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Efficacy and Tolerability of Integrase Inhibitors in Antiretroviral-Naive Patients

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Abstract

Integrase strand transfer inhibitors are a new class of antiretroviral agents recently licensed for the treatment of both naive and experienced HIV-infected patients. They inhibit the catalytic activity of the HIV-encoded enzyme integrase and prevent the integration of the HIV genome into the host cell genome, so slowing the propagation of the infection. Integrase strand transfer inhibitors cause a rapid drop in viral load, exhibit very low drug interactions (except elvitegravir/cobicistat), and have low pill burden and convenient dosing frequency. Drugs in this class have been compared to others in antiretroviral-naive patients with efavirenz and with protease inhibitors. Final results of the STARTMRK trial highlighted the better virologic and immunologic performance of raltegravir over efavirenz/emtricitabine/tenofovir disoproxil co-formulation. Raltegravir was also superior to atazanavir/ritonavir and darunavir/ritonavir in the ACTG 5257 study for the combined virologic/tolerability endpoint. Elvitegravir/cobicistat/emtricitabine/tenofovir was non-inferior to efavirenz/emtricitabine/tenofovir and to atazanavir/ritonavir plus emtricitabine/tenofovir in terms of confirmed virologic response in the GS-US-236-0102 and GS-US-236-0103 studies, respectively. Finally, dolutegravir showed non-inferiority compared to raltegravir in the SPRING-2 study and was superior to efavirenz and darunavir/ritonavir in the SINGLE and FLAMINGO trials, respectively. The aim of this review is to analyze the data on efficacy and safety of integrase strand transfer inhibitors in antiretroviral-naive HIV patients and discuss the strengths and weaknesses of drugs within this class. **(AIDS Rev. 2015;17:171-85)**

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Key words

Integrase inhibitor. Antiretroviral therapy. Naive patient. Efficacy. Safety. Dolutegravir. Raltegravir. Elvitegravir.

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Introduction

Infection with HIV is now a chronic disease, and mortality due to AIDS-related events has dramatically decreased after the introduction of HAART; however, eradication of the virus is not possible with currently available therapies. Until recently, the first-line HAART choice in untreated patients was based on the combination of two nucleoside reverse transcriptase inhibitors (NRTI) as backbone plus a third drug, either a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a ritonavir-boosted protease inhibitor (PI/r), or an integrase strand transfer inhibitor (INSTI). The latter are a new class of antiretroviral agents recently licensed for the treatment of both naive and experienced HIV-infected patients. Agents in this class inhibit the catalytic activity of the HIV-encoded enzyme integrase and prevent the integration of the HIV genome into the host cell genome, so slowing the propagation of the infection. Characteristically, drugs in this class produce a rapid drop in viral load and exhibit low drug interactions (except elvitegravir/cobicistat). The currently available INSTIs, except raltegravir, can be administered once daily. Moreover, elvitegravir and dolutegravir are marketed in some countries as fixed-dose combinations with a NRTI backbone in one tablet given once daily. This is a clear advantage that will promote adherence to therapy and reduce the pill burden.

In this review we analyze the results of the most important trials that have assessed the efficacy and tolerability of all the INSTIs available in antiretroviral-naive HIV-infected persons. We also discuss in detail the strengths and weaknesses of each of these drugs in clinical practice.

Raltegravir

Raltegravir (RAL) was the first approved drug within the INSTI class. It was originally licensed for the treatment of antiretroviral-experienced adults; the license was subsequently extended in September 2009 to include drug-naive patients. Raltegravir is the only INSTI that requires twice-daily dosing. It can be taken with or without food and is currently marketed as a 400 mg oral compressed tablet formulation given twice daily for a total daily dose of 800 mg (Isentress®). Grade 2-4 creatinine kinase laboratory abnormalities have been observed in patients receiving RAL, and there is a warning not to use (or use with caution) the drug in persons with high risk of myopathy or rhabdomyolysis, such as those receiving concomitant medications known to cause it (i.e., statins).

Development of rash mild-to-moderate in severity was observed in antiretroviral-experienced subjects receiving RAL plus darunavir/ritonavir (DRV/r). These rashes did not limit therapy and there were no drug discontinuations due to rash. However, rash that was considered drug-related occurred at similar rates in all the groups of patients receiving RAL plus DRV/r, RAL alone, or DRV/r without RAL. The drug can be used in pregnancy only if the potential benefit justifies the potential risk for the fetus[1].

STARTMRK study

Two studies have unequivocally demonstrated the effectiveness of RAL in drug-naive HIV patients: STARTMRK and ACTG 5257. The STARTMRK study[2-4] was a multicenter, double-blind, randomized, active-controlled, phase III, non-inferiority study. A total of 503 adult antiretroviral therapy (ART)-naive patients without baseline resistance to efavirenz (EFV), tenofovir disoproxil fumarate (TDF), or emtricitabine (FTC) were stratified by screening HIV-1 RNA levels (> 50,000 vs. ≤ 50,000 copies/ml) and viral hepatitis coinfection status. After stratification, patients were randomly assigned (1:1 ratio) to receive RAL or EFV. Although designed as a non-inferiority trial, the STARTMRK analysis determined that the regimen containing RAL would be considered non-inferior to EFV if the lower limit of the 95% confidence interval (CI) was greater than −12%, and superior if the lower limit exceeded zero. Virologic response was defined as two consecutive HIV-1 RNA tests < 50 copies/ml measured at least one week apart. Virologic failure could represent either a non-response at week 24 (or premature discontinuation) or a confirmed rebound ≥ 50 HIV-1 RNA copies/ml. Genotyping was planned to be performed in patients with HIV-1 RNA levels > 400 copies/ml at the time of failure. The primary endpoint of the study was a reduction in HIV-1 RNA to < 50 copies/ml at week 48. Secondary endpoints included the proportion of patients achieving HIV-1 RNA < 50 copies/ml at 96 weeks, as well as achieving < 400 copies/ml and change from baseline in CD4 counts, both measured at 48 and 96 weeks. Pre-specified exploratory endpoints also included the proportion of patients achieving HIV-1 RNA < 50 copies/ml at 240 weeks, as well as changes from baseline in CD4 counts at 240 weeks. Safety was evaluated throughout the study period.

At the study entry, mean plasma HIV-1 RNA for patients was > 100,000 copies/ml (103,205 copies/ml for patients on RAL and 106,215 for those on EFV). The final results of STARTMRK showed that RAL induced a better virologic suppression than EFV, confirmed in exploratory analyses at 192 and 240 weeks, respectively[3,4]. Results at week 48, 96, and 156 also proved the non-inferiority of RAL, although the lower margin was less than zero and therefore did not met the criteria for superiority. In the non-completer (NC) = failure (F) efficacy analysis at week 240, 71% of RAL recipients and 61.3% of EFV recipients had HIV-1 RNA < 50 copies/ml, yielding a significant difference (increment 9.5; 95% CI: 1.7-17.3). Pre-specified sensitivity analysis at week 240 confirmed the non-inferiority of RAL to EFV and was consistent with a superiority of RAL over EFV demonstrated by the primary NC = F approach. Time to achieve virologic response was significantly shorter in the RAL group than in the EFV group (log rank, p = 0.001). In patients experiencing virologic failure, comparable time to loss of virologic response was observed with each regimen. Mean (95% CI) changes from baseline CD4 counts at week 240 were 374 and 312 cells/mm^3 in the RAL and EFV groups, respectively. *Post hoc* analysis of virologic suppression rates to < 50 HIV-1 RNA copies/ml also confirmed the non-inferiority of RAL versus EFV using either a six-week or 12-week window around the scheduled week 240 visit. The snapshot analysis with a window of ± six weeks did not demonstrate superiority, most likely because of the exclusion of eight patients falling outside the window compared with the protocol-specified NC = F analysis. Another snapshot analysis using a ± 12 weeks window was also performed at week 240. This time the analysis was consistent with both the non-inferiority and the superiority of RAL compared with EFV.

