DOLUTEGRAVIR-BASED ANTIRETROVIRAL THERAPY FOR PATIENTS CO-INFECTED WITH TUBERCULOSIS AND HIV: A MULTICENTER, NONCOMPARATIVE, OPEN-LABEL, RANDOMIZED TRIAL

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Summary: Dolutegravir (given at a dose of 50 mg twice daily during tuberculosis treatment) demonstrated rapid virologic and immunologic response among HIV treatment-naïve individuals with drug-sensitive tuberculosis. Dolutegravir with rifampicin-containing TB treatment was well-tolerated with no deaths or discontinuations for toxicity.

ABSTRACT

Background

Concurrent treatment of tuberculosis and HIV is challenging owing to drug interactions, overlapping toxicities, and immune reconstitution inflammatory syndrome (IRIS). The efficacy and safety of dolutegravir were assessed in adults with HIV and drug-susceptible tuberculosis.

Methods

INSPIRING (NCT02178592) is a non-comparative, active-control, randomised, open-label study in HIV-1-infected ART-naïve adults (CD4+ ≥50 cells/mm^3). Participants on rifampicin-based tuberculosis treatment ≤8 weeks were randomised (3:2) to receive dolutegravir (50 mg twice-daily during and 2 weeks post-tuberculosis therapy, then 50 mg once-daily) or efavirenz (600 mg daily), with two NRTIs for 52 weeks. The primary endpoint was the proportion of dolutegravir-arm participants with plasma HIV-1-RNA <50 copies/mL (responders) by FDA Snapshot algorithm (intent-to-treat exposed population) at Week 48. The study was not powered to compare arms.

Results

For dolutegravir (N=69), Baseline HIV-1-RNA was >100,000 copies/mL in 64%, with median CD4+ 208 cells/mm^3; for efavirenz (N=44), 55% had HIV-1-RNA >100,000 copies/mL, median CD4+ count was 202 cells/mm^3. Week 48 response rate was 75% (52/69) (95% CI: 65%, 86%) for dolutegravir and 82% (36/44) (95% CI: 70%, 93%) for efavirenz. Dolutegravir non-response was driven by non-treatment-related discontinuations (n=10 lost-to-follow-up). There were no deaths or study drug switches. There were two discontinuations for toxicity (efavirenz). There were three protocol-defined virological failures (2 dolutegravir, no acquired resistance; 1 efavirenz, NRTI and NNRTI emergent resistance). Tuberculosis treatment success was high. TB-associated IRIS was uncommon (4/arm), with no discontinuations for IRIS.

Conclusions

Among adults with HIV receiving rifampicin-based tuberculosis treatment, twice-daily dolutegravir was effective and well-tolerated.

Key Words: HIV; Tuberculosis; HIV; Dolutegravir; Efavirenz; immune reconstitution inflammatory syndrome

INTRODUCTION

Tuberculosis (TB) is the leading cause of death among persons living with HIV (PLWH) (1). Clinical trials have demonstrated the benefit of treating HIV and TB concurrently (2-5). Among HIV treatment-naïve individuals, antiretroviral therapy (ART) should be started within two weeks of TB treatment initiation for patients with a CD4+ lymphocyte count less than 50 cells/mm^3 and within eight weeks for those with higher CD4+ values (6). Co-treatment, while reducing risk of death and new opportunistic infections, poses challenges, owing to overlapping toxicities, drug interactions, and immune reconstitution inflammatory syndrome (IRIS) (7).

Rifamycins (e.g. rifampicin) are the cornerstone of TB therapy because of their unique sterilizing activity against *Mycobacterium tuberculosis* (8,9). If a rifamycin cannot be used, treatment duration must be substantially prolonged. Rifampicin, however, is a potent inducer of the expression of cytochrome P450 (CYP) isoenzymes. It also induces phase 2 enzymes, such as UDP-glucuronosyltransferases (UGT) and sulfotransferases, and transporter proteins, such as P-glycoprotein. Non-nucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors (PI) are substrates of CYP450 enzymes and/or P-glycoprotein, and the plasma concentrations and effectiveness of many NNRTIs and PIs are significantly reduced when co-administered with rifampicin. ART options for patients with TB and HIV are, therefore, very limited (10,11). Dolutegravir is metabolized primarily by UGT1A1, with CYP3A playing a minor role; both enzymes are upregulated by rifampicin (12). In a Phase 1 trial involving healthy HIV-seronegative individuals without TB, rifampicin reduced the area under the concentration-time curve (AUC), maximum concentration (C_{max}), and trough concentration (C_τ) of dolutegravir given at standard dose (50 mg once daily) by 54%, 43%, and 72%, respectively. Increasing dolutegravir dosing frequency to 50 mg twice daily with rifampicin achieved similar trough concentrations to dolutegravir alone at standard dose (13).

