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Week 48 Resistance Analysis of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir DF Versus Atazanavir + Ritonavir + Emtricitabine/Tenofovir DF in HIV-1 Infected Women (WAVES Study GS-US-236-0128)

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Abstract

Background—Women and those with non-B subtype HIV-1 are typically underrepresented in clinical trials. WAVES (GS-US-236-0128) was a double-blind phase 3b study among treatment-naïve HIV-1-infected women that demonstrated that elvitegravir/cobicistat/emtricitabine/tenofovir DF (EVG/COBI/FTC/TDF; N=289) was superior to atazanavir+ritonavir+FTC/TDF (ATV+RTV +FTC/TDF; N=286) for HIV-1 RNA <50 copies/mL by FDA snapshot analysis at Week 48. Here, we describe resistance development through Week 48 in women with virologic failure and determine the impact of pre-existing mutations and HIV-1 subtype on viral suppression.

Methods—Genotypic analyses (population and deep sequencing) and phenotypic analyses of HIV-1 protease, reverse transcriptase (RT), and integrase (IN) were performed. The resistance analysis population (participants with HIV-1 RNA ≥400 copies/mL at confirmed virologic failure, at discontinuation ≥Week 8, or at Week 48) had genotypic and phenotypic analyses at failure and baseline.

Results—The proportion of women qualifying for resistance analyses was similar between treatment groups (6.2% EVG/COBI/FTC/TDF; 7.3% ATV+RTV+FTC/TDF). Emergent resistance was rare (0% EVG/COBI/FTC/TDF; 1% ATV+RTV+FTC/TDF—3 with M184V/I in RT). Deep sequencing of HIV-1 did not detect additional resistance development. Pre-existing mutations did

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Declaration of Interests: R. Kulkarni, H. Cao, S. Chang, M.D. Miller, and K.L. White are full-time employees and shareholders of Gilead Sciences, Inc.

S.L. Hodder has participated in advisory boards for Gilead Sciences, Inc., Bristol-Myers Squibb, and Janssen and has received personal fees from Gilead Sciences, Inc., ViiV, Bristol-Myers Squibb, and Janssen.

not lead to virologic failure; most with the polymorphic primary IN substitution T97A, or with substitutions in RT (i.e. A62V, V90I, K103N, or E138) demonstrated virologic suppression at Week 48, with no resistance development. Most participants (74%) had non-B HIV-1, and subtype did not affect outcome.

Conclusions—Emergent resistance to study drugs was rare in this global study of women, and no resistance was observed among EVG/COBI/FTC/TDF-treated participants, despite a high proportion of participants with natural or transmitted viral mutations and non-B HIV-1 subtypes.

Keywords

HIV-1; resistance; women; elvitegravir; cobicistat; tenofovir; emtricitabine

Subject classification codes

clinical trials; antiretroviral therapy – adult; HIV drug resistance; incl. geno-/phenotyping

Introduction

Women continue to be underrepresented in clinical trials of antiretroviral efficacy and safety, despite constituting roughly half of the world's HIV cases.(1) This limited representation can lead to research findings that may not detect gender-specific risks or benefits of different antiretroviral therapies.(2, 3) The selection of HIV treatment should be evidence-based and should consider a number of factors, such as potency, side effects, barrier to resistance, and, for women, use during pregnancy.(4-9) Current guidelines for treating antiretroviral-naïve HIV-1-infected individuals include the use of two nucleoside reverse transcriptase inhibitors (NRTIs) in combination with a third active antiretroviral drug from a different class.(10-12) The single-tablet regimen (STR) containing the integrase strand transfer inhibitor (INSTI) elvitegravir (EVG) with the NRTIs emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF), and the pharmacoenhancer cobicistat (COBI) is an approved regimen for treatment-naïve individuals with HIV, and the protease inhibitor atazanavir (ATV) boosted by ritonavir (RTV) with FTC/TDF is another regimen option that is well tolerated in HIV-1 infected women and is a recommended regimen during pregnancy.(10, 11, 13, 14)

The Women's Antiretroviral Efficacy and Safety study (WAVES) was the first international, randomized, double-blind, phase 3 trial that exclusively enrolled women. WAVES was designed to evaluate the efficacy, safety, and tolerability of EVG/COBI/FTC/TDF versus ATV+RTV+FTC/TDF in treatment-naïve HIV-1 infected women. At the primary efficacy endpoint of HIV-1 RNA <50 copies/mL by FDA snapshot analysis at 48 weeks, EVG/COBI/FTC/TDF was superior to ATV+RTV+FTC/TDF with response rates of 87.2% and 80.8%, respectively (6.5% adjusted difference; 95% CI: 0.4% to 12.6%), and demonstrated safety.(15) Resistance development was rare (0% EVG/COBI/FTC/TDF; 1% ATV+RTV +FTC/TDF).

Here, we report the detailed genotypic and phenotypic characterization of resistance patterns that developed in the HIV-1 *pol* gene from the plasma HIV-1 of participants with virologic failure or early discontinuation in both treatment arms of the WAVES study through Week

48. Analyses of baseline resistance substitutions were also conducted, using both population genotyping and deep sequencing, to determine the effect of pre-existing drug resistance substitutions on treatment response to both regimens. Deep sequencing analyses did not detect additional resistance development but revealed key mutations at baseline, such as the polymorphic primary T97A substitution in IN.