Subgroup analysis at week 240 demonstrated consistent virologic and immunologic treatment effects between groups across key pre-specified demographic and baseline prognostic factors, including gender, age, race, HIV-1 RNA levels (≤ vs. > 100,000 copies/ml), CD4 counts (≤ vs. > 200 cells/mm^3), HIV-1 subtype (B versus non-B clades), and hepatitis B virus (HBV) and/or C (HCV) co-infection.

Cumulatively through week 240, a total of 114 patients experienced virologic failure, including 23 of 55 RAL recipients and 20 of 59 EFV recipients with HIV-1 RNA > 400 copies/ml, allowing virus amplification for resistance. Raltegravir-resistant virus was demonstrated in four of the 23 patients in the RAL group; in three of these four cases the viruses had dual RAL and FTC resistance but remained sensitive to TDF. Emtricitabine resistance was detected in three additional cases (including one patient with RAL-susceptible virus and two other patients where the integrase gene was not amplified). Efavirenz-resistant virus was demonstrated in 10 of the 17 patients in the EFV group; the viruses were also FTC-resistant but susceptible to TDF in three of these 10 cases. Resistance to both FTC and TDF was found in one case. In two additional EFV recipients, only FTC resistance was detected. During the interval from week 192 to 240, seven additional patients (three RAL recipients and four EFV recipients) met the protocol definition for virologic failure. Resistance was not detected to any drugs of the regimen in all three RAL failures, whereas isolated EFV resistance was detected in the three evaluable EFV failures[3,4].

Through 240 weeks, there was a low incidence of drug-related adverse events (AE) of moderate-to-severe intensity that occurred in ≥ 2% of patients treated with RAL. These AEs as compared to EFV were insomnia (4% in both arms), headache (4 vs. 5%), nausea (3 vs. 4%), fatigue (2 vs. 3%), and dizziness (2 vs. 6%). Moderate reactions were defined as discomfort enough to cause interference with usual activity. Severe reactions were defined as incapacitating with inability to work or do usual activity. Patients on RAL also had a lower treatment discontinuation rate due to clinical AEs versus patients on EFV (5 vs. 10%, respectively; p = 0.023). Additionally, RAL had less effect on lipids (total cholesterol, low-density lipoprotein cholesterol [LDL-C] and high-density lipoprotein cholesterol [HDL-C]) and triglycerides fasting serum lipids[3]. The STARTMRK team concluded that in this exploratory analysis of combination therapy with FTC/TDF in treatment-naive patients at week 240, HIV-1 RNA suppression rates and CD4 count increases were significantly higher in RAL than EFV recipients. Over the entire study, fewer patients experienced neuropsychiatric and drug-related AEs in the RAL group than in the EFV group. Based on better virologic and immunologic outcomes after 240 weeks, RAL plus FTC/TDF seemed to have superior efficacy compared with EFV/FTC/TDF[4].

ACTG 5257 study

The ACTG 5257 study[5,6] was a multicenter, randomized, open label, 96-week study on ART-naive patients initiating HAART with three different third agents. The trial was conducted by the AIDS Clinical Trial Group (ACTG), a leading network of independent research in

HIV/AIDS in more than 1,800 adult ART-naive patients with HIV-1 RNA > 1,000 copies/ml randomly assigned (1:1:1 ratio) to receive RAL, atazanavir/ritonavir (ATV/r) or DRV/r, each with the fixed-dose combination of FTC plus TDF. The study population was stratified based on HIV-1 RNA values (< or > 100,000 copies/ml) and CD4 cell counts (< or > 200/mm^3) at baseline. The value of the ACTG 5257 study, other than the independence of the research team, comes from the fact that patients enrolled had a profile very similar to that seen in daily clinical practice. In ACTG 5257, first-line RAL proved superior to ATV/r or DRV/r in an endpoint combining virologic efficacy and safety (ATV/r was inferior to RAL and DRV/r in a tolerability endpoint, and DRV/r was superior to ATV/r in the combined efficacy/safety endpoint). The study was designed on a hypothesis of equivalence for the three groups, with 90% power to define any pairwise comparison. Equivalence meant a 97.5% CI entirely within ± 10% in the pairwise difference in 96-week cumulative incidence. Superiority required the upper limit of the 97.5% CI to be greater than 10% and the lower limit greater than zero. The primary objective of the ACTG 5257 was to demonstrate the equivalence of the three regimes as to virological efficacy and tolerability over 96 weeks. The trial had three endpoints: time to virologic failure, defined as time from entry to a confirmed viral load > 1,000 copies/ml from week 16 to before week 24, or > 200 copies/ml at or after week 24; time to toxicity failure, defined as time from entry to discontinuation of one of the three major study drugs for toxicity and a combined virologic/tolerability endpoint. The ACTG 5257 also had two important metabolic objectives: to compare the impact of the study regimens on fasting plasma lipid and glucose levels and to detect an association between plasma ritonavir (RTV) exposure and lipid levels. This analysis involved 1,809 eligible participants; of these, 1,797 with confirmed baseline fasting samples and clinical measures[7]. Baseline metabolic characteristics and lipid measures were well balanced between the arms. Mean age was 37 years; 24% of participants were women; ethnicity was 42% black, 36% white, and 22% Hispanic. Median CD4 count was 308/mm^3, although 30% had < 200 cells/mm^3. Median viral load stood at 4.6 $\log_{10}$ copies/ml, although 30% had > 100,000 copies/ml. Of the participants, 21% had evidence of metabolic syndrome at study entry, 6% were taking lipid-lowering agents, and 4% were on hypoglycemic therapy[4,5]. Approximately 8% of patients were lost to follow-up over two years, with 92% of patients in the 96-week analysis. Overall, the study performed better than the projections, with lower rates of virological failure (25 vs. 16%) and tolerability discontinuations (10 vs. ~7%) and less loss-to-follow-up (12 vs. 5%) in the projected versus actual rates, respectively. Atazanavir/r, RAL, and DRV/r proved equivalent in time to virologic failure at week 96. Viral suppression to < 50 copies/ml was achieved by 88, 94, and 89% (intent to treat [ITT] analysis, tolerability change allowed) and 63, 80, and 73% (ITT analysis, off-ART = failure), respectively. In pairwise comparisons, equivalence was demonstrated for the three regimens: ATV/r vs. RAL (difference 3.4%; 97.5% CI: –0.7 to 7.4%); ATV/r vs. DRV/r (difference –2.2%; 97.5% CI: –6.7 to 2.3%), and DRV/r vs. RAL (difference 5.6%; 97.5% CI: 1.3-9.9%). Approximate CD4 increase was similar between arms (+284, IQR 270, 300), though slightly non-statistically lower with DRV/r (+256, IQR 240, 271). Cumulative incidence of virologic failure at 96 weeks was 13% with ATV/r, 10% with RAL, and 15% with DRV/r. Among people with virologic failure, nine of 75 ATV/r isolates sampled (12%) had any detectable resistance mutation, as did 18 of 65 RAL isolates (28%), and four of 99 DRV/r isolates (4%). Proportions of people assigned to each drug who had virologic failure with resistance were 2.8% for ATV/r, 3.3% for RAL, and 2.0% for DRV/r. Overall 1, 16, and 5% discontinued RAL, ATV/r, and DRV/r, respectively, for toxicity largely due to clinical jaundice and hyperbilirubinemia with ATV/r and gastrointestinal symptoms with both ATV/r and DRV/r. Other discontinuations were similarly distributed across all arms. The primary tolerability endpoint of discontinuation was equivalent between RAL and DRV/r, while the incidence of discontinuation due to tolerability over 96 weeks in the ATV/r group was 13% (97.5% CI: 9.4-16.0) higher than RAL and 9.2% (97.5% CI: 5.5-13.0) higher than DRV/r. In pairwise comparisons of the cumulative incidence to either virologic or tolerability failure, RAL was superior to both ATV/r (largely due to elevated bilirubin) and DRV/r (driven by both virology and differences in gastrointestinal toxicity). In this composite analysis, ATV/r was inferior to both RAL by 15% (97.5% CI: 10-20) and DRV/r by 7.6% (97.5% CI: 2.3-13.0). Darunavir/r was inferior to RAL by 7.5% (97.5% CI: 3.2-12.0). Overall, 49% of the ATV/r toxicity discontinuations were attributed to jaundice or hyperbilirubinemia and 26% to gastrointestinal disorders. Gastrointestinal problems accounted for 44% of DRV/r toxicity discontinuations. Only two people assigned to RAL had gastrointestinal troubles. For the combined virologic failure/tolerability endpoint, RAL was superior to ATV/r (difference 15%;

