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MAJOR ARTICLE

Dolutegravir-based Antiretroviral Therapy for Patients Coinfected With Tuberculosis and Human Immunodeficiency Virus: A Multicenter, Noncomparative, Open-label, Randomized Trial

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

Methods. International Study of Patients with HIV on Rifampicin ING is a noncomparative, active-control, randomized, open-label study in HIV-1–infected antiretroviral therapy–naive adults (CD4+ ≥50 cells/mm^3). Participants on rifampicin-based tuberculosis treatment ≤8 weeks were randomized (3:2) to receive DTG (50 mg twice daily both during and 2 weeks after tuberculosis therapy, then 50 mg once daily) or efavirenz (EFV; 600 mg daily) with 2 nucleoside reverse transcriptase inhibitors for 52 weeks. The primary endpoint was the proportion of DTG-arm participants with plasma HIV-1-RNA <50 copies/mL (responders) by the Food and Drug Administration Snapshot algorithm (intent-to-treat exposed population) at Week 48. The study was not powered to compare arms.

Results. For DTG (n = 69), the baseline HIV-1 RNA was >100 000 copies/mL in 64% of participants, with a median CD4+ count of 208 cells/mm^3; for EFV (n = 44), 55% of participants had HIV-1 RNA >100 000 copies/mL, with a median CD4+ count of 202 cells/mm^3. The Week 48 response rates were 75% (52/69, 95% confidence interval [CI] 65–86%) for DTG and 82% (36/44, 95% CI 70–93%) for EFV. The DTG nonresponses were driven by non–treatment related discontinuations (n = 10 lost to follow-up). There were no deaths or study drug switches. There were 2 discontinuations for toxicity (EFV). There were 3 protocol-defined virological failures (2 DTG, no acquired resistance; 1 EFV, emergent resistance to nucleoside reverse transcriptase inhibitors and nonnucleoside reverse transcriptase inhibitors). The tuberculosis treatment success rate was high. Tuberculosis-associated IRIS was uncommon (4/arm), with no discontinuations for IRIS.

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

Clinical Trials Registration. NCT02178592.

Keywords. HIV; tuberculosis; dolutegravir; efavirenz; immune reconstitution inflammatory syndrome.

Tuberculosis (TB) is the leading cause of death among persons living with human immunodeficiency virus (PLWH; HIV) [1]. Clinical trials have demonstrated the benefit of treating HIV and TB concurrently [2–5]. Among HIV treatment-naive individuals, antiretroviral therapy (ART) should be started within 2 weeks of TB treatment initiation for patients with a CD4+ lymphocyte count less than 50 cells/mm^3 and within 8 weeks for those with higher CD4+ values [6]. Cotreatment, 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 (eg, rifampicin) are the cornerstone of TB therapy, because of their unique sterilizing activity against *Mycobacterium tuberculosis* [8, 9]. If a rifamycin cannot be used, the treatment duration must be substantially prolonged. Rifampicin,

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however, is a potent inducer of the expression of cytochrome P450 (CYP) isoenzymes. It also induces Phase II enzymes, such as uridine 5'-diphospho-glucuronosyltransfernases (UGT) and sulfotransferases, and transporter proteins, such as P-glycoprotein. Nonnucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) are substrates of CYP450 enzymes and/or P-glycoprotein, and the plasma concentrations and effectiveness of many NNRTIs and PIs are significantly reduced when coadministered with rifampicin. ART options for patients with TB and HIV are, therefore, very limited [10, 11]. Dolutegravir (DTG) is metabolized primarily by UGT1A1, with CYP3A playing a minor role; both enzymes are upregulated by rifampicin [12]. In a Phase I trial involving healthy, HIV-seronegative individuals without TB, rifampicin reduced the area under the concentration-time curve, maximum concentration, and trough concentration of DTG, given at standard dose (50 mg once daily), by 54%, 43%, and 72%, respectively. Increasing the DTG dosing frequency to 50 mg twice daily with rifampicin achieved similar trough concentrations to DTG alone at the standard dose [13].