The World Health Organization (WHO) recommends dolutegravir-based ART as a preferred first-line regimen for PLWH initiating ART. It is, thus, important to know whether dolutegravir is safe and effective for patients treated for HIV-associated TB. We conducted a multicentre trial to assess the antiviral activity and safety of dolutegravir-based ART among ART-naïve patients with HIV-associated, drug-sensitive TB. Previous data on the use of efavirenz for the treatment of HIV in individuals co-infected with TB were available (14-16), and so, to ensure good study conduct, a non-comparative efavirenz control arm was included.

METHODS

Study design. INSPIRING (NCT02178592) is a non-comparative, active control, randomised, open-label study in HIV-1 infected ART-naïve adults with drug-sensitive TB. The trial was approved by local ethics committees. Participants gave written informed consent.

Thirty-seven sites in seven countries (Argentina, Brazil, Mexico, Peru, Russia, South Africa, Thailand) participated. Adults (age $\geq$18) with culture- or Xpert MTB/RIF (Cepheid) proven, rifampicin-susceptible pulmonary, pleural or lymph node TB were included. An HIV-1 viral load of $\geq$1000 copies/mL and CD4+ count $\geq$50 cells/mm^3 were required. Participants with previous TB; central nervous system, miliary, or pericardial TB; Child-Pugh Class B or C hepatic impairment; positive hepatitis B surface antigen; alanine aminotransferase value twice the upper limit of normal; haemoglobin <7.4 g/dL; platelet count <50,000/mm^3; Grade 4 laboratory abnormality on Screening laboratory testing (chemistry, haematology) or primary HIV-1 viral resistance to nucleoside reverse transcriptase inhibitors (NRTI), NNRTI, or PI were excluded.

Randomisation and masking. Eligible participants were randomly assigned (3:2) to receive dolutegravir or efavirenz. A higher proportion was randomized to the dolutegravir arm to improve precision on estimates

in this group. A central randomization schedule was computer-generated using a validated SAS program. Randomization was stratified by screening plasma HIV-1 RNA ($\leq$ or $>$ 100,000 copies/mL) and CD4+ cell count ($\leq$ or $>$100 cells/mm^3). Participants and site investigators were not masked to allocation.

Procedures. Participants received rifampicin-based TB treatment ($\leq$ 8 weeks) prior to Baseline, through their local TB program, which continued during the study. Participants were randomized to receive either dolutegravir (50 mg twice daily during TB treatment and for two weeks post-TB treatment completion, then 50 mg once daily) or efavirenz (600 mg once daily), together with two NRTIs selected by the investigator in accordance with guidelines (HLA-B*5701 testing required for abacavir). Study HIV treatment was given for 52 weeks.

Participants underwent HIV-1 viral load, CD4+ and safety laboratory testing (chemistry, haematology) and clinical assessments at Baseline and Weeks 4, 8, 12, 24, 36, 48, and 52 (HIV-1 viral load at Week 52 only for participants with ≥50 copies/ml at the Week 48 visit). Plasma for HIV genotyping was assayed at Screening (Viroseq HIV-1 Genotyping System, Abbott Molecular). Further genotyping and phenotyping was performed at Baseline and time of virologic rebound for participants with protocol-defined virologic failure (PDVF) (PhenoSense GT, PhenoSense Integrase and GeneSeq Integrase assays (Monogram Biosciences)). Sparse PK sampling to determine plasma dolutegravir or efavirenz concentrations was performed at Weeks 8, 24, 36, 48. In the dolutegravir arm, samples were collected pre-dose, 1-3 and 4-12 hours post-dose at Weeks 8 and 36, and pre-dose at Weeks 24 and 48. In the efavirenz arm, mid-dosing interval samples were collected (10-14h post-dose). Sputum for acid fast bacilli (AFB) staining and mycobacterial culture were performed at Baseline, 2 and 4 months following TB treatment initiation and at the end of treatment (6 or 9 months, depending on local treatment guidelines). Solid or liquid media could be used for sputum cultures, but the medium had to be consistent across visits for individual patients. Study withdrawal criteria included: PDVF criteria met (see Outcomes); requirement for change or dose modification of study drug (dolutegravir or efavirenz; one NRTI substitution for toxicity was permitted); switch to TB treatment regimen that did not include rifampicin; pregnancy; or protocol-defined adverse events (liver toxicity, renal toxicity, rifampicin-induced thrombocytopenia, rash, hypersensitivity, drug-related grade 4 event).

