation of these major eligibility criteria.

	Switch group (n=293)	No-switch group (n=140)
Age (years)		
Median (IQR)	41 (33–48)	40 (35–47)
Mean (SD)	41 (10)	41 (9)
Male	250 (85%)	121 (86%)
Race		
Native American or Native Alaskan	2 (1%)	1 (1%)
Asian	7 (2%)	2 (1%)
Black or African heritage	43 (15%)	20 (14%)
Native Hawaiian or Pacific Islander	0	0
White	234 (80%)	113 (81%)
Other	5 (2%)	2 (1%)
Missing data	2 (1%)	2 (1%)
Ethnicity		
Hispanic or Latino	42 (14%)	17 (12%)
Weight (kg)		
Median (IQR)	79·0 (69·0–88·2)	76·6 (69·8–88·6)
Mean (SD)	79·9 (15·9)	78·9 (12·4)
Height (cm)		
Median (IQR)	175·3 (170·0–180·3)	175·3 (170·0–180·3)
Mean (SD)	174·7 (8·6)	175·0 (8·2)
Body-mass index (kg/m²)		
Median (IQR)	25·6 (23·0–28·4)	25·3 (23·6–27·8)
Mean (SD)	26·2 (5·0)	25·8 (3·7)
Estimated glomerular filtration rate (mL/min)		
Median (IQR)	111·2 (96·0–127·9)	111·1 (98·1–126·8)
Mean (SD) estimated glomerular filtration rate (mL/min)	114·6 (27·5)	113·1 (23·5)
Positive HBsAg	10 (3%)	3 (2%)
Positive hepatitis C virus antibody	19 (7%)	10 (7%)
AIDS diagnosis	41 (14%)	18 (13%)
CD4 cell count (cells per µL)		
Median (IQR)	564 (423–757)	585 (445–770)
Mean (SD)	604 (275)	624 (270)
Time since HIV diagnosis (years)		
Median (IQR)	4 (3–7)	4 (3–7)
Mean (SD)	6 (4·8)	5 (3·6)
Time since first antiretroviral therapy use (years)		
Median (IQR)	3 (2–4)	3 (1–4)
Mean (SD)	3 (2·8)	3 (2·2)
On first antiretroviral therapy regimen at random assignment	226 (77%)	116 (83%)
Protease inhibitor at random assignment		
Atazanavir	123 (42%)	51 (37%)
Darunavir	113 (39%)	60 (43%)
Lopinavir	49 (17%)	23 (16%)
Fosamprenavir	6 (2%)	5 (4%)
Saquinavir	2 (1%)	0

Data are n (%) unless otherwise stated. HBsAg=hepatitis B surface antigen.

***Table 1*: Baseline characteristics**

The primary endpoint was analysed in accordance with the snapshot algorithm defined by the US Food and Drug Administration (FDA).[17] We also did a per-protocol snapshot sensitivity analysis for the primary endpoint. The per-protocol population consisted of the modified intention-to-treat population, excluding participants with a protocol violation that met prespecified criteria (not having sensitivity to emtricitabine and tenofovir on historical genotype, not being virologically suppressed at both screening and baseline, not having viral load assessments in the week 48 analysis window for reasons other than discontinuation because of poor efficacy, or taking protocol-prohibited drugs).

In the primary efficacy analysis, non-inferiority would be established if the lower bound of a two-sided 95% CI for the difference in proportions (switch group minus no-switch group) of participants who maintained a viral load of less than 50 copies per mL at week 48 was greater than –12%. We calculated the two-sided 95% CI for the difference in proportions of virological success between treatment groups on the basis of an unconditional exact method by use of two inverted one-sided tests with standardised statistics using StatXact (version 8).[18] If non-inferiority was established in the primary efficacy analysis and the lower bound of 95% CI was greater than zero, then we would test superiority at the nominal 5% significance level using Fisher's exact test. A sample size of 420 participants would provide at least 85% power to establish non-inferiority for the proportion of participants maintaining virological suppression at week 48, with an assumed response rate of 82% in both groups, and a non-inferiority margin of 12%. We did sample size calculations with nQuery Advisor (version 6.0).

We summarised all safety data collected on or after the date of the first dose of study drug up to 30 days after the last dose of study drug using descriptive statistics. Adverse events were coded with the Medical Dictionary for Regulatory Activities (version 16.1). We estimated glomerular filtration rate using the Cockcroft-Gault method.[19] We tested treatment differences for continuous laboratory results using the Wilcoxon rank-sum test.