The World Health Organization (WHO) recommends DTG-based ART as a preferred first-line regimen for PLWH initiating ART. It is, thus, important to know whether DTG is safe and effective for patients treated for HIV-associated TB. We conducted a multicenter trial to assess the antiviral activity and safety of DTG-based ART among ART-naive patients with HIV-associated, drug-sensitive TB. Previous data on the use of efavirenz (EFV) for the treatment of HIV in individuals coinfected with TB were available [14–16]; to ensure good study conduct, a noncomparative EFV control arm was included.

METHODS

Study Design

International Study of Patients with HIV on Rifampicin ING (INSPIRING) (NCT02178592) is a noncomparative, active control, randomized, open-label study in HIV-1–infected, ART-naive adults with drug-sensitive TB. The trial was approved by local ethics committees. Participants gave written informed consent.

There were 37 sites in 7 countries (Argentina, Brazil, Mexico, Peru, Russia, South Africa, and Thailand) that participated. Adults (age ≥18) with culture-proven or Xpert *Mycobacterium tuberculosis* DNA and resistance to rifampicin (Cepheid)-proven, rifampicin-susceptible pulmonary, pleural, or lymph node TB were included. An HIV-1 viral load of ≥1000 copies/mL and a CD4+ count ≥50 cells/mm^3 were required. Participants with previous instances of TB; central nervous system, miliary, or pericardial TB; Child-Pugh Class B or C hepatic impairments; positive hepatitis B surface antigens; alanine aminotransferase values twice the upper limit of normal; hemoglobin measurements <7.4 g/dL; platelet counts <50 000/mm^3; Grade 4 laboratory abnormalities on screening laboratory testing (chemistry, hematology), or primary HIV-1 viral resistance to nucleoside reverse transcriptase inhibitors (NRTI), NNRTI, or PI were excluded.

Randomization and Masking

Eligible participants were randomly assigned (3:2) to receive DTG or EFV. A higher proportion was randomized to the DTG arm to improve the precision on estimates in this group. A central randomization schedule was computer-generated using a validated Statistical Analysis System program. Randomization was stratified by screening plasma HIV-1 RNA (≤ or ≥ 100 000 copies/mL) and CD4+ cell count (≤ or >100 cells/mm^3). Participants and site investigators were not masked to allocation.

Procedures

Participants received rifampicin-based TB treatment (≤8 weeks) prior to baseline, through their local TB program, which continued during the study. Participants were randomized to receive either DTG (50 mg twice daily during TB treatment and for 2 weeks after TB treatment completion, then 50 mg once daily) or EFV (600 mg once daily), together with 2 NRTIs selected by the investigator in accordance with guidelines (human leukocyte antigen-B*5701 testing required for abacavir). The study HIV treatment was given for 52 weeks.

Participants underwent HIV-1 viral load, CD4+, and safety laboratory testing (chemistry, hematology), as well as clinical assessments, at baseline and at Weeks 4, 8, 12, 24, 36, 48, and 52 (HIV-1 viral loads were tested 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 at the time of virologic rebound for participants with protocol-defined virologic failure (PDVF; PhenoSense GT, PhenoSense Integrase, and GeneSeq Integrase assays [Monogram Biosciences]). Sparse pharmacokinetic sampling to determine plasma DTG or EFV concentrations was performed at Weeks 8, 24, 36, and 48. In the DTG arm, samples were collected predose, at 1–3 and 4–12 hours postdose at Weeks 8 and 36, and predose at Weeks 24 and 48. In the EFV arm, mid-dosing interval samples were collected (10–14h postdose). Sputum were collected at baseline, at 2 and 4 months following TB treatment initiation, and at the end of treatment (6 or 9 months, depending on local treatment guidelines) for acid-fast bacilli staining and mycobacterial cultures. Solid or liquid media could be used for sputum cultures, but the medium had to be consistent across visits for individual patients. The study withdrawal criteria included: the PDVF criteria being met (see Outcomes); a requirement for a change or dose modification of the study drug (DTG or EFV; 1 NRTI substitution for toxicity was permitted); a switch to a TB treatment regimen that did not include rifampicin; pregnancy; or a protocol-defined adverse event (liver toxicity, renal toxicity, rifampicin-induced thrombocytopenia, a rash, hypersensitivity, or a drug-related Grade 4 event).