Following participation in the Randomized phase of the study (i.e. period up to and including the Week 52 visit), individuals in the dolutegravir arm who lived in a setting where dolutegravir was not yet available could continue in the Open Label Extension (OLE) phase of the study and receive dolutegravir until it was available. Participants in the efavirenz arm received study efavirenz up to the Week 52 visit only; however, in South Africa, as per local regulations, provision of efavirenz was extended for 2 years. The OLE phase is ongoing. Only results from the Randomized phase of the trial are presented.

Outcomes. The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 48 (responders) in the dolutegravir arm using a modified version of the U.S. Food and Drug Administration (FDA) Snapshot algorithm for the intention-to-treat exposed (ITT-E) population. The ITT-E population consisted of all participants who received least one dose of study drug.

Secondary efficacy outcomes included Week 24 plasma HIV-1 RNA <50 copies/mL in the dolutegravir arm and Week 24 and 48 plasma HIV-1 RNA <50 copies/mL in the efavirenz arm (ITT-E). Analyses based on per-protocol (PP) populations were also performed. The PP population included individuals without any of the following: (i) inclusion/exclusion criteria deviation (ii) interruption of study drug for >10% of total time on-treatment (calculated based on study drug start and stop dates as recorded in the eCRF) for reasons other than treatment-related adverse events/laboratory abnormalities (iii) permanent discontinuation of study drug due to a protocol deviation or (iv) receipt of prohibited concomitant medications. Other outcomes included change from Baseline in CD4+ counts; proportion of participants with IRIS; incidence and severity of adverse events; and proportion of participants discontinuing study

drug due to adverse event or death. IRIS events were adjudicated by an independent committee masked to treatment arm. Participants with plasma HIV-1 RNA levels ≥400 copies/mL at Week 24 or beyond (confirmed 2 to 6 weeks later) were considered to have met PDVF criteria and discontinued the study once resistance test results were available or earlier at investigator discretion. TB treatment outcomes were defined in accordance with WHO guidelines: treatment success (cure or treatment completion), failure (positive sputum AFB smear at or after 5 months of treatment), death, loss to follow-up, or not-evaluated (e.g. transferred out).

Statistical considerations. The proportion of participants with plasma HIV-1 RNA <50 copies/mL at any time point was derived using a modified version of the FDA Snapshot algorithm (i.e. approved, single protocol-defined background NRTI component switch was not penalized). The Snapshot algorithm treats all participants without HIV-1 RNA data at the visit of interest as non-responders. The trial was not powered to show a difference between study arms; no formal statistical hypothesis was tested. A sample size of 66 to 72 participants in the dolutegravir arm was estimated to have >85% power to detect a response rate of greater than 70%, assuming an 85% response rate at Week 48.

RESULTS

Between January 23, 2015, and October 13, 2017, 113 participants (69 dolutegravir, 44 efavirenz) were enrolled (Figure 1). Demographics, Baseline CD4+ cell count, and proportion with Baseline viral load >100,000 copies/mL are shown in Table 1.