Methods

WAVES Study Design

WAVES (GS-US-236-0128) was a phase 3b, randomized, double-blind, multi-center, international study to evaluate the safety and efficacy of the STR EVG/COBI/FTC/TDF versus ATV+RTV+FTC/TDF in 575 HIV-1 infected, antiretroviral treatment-naïve adult women. The study was conducted at 80 sites located in Belgium, Dominican Republic, France, Italy, Mexico, Portugal, Puerto Rico, Russia, Thailand, Uganda, the United Kingdom, and the United States. Participants were randomized 1:1 to EVG/COBI/FTC/TDF or ATV+RTV+FTC/TDF. Eligibility criteria included screening HIV-1 RNA ≥1,000 copies/mL, no prior ARV therapy, and genotypic sensitivity to FTC, TDF, and ATV. Randomization was stratified by screening HIV-1 RNA level (≤100,000 copies/mL, >100,000 to ≤400,000 copies/mL, or >400,000 copies/mL) and race (Black vs. non-Black). The primary endpoint was the proportion of participants with HIV-1 RNA <50 copies/mL at Week 48 as determined by the FDA snapshot algorithm.(15)

Virologic Failure Definition and Resistance Analysis Population

Participants with HIV-1 RNA ≥400 copies/mL who were on study drugs and experienced either suboptimal virologic response or virologic rebound, as defined below, were considered to have virologic failure and were included in the resistance analysis population (RAP). Suboptimal virologic response was assessed at Week 8 (with confirmation at a subsequent visit) and was defined as having HIV-1 RNA ≥50 copies/mL and <1 log10 reduction from baseline. Virologic rebound was defined as having 2 consecutive visits with HIV-1 RNA ≥50 copies/mL after achieving HIV-1 RNA <50 copies/mL, or as having 2 consecutive visits with >1 log10 increase in HIV-1 RNA from their nadir. The sample from the confirmation visit was analyzed for resistance development if the HIV-1 RNA value was ≥400 copies/mL; the assay is validated at ≥500 copies/mL. In addition, participants who were on study drugs, had not been analyzed previously, and who had HIV-1 RNA ≥400 copies/mL at Week 48 or their last visit (at or after Week 8) were analyzed for resistance at their last visit. At Week 48, participants in the resistance analysis population who resuppressed HIV-1 RNA to <50 copies/mL while on study drugs and without emergent resistance were also tabulated.

Resistance Testing

Viral load (HIV-1 RNA copies/mL) was assessed at screening, every visit during the treatment period, and at the final or early study drug discontinuation (ESDD) visit using the COBAS TaqMan HIV-1 Test, v2.0 (Roche Diagnostics, Basel, Switzerland).

At screening, pre-existing (transmitted) resistance in the protease (PR) and RT portion of the *pol* gene was assessed by population genotyping using the GenoSure® MG assay (Monogram Biosciences, South San Francisco, CA). This assay also determines the HIV-1 subtype. These screening data were used for baseline resistance analyses. For post-baseline resistance analyses of participants included in the resistance analysis population, PR, RT, and IN genotyping and phenotyping assays were performed. The PhenoSense GT®, PhenoSense® IN, and GeneSeq® IN assays (Monogram Biosciences) were used for this purpose. Genotypic and phenotypic PR, RT, and IN testing was also conducted at baseline for those participants in the resistance analysis population.

Deep sequencing of HIV-1 PR, RT, and IN was performed retrospectively on baseline and virologic failure timepoint samples from participants in both treatment arms in the resistance analysis population who did not later resuppress their HIV-1, and on baseline samples from all participants in the EVG/COBI/FTC/TDF treatment arm. This analysis used the deepTypeHIV assay and Illumina MiSeq (SeqIT GmbH & Co. KG, Kaiserlautern, Germany) and was analyzed internally, as described previously.(16) Resistance substitutions were analyzed at mutation frequency cutoffs of 15% and 2%.

Drug resistance substitutions in these analyses were based on the IAS-USA Guidelines with some modifications.(17) Primary INSTI-R substitutions assessed were T66A/I/K, E92G/Q, T97A, Y143C/H/R, S147G, Q148H/K/R, and N155H/S in IN. Secondary INSTI-R substitutions assessed were M50I, H51Y, L68I/V, V72A/N/T, L74M, Q95K/R, G118R, S119P/R/T, F121C/Y, A128T, E138A/K, G140A/C/S, P145S, Q146I/K/L/P/R, V151A/L, S153A/F/Y, E157K/Q, G163K/R, E170A, and R263K in IN. Primary NRTI-R substitutions assessed were M41L, A62V, K65R, D67N, T69 insertions, K70E/R, L74I/V, V75I, F77L, Y115F, F116Y, Q151M, M184V/I, L210W, T215F/Y, and K219E/N/Q/R in RT. Primary NNRTI-R substitutions assessed were V90I, A98G, L100I, K101E/H/P, K103N/S, V106A/I/M, V108I, E138A/G/K/Q/R, V179D/F/L/T, Y181C/I/V, Y188C/H/L, G190A/E/Q/S, H221Y, P225H, F227C, and M230I/L in RT. Primary PI-R substitutions assessed were D30N, V32I, L33F, M46I/L, I47A/V, G48V, I50L/V, I54L/M, Q58E, T74P, L76V, V82A/F/L/S/T, I84V, N88S, and L90M in PR.

Results

Baseline Genotypic Analyses

Among the 575 participants in the intent-to-treat (ITT) analysis set, all participants showed genotypic sensitivity to FTC, TDF, and ATV at screening, as required by the enrollment criteria. Consistent with these enrollment criteria, no participant had K65R or M184V/I RT substitutions at study entry. Primary NRTI and NNRTI resistance substitutions were observed in 15.3% and 20% of participants, respectively. The most common pre-existing NRTI-associated substitution was A62V, observed in 13.6% of participants, all located in Russia (Table 1; Supp. Table 1). The most common NNRTI-associated substitutions were V90I, E138A, and K103N. The V90I substitution was seen primarily in participants from Russia (31 of 41 participants with V90I, 75.6%). Primary PI resistance substitutions were observed in 1.7% of participants, most commonly M46I/L and L33F in protease. Per protocol, there was no analysis of IN genotype at screening.

HIV-1 Subtype

The HIV-1 subtype was determined for participants by the screening genotype. Almost half the participants had HIV-1 subtype A or A1 (265 of 575, 46.1%). Other subtypes present were subtypes B (147 of 575, 25.6%), D (45 of 575, 7.8%), AE (28 of 575, 4.9%), AG or C (27 of 575 each, 4.7%), G (11 of 575, 1.9%), F1 (1 of 575, 0.2%), and “complex” mixtures of subtypes (24 of 575, 4.2%). Most subtype B participants were from the United States (104 of 147, 70.7%) or the Dominican Republic (19 of 147, 12.9%). Most subtype A or A1 participants were from Russia (168 of 265, 63.4%) or Uganda (88 of 265, 33.2%).