Following participation in the randomized phase of the study (ie, the period up to and including the Week 52 visit), individuals in the DTG arm who lived in a setting where DTG was not yet available could continue in the open-label extension phase of the study and receive DTG until it was available. Participants in the EFV arm received study EFV up to the Week 52 visit only; however, in South Africa, as per local regulations, the provision of EFV was extended for 2 years. The open-label extension 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 DTG arm, using a modified version of the US Food and Drug Administration Snapshot algorithm for the intention-to-treat exposed (ITT-E) population. The ITT-E population consisted of all participants who received at least 1 dose of a study drug.

The secondary efficacy outcomes included Week 24 plasma HIV-1 RNA <50 copies/mL in the DTG arm and Week 24 and 48 plasma HIV-1 RNA <50 copies/mL in the EFV arm (ITT-E). Analyses based on per-protocol (PP) populations were also performed. The PP population included individuals without: (1) an inclusion/exclusion criteria deviation; (2) an interruption of study drug for >10% of the total time on treatment (calculated based on the study drug start and stop dates as recorded in the electronic case report form) for reasons other than treatment-related adverse events/laboratory abnormalities; (3) the permanent discontinuation of a study drug due to a protocol deviation; or (4) the receipt

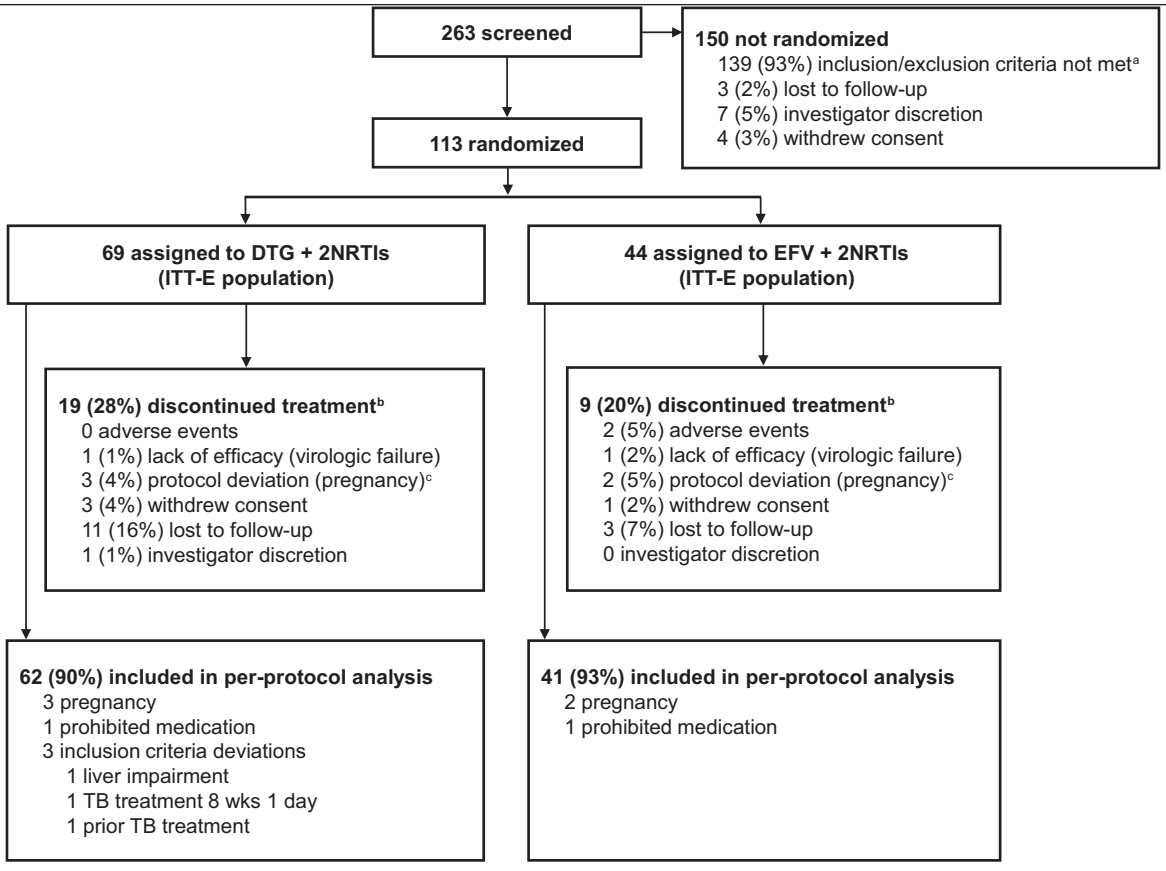

Figure 1. Trial profile. Abbreviations: DTG, dolutegravir; EFV, efavirenz; HIV-1, human immunodeficiency virus–1; ITT-E, intent-to-treat exposed; NRTI, nucleoside reverse transcriptase inhibitors; PDVF, protocol-defined virologic failure; SAE, serious adverse event; TB, tuberculosis.

[a]Among the 139 participants for whom the inclusion criteria were not met, the most common reason for exclusions were transmitted drug resistance (29/139, 21%), CD4+ <50 cells/mm3 (18%), and hepatitis B coinfection (15%).

[b]The figure shows all discontinuations up to the end of the randomized phase. There was 1 DTG subject who met PDVF at Week 36 and discontinued the study due to lack of efficacy, but the subject had HIV-1 RNA <50 c/mL at the 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. There was 1 EFV subject who met PDFV at Week 36 and had HIV RNA ≤50 c/ml at the withdrawal visit (within Week 48) and classified as Snapshot "Data in window not <50 c/mL."