This study is registered with ClinicalTrials.gov, number NCT01475838.

Role of the funding source

The funder manages all operational aspects of the study, including study design, data collection and analysis, interpretation, and the writing of the report. Upon request, all authors are given access to all the data in the study. The corresponding author had final responsibility for the decision to submit for publication.

Results

632 individuals were screened between Nov 18, 2011, and Nov 23, 2012, and 438 were randomly assigned treatment (figure 1). The trial profile (figure 1) does not include participants who had adverse events that resulted in

discontinuation after Oct 31, 2013, the week 48 data cutoff date; all adverse events with onset before this date were included in the safety analysis. 433 participants received at least one dose of study drug and were therefore included in the safety population (figure 1). On the basis of the enrolment survey (self-administered at screening), the most common reasons for enrolment in the study were participants' desire to simplify their existing regimen (371 [86%] of 433) and concern about the long-term side-effects of their existing regimen (53 [12%] of 433). Baseline characteristics were similar in the two treatment groups (table 1). Three participants were excluded from the switch group with pre-existing prohibited resistance to study drugs on their historical genotype (one participant had Val118Ile and Met184Val, one had Asp67Asn, Lys70Arg, Thr69Asp, Lys219Gln, and Met184Val, and one had Met41Leu, Glu44Glu/Asp, Leu210Glu/Gly/Trp, and Thr215Cys/Asp/Gly/Tyr); all discontinued the study drug because of protocol violation (at weeks 2, 27, and 12, respectively), and all had viral loads of less than 50 copies per mL at all study visits including the discontinuation visit. One participant not on a protease inhibitor-containing regimen at screening was excluded from the no-switch group. This participant had a viral load of less than 50 copies per mL at the time of discontinuation on study day 57.

Switching to the simplified regimen was non-inferior to remaining on existing regimens at week 48 (table 2). The treatment difference was 6·7% (95% CI 0·4–13·7; p=0·025). The lower bound of the 95% CI for the difference in rates of virological success was greater than zero, suggesting the statistical superiority of the simplified regimen over the existing regimens. The proportion of participants with virological failure at week 48 was low in both groups (table 2). A larger proportion of participants in the no-switch group than in the switch group had no virological data for the week 48 analysis, mainly because of participants who withdrew consent or were lost to follow-up, but whose last measurement of viral load was less than 50 copies per mL (table 2).

Virological suppression was high in both groups in the sensitivity per-protocol analysis, in which 265 (99·3%) of 267 participants in the switch group and 117 (99·2%) of 118 in the no-switch group maintained viral loads of less than 50 copies per mL at week 48 (difference 0·1%, 95% CI –2·1 to 3·7), lending support to the finding of non-inferiority. In the secondary efficacy analysis, based on the FDA-defined TLOVR algorithm, 266 (91·7%) of 290 participants in the switch group and 117 (84·2%) of 139 in the no-switch group were responders at week 48 (difference 7·6%, 95% CI 0·9–15·0). Rates of virological success by FDA snapshot analysis and differences by subgroup according to age, sex, race, protease inhibitor used at random assignment, and number of previous regimens generally favoured the simplified regimen (figure 2). Differences in rates of virological success were significant in participants aged 40 years and older (p=0·044), men (p=0·020), white participants (p=0·037), and those taking atazanavir at random assignment (p=0·010). No participants met the criteria for resistance testing in either group; therefore, we noted no evidence of treatment-emergent resistance. Increases from baseline at week 48 in CD4 cell count were similar between groups (mean 40 [SD 170] cells per μL in the switch group *vs* 32 [166] cells per μL in the no-switch group).

	Switch group (n=290)	No-switch group (n=139)
HIV-1 RNA concentration <50 copies per mL	272 (94%)	121 (87%)
HIV-1 RNA ≥50 copies per mL	2 (1%)	2 (1%)
HIV-1 RNA ≥50 copies/mL (virological failure)	2	1
Discontinued because of poor efficacy	0	0
Discontinued for other reasons and last available HIV-1 RNA concentration ≥50 copies per mL*	0	1
No virological data	16 (6%)	16 (12%)
Discontinued because of adverse event or death	5†	2‡
Discontinued for other reasons and last available HIV-1 RNA <50 copies per mL*	11	14
Missing data for week 48, but on study drug	0	0

Data are n or n (%). *Other reasons included withdrawal of consent, loss to follow-up, and protocol violation. †One additional participant had an adverse event that led to study drug discontinuation, but had a viral load of less than 50 copies per mL in the week 48 analysis window and was therefore counted as a virological success. ‡Two additional participants had an adverse event that led to study drug discontinuation, but had viral loads less than 50 copies per mL in the week 48 analysis window and were therefore counted as virological successes.