Genotypic and Phenotypic Resistance Development at Week 48

Of the 575 randomized and treated participants, a total of 39 participants met the criteria for inclusion in the RAP (6.8%) (Table 2). By treatment group, 18 of 289 (6.2%) and 21 of 286 (7.3%) participants were analyzed in the EVG/COBI/FTC/TDF and ATV+RTV+FTC/TDF arms, respectively. Of these 39 women, 11 of 18 (61%) participants in the EVG/COBI/FTC/TDF arm and 9 of 21 (43%) participants in the ATV+RTV+FTC/TDF arm resuppressed HIV-1 RNA to <50 copies/mL while on study drugs.

In the EVG/COBI/FTC/TDF arm, of the 18 participants analyzed for resistance development, no participant developed genotypic or phenotypic resistance to a study drug. One participant developed the NRTI resistance substitution D67D/N, but remained phenotypically susceptible to all drugs in their regimen. This participant discontinued after her failure timepoint and had no follow-up data. In addition, there was no development of primary NNRTI or primary PI resistance substitutions within the EVG/COBI/FTC/TDF arm.

In the ATV+RTV+FTC/TDF arm, of the 21 participants analyzed for resistance development, 3 participants (RAP: 3/21, 14%; treated: 3/286, 1%) developed resistance to a study drug. All 3 participants developed M184V/I in RT. The phenotypic resistance to FTC was high for two participants, with a mean of 53-fold reduced susceptibility. One participant had an M184M/I/V mixture and showed a 2.1-fold change in susceptibility to FTC, which is below the biological cutoff of the PhenoSense GT® assay for FTC. Two of the participants that developed resistance at Week 48 had HIV-1 subtype A1 and one participant had subtype B. The remaining 18 participants in the ATV+RTV+FTC/TDF arm lacked new resistance substitutions in RT and PR and remained phenotypically susceptible to all drugs in their regimen. One participant developed the NNRTI resistance substitution A98A/G, but this participant resuppressed HIV-1 RNA to <50 copies/mL while on study drugs.

Baseline Deep Sequencing Genotypic Analyses

As part of an exploratory analysis, deep sequencing of HIV-1 PR, RT, and IN was performed on 309 baseline samples, 288 of the 289 from the EVG/COBI/FTC/TDF arm (1 had no sample available for testing) and 21 of the 286 from the ATV+RTV+FTC/TDF arm (only those in the RAP). For the PR and RT genes where population sequencing data was also available, results were roughly similar at a deep sequencing cutoff of 15% (Table 3). At a 15% cutoff, primary NRTI and NNRTI resistance substitutions were observed in 15.2% and 17.8% of participants, respectively. The most common pre-existing NRTI- and NNRTI-associated substitutions were A62V, V90I, and E138A. Primary PI resistance substitutions

were observed in 1.3% of participants. At a 2% cutoff, primary NRTI, NNRTI, and PI resistance substitutions were observed at slightly higher frequencies of 16.5%, 27.8%, and 8.1%, respectively. Four participants (4 of 309, 1.3%) had the exclusion mutation M184I at baseline by deep sequencing at frequencies ranging from 2.0% to 9.7% (mutational viral loads of 44 copies/mL, 620 copies/mL, 2020 copies/mL, and 10590 copies/mL).

Cases of pre-existing primary INSTI-associated resistance substitutions were observed by deep sequencing (Table 4). At a 2% cutoff, E92G and N155H were observed in 1 participant each, and S147G was observed in 2 participants, at low percentages ranging from 2.1% to 3.7% (mutational viral loads: E92G, 920 copies/mL; S147G, 430 copies/mL and 490 copies/mL; N155H, 770 copies/mL). At a 15% cutoff, 10 participants had T97A (EVG/COBI/FTC/TDF: 9 of 288, 3.1%; ATV+RTV+FTC/TDF: 1 of 21, 4.8%), and at a 2% cutoff, 11 participants had T97A (EVG/COBI/FTC/TDF: 10 of 288, 3.5%; ATV+RTV+FTC/TDF: 1 of 21, 4.8%) by deep sequencing, at percentages ranging from 6.1% to 99.8%. Baseline samples from the 10 participants with T97A at ≥15% (9 EVG/COBI/FTC/TDF; 1 ATV +RTV+FTC/TDF) were sent for population sequencing using the GeneSeq® IN assay, and the presence of T97A was confirmed. Phenotyping of these samples found that 5 of these samples showed a >2.5-fold change in susceptibility to EVG (range: 2.8 to 4.2-fold), though all of these participants were virologically suppressed at 48 weeks. Secondary IN resistance substitutions were observed in 173 of 309 participants (56.0%) at a deep sequencing cutoff of 15% and in 194 of 309 participants (62.8%) at a deep sequencing cutoff of 2%. The most prevalent secondary IN resistance substitutions observed were S119P and M50I, which are known polymorphisms.(18)

Baseline Resistance Substitutions and Clinical Outcome at Week 48

At screening, participants were required to show genotypic sensitivity to FTC, TDF, and ATV. However, participants with HIV-1 isolates having NRTI-R or PI-R substitutions not associated with resistance to these drugs were allowed to enroll in the study. The presence of pre-existing primary drug resistance substitutions did not affect the clinical outcome of participants. Specifically, those participants with A62V, V90I, K103N, or E138A/G/K/Q/R in RT, or M46I/L or L33F in PR, had HIV-1 RNA <50 copies/mL at Week 48 after treatment with EVG/COBI/FTC/TDF or ATV+RTV+FTC/TDF at proportions similar to the overall treated population (Table 5). These analyses were also performed by treatment arm and showed that this pre-existing resistance did not affect durable viral suppression regardless of regimen studied. In addition, 4 participants had the exclusion mutation M184I at low levels by deep sequencing, and 3 of these participants were virologic successes at Week 48, and one participant was lost to follow up with the last available HIV-1 RNA <50 copies/mL.