[c]There were 5 participants (n = 3 DTG; n = 2 EFV) who became pregnant during the randomized phase of the study: 3 delivered healthy babies; 1 DTG participant experienced an SAE of ectopic pregnancy; and 1 EFV participant experienced an SAE of spontaneous abortion.

of prohibited concomitant medications. Other outcomes included changes from baseline in CD4+ counts; the proportion of participants with IRIS; the incidence rate and severity of adverse events; and the proportion of participants discontinuing a study drug due to an adverse event or death. IRIS events were adjudicated by an independent committee masked to the 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 the PDVF criteria and discontinued the study once resistance test results were available or earlier, at investigator discretion. The TB treatment outcomes were defined, in accordance with WHO guidelines, as treatment success (cure or treatment completion), failure (positive sputum acid-fast bacilli smear at or after 5 months of treatment), death, loss to follow-up, or not evaluated (eg, 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 Food and Drug Administration Snapshot algorithm (ie, an 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 nonresponders. 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 DTG 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 23 January 2015 and 13 October 2017, 113 participants (69 DTG, 44 EFV) were enrolled (Figure 1). Demographics, baseline CD4+ cell counts, and the proportion of participants with baseline viral loads >100 000 copies/mL are shown in Table 1.

At Week 48, the percentage of responders (ITT-E population) was 75% (52/69, 95% confidence interval [CI] 65–86%) in the DTG arm and 82% (36/44, 95% CI 70–93%) in the EFV arm (Table 2). Virologic responses were rapid in the DTG arm (Figure 2). All 17 Snapshot nonresponders in the DTG arm were due to non–treatment related reasons (eg, 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 DTG arm. In the EFV arm, among the 8 participants classified as Snapshot nonresponders, 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.