Table 2: **Virological outcome at week 48**

Adverse events occurred at similar frequencies in the switch and no-switch groups, and most were grade 1 or 2 in severity (table 3). Adverse events that were reported in at least 5% of participants in either group were generally similar in frequencies between groups (table 3). Adverse events that led to study drug discontinuation were rare in both groups (table 3). One participant in the no-switch group had a renal adverse event of decreased glomerular filtration rate without proximal renal tubular laboratory abnormalities. One participant in the no-switch group died during the study from bronchial carcinoma with liver metastases, which the investigator did not regard as related to study drug.

Most participants had at least one treatment-emergent laboratory abnormality reported during the study, most of which were grade 1 or 2 in severity. Grade 3 or 4 laboratory abnormalities were reported for a smaller proportion of participants in the switch group than in the no-switch group (table 4), largely caused by a higher incidence of grade 3 or 4 hyperbilirubinaemia in the no-switch group.

Starting at week 4, we noted increases in serum creatinine concentration in the switch group, but these increases generally stabilised and were non-progressive up to week 48 (median change 6 μmol/L [IQR –1 to 12] at

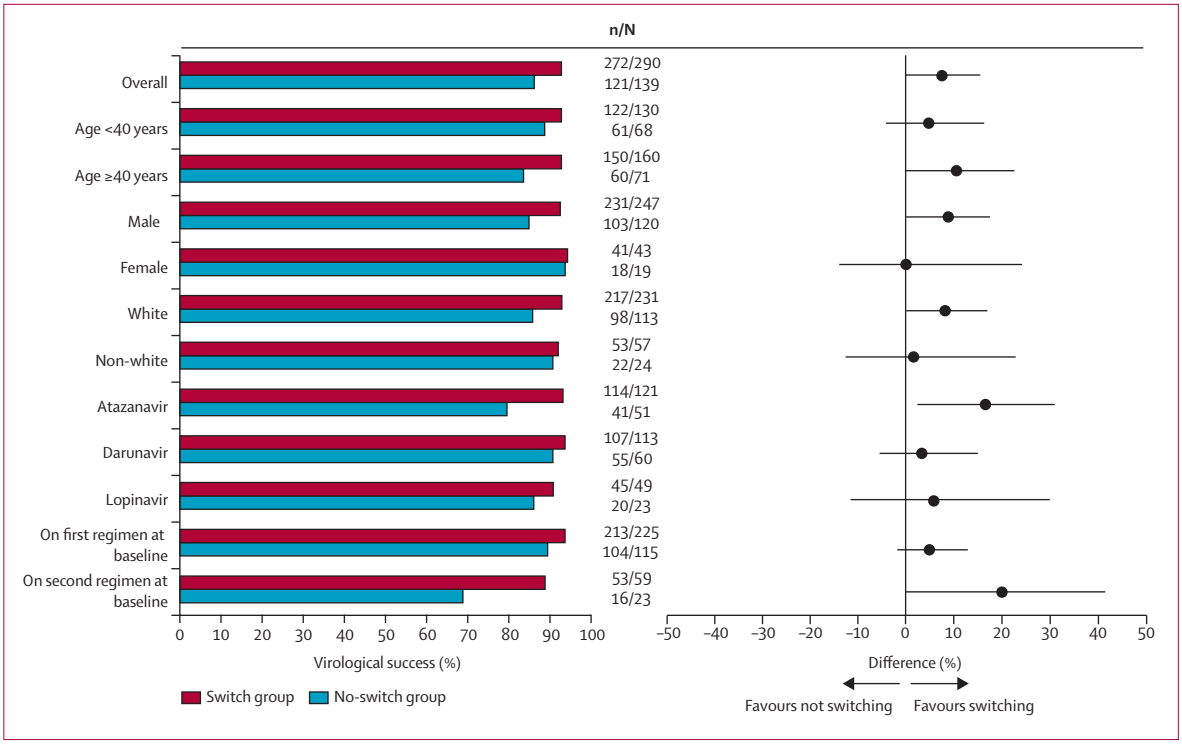

Figure 2: **Virological success and difference by subgroup at week 48**
Data are for the modified intention-to-treat population. n=number of participants with a viral load of less than 50 copies per mL. N=total number of participants. Subgroups not summarised because of low numbers include four patients who did not report their race, eight who had been on more than two previous regimens, and 13 who took protease inhibitors other than atazanavir, darunavir, or lopinavir.