At Week 48, the percentage of responders (ITT-E population) was 75% (52/69, 95% CI 65%-86%) in the dolutegravir arm and 82% (36/44, 95% CI 70%-93%) in the efavirenz arm (Table 2). Virologic response was rapid in the DTG arm (Figure 2). All 17 Snapshot non-responders in the dolutegravir arm were due to non-treatment-related reasons, e.g. 10 being lost to follow-up, most after completing their TB treatment (Table 3). There were no deaths, changes in ART, or discontinuations for protocol-defined adverse events in the dolutegravir arm. In the efavirenz arm, among the 8 participants classified as Snapshot non-responders, 2 had HIV-1 RNA ≥50 copies/mL at Week 48, 2 discontinued for drug-related adverse events and 4 discontinued for non-treatment related reasons; there were no deaths or treatment switches. PP and 24-week ITT-E response rates are shown in Table 2.

Three participants (2 dolutegravir, 1 efavirenz) met PDVF criteria. Only the efavirenz arm participant demonstrated acquired resistance mutations (to NNRTI and NRTI, Supplemenary Figure S1). Median CD4 count increases were 146 (IQR 71, 214) and 220 (IQR 111, 271) cells/mm^3 (dolutegravir) and 93 (IQR 47, 178) and 190 (IQR 104, 252) cells/mm^3 (efavirenz) by Weeks 24 and 48, respectively. Dolutegravir trough concentrations were similar when dosed twice-daily with TB treatment vs. once daily dosing alone (Table 4). In the dolutegravir arm, 88% achieved TB treatment success, with no treatment failures. In the efavirenz arm, 91% had treatment success (one patient with treatment failure (positive cultures months 4 and 6) had negative culture at 9 months).

Adverse events were common (75% dolutegravir arm, 91% efavirenz arm). Grade 3 or 4 adverse events and serious adverse events were rare. There were two drug-related adverse events that resulted in discontinuation of therapy, both in the efavirenz arm. Four (6%) participants in the dolutegravir arm and 4 (9%) participants in the efavirenz arm met criteria for TB-associated IRIS. Two participants in the dolutegravir arm met criteria for non-TB IRIS, one with strongyloidiasis (also met TB IRIS criterion mentioned above) and one with herpes zoster, making a total of 5 participants (7%) with any IRIS. No participant discontinued the study due to IRIS. Two participants had Grade 3 elevations in alanine aminotransferase (ALT) values (with normal bilirubin), one in each arm, neither resulting in treatment discontinuation (Table 5).

DISCUSSION

In our trial, dolutegravir 50 mg twice daily in combination with two NRTIs produced rapid virologic and immunologic responses in treatment-naïve patients with TB and HIV. It was well-tolerated, with no discontinuations for adverse events, including IRIS or liver toxicity, no deaths and no emergence of drug resistance.

Options for persons with HIV-associated TB remain limited. While substituting rifampicin with rifabutin to avoid drug interactions is clinically acceptable, it is rarely possible in high TB burden countries because of cost, availability, and lack of rifabutin-containing fixed-dose combinations. Efavirenz, given with an NRTI backbone can be used without dose adjustment with rifampicin (17). Double-dose raltegravir is also an option (16). Most other antiretrovirals, including the recently approved bictegravir, either cannot be used with rifampicin because of drug interactions or must be used with caution because of toxicity (18-22). A previous study conducted among healthy HIV-uninfected volunteers without TB showed that rifampicin reduced concentrations of dolutegravir when the two drugs were co-administered but that doubling the dose mitigated the drug interaction (13). Average trough concentrations of dolutegravir 50 mg twice daily were similar to trough concentrations when dolutegravir was given at 50 mg once a day without TB treatment and were well above target trough concentrations (>300 ng/mL, achieved with a DTG 10 mg daily dose) and the protein-adjusted 90% inhibitory concentration of 64 ng/mL) (23). Virologic suppression and higher-than-target median DTG C_{12h} concentrations in this study and in the eight participants with TB and HIV in the ANRS-12313 NAMSAL study taking twice-daily dolutegravir (DTG C_{12h} 1123 ng/mL (IQR, 820-1746)) (23) provide support for this dosing strategy.