95% CI: 10-20) and to DRV/r (difference 7.5%; 95% CI; 3.2-12.0), and DRV/r was superior to ATV/r (difference 7.5%; 95% CI: 2.3-13.0). The ACTG investigators noted that virologic differences and toxicity largely explained the superiority of RAL to DRV/r in this analysis[5,6]. Raltegravir produced the most favorable lipid profile compared with ATV/r- or DRV/r-based regimens. In pairwise comparisons, there were no significant differences in the mean change from baseline to all study weeks in any of the lipid measures between the ATV/r and the DRV/r arms. However, each of the RTV-boosted PI arms had greater increases relative to the RAL arm in total cholesterol, triglycerides, non-HDL-C and LDL-C (all $p < 0.001$). From baseline to week 96, the percentage of patients who had taken lipid-lowering agents increased from 5 to 11% in the ATV/r arms, from 6 to 14% in the DRV/r arm, and from 6 to 9% in the RAL group. In pairwise comparisons, larger increases in waist circumference were observed with the RAL arm compared to the DRV/r arm at weeks 48 and 96 (all $p \leq 0.023$), but not compared with the ATV/r arm ($p \geq 0.07$); no other treatment group differences were apparent. The cumulative probability of incident metabolic syndrome by week 96 (~22%) was not different across arms, and there was no apparent relationship between RTV exposure and lipid levels at either weeks 48 or 96[7]. As concluded by the ACTG team, RAL proved superior to both PI arms for the combined virologic/tolerability endpoint, and DRV/r proved superior to ATV/r for this endpoint. In summary, RAL clearly emerged as a potent drug with minimal side effects in previously untreated people; ATV/r suffered in the comparison because of well-known and easily reversed problems like jaundice and high bilirubin, which the investigators made a point of calling "cosmetic hyperbilirubinemia".

In a subset of 328 individuals randomized equally to FTC/TDF plus ATV/r or DRV/r or RAL, the percentage change in body mass density (BMD) was also compared over 96 weeks and it was determined whether baseline levels of inflammation markers and immune activation were independently associated with BMD loss. At week 96, the mean percentage changes from baseline in spine and hip BMD were similar in the PI arms (spine: –4.0% in the ATV/r group vs. –3.6% in the DRV/r group, $p = 0.42$; hip: –3.9% in the ATV/r group vs. –3.4% in the DRV/r group, $p = 0.36$) but were greater in the combined PI arms than in the RAL arm (spine: –3.8 vs. –1.8%, $p < 0.001$; hip: –3.7 vs. –2.4%, $p = 0.005$). In multivariable analysis, higher baseline concentrations of high-sensitivity C-reactive protein, interleukin 6, and soluble CD14 were associated with greater total hip BMD loss, whereas markers of CD4 T-cell senescence and exhaustion ($CD4^+CD28^-CD57^+PD1^+$) and CD4 T-cell activation ($CD4^+CD38^+HLA\text{-}DR^+$) were associated with lumbar spine BMD loss. In conclusion, BMD losses 96 weeks after HAART initiation were similar in magnitude among patients receiving PIs, either ATV/r or DRV/r, but lowest among those receiving RAL. Inflammation and immune activation/senescence before HAART initiation independently predicted subsequent BMD loss[8]. Table 1 summarizes the strengths and weaknesses related to the use of RAL.

Elvitegravir/cobicistat

Elvitegravir (EVG) is a new chemical entity that belongs to the class of HIV-1 INSTIs. Elvitegravir is metabolized via cytochrome P450 (CYP), enzymes of the CYP3A family, and to a lesser extent by UGT1A1; so it is expected that compounds inducing the activity of CYP3A increase the clearance of EVG with a consequent reduction in plasma concentration of the drug and possibly loss of its therapeutic effect. Elvitegravir is not available as a single component and is marketed in fixed combination with FTC/TDF, which represents the backbone of the therapy (Stribild®). The drug must be taken with food and requires the pharmacological boosting of cobicistat (COBI), a potent CYP3A inhibitor that enables its once-daily administration, but can lead to substantial drug interactions with substrates of the latter[9,10]. Elvitegravir was approved by Food and Drug Administration (FDA) in August 2012 for the use both in HIV-1-infected adult naive and ART-experienced patients without known mutations associated with resistance to any of the three antiretroviral agents that make it up. Patients treated with EVG might have an increased risk of developing proximal renal tubulopathy and kidney failure. Rise in serum creatinine concentration has been observed during the first weeks of therapy due to a reversible COBI-related inhibition of the apical transporter MATE-1 involved in active tubular secretion of creatinine. Serum creatinine concentrations remain successively stable over time and there is no damage of glomerular function. However, therapy with EVG/COBI/FTC/TDF cannot be initiated in subjects with creatinine clearance < 70 ml/minute, and its discontinuation is mandatory in case of reduction in creatinine clearance < 50 ml/minute. Furthermore, EVG/COBI/FTC/TDF is not recommended in patients with severe hepatic impairment[9,10]. Notably, it should be remembered that EVG has a lower genetic barrier than the RTV-boosted

Table 1. Advantages and disadvantages of therapy with raltegravir

Advantages	Disadvantages
INSTI with more clinical experience	Administration two times a day
Rapid drop in viral load	Not available as one-tablet once-daily complete regimen
Less CNS side effects compared to EFV. Lower incidence of skin rash and metabolic effects on lipids, kidney, and bones than PI/r	Lower genetic barrier than RTV-boosted PI and dolutegravir. Risks of development of resistance at virologic failure, especially in treatment-experienced patients
Administration with or without food	Inferior to dolutegravir in treatment-experienced patients with HIV-1 RNA levels > 100,000 copies/ml
Better immune recovery compared to EFV	Experience only in combination with FTC/TDF. Limited data for association with ABC/LAM
Low number of drug interactions.	Rare cases of hypersensitivity reaction including Stevens-John syndrome.
No interactions with the second generation anti-HCV DAA agents	Increased risk of myopathy and rhabdomyolysis when used in combination with medication known to cause this condition in patient at increased risk for these events
	Antacids containing metals may decrease absorption of RAL. Never administered together with antacids containing polyvalent cations (Al^{+++}, Mg^{++})

INSTI: integrase strand transfer inhibitor; CNS: central nervous system; EFV: efavirenz; PI/r: ritonavir boosted protease inhibitor; DAA: direct-acting antiviral; RTV: ritonavir; FTC: emtricitabine; TDF: tenofovir disoproxil fumarate; ABC: abacavir; LAM: lamivudine; RAL: raltegravir.

PI and dolutegravir (DTG) so there is a high risk of developing resistance mutations in case of virologic failure.