See Online for appendix

	Switch group (n=293)	No-switch group (n=140)
Summary of adverse events		
Adverse event	232 (79%)	104 (74%)
Grade 3 or 4	12 (4%)	11 (8%)
Serious adverse event	17 (6%)	9 (6%)
Discontinuation because of adverse event	6 (2%)*	4 (3%)†
Death	0	1 (1%)
Adverse events that occurred in at least 5% of participants in either group		
Nasopharyngitis	35 (12%)	14 (10%)
Upper-respiratory infection	24 (8%)	6 (4%)
Diarrhoea	21 (7%)	11 (8%)
Nausea	21 (7%)	4 (3%)
Headache	19 (6%)	9 (6%)
Anxiety	17 (6%)	5 (4%)
Back pain	16 (5%)	2 (1%)
Cough	15 (5%)	4 (3%)
Depression	12 (4%)	8 (6%)
Insomnia	10 (3%)	7 (5%)

Data are n (%). *Anxiety (n=1); depression (n=1); Hodgkin's disease (n=1); major depression and suicide attempt (n=1); myalgia, nausea, and headache (n=1); and reduced visual acuity (n=1). †Bronchial carcinoma with liver metastases (n=1), diarrhoea (n=1), bipolar disorder (n=1), and decreased glomerular filtration rate (n=1).

Table 3: **Adverse events overview**

week 48), compared with no trend in median change from baseline in the no-switch group (–1 µmol/L [–6 to 6]; appendix).

Fasting triglycerides fell in the switch group, whereas they did not change in the no-switch group (appendix). Subgroup analyses showed decreases at week 48 in fasting total and high-density lipoprotein cholesterol and triglycerides in participants in the lopinavir switch subgroup compared with no changes from baseline in those who continued on a lopinavir-based regimen (appendix). Additionally, we noted a small decrease from baseline at week 48 in fasting triglycerides for participants in the atazanavir switch subgroup and a small decrease from baseline in the total-to-high-density-lipoprotein-cholesterol ratio for participants in the darunavir switch subgroup compared with no change from baseline in these parameters for those who continued on an atazanavir-based or darunavir-based regimen, respectively (appendix).

Results of the HIV Symptom Index showed that rates of diarrhoea and bloating decreased compared with baseline from week 4 to week 48 in the switch group, whereas there were generally no changes for these symptoms in the no-switch group (appendix). Rates of other HIV symptoms did not change compared with baseline in either group. Participants in the switch group had higher treatment satisfaction scores (range –30 to 30) than those in the no-

	Switch group (n=293)	No-switch group (n=140)
Any grade 3 or 4 laboratory abnormality	42 (14%)	32 (23%)
Gamma-glutamyl transpeptidase (>5×ULN)	8 (3%)	2 (1%)
Creatine kinase (≥10×ULN)	7 (2%)	9 (6%)
Alanine aminotransferase (>5×ULN)	6 (2%)	1 (1%)
Haematuria (RBC/HPF >75)	7 (2%)	2 (1%)
Total bilirubin (>2·5×ULN)	0	17 (12%)

Data are n (%) for treatment-emergent grade 3 or 4 laboratory abnormalities that occurred in at least 2% of participants in either treatment group (safety population). ULN=upper limit of normal. RBC/HPF=red blood cells/high power field.

Table 4: **Grade 3 or 4 laboratory abnormalities**

switch group at week 4 (mean 21·5 [SD 9·4] *vs* 13·3 [11·8]; p<0·0001) and week 24 (23·1 [8·8] *vs* 14·5 [12·9]; p<0·0001). Patient-reported outcomes from the Short Form 36 and visual analog scale adherence questionnaires were generally favourable in both treatment groups, did not change from baseline within groups, and did not differ between the groups (data not shown).