There has been concern that IRIS, particularly among patients with TB, would be more common among patients receiving INSTI than other ARVs given the rapid virologic decline observed with INSTIs and the association between rate of virologic decline and IRIS (24). In our trial, IRIS incidence was low, which is similar to the results of a recent meta-analysis of HIV-1-mononifected patients and the 1800-participant REALITY trial (25)(26). Perhaps rapid virologic decline is not the trigger for IRIS, and we should think about IRIS in a more sophisticated way (2,3,5). Whether or not IRIS incidence and/or severity would be different for dolutegravir vs. efavirenz in patients with severe immunosuppression - who also require earlier initiation of ART after starting TB treatment - is unknown and remains an area for further investigation.

Recently, WHO recommended dolutegravir as first-line therapy for initiation of ART (27,28), due to increasing levels of transmitted NNRTI drug resistance in low- and middle-income countries (29), as well as its high barrier to resistance and improved tolerability compared to efavirenz. Through PEPFAR and other programs, generic dolutegravir is increasingly available in resource-limited countries (30). In many settings, particularly in those areas where HIV treatment is provided on a large scale via public health clinics, HIV treatment is standardized, with a preference for drugs that can be used for all patients, including pregnant women and patients with TB. Our data suggest that dolutegravir can also be used in adults with TB, provided the dose is adjusted.

INSPIRING was not powered to assess differences between arms. Rather it was designed to see if dolutegravir can be used in patients with TB. At the time this study was designed, there were few randomized controlled trials of different HIV regimens in this population, with the majority of data from studies of EFV. A study designed to formally compare the two regimens, assuming a non-inferiority margin of 10% and 85% treatment success in each arm, with 2.5% one-sided significance, would have required 536 patients (268 in each arm). Enrolling a trial involving participants with HIV/TB co-infection

is challenging, even in settings with high burdens of both diseases—in our study enrolment of 113 patients at 37 sites in 7 countries took almost 2 years. Instead, we included an efavirenz arm as a non-comparative active control arm to assess and confirm the good conduct of the study as several historical data exist for EFV in this population. Having a smaller sample size, while not allowing for a statistically-powered comparison, allowed for more rapid generation of efficacy and safety information. Further work to assess tolerability in larger patient populations is needed and should be part of pharmacovigilance efforts with rollout.

In INSPIRING, we observed a high number of participants discontinuing for non-treatment-related reasons in the dolutegravir arm with most being virologically-suppressed at the time of discontinuation. Detailed investigation revealed no pattern or specific treatment-related reason for withdrawal. Tolerability appeared to be good, though it is not possible to know if dropouts were related to unreported side effects. It is reassuring that dropouts occurred at variable time points (Days 25, 80, 118, 177, 181, 192, 223, 253, 255, 256, 268, 326, and 337), most following completion of TB treatment, when IRIS or drug interactions are less likely. Participants in the efavirenz arm achieved higher rates of virologic suppression at Weeks 24 (89%) and 48 (82%), than are typically seen in studies involving this population receiving efavirenz (2,3,14,16,31,32), demonstrating that sites were attentive to TB/HIV co-management challenges and that adherence was good. In REFLATE, a similar trial of INSTI-based ART in TB/HIV, Week 48 response rates were 63% (raltegravir 800 mg twice daily), 76% (raltegravir 400 mg twice daily), and 67% (efavirenz) (13). In REFLATE, non-response by snapshot was driven by discontinuations due to AEs as well as PDVF with development of treatment-emergent resistance, which is in contrast with the INSPIRING results that are in line with the recognised high barrier to resistance of dolutegravir.

To use dolutegravir-based ART with rifampicin-containing TB treatment will require resources and coordination. Dolutegravir dosing should be increased to 50 mg twice daily during TB treatment (and for two weeks following TB treatment completion), and so an additional (non-FDC) dose of dolutegravir must be available. Additionally, coordination between HIV and TB providers is critical to ensure that dose adjustments are made (at the beginning and end of co-treatment, and in situations of prolonged treatment interruption). However, the logistics of different dosing for patients is less complicated than the logistics of providing different regimens and requiring an ART regimen switch upon TB diagnosis in patients stable and suppressed on their current regimen. Whether giving dolutegravir at a dose of 50mg or100mg once-daily (rather than 50mg twice-daily) will be efficacious requires further study (33). In addition, children are a subpopulation with few treatment options for HIV/TB co-treatment, especially since efavirenz cannot be given to children under the age of 3 years and pediatric formulations are lacking (34); further study of dolutegravir-containing regimens in children is a priority.