The efficacy and safety of EVG/COBI/FTC/TDF in ART-naive patients is based on the data of two randomized, double-blind, active controlled trials, GS-US-236-0102 and GS-US-236-0103. In the analysis at 48 weeks, EVG/COBI/FTC/TDF was non-inferior to EFV and ATV/r in terms of percentage of confirmed virologic response.

GS-US-236-0102 study

GS-US-236-0102[11-14] was a randomized, double-blind, double-dummy, active-controlled, phase III study conducted in 700 ART-naive adults with HIV-1 RNA ≥ 5,000 copies/ml, an estimated glomerular filtration rate (eGFR) ≥ 70 ml/minute, and susceptibility of the virus to EFV, FTC, and TDF at screening. Eligible patients were randomized in a 1:1 ratio to receive either EVG/COBI/FTC/TDF or EFV/FTC/TDF with matching placebo tablets. Primary endpoint was the proportion of patients in the ITT population with HIV-1 RNA < 50 copies/ml at week 48 and was assessed with a pre-specified non-inferiority margin of 12% according to snapshot analysis as defined by the FDA[11]. The difference, weighted by baseline HIV-1 RNA stratum, for response rate and its 95% CI were calculated based on stratum-adjusted Mantel-Haenszel proportions. The snapshot analysis was also conducted in subgroups. At baseline, the mean HIV-1 RNA level was 4.75 $\log_{10}$/ml in the EVG/COBI/FTC/TDF arm, and 4.78 $\log_{10}$/ml in the EFV/FTC/TDF group; mean CD4 cell counts were 391 and 382 cells/mm^3, respectively. Results from the primary efficacy analysis demonstrated that EVG/COBI/FTC/TDF was non-inferior to EFV/FTC/TDF after 48 weeks of therapy. Based on the FDA-defined snapshot analysis, 87.6% of subjects in the EVG/COBI/FTC/TDF group and 84.1% in the EFV/FTC/TDF group had virologic success (ITT analysis set; difference 3.6%; 95% CI: –1.6 to 8.8%). Sensitivity analysis to evaluate the effects of study drug discontinuations not related to virologic response and late discontinuations also demonstrated the superiority of EVG/COBI/FTC/TDF. Subgroup analysis (i.e., age, sex, race, baseline HIV-1 RNA level, and baseline CD4 cell count) based on the FDA-defined snapshot analysis revealed high and generally comparable rates of virologic success with those observed for the overall study population. The FDA-defined time to loss of virological response (TLOVR) analysis results confirmed the comparable rates of virologic response between the two groups, with 85.9% of subjects in the EVG/COBI/FTC/TDF group and 83.2% of subjects in the EFV/FTC/TDF group that

achieved and maintained HIV-1 RNA values < 50 copies/ml through week 48 (difference 2.7%; 95% CI: –2.6 to 8.1%). The percentage of patients with HIV-1 RNA < 50 copies/ml at week 48 using missing = failure (M = F) and missing = excluded (M = E) methods were also similar between treatments. The mean increase in CD4 cell count was similar between the EVG/COBI/FTC/TDF and EFV/FTC/TDF groups; however, it was numerically higher in the EVG/COBI/FTC/TDF arm at all time points[12]. The non-inferior efficacy of EVG/COBI/FTC/TDF compared to EFV/FTC/TDF was confirmed at week 96 (margin 12%) using the week 96 data set (88 vs. 84%; difference 3.6%; 95% CI: –1.6 to 8.8)[13]. Results of virologic outcome using other efficacy endpoints at week 96 were the following: snapshot (per protocol), EVG/COBI/FTC/TDF 96.9% versus EFV/FTC/TDF 96.3% (difference: 0.7%; 95% CI: –2.4 to 3.7); time to loss of virologic response (ITT) 79.3 vs. 77.3% (difference 2.1%; 95% CI: –4.0 to 8.2); M = F (ITT) 86.2 vs. 83.2% (difference 3.0%; 95% CI: –2.4 to 8.3). The efficacy of EVG/COBI/FTC/TDF relative to EFV/FTC/TDF was consistent across pre-specified subgroups[13]. Proportions of patients discontinuing drugs for AEs did not differ substantially between the two groups: at week 48, 3.7% of people in the EVG/COBI/FTC/TDF group versus 5.11% in the EFV/FTC/TDF group dropped the treatment for AEs. The most frequent AEs reported were nausea (more common with EVG/COBI/FTC/TDF than with EFV/FTC/TDF, 20.7 vs. 13.3%) and dizziness (6.6 vs. 24.4%); abnormal dreams, insomnia, and rash were less common. The percentage of AE-related drug discontinuations remained similar between the groups (4.9 vs. 6.8%, respectively) through week 96, with only minimal increases in frequency in the two groups since week 48. Nausea remained more frequent in the EVG/COBI/FTC/TDF group (21.8 vs. 15.1%), but only a few patients from each group reported new nausea since week 48 (1.1 vs. 1.4%) and none of them discontinued study drugs due to this problem. Also, the rates of prespecified neuropsychiatric events and rash continued to be lower in the EVG/COBI/FTC/TDF group (46.6 vs. 65.9%, p < 0.001, and 21.3 vs. 30.7%, p = 0.006, respectively). Overall, study drug discontinuation due to neuropsychiatric events occurred in 0.9% of receiving EVG/COBI/FTC/TDF versus 2.8% in the EFV/FTC/TDF group; drug discontinuation due to rash occurred in 0 vs. 1.1%, respectively. Less than 1% of patients discontinued EVG/COBI/FTC/TDF due to renal events after week 48. Serum creatinine concentration was consistent with reversible inhibition; COBI-related tubular creatinine secretion by week 48 significantly increased more in the EVG/COBI/FTC/TDF group than in the EFV/FTC/TDF group (p < 0.001). Moreover, no patients had laboratory findings of proximal tubulopathy[13]. After 144 weeks of therapy by snapshot analysis, virologic response was maintained in 80% of the EVG/COBI/FTC/TDF subjects versus 75% of the patients receiving EFV/FTC/TDF[14]. Virologic success was similar for participants with high baseline viral load (77 vs. 78%) and CD4 counts ≤ 350/mm^3 (76% for both). Resistance was present in 3 and 4% of patients, respectively, and no new resistance emerged after week 96 in subjects receiving EVG/COBI/FTC/TDF. Drug discontinuation due to AEs was low and similar in both EVG/COBI/FTC/TDF and EFV/FTC/TDF arms (6 vs. 7%, respectively). Four and two additional patients discontinued treatment after week 96. Median changes in serum creatinine at week 144 were similar to those at week 48 and 96; renal discontinuation occurred in 8 vs. 0 patients, but no cases of proximal tubulopathy were reported. Neuropsychiatric disorders and rash remained lower in the EVG/COBI/FTC/TDF arm (51 vs. 68%, p = < 0.001, and 25 vs. 32%, p = 0.044, respectively). Finally, EVG/COBI/FTC/TDF treatment was associated with smaller median increases in total cholesterol and LDL-C (p = 0.007) and similar increases in triglycerides and total cholesterol to HDL-C ratio[14].