Analyses of the HIV IN genotype at baseline were conducted retrospectively by deep sequencing, with data available for 309 participants, 288 from the EVG/COBI/FTC/TDF arm and 21 from the ATV+RTV+FTC/TDF arm. Additionally, HIV IN population sequencing data was available for 59 participants (33 of whom also had IN deep sequencing data), 30 from the EVG/COBI/FTC/TDF arm and 29 from the ATV+RTV+FTC/TDF arm. Ten participants treated with EVG/COBI/FTC/TDF had the polymorphic primary IN resistance substitution T97A by deep sequencing, at percentages ranging from 6.1% to

99.8%, and all of these participants had <50 copies/mL HIV-1 RNA at Week 48 (Table 5). Of the two participants with T97A that were treated with ATV+RTV+FTC/TDF, one had <50 copies/mL HIV-1 RNA at Week 48, and one had ≥50 copies/mL at Week 48. Four other EVG/COBI/FTC/TDF participants had primary IN resistance substitutions (2 with S147G, 1 with E92G, 1 with N155H) present at low percentages ranging from 2.1% to 3.7%, and all four of these participants were virologic successes at Week 48. Secondary IN resistance substitutions such as S119P and M50I were observed in greater than 50% of participants, and these participants had HIV-1 RNA <50 copies/mL at Week 48 at proportions similar to the overall population, and no development of IN resistance.

Resistance Development at Week 48 by Deep Sequencing

Deep sequencing of HIV-1 PR, RT, and IN was performed on baseline and virologic failure timepoint samples from participants in the RAP. The three ATV+RTV+FTC/TDF participants who developed M184V/I by population sequencing also had this resistance substitution in their failure sample deep sequencing results (Table 6). The EVG/COBI/FTC/TDF participant who developed D67D/N did not have post-baseline deep sequencing data available, so this substitution development could not be confirmed. One participant treated with EVG/COBI/FTC/TDF had the NNRTI substitution K101E present at 23.1% in their failure sample; this mutation was not detected by population sequencing and the sample did not show phenotypic resistance to any approved NNRTIs. No additional developed resistance substitutions were detected by deep sequencing that were not detected by population sequencing in either arm.

Discussion

WAVES was the first HIV-1 clinical study to evaluate the efficacy, safety, and tolerability of two approved antiretroviral regimens in treatment-naïve women in a randomized, double-blind trial. The population of women in the study was geographically and ethnically diverse, providing a better understanding of different factors that affect clinical outcome. At the primary efficacy endpoint of 48 weeks, EVG/COBI/FTC/TDF was superior to ATV+RTV +FTC/TDF. Thirty-nine women (39 of 575, 6.8%) were included in the resistance analysis population (participants with HIV-1 RNA ≥400 copies/mL at confirmed virologic failure, discontinuation ≥Week 8, or Week 48), with 18 women (18 of 289, 6.2%) in the EVG/COBI/FTC/TDF arm and 21 women (21 of 286, 7.3%) in the ATV+RTV+FTC/TDF arm. No women developed resistance to study drugs in the EVG/COBI/FTC/TDF group, compared to 1% in the ATV+RTV+FTC/TDF group.

Study GS-US-236-0103 was an earlier phase 3, randomized, double-blind study comparing EVG/COBI/FTC/TDF to ATV+RTV+FTC/TDF in a population of men and women. In this study, 20 participants (20 of 708, 2.8%) qualified for resistance analyses using the same criteria used in WAVES, with 12 participants (12 of 353, 3.4%) in the EVG/COBI/FTC/TDF arm and 8 participants (8 of 355, 2.3%) in the ATV+RTV+FTC/TDF arm.(19) The size of the WAVES resistance analysis population was significantly larger than the resistance analysis population from GS-US-236-0103 ($p = 0.0011$), but the number of participants developing resistance to study drug was similar in the two studies (3 participants vs. 5

participants, p = 0.7374). Twenty of the participants in the WAVES resistance analysis population (20 of 39, 51%) resuppressed HIV-1 RNA to <50 copies/mL while on study drug, suggesting that these women were temporarily not adherent to their drugs but responded once treatment was resumed.

WAVES was a global study spanning 11 countries on 4 continents, with most participants located in the United States, Russia, and Uganda. This distribution of participants around the world also led to participants with various HIV-1 subtypes being enrolled in the study. The majority of participants (74%) had non-B subtype HIV-1, primarily consisting of subtype A and A1 in Russia, and A1 and D in Uganda. Twenty-six percent of participants had HIV-1 subtype B, primarily in the United States. Although women with pre-existing HIV-1 resistance to FTC, TDF, or ATV were excluded from this study, primary NRTI-R substitutions not causing resistance to FTC or TDF were common, observed in 15.3% of participants. The most common pre-existing NRTI-associated substitution was A62V, observed in 13.6% of participants, all located in Russia and all with subtypes A or A1. A62V is a known polymorphism in Russia and has been previously described as a fitness compensatory mutation associated with K65R (20). Therefore, A62V might predispose participants to developing K65R; however, no participant in this study developed this TDF resistance mutation. NRTI-R substitutions were more frequent in non-B HIV-1 subtypes (Supp. Table 2), but did not impact genotypic sensitivity assessments. NNRTI-associated substitutions were also common, observed in 20% of participants. The most common NNRTI-associated substitutions were V90I and E138A/G/K/Q/R, observed most frequently in subtypes A and A1, but these did not impact genotypic sensitivity to most NNRTIs. The primary efavirenz resistance substitution K103N was present in 3.0% of women, mostly with subtype B and located in the United States. Primary PI resistance substitutions not causing resistance to ATV were rare, observed in 1.7% of participants, but 13% of women had a genotypic assessment of ‘resistance possible’ or ‘resistance’ to protease inhibitors. Most of these genotypic assessments for resistance were called for nelfinavir and/or tipranavir due to the presence of several secondary resistance mutations.

Although not a treatment-experienced population, this group of participants had pre-existing resistance mutations, as mentioned above. The presence of these mutations did not lead to virologic failure with resistance development to the treatment regimens studied here. A total of 80 participants had the NRTI-associated substitution A62V at baseline, detected by either population or deep sequencing. Of these participants, 63 had HIV-1 RNA <50 copies/mL at Week 48 (63 of 80, 78.8%), which is comparable to the percent of participants in the overall study who had HIV-1 RNA <50 copies/mL at Week 48. In addition, 7 of these participants were analyzed for resistance, and none of them developed additional resistance mutations or had phenotypic resistance to the drugs in their regimen. Outcome analyses were done for other resistance mutations seen at baseline, including the NNRTI-associated substitutions K103N and E138A/G/K/Q/R, and the PI-associated substitutions M46I/L and L33F, and similar results were observed. Four participants had the exclusion mutation M184I at low levels by deep sequencing, and 3 of these participants were virologic successes at Week 48, and one participant was lost to follow up with the last available HIV-1 RNA <50 copies/mL. Deep sequencing of IN revealed the presence of INSTI-associated resistance substitutions at baseline, and these mutations also had no impact on virologic failure with resistance

development through Week 48. Ten participants treated with EVG/COBI/FTC/TDF had the polymorphic primary IN resistance substitution T97A by deep sequencing, and all of these participants had <50 copies/mL HIV-1 RNA at Week 48. Secondary IN resistance substitutions such as S119P and M50I were observed in greater than 50% of participants by deep sequencing, and these participants had HIV-1 RNA <50 copies/mL at Week 48 at proportions similar to the overall population, and no development of IN resistance.