Table 1. Demographic and Baseline Characteristics, by Treatment Arm

Characteristic	DTG (n = 69)	EFV (n = 44)
Age, median (min, max),	33 (18, 62)	32 (20, 50)
years ≥50 years, n (%)	9 (13)	2 (5)
Female, n (%)	30 (43)	16 (36)
African-Heritage/African, n (%)	47 (68)	29 (66)
HIV-1 RNA, median (IQR), $\log_{10}$	5.10 (4.74, 5.47)	5.24 (4.50, 5.67)
copies/mL >100 000 copies/mL, n (%)	44 (64)	24 (55)
CD4+ cell count, median (IQR),	208 (128, 410)	202 (92, 354)
cells/mm^3 ≤100 cells/mm^3, n (%)	13 (19)	12 (27)
Current TB conditions, n (%): Pulmonary TB, Lymph node TB, Pleural TB	65 (94), 5 (7), 5 (7)	44 (100), 1 (2), 0
Time from start of TB therapy to Day 1, median (IQR), 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

Abbreviations: 3TC, lamivudine; ABC, abacavir; AZT, zidovudine; d4T, Stavudine; ddI, didanosine; DTG, dolutegravir; EFV, efavirenz; FTC, Emtricitabine; HIV-1, human immunodeficiency virus–1; IQR, interquartile range; NRTI, nucleoside reverse transcriptase inhibitors; TB, tuberculosis; TDF, tenofovir disoproxil fumarate.

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

Adverse events were common (75% in the DTG arm and 91% in the EFV arm). Grade 3 or 4 adverse events and serious adverse events were rare. There were 2 drug-related adverse

Table 2. Summary of Snapshot Study Outcomes, by Visit, Treatment Group, and Study Population

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

Outcomes data indicate participants with plasma HIV-1 RNA < 50 c/mL.

Abbreviations: CI, confidence interval; HIV-1, human immunodeficiency virus–1; ITT-E, intent-to-treat exposed; PP, per protocol.

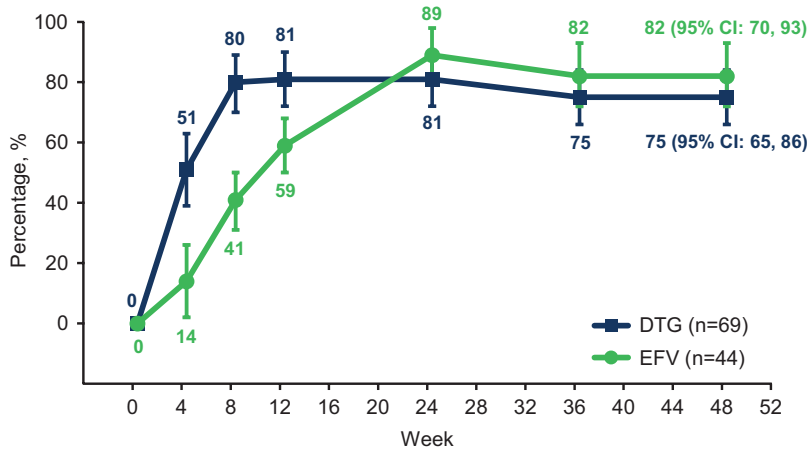

Figure 2. Proportion of participants in the ITT-E population with Snapshot HIV-1 RNA ≤50 copies/mL, by week following initiation of antiretroviral therapy with DTG or EFV. Abbreviations: CI, confidence interval; DTG, dolutegravir; EFV, efavirenz; HIV-1, human immunodeficiency virus–1; ITT-E, intent-to-treat exposed.

events that resulted in the discontinuation of therapy; both were in the EFV arm. There were 4 (6%) participants in the DTG arm and 4 (9%) participants in the EFV arm that met the criteria for TB-associated IRIS. There were 2 participants in the DTG arm that met the criteria for non-TB IRIS: 1 with strongyloidiasis (also met TB IRIS criterion mentioned above) and 1 with herpes zoster. Thus, there was a total of 5 participants (7%) with any IRIS. No participant discontinued the study due to IRIS. There were 2 participants who had Grade 3 elevations in alanine aminotransferase values (with normal bilirubin), with 1 in each arm and neither resulting in treatment discontinuation (Table 5).