GS-US-236-0103 study

GS-US-236-0103[15-17] was a randomized, double-blind, active-controlled international phase III trial designed to evaluate the efficacy, safety, and tolerability of EVG/COBI/FTC/TDF compared to ATV/r in ART-naive adults with an estimated eGFR rate ≥ 70 ml/minute and susceptibility to ATV, FTC, and TDF at screening. Eligible patients (n = 715) were stratified by HIV-1 RNA (≤ or > 100,000 copies/ml) and randomized in a 1:1 ratio to either EVG/COBI/FTC/TDF or ATV + FTC/TDF. Primary endpoint was the proportion of patients in the ITT population with HIV-1 RNA < 50 copies/ml at week 48, according to snapshot analysis as defined by the FDA, with a 12% non-inferiority margin. Other endpoints included treatment differences by subgroup, achievement and maintenance of HIV-1 RNA < 50 copies/ml (based on the FDA defined TLOVR algorithm), proportion of patients with HIV-1 RNA < 50 copies/ml when treating M = F and M = E, change in HIV-1 RNA from baseline, and change in CD4 cell count from baseline. Patients on EVG/COBI/FTC/TDF had a mean HIV-1 RNA level of 4.88 $\log_{10}$/ml and a mean CD4

count of 364 cells/mm^3; those in the ATV/r arm had a mean HIV-1 RNA level of 4.86 $\log_{10}$/ml and a mean CD4 count of 375 cells/mm^3. Overall for both arms, 41% of patients had HIV-1 RNA > 100,000 copies/ml and 13% had a CD4 count ≤ 200 cells/mm^3. At week 48, EVG/COBI/FTC/TDF was non-inferior to ATV/r + FTC/TDF: 87.6 vs. 84.1% of patients had HIV-1 RNA < 50 copies/ml at week 48 (difference 3.6%, 95% CI: –1.6 to 8.8)[15]. Proportions of patients discontinuing drugs for AEs did not differ substantially among the two groups. Nausea (more common with EVG/COBI/FTC/TDF than with ATV/r + FTC/TDF) and dizziness were the most common AEs. Serum creatinine concentration significantly increased more in the EVG/COBI/FTC/TDF group than in the ATV/r + FTC/TDF arm ($p < 0.001$)[15]. The non-inferior efficacy of EVG/COBI/FTC/TDF to ATV/r + FTC/TDF was confirmed at week 96 (margin: 12%) using the week 96 dataset (89.5 vs. 87.0%, difference 2.7%; 95% CI: –2.1 to 7.5)[16]. The percentage of virologic failure was similar in the two groups both at week 48 (5.4 vs. 5.1%) and 96 (6.8 vs. 7.3%). Reasons for virologic failure and lack of virologic data in the week 96 analysis were balanced between the treatment groups. The recovery of CD4 cell count persisted through week 96, with mean (SD) increases, from baseline, of 256 cells/mm^3 in the EVG/COBI/FTC/TDF group and 261 cells/mm^3 in the ATV/r + FTC/TDF group[16]. At week 96, the 95% CI was zero for all subgroups, suggesting no treatment difference according to age, sex, race, baseline HIV-1 RNA level, baseline CD4 cell count, or study-drug adherence rate. The overall safety findings at 96 weeks were generally consistent with those observed at week 48[15,16]. Through week 96, 4.2% of participants discontinued study drug due to AEs in EVG/COBI/FTC/TDF versus 5.9% of those treated with ATV/r + FTC/TDF); two and three additional subjects from each group, respectively, discontinued study drug due to AEs since week 48. Rates of study drug discontinuation due to renal events remained low and similar through week 96 (0.8 vs. 0.6%), including one subject in each group since week 48. Neither subject had evidence of proximal tubulopathy. Serious AEs were reported for a slightly lower percentage of subjects in the EVG/COBI/FTC/TDF group (9.6%) than in the ATV/r + FTC/TDF group (14.1%). There were small increases in the rates of most AEs in both groups since week 48. Differences of > 5% in ATV/r + FTC/TDF versus EVG/COBI/FTC/TDF, respectively, included scleral icterus (14.4 vs. 0.6%); diarrhea, (31.1% vs. 24.9%), and back pain (4.4 vs. 11.6%). A difference in fasting metabolic assessments was observed between treatment groups at 96 weeks. Renal laboratory assessments showed changes consistent with COBI's expected effect on eGFR rates, which were seen as early as week 2-4, and appeared to stabilize after week 24 through week 96. Median increases from baseline in serum creatinine at week 96 were similar to those at week 48[15,16]. High rates of virologic success in both groups were maintained at week 144[17]. Seventy-nine percent of patients with EVG/COBI/FTC/TDF and 75% of those in the ATV/r + FTC/TDF arm had viral load < 50 copies/ml (difference: 3.1%, 95% CI: –3.2 to 9.4). The 95% CI for the treatment difference in virologic response in the subgroup analysis contained zero for all subgroups, suggesting no therapy difference according to age, sex, race, baseline HIV-1 RNA level, and baseline CD4 cell count, except for the study adherence rate, where subjects with ≥ 95% adherence had a treatment difference of 6.8% (95% CI: –0.1 to 13.6) favoring EVG/COBI/FTC/TDF. Development of resistance to one or more components of the EVG/COBI/FTC/TDF regimen was infrequent. Overall, 2.3% of subjects in the EVG/COBI/FTC/TDF group failed with emergence of resistance mutations versus 0.6% in the ATV/r + FTC/TDF group through week 144. The overall safety findings through week 144 were generally consistent with those observed through week 96[16,17]. Serious AEs (14.4 vs. 16.0%) and rates of AEs leading to discontinuation (5.9 vs. 8.5%) were similar for the two groups of patients. Renal laboratory assessments showed changes consistent with COBI's expected effects on eGFR, which remained stable through week 144; drug discontinuation due to renal events remained low and similar through week 144 (1.9 vs. 2.3%). There were no cases of renal tubulopathy among people taking EVG/COBI/FTC/TDF, but three cases among people taking ATV/r + FTC/TDF. Median increases from baseline in serum creatinine at 144 week were similar to week 96 in the two groups. At 144 weeks, a lower proportion of people randomized to EVG/COBI/FTC/TDF than to ATV/r + FTC/TDF had diarrhea (26.8 vs. 33.2%; $p = 0.03$). The mean percent decrease from baseline in spine and hip BMD were –1.43 vs. –3.68% and –3.77 vs. 2.83% in the two arms, respectively ($p = 0.23$); fractures occurred in 2.8% of patients receiving EVG/COBI/FTC/TDF and in 5.4% of those treated with ATV/r + FTC/TDF ($p = 0.13$). All fractures in the EVG/COBI/FTC/TDF were trauma-related. Finally, there were no significant treatment differences from baseline through week 144 in change of median fasting LDL-C, HDL-C, or total cholesterol to fasting HDL-C ratio between the two arms[17]. Table 2

Table 2. Advantages and disadvantages of therapy with elvitegravir/cobicistat plus emtricitabine/tenofovir disoproxil fumarate

Advantages	Disadvantages
Administration once a day	Not available as a single component. It requires the pharmacological boosting of cobicistat, potent CYP3A inhibitor. This can lead to substantial drug interactions if EVG/COBI/FTC/TDF is co-administered with other drugs mainly metabolized by CYP3A
Rapid drop in viral load	EVG/COBI/FTC/TDF cannot be used in people with eGFR < 70 ml/minute (stop the treatment if eGFR < 50 ml/minute)
Available as one-tablet once-daily complete regimen with FTC plus TDF	Increased risk of renal failure and proximal tubulopathy
Lower hyperlipidemic effects than PI/r	Lower genetic barrier than RTV-boosted PI and dolutegravir. Risks of development of resistance at virologic failure
Can be used with sofosbuvir. Drug interactions for daclatasvir are generally moderate and can be managed with dose adjustments	Antacids reduce plasma concentrations of EVG/COBI not due to changes in gastric pH but because of local formation of complexes in the gastrointestinal tract. An interval of at least 4 hours is recommended between the administration of EVG/COBI and antacids
	Must be administered with food
	Cobicistat has pharmacokinetic interactions with the second-generation anti-HCV DAA agents but not sofosbuvir. Drug interactions for daclatasvir are generally moderate
	Clinical experience still limited

FTC: emtricitabine; TDF: tenofovir disoproxil fumarate; PI/r: ritonavir boosted protease inhibitor; EVG: elvitegravir; COBI: cobicistat; eGFR: estimated glomerular filtration rate; RTV: ritonavir; DAA: direct-acting antiviral.

summarizes the strengths and weaknesses related to the use of EVG/COBI/FTC/TDF.