Deep sequencing results were generally concordant with population sequencing results in the tested samples, both at baseline and virologic failure. The discrepant results between deep sequencing (mutations with frequencies ≥15%) and population sequencing may be assay related. Given that both assays were performed at different sites with distinct sets of primers for reverse transcription and PCR amplification, it is possible that different populations of virus may have been amplified. The three ATV+RTV+FTC/TDF participants who developed M184V/I by population sequencing also had this resistance substitution by deep sequencing at the failure time point, and no additional resistance substitutions to study drug were detected by deep sequencing that were not detected by population sequencing. There was only one virologic failure sample with a sequencing discrepancy; the NNRTI resistance substitution K101E was detected by deep sequencing at 23.1% in one sample but was not detected by population sequencing. This again could be explained by differential amplification of virus by the two assays.

In this global study of antiretroviral-naïve, HIV-1 infected women, treatment with EVG/COBI/FTC/TDF and ATV+RTV+FTC/TDF showed low rates of emergent resistance, despite having relatively large numbers of women who required resistance testing. These low rates of emergent resistance are consistent with the high efficacy of the drug regimens used in this study. The results of this study also suggest that testing for resistance substitutions at baseline by deep sequencing is a viable approach, but the clinical relevance of minority resistance variants remains uncertain. Finally, though A62V is a known polymorphism that has previously been described as a fitness compensatory mutation associated with K65R (20), there was no evidence that the presence of A62V predisposed participants to developing K65R.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1
Baseline Genotypic Analysis (Intent-to-Treat Population)

	Percent of Subjects (n)		
Resistance Mutations at Baseline	**EVG/COBI/FTC/TDF (n=289)**	**ATV+RTV+FTC/TDF (n=286)**	**All (n=575)**
NRTI-Associated[a]	15.2% (44)	15.4% (44)	15.3% (88)
M41L	0	1.7% (5)	0.9% (5)
A62V	14.9% (43)	12.2% (35)	13.6% (78)
K65R	0	0	0
D67N	0	0.3% (1)	0.2% (1)
F77L	0.3% (1)	0	0.2% (1)
M184V/I	0	0	0
L210W	0	0.3% (1)	0.2% (1)
K219E/N/Q/R	0	0.7% (2)	0.3% (2)
NNRTI-Associated[b]	18.0% (52)	22.0% (63)	20.0% (115)
V90I	6.9% (20)	7.3% (21)	7.1% (41)
A98G	0.3% (1)	0.3% (1)	0.3% (2)
K101E/H/P	0.7% (2)	0.7% (2)	0.7% (4)
K103N	2.4% (7)	3.5% (10)	3.0% (17)
K103S	0.3% (1)	0.7% (2)	0.5% (3)
V106A/M/I	1.4% (4)	2.4% (7)	1.9% (11)
V108I	0.7% (2)	0.3% (1)	0.5% (3)
E138A/G/K/Q/R	6.2% (18)	7.0% (20)	6.6% (38)
V179D/F/L/T	1.7% (5)	1.0% (3)	1.4% (8)
G190A/E/Q/S	0.3% (1)	0.7% (2)	0.5% (3)
Primary PI-Associated[c]	1.4% (4)	2.1% (6)	1.7% (10)
L33F	0	1.0% (3)	0.5% (3)
M46I/L	0.3% (1)	1.0% (3)	0.7% (4)
I50L/V	0	0.3% (1)	0.2% (1)
Q58E	0.7% (2)	0	0.3% (2)
L90M	0.3% (1)	0	0.2% (1)

[a] NRTI resistance substitutions (NRTI-R) are M41L, A62V, K65R, D67N, T69 insertions, K70E/R, L74I/V, V75I, F77L, Y115F, F116Y, Q151M, M184V/I, L210W, T215F/Y, K219E/N/Q/R in RT.

[b] NNRTI resistance substitutions (NNRTI-R) are V90I, A98G, L100I, K101E/H/P, K103N/S, V106A/I/M, V108I, E138A/G/K/Q/R, V179D/F/L/T, Y181C/I/V, Y188C/H/L, G190A/E/Q/S, H221Y, P225H, F227C, M230I/L in RT.

[c] Primary protease inhibitor resistance substitutions (PI-R) are D30N, V32I, L33F, M46I/L, I47A/V, G48V, I50L/V, I54L/M, Q58E, T74P, L76V, V82A/F/L/S/T, I84V, N88S, L90M in protease.

Table 2
Development of Genotypic Resistance at Week 48

	Number of Subjects (% of RAP; % of All Subjects)		
Resistance Substitution Development	**EVG/COBI/FTC/TDF (n=289)**	**ATV+RTV+FTC/TDF (n=286)**	**All (n=575)**
Resistance Analysis Population (RAP)	18 (6.2%)	21 (7.3%)	39 (6.8%)
Subjects who resuppressed HIV-1 RNA to <50 copies/mL while on study drugs	11 (61.1%; 3.8%)	9 (42.9%; 3.1%)	20 (51.3%; 3.5%)
Developed Resistance Substitutions to Study Drugs	0	3 (14.3%; 1.0%)	3 (7.7%; 0.5%)
M184V/I in RT	0	3 (14.3%; 1.0%)	3 (7.7%; 0.5%)