Discussion

Coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir is an effective, safe, and tolerable simplification from a ritonavir-boosted protease inhibitor plus emtricitabine and tenofovir regimen in virologically suppressed, HIV-infected adults with no history of virological failure or resistance to emtricitabine or tenofovir.

At baseline, participants were virologically suppressed and differed from treatment-naive participants who were viraemic in the pivotal phase 3 studies of the coformulated regimen.[8,9] We obtained historical genotypes to confirm sensitivity to emtricitabine and tenofovir, which might not always be possible in clinical practice. Nevertheless, the low frequency of virological failure and absence of emergent resistance in the switch group over 48 weeks in participants who switched from a ritonavir-boosted protease inhibitor, which have a high barrier to resistance, is reassuring.

Coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir was well tolerated; discontinuations because of adverse events were rare. Nausea was more common in the switch group than in the no-switch group, but its frequency was consistent with the known safety profile of the coformulated regimen from phase 3 studies.[8,9] Participants in the switch group had decreased rates of diarrhoea and bloating from week 4 to week 48, compared with baseline. The rates of gastrointestinal disturbance ascertained from the HIV Symptom Index were higher than those identified from the investigator-reported adverse events, suggesting that patients on a regimen containing a ritonavir-boosted protease inhibitor might have gastrointestinal disturbances for years without voicing the complaint to their physician. In this study, the tolerability profile of coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir, as defined by patient-reported outcomes, further differentiated this regimen from ritonavir-boosted protease inhibitor regimens. Coformulated rilpivirine, emtricitabine, and tenofovir is the only regimen with an FDA-approved switch indication, based on the findings of the SPIRIT study, in which patients switched from a regimen containing a ritonavir-boosted protease inhibitor.[20] In the SPIRIT study, only 12 (3%) of 469 patients who switched to rilpivirine, emtricitabine, and tenofovir discontinued the study drugs because of adverse events, which is similar to the proportion seen for elvitegravir, cobicistat, emtricitabine, and tenofovir in this study.[21] These findings add to the totality of evidence to show that this coformulated regimen is a well tolerated alternative to those based on a ritonavir-boosted protease inhibitor.

No participants in this study had renal laboratory findings consistent with proximal renal tubulopathy. We noted increases in serum creatinine in the switch group, consistent with the inhibitory effect of cobicistat on renal tubular creatinine secretion. The size of the serum creatinine increase in this study was smaller than those seen in phase 3 studies of elvitegravir, cobicistat, emtricitabine, and tenofovir in treatment-naive patients.[8,9] In an in-vitro study, ritonavir was a weaker inhibitor than cobicistat of the multidrug and toxin extrusion-1 (MATE-1; also known as SLC47A1) renal transporter, which mediates renal tubular creatinine secretion.[22,23] Participants in our study switched from ritonavir to cobicistat, which further inhibited MATE-1, translating into an additional but smaller increase in serum creatinine concentration. We noted a small decrease from baseline at week 48 in fasting triglycerides for participants who switched from a protease inhibitor plus emtricitabine and tenofovir regimen to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir. Switching to this coformulated regimen from one containing lopinavir and ritonavir was associated with improvement in some fasting lipid parameters, which is consistent with the results of the SWITCHMRK studies.[6] However, the changes in these fasting lipid parameters were small and might not be clinically significant.

We acknowledge several limitations of our study, the most important of which is its open-label study design. Our finding that switching to the simplified regimen was superior to not switching might have been different if the trial had been double blinded. Additionally, a potential for bias exists if participants can be excluded from the intention-to-treat population after random assignment. However, only participants with major protocol violations (ie, prohibited resistance mutations to study drugs or not taking a protease inhibitor-containing regimen at baseline) were excluded from the modified intention-to-treat population in our study. Similarly, participants who were not assigned to switch might feel deprived and be more likely to withdraw from the study. A potential for bias might exist with the use of patient-reported symptoms to assess treatment tolerability. Although we