Dolutegravir

Dolutegravir (Tivicay®) was recently licensed. The third drug of the INSTI class, dolutegravir (DTG) is a powerful new-generation INSTI, indicated both in ART-naive and experienced patients. The mutational profile of DTG allows its use even in patients already treated with RAL or EVG and having become resistant to these drugs, although in these patients the dose of DTG must be doubled (50 mg twice daily). The effectiveness of DTG is significantly reduced in patients with the Q148 mutation associated with two or more secondary mutations. Dolutegravir has a higher genetic barrier than RAL and EVG, comparable to PI/r, and a favorable pharmacokinetic profile, with a plasma half-life of approximately 14 hours; this supports the once-daily 50 mg dose without pharmacological boosting. No relevant inhibition or induction of cytochrome CYP3A4 or food effect has been reported, suggesting low potential drug interactions. In the studies published to date, patients treated with DTG showed an increase in serum creatinine concentration, neither clinically significant nor progressive, due to the inhibition of the organic cation transporter-2 (OCT-2) involved in the renal excretion of creatinine. An increase in serum liver transaminases has also been reported in HBV- or HCV-coinfected patients receiving DTG, but it was generally lower than that observed with RAL and EFV and similar to that described with DRV/r[18-21].

The effectiveness of DTG in ART-naive patients has been demonstrated based on the data at 96 weeks of two randomized, double-blind, active-controlled studies (SPRING-2 and SINGLE) and on the results of an open label study (FLAMINGO). Overall, these studies involved more than 2,100 patients and had a primary objective to demonstrate the non-inferiority of DTG plus FTC/TDF or plus abacavir/lamivudine (ABC/LAM) with respect to a comparator as RAL plus two NRTI in the SPRING-2 study, EFV/TDF/FTC in the SINGLE study, and DRV/r plus two NRTI in the FLAMINGO study.

SPRING-2 study

SPRING-2[22,23] was the first randomized, double-blind, active-controlled, non-inferiority study in HIV-1 ART-naive patients to compare the efficacy and safety of two regimens containing INSTIs. A total of 822 ART-naive

adults with HIV-1 RNA concentrations of ≥ 1,000 copies/ml were randomly assigned (1:1) to receive either DTG or RAL. Study drugs were given with co-formulated FTC/TDF or ABC/LAM. Randomization was stratified by screening HIV-1 RNA (≤ or > 100,000 copies/ml) and NRTI backbone. Primary endpoint was the proportion of participants with HIV-1 RNA < 50 copies/ml at 48 weeks, with a 10% non-inferiority margin. Main secondary endpoints were changes from baseline in CD4 cell counts, incidence and severity of AEs, changes in laboratory parameters, and genotypic or phenotypic evidence of resistance. At week 8, 85% of patients on DTG and 79% on RAL achieved HIV-1 RNA < 50 copies/ml; at week 48, these percentages were 88% on DTG and 85% on RAL (difference 2.5%; 95% CI: –2.2 to 7.1). This meets the non-inferiority criterion. Secondary efficacy analysis and virologic outcome by baseline stratification supported the primary results by showing non-inferiority of DTG. The number of patients who achieved the primary endpoint was similar between subgroups in analysis that combined high and low HIV-1 RNA strata and backbone NRTI. The CD4 cell count increased from baseline to week 48 in both treatment groups by a median of 230 cells/mm^3 (IQR: 128-338 in the DTG group, 139-354 in the RAL group). Similar rates of virologic response across subgroups stratified by baseline CD4 cell counts were observed; however, a more favorable numerical response was shown in patients in the DTG group, with baseline CD4 cell count of < 350 cells/mm^3 (86% of patients given DTG vs. 80% of those given RAL), or baseline CD4 count < 200 cells/mm^3 (78 vs. 68%). Fewer patients had protocol-defined virologic failure in the DTG group than in the RAL arm, and no patient on DTG had treatment-emergent integrase or NRTI resistance. Over 48 weeks, both study drugs had similar safety profiles, similar rates of all grade AEs, and low rates of events leading to drug discontinuation (2% in each group). The most frequent reported AEs (usually ranging from grade 1-2 in severity) were nausea (14 vs. 13%), headache (12 vs. 12%), nasopharyngitis (11 vs. 12%), and diarrhea (11% in each group). Also, rates of serious AEs were similar between treatment groups. No clinically significant changes were noted over time in the fasting lipid profile in either group. Increases in serum creatinine were reported in both groups by week 2 but remained stable to week 48. Similar numbers of patients in each treatment group had maximum treatment-emergent increases in alanine aminotransferase (ALT) of at least three-times or more the upper limit of normal (ULN); seven cases (five in the DTG group and two in the RAL group) met the liver stopping criteria with ALT values of 10 or more times greater than the ULN[22]. The non-inferiority of DTG versus RAL was confirmed at week 96: 81% of patients on DTG and 76% of patients on RAL maintained virologic success (difference 4.5%; 95% CI: –1.1 to 10.0)[23]. The difference between week 48 and week 96 responses was driven mainly by discontinuations for reasons other than AEs. The proportion of virologic non-response was unchanged for DTG from week 48 to week 96, whereas it rose by 2% for RAL. Secondary efficacy analysis was supportive of the primary results. Analysis of virologic outcomes by baseline viral load or NRTI backbone also supported non-inferiority of DTG to RAL. The proportions of patients with virologic success were similar across CD4 cell count subgroups, although in patients with baseline CD4 count < 350 cells/mm^3, 78% in the DTG group versus 69% in the RAL group had HIV-1 RNA < 50 copies/ml; in patients with baseline CD4 counts < 200 cells/mm^3 these percentages were 71 and 56%, respectively. The CD4 cell counts increased similarly in the two groups (276 cells/mm^3 on DTG, 264 cells/mm^3 on RAL). The proportion of patients with clinically optimum CD4 cell count (i.e. > 500 cells/mm^3) at week 96 was high and similar in both groups, providing further benefit of this INSTI-containing regimen strategy. As noted, at week 96 the exploratory analysis of efficacy in patients with low baseline CD4 cell count showed a higher response rate for DTG than for RAL, confirming the trend observed at week 48. Among participants taking DTG who developed virologic failure, no one developed detectable resistance to any class of anti-HIV therapy. Conversely, among patients on RAL with virologic failure, 6% presented resistance to integrase inhibitors and 21% had HIV that had become resistant to nukes. This all occurred during the first year of the study. In the second year of study, development of detectable resistance mutations to any drug was comparatively uncommon. The safety and tolerability of the two study drugs were similar through the 96 weeks, with a comparable incidence of AEs and a low rate of treatment discontinuation (2% in each group). No participant taking DTG left prematurely because of side effects; however, three patients who were taking RAL had to stop due to side effects. Side effects reported in the second year of the study, usually of mild-to-moderate intensity, were nausea (15% in the DTG group vs. 14% in the RAL group), headache (14 vs. 13%), nasopharyngitis (13 vs. 14%), and diarrhea (14 vs. 13%). Few patients had drug-related serious AEs (< 1 vs. 1%), and few

had AEs leading to discontinuation (2% in each group). Rates of graded laboratory toxic effects were similar in both arms; between weeks 48 and 96, incidence of ALT > 3-times the ULN was low in both groups; only two additional patients (in the RAL group) discontinued therapy for liver toxicity[23]. Overall, the risk of drug-induced liver injury over 96 weeks was similar for DTG and RAL[20,23].