Table 3
Baseline PR and RT Genotypic Analysis by Deep Sequencing

Resistance Mutations at Baseline	Percent of Subjects (n)		
	Deep Sequencing, 15% Cutoff (n=309)[a]	Deep Sequencing, 2% Cutoff (n=309)[a]	Population Sequencing (n=575)
NRTI-Associated[b]	15.2% (47)	16.5% (51)	15.3% (88)
M41L	0	0	0.9% (5)
A62V	14.9% (46)	14.9% (46)	13.6% (78)
K65R	0	0	0
D67N	0	0.3% (1)	0.2% (1)
F77L	0	0	0.2% (1)
M184V/I	0	1.3% (4)[c]	0
L210W	0.3% (1)	0.3% (1)	0.2% (1)
K219E/N/Q/R	0.3% (1)	0.3% (1)	0.3% (2)
NNRTI-Associated[d]	17.8% (55)	27.8% (86)	20.0% (115)
V90I	5.8% (18)	9.1% (28)	7.1% (41)
A98G	0.3% (1)	0.6% (2)	0.3% (2)
K101E/H/P	1.0% (3)	1.3% (4)	0.7% (4)
K103N	2.9% (9)	3.2% (10)	3.0% (17)
K103S	0.3% (1)	0.3% (1)	0.5% (3)
V106A/M/I	1.9% (6)	3.9% (12)	1.9% (11)
V108I	0.6% (2)	1.0% (3)	0.5% (3)
E138A/G/K/Q/R	6.1% (19)	7.4% (23)	6.6% (38)
V179D/F/L/T	1.3% (4)	1.9% (6)	1.4% (8)
G190A/E/Q/S	0.3% (1)	1.0% (3)	0.5% (3)
P225H	0	0.3% (1)	0
M230I/L	0	3.6% (11)	0
Primary PI-Associated[e]	1.3% (4)	8.1% (25)	1.7% (10)
D30N	0	0.3% (1)	0
V32I	0.3% (1)	0.6% (2)	0
L33F	0.3% (1)	0.6% (2)	0.5% (3)
M46I/L	0	2.3% (7)	0.7% (4)
G48V	0	3.9% (12)	0
I50L/V	0	0	0.2% (1)
Q58E	0.6% (2)	0.6% (2)	0.3% (2)
L90M	0.3% (1)	0.3% (1)	0.2% (1)

[a] Baseline deep sequencing data was available for 288/289 subjects in the EVG/COBI/FTC/TDF group and for 21/286 subjects in the ATV+RTV +FTC/TDF group.

[b] NRTI resistance substitutions (NRTI-R) are M41L, A62V, K65R, D67N, T69 insertions, K70E/R, L74I/V, V75I, F77L, Y115F, F116Y, Q151M, M184V/I, L210W, T215F/Y, K219E/N/Q/R in RT.

[c] Four subjects had M184I by deep sequencing, at percentages ranging from 2.0% to 9.7%. The mutational viral loads of the samples were 44 copies/mL, 620 copies/mL, 2020 copies/mL, and 10590 copies/mL.

[d] NNRTI resistance substitutions (NNRTI-R) are V90I, A98G, L100I, K101E/H/P, K103N/S, V106A/I/M, V108I, E138A/G/K/Q/R, V179D/F/L/T, Y181C/I/V, Y188C/H/L, G190A/E/Q/S, H221Y, P225H, F227C, M230I/L in RT.

[e] Primary protease inhibitor resistance substitutions (PI-R) are D30N, V32I, L33F, M46I/L, I47A/V, G48V, I50L/V, I54L/M, Q58E, T74P, L76V, V82A/F/L/S/T, I84V, N88S, L90M in protease.

Table 4
Baseline IN Genotypic Analysis by Deep Sequencing

Resistance Mutations at Baseline	Percent of Subjects (n)		
	Deep Sequencing, 15% Cutoff (n=309)[a]	Deep Sequencing, 2% Cutoff (n=309)[a]	Resistance Subset Population Sequencing (n=59)[b]
Primary INSTI-Associated[c]	3.2% (10)	4.9% (15)	18.6% (11)
E92G/Q	0	0.3% (1)[e]	0
T97A	3.2% (10)[d]	3.6% (11)[d]	18.6% (11)
S147G	0	0.6% (2)[e]	0
N155H/S	0	0.3% (1)[e]	0
Secondary INSTI-Associated[f]	56.0% (173)	62.8% (194)	55.9% (33)
M50I	16.8% (52)	23.6% (73)	23.7% (14)
H51Y	0	0.3% (1)	0
L68I/V	0.6% (2)	2.3% (7)	0
V72A/N/T	1.6% (5)	2.3% (7)	0
L74M	2.6% (8)	2.9% (9)	1.7% (1)
Q95K/R	0.3% (1)	0.6% (2)	1.7% (1)
S119P/R/T	40.1% (124)	40.1% (124)	33.9% (20)
F121C/Y	0	0.3% (1)	0
A128T	0	1.3% (4)	0
E138A/K	0.3% (1)	0.3% (1)	0
G140A/C/S	0	0.3% (1)	0
Q146I/K/L/P/R	0	1.3% (4)	0
S153A/F/Y	0	1.3% (4)	0
E157K/Q	3.2% (10)	6.5% (20)	0
E170A	0	0.3% (1)	0
R263K	0	0.6% (2)	0

[a] Baseline deep sequencing data was available for 288/289 subjects in the EVG/COBI/FTC/TDF group and for 21/286 subjects in the ATV+RTV +FTC/TDF group.

[b] Baseline population sequencing was performed retrospectively on 69 samples, with 10 assay failures. These samples included those from subjects on both treatment arms in the resistance analysis population, and those that had primary IN resistance by deep sequencing at ≥15%.

[c] Primary integrase strand transfer inhibitor resistance substitutions (INSTI-R) are T66A/I/K, E92G/Q, T97A, Y143C/H/R, S147G, Q148H/K/R, N155H/S in IN.

[d] Eleven subjects had T97A by deep sequencing, at percentages ranging from 6.1% to 99.8%.

[e] Four subjects had E92G, S147G, or N155H by deep sequencing, at percentages ranging from 2.1% to 3.7%. The mutational viral load of the E92G-containing sample was 920 copies/mL. The mutational viral loads of the S147G-containing samples were 430 copies/mL and 490 copies/mL. The mutational viral load of the N155H-containing sample was 770 copies/mL.