In conclusion, our trial provides efficacy, safety and pharmacokinetic evidence that dolutegravir is effective and well-tolerated in HIV treatment naïve patients who have drug-susceptible TB and are taking rifampicin-containing TB treatment, provided the dolutegravir dose is increased to 50 mg twice-daily during (and for two weeks after) TB treatment. More work is needed to characterize the safety and tolerability of dolutegravir-based ART in children and in patients with low CD4 counts.

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CONFLICTS OF INTERESTS

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APPENDIX

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Figure Legends:

Figure 1: Trial profile

* Among 139 for whom inclusion/exclusion criteria were not met, the most common reasons were transmitted drug resistance (29/139, 21%), CD4+ <50 cells/mm_3 (18%), and hepatitis B co-infection (15%).

† Figure shows all discontinuations up to end of Randomized Phase. One DTG subject met PDVF at Week 36 and discontinued study due to lack of efficacy, but subject had HIV-1 RNA <50 c/mL at withdrawal visit (within Week 48) and classified as a Snapshot responder. Another DTG subject was lost to follow-up within the Randomized Phase after having HIV-1 RNA <50 c/mL at Week 48. One EFV subject met PDFV at Week 36 and had HIV RNA ≤50 c/ml at withdrawal visit (within Week 48) and classified as Snapshot "Data in window not <50 c/mL."

‡ Five participants (n=3, dolutegravir; n=2, efavirenz) became pregnant during the randomized phase of the study and three delivered healthy babies. One dolutegravir participant experienced an SAE of ectopic pregnancy. One efavirenz participant experienced an SAE of spontaneous abortion.

Figure 2: Proportion of participants in the ITT-E population with Snapshot HIV-1 RNA ≤50 copies/mL,

by week following initiation of antiretroviral therapy with dolutegravir (DTG) or efavirenz (EFV).

TABLES

Table 1. Demographic and baseline characteristics, by treatment arm.

Characteristic	DTG (N=69)	EFV (N=44)
Age, median (min, max), years	33 (18, 62)	32 (20, 50)
≥50 years, n (%)		2 (5)
	9 (13)	
Female, n (%)	30 (43)	16 (36)
African-Heritage/African, n (%)	47 (68)	29 (66)
HIV-1 RNA, median (Q1, Q3), $\log_{10}$ copies/mL	5.10 (4.74, 5.47)	5.24 (4.50, 5.67)
>100,000 copies/mL, n (%)	44 (64)	24 (55)
CD4+ cell count, median (Q1, Q3), cells/mm^3	208 (128, 410)	202 (92, 354)
≤100 cells/mm^3, n (%)		
	13 (19)	12 (27)
Current TB conditions, n (%)		
Pulmonary TB	65 (94)	44 (100)
Lymph node TB	5 (7)	1 (2)
Pleural TB	5 (7)	0
Time from start of TB therapy to Day 1, median (Q1, Q3), days	35.0 (28.0, 44.0)	33.5 (26.0, 52.0)
NRTI backbone, n (%)		
TDF/FTC	50 (72)	33 (75)
TDF/3TC	12 (17)	9 (20)
ABC/3TC	3 (4)	1 (2)
AZT/3TC	2 (3)	1 (2)
d4T/3TC	1 (1)	0
ddI/3TC	1 (1)	0

Table 2. Summary of Snapshot study outcomes (plasma HIV-1 RNA < 50 c/mL), by visit, treatment group, and study population.

Arm	ITT-E 24 weeks	ITT-E 48 weeks	PP 48 weeks
Dolutegravir	56/69 (81%) 95% CI 72-90%	52/69 (75%) 95% CI 65-86%	49/62 (79%) 95% CI 69-89%
Efavirenz	39/44 (89%) 95% CI 79-98%	36/44 (82%) 95% CI 70-93%	33/41 (80%) 95% CI 68-93%

*ITT-E=intent-to-treat exposed; PP=per protocol

Table 3. Modified FDA Snapshot Outcomes at Week 48, ITT-E population.