SINGLE NG114467 study

The SINGLE NG114467 study[24-27] was a randomized, double-blind, double dummy, active-controlled, multicenter phase III study conducted in approximately 800 HIV-1-infected ART-naive subjects with viral load > 1,000 copies/ml, to compare efficacy and safety of DTG plus ABC/LAM fixed-dose combination to co-formulated EFV/TDF/FTC. From week 96 to 144, subjects were treated in an open-label extension (original randomization). Eligible patients were randomly assigned (1:1) to receive either DTG or EFV/TDF/FTC. Randomization was stratified by plasma HIV-1 RNA (< vs. > 100,000 copies/ml) and CD4 cell count (< vs. > 200 cells/mm^3) at baseline. In each arm, 14% of participants had CD4 cell counts < 200/mm^3; 31 and 32% of patients with HIV-1 RNA > 100,000 copies/ml were enrolled in the DTG arm and in the EFV/TDF/FTC arm, respectively. The primary endpoint of the study was the proportion of participants with HIV-1 RNA < 50 copies/ml at 48 weeks, with a 10% non-inferiority margin. After 48 weeks, 88% of the patients on DTG and 81% of those receiving EFV/TDF/FTC had HIV-1 RNA < 50 copies/ml, thus meeting the criteria for non-inferiority. Dolutegravir was, however, statistically superior to EFV/TDF/FTC (p = 0.003). The DTG group had a shorter median time to viral suppression than did the EFV/TDF/FTC group (28 vs. 84 days; p = <0.001); the difference was mainly due to the high rate of treatment discontinuation in the EFV/TDF/FTC arm (10 vs. 2%). The DTG arm also showed a better immunological recovery (267 vs. 208 CD4/mm^3; p ≤ 0.0001)[24]. At week 96, DTG maintained the superiority versus EFV/TDF/FTC with respect to snapshot (< 50 copies/ml). Eighty percent of subjects on DTG versus 72% on EFV/TDF/FTC achieved virologic success (p = 0.006)[25]. This difference was again driven by a lower rate of drug discontinuation due to AEs in the DTG arm, which was independent of baseline viral load. In the high viral load subgroup, tolerability advantages were attenuated by reasons unrelated to treatment. Dolutegravir was statistically superior to EFV/TDF/FTC also in CD4 cell count change from baseline. Furthermore, DTG had a more favorable safety and tolerability profile than EFV/TDF/FTC, with a lower rate of central nervous system (CNS) disorders and rash and fewer drug discontinuations due to AEs. In the DTG arm, the rate of liver chemistry elevations was also lower. No major treatment-emergent INSTI or NRTI resistance mutations were detected through 96-weeks with DTG[25]. The long-term superiority of DTG was still confirmed at week 144 when 71% randomized to the DTG regimen and 63% randomized to EFV/TDF/FTC had viral load < 50 copies/ml (difference 8.3%; 95% CI: 2.0-14.6; p = 0.01)[26,27]. Among people who began treatment with viral load > 100,000 copies/ml, the 144-week response rate was 69% in the DTG arm and 61% in the EFV/TDF/FTC arm. Among women, 69% assigned to DTG and 48% assigned to EFV/TDF/FTC had a week-144 virologic success. Among nonwhites, respective 144-week response rates were 71 and 47%. Also, the recovery of CD4 remained higher in the DTG arm through 144 weeks (379 vs. 332; p = 0.003), though this difference may not be clinically meaningful. Four percent of people on DTG versus 14% of those randomized to EFV/TDF/FTC withdrew from the study because of AEs. Rates of psychiatric disorders (6 vs. < 1%), CNS disorders (4 vs. < 1%), skin and subcutaneous tissue disorders (2 vs. < 1%) and gastrointestinal troubles (2 vs. 0) were higher with EFV/TDF/FTC than with the DTG-containing regimen. Protocol-defined virologic failure did not differ between treatment arms (9% with DTG and 8% with EFV/TDF/FTC). Among people genotyped after failure, no integrase inhibitor or nucleoside mutations could be detected in the DTG arm, while nucleoside mutations could be detected in one person and non-nucleoside mutations in six people randomized to EFV/TDF/FTC[26,27].

FLAMINGO (NCT01449929) study

The third study, FLAMINGO (NCT01449929)[28,29], was a 96-week, randomized, open label, active controlled, multicenter, non-inferiority phase III study. In total, 484 ART-naive adults with HIV-1 RNA > 1,000 copies/ml and without primary resistance to NRTIs or protease inhibitors were randomly assigned with a 1:1 ratio to receive DTG or DRV/r plus an NRTI backbone of co-formulated FTC/TDF or ABC/LAM at the investigators' discretion. Randomization was by HIV-1 RNA < vs. > 100,000 copies/ml and NRTI backbone. Study participants had a median age of 34 years, 15% were women, and 28% were nonwhites. One-quarter of patients had

a pre-treatment viral load > 100,000 copies/ml, and median pre-treatment CD4 count stood at a relatively high 395 cells/mm^3. One-third of participants started ABC/LAM. Primary endpoint was the proportion of patients with viral load < 50 copies/ml at week 48 using the FDA snapshot algorithm MSDF (missing, switch or discontinuation = failure). Secondary endpoints included changes from baseline CD4 cell counts, incidence and severity of AEs, changes in laboratory variables, time to virological suppression, and treatment-emergent genotypic or phenotypic evidence of resistance. The non-inferiority margin was set as 12%; non-inferiority of DTG to DRV/r was to be concluded if the lower bound of a two-sided 95% CI for the difference in proportions (DTG-DRV/r) of patients with HIV-1 RNA of < 50 copies/ml was greater –12%. Compared to DRV/r, DTG demonstrated a statistically significant superiority of efficacy. At week 48, 90% in the DTG group versus 83% in the DRV/r arm achieved HIV-1 RNA values < 50 couples/ml (difference 7.1%; 95% CI: 0.9-13.2), establishing the superiority of DTG to DRV/r (p = 0.025)[28]. Dolutegravir also determined a more rapid drop in viral load already at week 8 (87 vs. 31%). Instead, the immune recovery with a median CD4 count increase of 210 cells/mm^3 was similar for both groups. The HIV-1 RNA strata showed a significantly higher treatment difference in patients with high baseline viral load (p = 0.005). Among people with pre-treatment HIV-1 RNA < 100,000, snapshot analysis determined a 48-week sub-50-copy response rate of 88% in the DTG group and 87% in the DRV/r group. Among people with baseline viral load > 100,000, the 48-week sub-50 response rates were 93 and 70%, respectively. Whether a person took ABC/LAM or FTC/TDF did not affect virologic results. As the investigators proposed, the superiority of DTG to DRV/r reflected fewer withdrawals due to AEs and other reasons before week 48 in the DTG arm, and a better DTG response rate among people starting treatment with viral load > 100,000 copies/ml. Four percent of people withdrew from the DRV/r group because of AEs or death, compared with 1% from the DTG arm. Drug-related grade 2 to 4 AEs affected 12% of people in the DRV/r arm and 10% in the DTG arm. Serious AEs were reported more frequently in the DTG group (11%) than in the DRV/r group (5%), but only in one case was the event judged to be drug-related. The most frequent reported AEs (occurring in > 10% of patients and usually of mild-to-moderate intensity) were diarrhea (17 vs. 29%), nausea (16 vs. 18%), headache (15 vs. 10%), and nasopharyngitis. Patients on DTG presented better lipid profile with an average increase of less LDL-C (p ≥ 0.0001). An increase in serum creatinine (not clinically significant) was observed in 4% of patients treated with DTG after two weeks of therapy, but the change remained stable in subsequent weeks. No patient in either group discontinued treatment because of renal events during the study period[28]. Eighty-six percent of participants in the DTG arm and 79% of participants in the DRV/r arm completed the 96-week study[29]. At this time, the proportion of participants with HIV-1 RNA < 50 copies/ml was 80% in the DTG arm versus 68% in the DRV/r arm (difference 12.4%; 95% CI: 4.7-20.2; p = 0.002). Secondary analysis supported primary results: per-protocol (DTG 83% vs. DRV/r 70%; 95% CI: 12.9; 5.3-20.6) and treatment-related discontinuation = failure (98 vs. 95%; 95% CI: 3.2; –0.3 to 6.7). As at week 48, the difference between arms was most pronounced in participants with high baseline viral load (82 vs. 52%) and in the FTC/TDF stratum (79 vs. 64%). Consistent responses were seen in the ABC/LAM stratum (82 vs. 75%). Six participants (DTG two, none post-week 48; DRV/r four, two post-week 48) experienced protocol-defined virologic failure: none had treatment-emergent resistance to study-drugs. The most frequent drug-related AEs reported at week 96 were diarrhea (significantly more common on DRV/r at 24% than on DTG 10%), nausea, and headache. More participants had grade 2 fasting LDL toxicities on DRV/r than with DTG (22 vs. 7%; p < 0.001); finally, mean changes in creatinine for patients receiving DTG (~ 0.18 mg/dl) were stable through week 96[29]. Table 3 summarizes the strengths and weaknesses of DTG in clinical practice.