[f] Secondary INSTI-R are M50I, H51Y, L68I/V, V72A/N/T, L74M, Q95K/R, G118R, S119P/R/T, F121C/Y, A128T, E138A/K, G140A/C/S, P145S, Q146I/K/L/P/R, V151A/L, S153A/F/Y, E157K/Q, G163K/R, E170A, R263K in IN.

Table 5

Baseline PR, RT, and IN Genotypic Substitutions and Virologic Outcome Through Week 48, n=575

Resistance Substitutions at Baseline	Subjects with Substitutions by Population or Deep Sequencing, ≥2%, n (%)[a]	Week 48 Snapshot Outcome			Week 48 Resistance Analysis (Resistance Developed/ Analyzed)	
		HIV-1 RNA <50 copies/mL	HIV-1 RNA ≥50 copies/mL	No virologic data in window	EVG/COBI/FTC/TDF	ATV+RTV+ FTC/TDF
NRTI-Associated[b]	95 (16.5%)	75 (78.9%)	12 (12.6%)	8 (8.4%)	0/5	0/3
M41L	5 (0.9%)	3 (60.0%)	1 (20.0%)	1 (20.0%)	0/0	0/0
A62V	80 (13.9%)	63 (78.8%)	11 (13.8%)	6 (7.5%)	0/4	0/3
D67N	2 (0.3%)	2 (100%)	0	0	0/0	0/0
F77L	1 (0.2%)	1 (100%)	0	0	0/1	0/0
M184V/I	4 (0.7%)	3 (75.0%)	0	1 (25.0%)	0/0	0/0
L210W	2 (0.3%)	2 (100%)	0	0	0/0	0/0
K219E/N/Q/R	3 (0.5%)	3 (100%)	0	0	0/0	0/0
NNRTI-Associated[c]	148 (25.7%)	111 (75.0%)	25 (16.9%)	12 (8.1%)	0/8	3/10
V90I	50 (8.7%)	34 (68.0%)	12 (24.0%)	4 (8.0%)	0/5	0/3
A98G	3 (0.5%)	3 (100%)	0	0	0/0	0/0
K101E/H/P	7 (1.2%)	7 (100%)	0	0	0/0	0/1
K103N	18 (3.1%)	14 (77.8%)	3 (16.7%)	1 (5.6%)	0/2	1/3
K103S	3 (0.5%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	0/1	0/0
V106A/M/I	17 (3.0%)	14 (82.4%)	1 (5.9%)	2 (11.8%)	0/0	1/1
V108I	4 (0.7%)	2 (50.0%)	1 (25.0%)	1 (25.0%)	0/0	0/0
E138A/G/K/Q/R	44 (7.7%)	36 (81.8%)	6 (13.6%)	2 (4.5%)	0/0	1/3
V179D/F/L/T	10 (1.7%)	6 (60.0%)	3 (30.0%)	1 (10.0%)	0/0	0/0
G190A/E/Q/S	5 (0.9%)	4 (80.0%)	1 (20.0%)	0	0/0	0/0
P225H	1 (0.2%)	1 (100%)	0	0	0/0	0/0
M230I/L	11 (1.9%)	9 (81.8%)	1 (9.1%)	1 (9.1%)	0/1	0/0
Primary PI-Associated[d]	30 (5.2%)	23 (76.7%)	5 (16.7%)	2 (6.7%)	0/2	0/0
D30N	1 (0.2%)	1 (100%)	0	0	0/0	0/0
V32I	2 (0.3%)	1 (50.0%)	0	1 (50.0%)	0/0	0/0

Resistance Substitutions at Baseline	Subjects with Substitutions by Population or Deep Sequencing, ≥2%, n (%)[a]	Week 48 Snapshot Outcome			Week 48 Resistance Analysis (Resistance Developed/ Analyzed)	
		HIV-1 RNA <50 copies/mL	HIV-1 RNA ≥50 copies/mL	No virologic data in window	EVG/COBI/FTC/TDF	ATV+RTV+ FTC/TDF
L33F	4 (0.7%)	3 (75.0%)	1 (25.0%)	0	0/0	0/0
M46I/L	10 (1.7%)	8 (80.0%)	1 (10.0%)	1 (10.0%)	0/1	0/0
G48V	12 (2.1%)	10 (83.3%)	1 (8.3%)	1 (8.3%)	0/1	0/0
I50L/V	1 (0.2%)	1 (100%)	0	0	0/0	0/0
Q58E	2 (0.3%)	1 (50.0%)	1 (50.0%)	0	0/0	0/0
L90M	1 (0.2%)	0	1 (100%)	0	0/0	0/0
Primary INSTI-Associated[e]	16 (4.8%)	15 (93.8%)	1 (6.3%)	0	0/0	1/1
E92G/Q	1 (0.3%)	1 (100%)	0	0	0/0	0/0
T97A	12 (3.6%)	11 (91.7%)	1 (8.3%)	0	0/0	1/1
S147G	2 (0.6%)	2 (100%)	0	0	0/0	0/0
N155H/S	1 (0.3%)	1 (100%)	0	0	0/0	0/0
Secondary INSTI-Associated[f]	212 (63.3%)	176 (83.0%)	28 (13.2%)	8 (3.8%)	0/12	3/15
M50I	83 (24.8%)	68 (81.9%)	12 (14.5%)	3 (3.6%)	0/3	0/7
H51Y	1 (0.3%)	1 (100%)	0	0	0/0	0/0
L68I/V	7 (2.1%)	7 (100%)	0	0	0/0	0/0
V72A/N/T	7 (2.1%)	7 (100%)	0	0	0/0	0/0
L74M	10 (3.0%)	8 (80.0%)	1 (10.0%)	1 (10.0%)	0/1	0/0
Q95K/R	2 (0.6%)	1 (50.0%)	1 (50.0%)	0	0/1	0/0
S119P/R/T	135 (40.3%)	111 (82.2%)	20 (14.8%)	4 (3.0%)	0/8	2/9
F121C/Y	1 (0.3%)	0	1 (100%)	0	0/0	0/0
A128T	4 (1.2%)	3 (75.0%)	1 (25.0%)	0	0/0	0/0
E138A/K	1 (0.3%)	1 (100%)	0	0	0/0	0/0
G140A/C/S	1 (0.3%)	1 (100%)	0	0	0/0	0/0
Q146I/K/L/P/R	4 (1.2%)	4 (100%)	0	0	0/0	0/0
S153A/F/Y	4 (1.2%)	2 (50.0%)	1 (25.0%)	1 (25.0%)	0/1	0/0
E157K/Q	20 (6.0%)	17 (85.0%)	2 (10.0%)	1 (5.0%)	0/0	1/1
E170A	1 (0.3%)	1 (100%)	0	0	0/0	0/0