Panel: Research in context

Systematic review

We searched Medline, Embase, Biosis, and Current Contents for randomised controlled trials of ritonavir-boosted protease inhibitor to integrase inhibitor switch in virologically suppressed HIV-infected patients using the search terms "elvitegravir" or "vitekta, raltegravir" or "isentress, dolutegravir" or "tivicay, HIV integrase inhibitor" or "integrase strand transfer inhibitor, HIV protease inhibitor, switch, and simplification". We included only reports published in English up to March 25, 2014. Excluding reviews, we identified two reports.[6,7] The first report[6] was of two phase 3, randomised, double-blinded clinical trials (SWITCHMRK 1 and 2) in which 707 virologically suppressed patients on lopinavir and ritonavir in combination with two nucleoside or nucleotide reverse transcriptase inhibitors were randomly assigned (1:1) to either switch to raltegravir or to continue on the baseline regimen. Switching to raltegravir resulted in improved fasting lipid parameters, but the efficacy results did not establish non-inferiority (as measured by the proportion of patient with an HIV-1 viral load of less than 50 copies per mL at week 24),[6] requiring the data safety monitoring board to recommend early termination of these studies. The second report[7] was of a trial (SPIRAL) in which 273 virologically suppressed patients on a ritonavir-boosted protease inhibitor regimen were randomly assigned (1:1) to either switch to raltegravir or to continue the baseline regimen. The results showed that switching to raltegravir was non-inferior at maintaining virological suppression, with an improvement in lipid profiles noted at week 48. These three switch studies involved participants on a ritonavir-boosted protease inhibitor with various combinations of nucleoside or nucleotide reverse transcriptase inhibitors, with or without non-nucleoside reverse transcriptase inhibitors (with some having had previous virological failure on these treatments) being switched to a twice daily, multitablet integrase inhibitor-based regimen. A history of virological failure on previous antiretroviral therapy was not consistently predictive of virological efficacy on an integrase inhibitor-based regimen in these studies.[6,7]

Interpretation

STRATEGY-PI is being done in parallel with STRATEGY-NNRTI, another fully powered, randomised, open-label, non-inferiority trial to assess the safety and efficacy of switching to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir from a non-nucleoside reverse transcriptase inhibitor in combination with emtricitabine, and tenofovir in virologically suppressed adults with HIV.[29] In both studies, switching to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir was non-inferior to continuing the baseline regimen at maintaining virological suppression at week 48. Coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir was well tolerated and had favourable patient-reported outcomes. The limitations of both studies are similar and stem from the open-label study design, which might have contributed to the larger numbers of discontinuations for non-virological reasons in the comparator groups. The results of these phase 3b switch trials suggest that coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir is a switch option that is effective and well tolerated for virologically suppressed, HIV-infected adults on regimens containing a ritonavir-boosted protease inhibitor or a non-nucleoside reverse transcriptase inhibitor plus emtricitabine and tenofovir who might want to simplify or switch to an integrase inhibitor-based, single-tablet regimen.

recognise that these limitations can be ameliorated by double blinding, it is also true that a double-blinded study design using placebo pills would make it impossible to study the benefits of a regimen simplification strategy that consists of a single tablet. Additionally, we enrolled people taking various different ritonavir-boosted protease inhibitor regimens, which consist of different numbers of pills with once or twice daily dosing; therefore, a double-blinded study with many placebo pills would be an obstacle to enrolment and might lead to high rates of withdrawal. Finally, the well described side-effects and lipid profile of ritonavir and the serum creatinine increase associated with a cobicistat-containing regimen would undermine the effectiveness of double blinding.

Although the primary endpoint showed the statistical superiority of the simplified regimen, this finding is not necessarily clinically significant. The similar rates of virological failure and absence of emergent resistance in both groups suggest that the virological efficacy of these two regimens is similar. Furthermore, the inclusion of several different protease inhibitors in the comparator group limits the power for head-to-head comparison between individual protease inhibitors and the simplified regimen. Lastly, the low number of women in the study restricts definitive assessment of the safety and tolerability of coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir in women.

Most participants in this study enrolled with the goal of simplifying a multitablet regimen to a single-tablet regimen. Findings from studies of regimen simplification strategies have shown that patients prefer to take fewer pills, and results of observational studies suggest that virological and clinical outcomes are better for patients treated with single-tablet regimens than for those on multitablet regimens, even among the most difficult to treat patient population.[24–27] The benefits of a single-tablet regimen include improved adherence, reduced risk of selective non-compliance, and lowered risk of prescription error, all of which might decrease the risk of treatment failure and drug resistance.[28]

Overall, the results of this study support the use of coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir as a switch option in virologically suppressed patients with no history of virological failure who want to simplify their existing ritonavir-boosted protease inhibitor regimen, or who have concerns about the long-term safety and side-effects of their existing regimen (panel).