N(%)	Dolutegravir arm (N=69)	Efavirenz arm (N=44)
Virologic success (HIV-1 RNA <50 copies/mL)	**52 (75)**	**36 (82)**
Snapshot non-responders	**6 (9)**	**3 (7)**
Data in window not <50 copies/mL	0	2 (5)
Discontinued for other reason while not <50 copies/mL	6 (9)[a]	1 (2)[b]
Change in antiretroviral treatment	0	0
No virologic data	**11 (16)**	**5 (11)**
Discontinued because of adverse event or death	0	2 (5)[c]
Discontinued for other reasons	11 (16)[d]	3 (7)[e]
Missing data during window but on study	0	0

[a]3 lost to follow-up; 2 withdrawal of consent; 1 pregnancy; [b]1 lost to follow-up; [c]1 hypersensitivity to EFV; 1 increased gamma-glutamyltransferase; [d]7 lost to follow-up (2 of whom had no on-treatment HIV-1 RNA assessment); 2 pregnancies; 1 based on physician decision; 1 withdrawal of consent; [e]2 lost to follow-up; 1 withdrawal of consent.

Table 4. Geometric mean (with 90% confidence interval) plasma concentrations for dolutegravir (trough, C_t)(ng/mL) and efavirenz (mid-dose interval, 10-14h)(mcg/mL), during concurrent TB treatment (Week 8 and 24) versus during treatment for HIV alone (Weeks 36 and 48).

	Dolutegravir 50mg twice daily		Dolutegravir 50mg once daily		Efavirenz 600mg once daily		
	C12h, Week 8	C12h Week 24	C24h, Week 36	C24h, Week 48	Week 8	Week 36	Week 48
N	42	23	27	26	24	21	20
Geometric mean (SD)	870 (2.54)	964 (4.22)	854 (3.64)	881 (4.38)	3.37 (2.37)	2.89 (2.22)	2.52 (2.81)
90% confidence interval (CI)	208, 2340	<LLQ, 3380	64.7, 3310	47.1, 3310	1.35, 23.4	1.30, 11.0	0.63, 19.6

*SD, standard deviation; LLQ, lower limit of quantification (LLQ=20 ng/mL)

Table 5. Number (%) of participants with adverse events (AE), by arm.

n (%)	DTG (n=69)	EFV (n=44)
Any AE	52 (75)	40 (91)
AEs occurring in ≥10% of participants in either group		
Headache	9 (13)	6 (14)
Upper respiratory tract infection	5 (7)	8 (18)
Diarrhea	3 (4)	10 (23)
Vomiting	5 (7)	3 (7)
Dizziness	3 (4)	6 (14)
Arthralgia	7 (10)	0
Gastroenteritis	1 (1)	5 (11)
Any serious AE (SAE)[a]	5 (7)	5 (11)
Drug-related SAEs[b]	2 (3)	1 (2)
Any drug-related AE	19 (28)	14 (32)
Grades 1-2	16 (23)	12 (27)
Grade 3	2 (3)	1 (2)
Grade 4	1 (1)	1 (2)
AEs leading to withdrawal	0	2 (5)[c]
Any psychiatric AE	5 (7)	6 (14)
Grade 1-2	5 (7)	6 (14)
Grade 3-4	0	0
SAE	0	1 (2)[d]

[a] DTG arm: TB-associated IRIS, GI tuberculosis, ruptured ectopic pregnancy, bronchospasm, and cellulitis and skin abrasion, which were both experienced by one participant; EFV arm: pneumonia, patella fracture, spontaneous abortion, suicidal ideation, and IRIS and acute kidney injury, which were both experienced by one participant;

[b] DTG arm: TB-associated IRIS, Day 15; ruptured ectopic pregnancy; EFV arm: IRIS Day 8