Resistance Substitutions at Baseline	Subjects with Substitutions by Population or Deep Sequencing, ≥2%, n (%)[a]	Week 48 Snapshot Outcome			Week 48 Resistance Analysis (Resistance Developed/ Analyzed)	
		HIV-1 RNA <50 copies/mL	HIV-1 RNA ≥50 copies/mL	No virologic data in window	EVG/COBI/FTC/TDF	ATV+RTV+ FTC/TDF
R263K	2 (0.6%)	2 (100%)	0	0	0/0	0/0

[a]This analysis includes any subject with resistance detected by either population or deep sequencing. PR and RT data was available for 575 subjects total, 575 with population sequencing data and 309 with deep sequencing data. IN data was available for 335 subjects total, 59 with population sequencing data and 309 with deep sequencing data.

[b]NRTI resistance substitutions (NRTI-R) are M41L, A62V, K65R, D67N, T69 insertions, K70E/R, L74I/V, V75I, F77L, Y115F, F116Y, Q151M, M184V/I, L210W, T215F/Y, K219E/N/Q/R in RT.

[c]NNRTI resistance substitutions (NNRTI-R) are V90I, A98G, L100I, K101E/H/P, K103N/S, V106A/I/M, V108I, E138A/G/K/Q/R, V179D/F/L/T, Y181C/I/V, Y188C/H/L, G190A/E/Q/S, H221Y, P225H, F227C, M230I/L in RT.

[d]Primary protease inhibitor resistance substitutions (PI-R) are D30N, V32I, L33F, M46I/L, I47A/V, G48V, I50L/V, I54L/M, Q58E, T74P, L76V, V82A/F/L/S/T, I84V, N88S, L90M in protease.

[e]Primary integrase strand transfer inhibitor resistance substitutions (INSTI-R) are T66A/I/K, E92G/Q, T97A, Y143C/H/R, S147G, Q148H/K/R, N155H/S in IN.

[f]Secondary INSTI-R are M50I, H51Y, L68I/V, V72A/N/T, L74M, Q95K/R, G118R, S119P/R/T, F121C/Y, A128T, E138A/K, G140A/C/S, P145S, Q146I/K/L/P/R, V151A/L, S153A/F/Y, E157K/Q, G163K/R, E170A, R263K in IN.

Table 6
Genotypic Resistance at Week 48 by Deep Sequencing

Resistance Substitution Development	Number of Subjects (% of RAP; % of All Subjects)		
	Deep Sequencing, 15% Cutoff (n=575)	Deep Sequencing, 2% Cutoff (n=575)	Population Sequencing (n=575)
Resistance Analysis Population (RAP)		39 (6.8%)	
Subjects who resuppressed HIV-1 RNA to <50 copies/mL while on study drugs		20 (51.3%; 3.5%)	
Subjects who did not resuppress HIV-1 RNA to <50 copies/mL while on study drugs		19 (48.7%; 3.3%)	
Subjects with data, of those who did not resuppress HIV-1 RNA to <50 copies/mL while on study drugs	18	18	19
Developed Resistance Substitutions to Study Drugs	3 (16.7%; 0.5%)	3 (16.7%; 0.5%)	3 (15.8%; 0.5%)
No Change from Baseline (Primary Substitutions)[a]	15 (83%; 2.6%)	15 (83%; 2.6%)	16 (84%; 2.8%)
Any Primary INSTI-R[b]	0	0	0
E92G/Q	0	0	0
Q148H/K/R	0	0	0
N155H/S	0	0	0
Any NRTI-R[c]	3 (16.7%; 0.5%)	3 (16.7%; 0.5%)	4 (21%; 0.7%)
K65R	0	0	0
D67N	0	0	1 (5.3%; 0.2%)[d]
M184V/I	3 (16.7%; 0.5%)[e]	3 (16.7%; 0.5%)[e]	3 (15.8%; 0.5%)[e]
Any NNRTI-R[f]	1 (5.6%; 0.2%)	1 (5.6%; 0.2%)	0
K101E	1 (5.6%; 0.2%)[g]	1 (5.6%; 0.2%)[g]	0
Any Primary PI-R[h]	0	0	0

[a] No change from baseline at INSTI-R, NRTI-R, NNRTI-R, or primary PI-R sites.

[b] Primary integrase strand transfer inhibitor resistance substitutions (INSTI-R) are T66A/I/K, E92G/Q, T97A, Y143C/H/R, S147G, Q148H/K/R, N155H/S in IN.

[c] NRTI resistance substitutions (NRTI-R) are M41L, A62V, K65R, D67N, T69 insertions, K70E/R, L74I/V, V75I, F77L, Y115F, F116Y, Q151M, M184V/I, L210W, T215F/Y, K219E/N/Q/R in RT.

[d] One EVG/COBI/FTC/TDF subject developed D67D/N by population sequencing, but there was no additional sample available for confirmation by deep sequencing.

[e] Three ATV+RTV+FTC/TDF subjects developed M184V/I by population sequencing and deep sequencing.

[f] NNRTI resistance substitutions (NNRTI-R) are V90I, A98G, L100I, K101E/H/P, K103N/S, V106A/I/M, V108I, E138A/G/K/Q/R, V179D/F/L/T, Y181C/I/V, Y188C/H/L, G190A/E/Q/S, H221Y, P225H, F227C, M230I/L in RT.

[g] One EVG/COBI/FTC/TDF subject developed K101E by deep sequencing, at 23.1%, but this substitution was not observed by population sequencing and did not confer phenotypic resistance to any approved NNRTIs.

[h]Primary protease inhibitor resistance substitutions (PI-R) are D30N, V32I, L33F, M46I/L, I47A/V, G48V, I50L/V, I54L/M, Q58E, T74P, L76V, V82A/F/L/S/T, I84V, N88S, L90M in protease.