Contributors

JRA, GP, JG, GDP, JR, and PT enrolled participants and reviewed and interpreted analyses of data. KW, RE, and DP designed the study. KW, RE, DP, and TN oversaw data collection, and KW, RE, and TN analysed data, which were reviewed and interpreted by KW, RE, DP, and TN. JRA and TN wrote the first draft of this report; all authors reviewed and amended the draft report.

Declaration of interests

JRA received a research grant from Gilead Sciences related to this work, and has received consulting fees and speaking honoraria from AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck Sharp & Dohme, Tibotec, Tobira, and ViiV, and grants from Janssen, all unrelated to this work. GP received a research grant from Gilead Sciences related to this work, and has received a research grant from Bristol-Myers Squibb (unrelated to this work), as well as payment for the development of educational materials and speaking honoraria from Abbott Laboratories, Bristol-Myers Squibb, Gilead Sciences, and ViiV (all unrelated to this work). JG received a research grant from Gilead Sciences related to this work, and has received speaking honoraria from AbbVie, Boehringer Ingelheim, Gilead Sciences, and GlaxoSmithKline, all unrelated to this work. GDP received a research grant from Gilead Sciences related to this work, and has received consulting fees, speaking honoraria, and payment for the development of educational materials from Abbvie, Bristol-Myers

Squibb, Gilead Sciences, Janssen Therapeutics, and Merck Sharp & Dohme, all unrelated to this work. JR received a research grant from Gilead Sciences related to this work, and has received consulting fees from Abbvie, Gilead Sciences, Janssen, Merck, Splicos, and ViiV (all unrelated to this work), as well as travel grants and payment for the development of educational materials from Abbvie, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck, Pfizer, and ViiV (all unrelated to this work). PT received a research grant from Gilead Sciences related to this work, and has received consulting fees from GlaxoSmithKline, Merck, Janssen, and AstraZeneca, all unrelated to this work. TN, RE, KW, and DP are employed by and hold stocks in Gilead Sciences.

Acknowledgments

The study was funded by Gilead Sciences. We thank Javier Szwarcberg and Martin S Rhee for their critical review of the report. We also thank Andrew Plummer, Will Garner, Helen Kuo, Yu Ning, Eric Wang, Ting Bai, Sandy Shen, Desiree Benavente, and the STRATEGY-PI study team. Parts of this study were presented at the Conference on Retroviruses and Opportunistic Infections (Boston, MA, USA; March 3–6, 2014).

References

1 Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. US Department of Health and Human Services, 2014. http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf (accessed May 22, 2014).

2 European AIDS Clinical Society. EACS guidelines version 7.0. European AIDS Clinical Society, 2013. http://www.eacsociety.org/Portals/0/Guidelines_Online_131014.pdf (accessed on March 25, 2014).

3 Thompson MA, Aberg JA, Hoy JF, et al. Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral Society–USA Panel. *JAMA* 2012; **308:** 387–402.

4 The DAD Study Group. Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med* 2007; **356:** 1723–35.

5 Boesecke C, Cooper DA. Toxicity of HIV protease inhibitors: clinical considerations. *Curr Opin HIV AIDS* 2008; **3:** 653–59.

6 Eron JJ, Young B, Cooper DA, et al, for the SWITCHMRK 1 and 2 investigators. Switch to a raltegravir-based regimen versus continuation of a lopinavir-ritonavir-based regimen in stable HIV-infected patients with suppressed viraemia (SWITCHMRK 1 and 2): two multicentre, double-blind, randomised controlled trials. *Lancet* 2010; **375:** 396–407.

7 Martinez E, Larrousse M, Llibre JM, et al, for the SPIRAL Study Group. Substitution of raltegravir for ritonavir-boosted protease inhibitors in HIV-infected patients: the SPIRAL study. *AIDS* 2010; **24:** 1697–707.

8 Sax PE, DeJesus E, Mills A, et al, for the GS-US-236-0102 study team. 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. *Lancet* 2012; **379:** 2439–48.

9 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.