[c] Drug hypersensitivity; gamma-glutamyltransferase (GGT) elevation

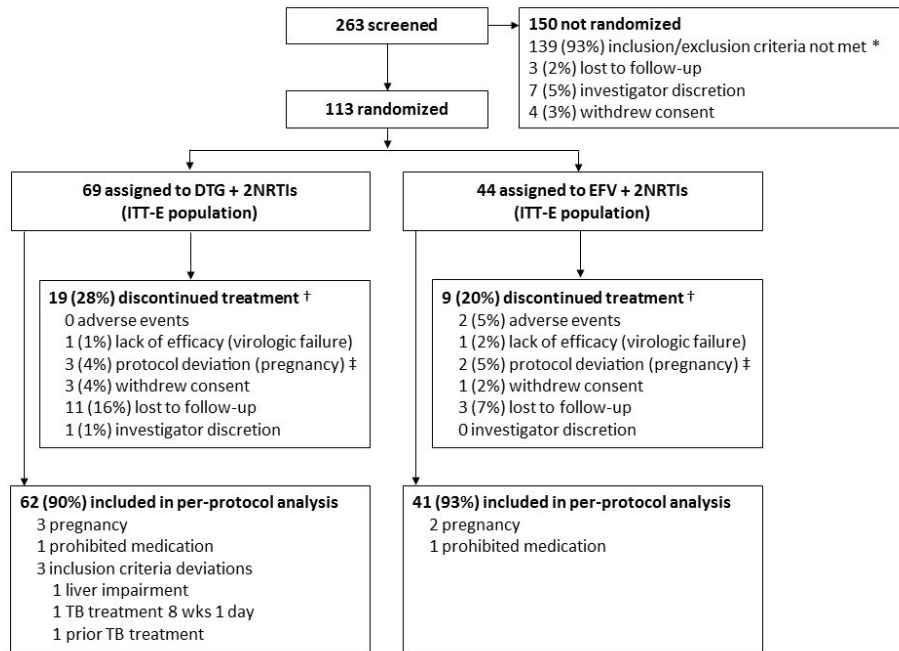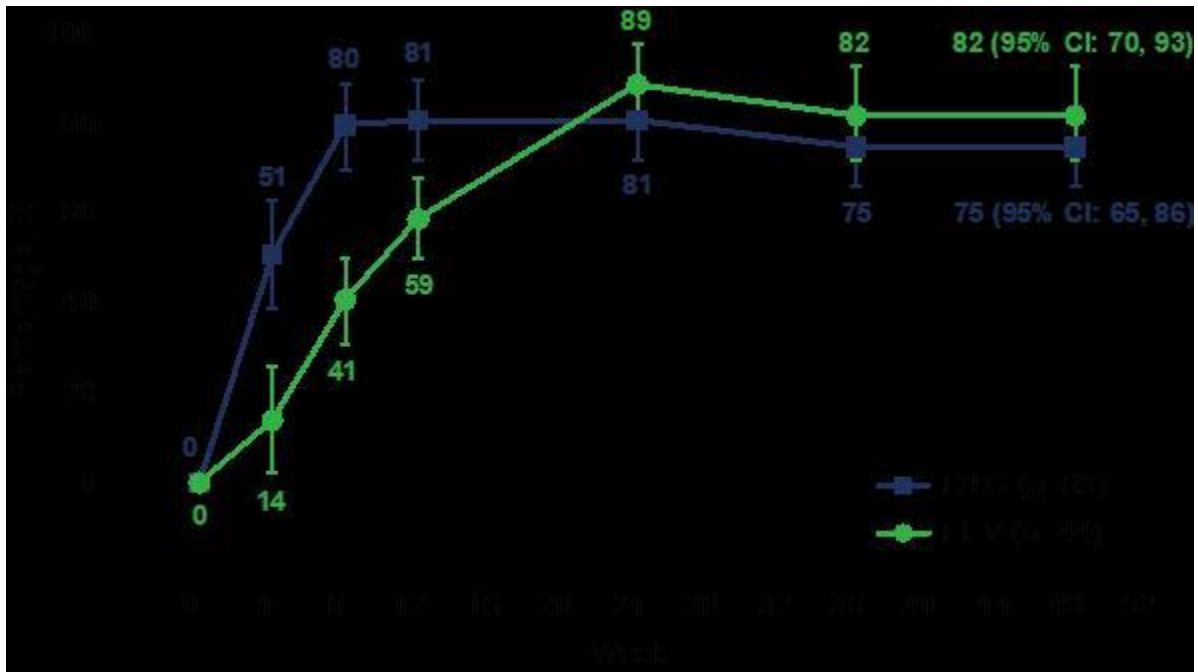[d] Suicidal ideation, considered unrelated to study drug and resolving the same day

Figure 1

Figure 2