Integrase strand transfer inhibitors between present and future

Both EVG and DTG still have limited clinical experience; however, usage experience will increase rapidly over time. Integrase strand transfer inhibitors were originally designed for the treatment of drug-resistant HIV patients; today the INSTI-based regimens are recommended by all International Guidelines for first-line therapy in untreated subjects because of their high virologic efficacy, excellent safety, tolerability profiles, and (with RAL and DTG) low number of drug interactions[30-33]. Four INSTI-based regimens (except RAL plus ABC/LAM) and the DRV/r plus FTC/TDF association are the only schemes recommended for the treatment of naive HIV adults in the last edition of the Antiretroviral Guidelines for Adults and Adolescents of Department

Table 3. Advantages and disadvantages of therapy with dolutegravir

Advantages	Disadvantages
Administration once a day with or without food	Inhibition of the OCT-2 transporter involved in the renal excretion of creatinine with increase in serum creatinine levels without interfering with the glomerular function
Virological power with rapid drop in viral load	Substrate UGB: possible drug interactions
Marketed also in some countries as one-tablet once-daily complete regimen with ABC/LAM	Increased risk of renal failure and proximal tubulopathy
Virological efficacy demonstrated regardless of the nucleoside backbone	Antacids including the magnesium/aluminum and calcium must be administered well separated in time from taking dolutegravir (at least 2 hours after or 6 hours before) (risk of reduced absorption) Never give together with multivitamin containing minerals (risk of reduced absorption)
Non-inferior to RAL. More effective than EFV and DRV/r	Double the dose in patients treated with rifampicin. In presence of resistance mutations in the integrase gene avoid the association
High genetic barrier with lower incidence of mutations at virologic failure than NRTI, RAL, and EVG; comparable to RTV-boosted PI	Significant interference with metformin, which concentrations increase by inhibition of the transporter OCT-2. You may need a dose adjustment of metformin
Better lipid profile than EFV and DRV/r	Clinical experience still limited
Minimal interactions with cytochrome CYP3A4. No dose adjustment of oral contraceptives required when administered with DTG	
Can be used with all second generation anti-HCV DAA	

ABC: abacavir; LAM: lamivudine; RAL: raltegravir; EFV: efavirenz; DRV: darunavir; NRTI: nucleoside reverse transcriptase inhibitor; DTG: dolutegravir; DAA: direct-acting antiviral; UGB: Upper gastrointestinal bleeding; OCT: organic cation transporter.

of Health and Human Services (DHHS. April 2015)[34]. However, these very restrictive indications have raised many doubts and questions because the results, influenced by the superiority of INSTI, are sometimes related to high discontinuation rates of competitors rather than pure virological failure.

The large-scale use of RAL in naive patients has long been delayed by the cost of therapy compared with other equally effective and less expensive systems (EFV/FTC/TDF or rilpivirine/FTC/TDF co-formulated). Its cost reduction has removed this obstacle, but there remains the Damocles' sword of twice-daily administration and the lack of a one-tablet once-daily complete regimen that includes RAL. There is, however, the suggestion that increasing the dose of RAL may result in a feasible once-daily regimen. A small open-label, multiple-dose, randomized, three-period, three-treatment, crossover study performed on 24 healthy male and female adult subjects has characterized the steady state pharmacokinetic (PK) profile of 1,200 mg doses of RAL to support once-daily administration. In this study, subjects received either 1,200 mg once daily of the oral compressed tablet formulation (three 400 mg tablets), 1,200 mg once daily of a reformulated RAL formulation (two 600 mg tablets), or 400 mg twice daily of the oral compressed tablet formulation for five days. Results from this study show that 1,200 mg of either formulation represents a once-daily option that is very likely to achieve non-inferiority to twice-daily RAL. These data in combination with other completed phase I studies and PK viral dynamics modeling and simulation will be utilized to further assess whether once-daily dosing with these formulations would have a high likelihood of exerting antiviral activity similar to that of the current twice-daily regimen and provide insights into the feasibility of these formulations for once-daily administration[35].

Paradoxically, the availability of EVG only in one-tablet once-daily complete regimen with the PK enhancer (COBI) and FTC/TDF is its Achilles heel. So, if the patient develops side effects or renal toxicity, you cannot use the drug alone and you need to change the whole regime. Moreover, co-administration of EVG/COBI with drugs mainly metabolized by CYP3A (such as atorvastatin amiodarone, quinidine, cisapride, pimozide, alfuzosin, and sildenafil for pulmonary arterial

hypertension) could increase plasma concentrations of these drugs, determining severe and/or life-threatening reactions[10]. Cobicistat also has interactions with the second-generation anti-HCV direct-acting antiviral (DAA) agents, but not sofosbuvir[36]. In the near future, EVG/COBI will be available in co-formulation with the new tenofovir alafenamide fumarate (TAF), a targeted tenofovir pro-drug with a 90% reduction in plasma tenofovir concentrations that significantly improves renal and bone safety compared with TDF-containing regimens[37].

Dolutegravir, the last and most powerful of the INSTI, now represents an effective alternative option to RTV-boosted PIs in treatment-naive patients. Like the RTV boosted-PIs, DTG has a high genetic barrier that minimizes the risks of resistance in case of virologic failure. Dolutegravir is effective in combination with either ABC/LAM or FTC/TDF in a wide variety of HIV-positive individuals, as concluded in a recent retrospective exploratory analysis of the data from the three large, randomized, comparative Spring-2, Single, and FLAMINGO trials. Authors explored the factors (sex, age, race, chronic hepatitis coinfection, HIV stage, as well as baseline CD4 cell count and HIV-1 RNA value) that can influence the efficacy and tolerability of HAART and predict treatment success; the consistency of observed treatment differences across subgroups and the impact of the NRTI backbone on treatment outcome were also analyzed, using the primary endpoint from the studies (FDA snapshot) and secondary endpoints that examine specific elements of therapy response. In particular, the authors examined the relationship between baseline viral load, NRTI backbone, and virologic response. Snapshot response results were affected by age, hepatitis coinfection, HIV risk factor, baseline CD4 cell count, HIV-1 RNA value, and by the third drug of the combination. Differences between DTG and other third agents were generally consistent across the subgroups, and no difference in snapshot response between ABC/LAM and FTC/TDF overall (ABC/LAM 86% vs. FTC/TDF 85%; difference 1.1%; 95% CI: –1.8 to 4.0; p = 0.61) or at high viral load (difference –2.5%; 95% CI: –8.9 to 3.8; p = 0.429) were observed, confirming the efficacy of DTG regardless of the NRTI backbone[38]. Dolutegravir could become the main treatment for HIV-infected patients by 2016.

Declaration of interest

The authors declare no conflict of interest.

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