10 Wohl D, Cohen C, Gallant JE, et al. Elvitegravir/cobicistat/emtricitabine/tenofovir DF (STB) demonstrates durable efficacy and favorable long-term safety profile versus efavirenz/emtricitabine/tenofovir DF (ATR) at week 144 in treatment-naive HIV patients. 53rd Interscience Conference on Antimicrobial Agents and Chemotherapy; Denver, CO, USA; Sept 10–13, 2013. H-672A.

11 Clumeck N, Molina JM, Henry K, et al. Elvitegravir/cobicistat/emtricitabine/tenofovir DF (STB) has durable efficacy and differentiated safety compared to atazanavir boosted by ritonavir plus emtricitabine/tenofovir DF in treatment-naïve HIV-1 infected patients: week 144 results. 14th European AIDS Conference; Brussels, Belgium; Oct 16–19, 2013. LBPS7/2.

12 Williams I, Churchill D, Anderson J, et al. British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2012. *HIV Med* 2014; **15** (suppl 1)**:** 1–85.

13 Maggiolo F, Ripamonti D, Arici C, et al. Simpler regimens may enhance adherence to antiretrovirals in HIV infected patients. *HIV Clin Trials* 2002; **3:** 371–78.

14 Stone VE, Jordan J, Tolson J, Miller R, Pilon T. Perspectives on adherence and simplicity for HIV-infected patients on antiretroviral therapy: self-report of the relative importance of multiple attributes of highly active antiretroviral therapy (HAART) regimens in predicting adherence. *J Acquir Immune Defic Syndr* 2004; **36:** 808–16.

15 Smith F, Hammerstrom T, Soon G, et al. A meta-analysis to assess the FDA DAVP's TLOVR algorithm in HIV submissions. *Drug Inf J* 2011; **45:** 291–300.

16 US DHSS, FDA, CDER, CBER. Guidance for industry: E9 statistical principles for clinical trials. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, 1998. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073137.pdf (accessed April 29, 2014).

17 US DHSS, FDA, CDER, CBER. Guidance for industry: antiretroviral drugs using plasma HIV RNA measurements—clinical considerations for accelerated and traditional approval. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, 2002. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070968.pdf (accessed March 25, 2014).

18 Chan IS, Zhang Z. Test-based exact confidence intervals for the difference of two binomial proportions. *Biometrics* 1999; **55:** 1202–09.

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

20 Gilead Sciences. COMPLERA (emtricitabine/rilpivirine/tenofovir disoproxil fumarate) tablets, for oral use. US prescribing information. Foster City: Gilead Sciences, 2013. http://www.gilead.com/~/media/Files/pdfs/medicines/hiv/complera/complera_pi.PDF (accessed May 22, 2014).

21 Palella FJ Jr, Fisher M, Tebas P, et al. Simplification to rilpivirine/emtricitabine/tenofovir disoproxil fumarate from ritonavir-boosted protease inhibitor antiretroviral therapy in a randomized trial of HIV-1 RNA-suppressed participants. *AIDS* 2014; **28:** 335–44.

22 German P, Liu HC, Szwarcberg J, et al. Effect of cobicistat on glomerular filtration rate in subjects with normal and impaired renal function. *J Acquir Immune Defic Syndr* 2012; **61:** 32–40.

23 Stray KM, Bam RA, Birkus G, et al. Evaluation of the effect of cobicistat on the in vitro renal transport and cytotoxicity potential of tenofovir. *Antimicrob Agents Chemother* 2013; **57:** 4982–89.

24 Hodder SL, Mounzer K, DeJesus E, et al, for the AI266073 Study Group. Patient-reported outcomes after simplification to a single-tablet regimen of efavirenz, emtricitabine, and tenofovir DF. *AIDS Patient Care STDS* 2010; **24:** 87–96.

25 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.

26 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.

27 Cohen CJ, Meyers JL, Davis KL. Association between daily antiretroviral pill burden and treatment adherence, hospitalization risk, and other health utilisation and costs in a US medicaid population with HIV. *BMJ Open* 2013; **3:** e003028.

28 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.

29 Pozniak A, Markowitz M, Mills A, et al. Switching to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus continuation of non-nucleoside reverse transcriptase inhibitor with emtricitabine and tenofovir in virologically suppressed adults with HIV (STRATEGTY-NNRTI): 48 week results of a randomised, open-label, phase 3b, non-inferiority trial. *Lancet Infect Dis* 2014; published online June 5. http://dx.doi.org/10.1016/S1473-3099(14)70796-0.