Table 3. Modified Food and Drug Administration Snapshot Outcomes at Week 48, Intent-to-treat Exposed Population

n (%)	Dolutegravir arm (n = 69)	EFV arm (n = 44)
Virologic success (HIV-1 RNA <50 copies/mL)	52 (75)	36 (82)
Snapshot nonresponders	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

Abbreviations: EFV, efavirenz; HIV-1, human immunodeficiency virus–1.

[a]Data represent 3 participants lost to follow-up; 2 withdrawals of consent; and 1 pregnancy.

[b]Data represent 1 participant lost to follow-up.

[c]Data represent hypersensitivity to EFV and 1 participant with increased gamma-glutamyltransferase.

[d]Data represent 7 participants lost to follow-up (2 of whom had no on-treatment HIV-1 RNA assessment); 2 pregnancies; 1 withdrawal based on physician decision; and 1 withdrawal of consent.

[e]Data represent 2 participants lost to follow-up and 1 withdrawal of consent.

DISCUSSION

In our trial, DTG at 50 mg twice daily, in combination with 2 NRTIs, produced rapid virologic and immunologic responses in treatment-naive 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 countries with high TB burdens because of a high cost, limited availability, and a lack of rifabutin-containing fixed-dose combinations. EFV, given with an NRTI backbone, can be used without dose adjustments 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 DTG when the 2 drugs were coadministered, but that doubling the dose mitigated the drug interaction [13]. Average trough concentrations of DTG at 50 mg twice daily were similar to trough concentrations when DTG was given at 50 mg once a day without TB treatment, and were well above the target trough concentrations (>300 ng/mL, achieved with a DTG 10 mg daily dose) and the protein-adjusted 90% inhibitory concentration (64 ng/mL) [23]. Virologic suppression and higher-than-target median DTG C_{12h} concentrations in this study and in the 8 participants with TB and HIV in the French National Agency for Research on AIDS and Viral Hepatitis (ANRS) 12 313 New Antiretroviral and Monitoring Strategies in HIV-infected Adults in Low-income countries study, taking twice-daily DTG (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 integrase strand transfer inhibitor (INSTI) than other antiretroviral, given the rapid virologic decline observed with INSTIs and the association between rates of virologic decline and IRIS [24]. In our trial, the IRIS incidence was low and was similar to the results of a recent meta-analysis of HIV-1–mononifected patients and the 1800-participant reduction of early mortality in HIV infected adults and children starting ART 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 incidences and/or severities would be different for DTG vs EFV 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, the WHO recommended DTG as a first-line therapy for the 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 EFV. Through U.S. President's Emergency Plan for AIDS Relief and other programs, generic DTG 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 DTG 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 whether DTG could 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 2 regimens, assuming a noninferiority margin of 10% and 85% treatment success in each arm, with 2.5% 1-sided significance, would have required 536 patients (268 in each arm). Enrolling a trial involving participants with HIV/TB coinfections is challenging, even in settings with high burdens of both diseases; in our study, the enrollment of 113 patients at 37 sites in 7 countries took almost 2 years. Instead, we included an EFV arm as a noncomparative, 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 the 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 rollouts.

In INSPIRING, we observed a high number of participants discontinuing for non–treatment related reasons in the DTG arm, with most being virologically suppressed at the time of discontinuation. A detailed investigation revealed no pattern or specific treatment-related reasons for withdrawal. Tolerability appeared to be good, though it is not possible to know whether 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 the completion of TB treatment, when IRIS or drug interactions are less likely. Participants in the EFV arm achieved higher rates of virologic suppression at Weeks 24 (89%) and 48 (82%) than are typically seen in studies where this population has received EFV [2, 3, 14, 16, 31, 32], demonstrating that the sites were attentive to TB/HIV comanagement challenges and that adherence was good. In ANRS 12 180 Raltegravir for the treatment of patients co-infected with HIV and tuberculosis (REFLATE TB) a similar trial of INSTI-based ART in TB/HIV, Week 48 response rates were 63% (raltegravir at 800 mg twice daily), 76% (raltegravir at 400 mg twice daily), and 67% (EFV) [13]. In REFLATE, nonresponses by Snapshot were driven by discontinuations due to AEs, as well as PDVF, with the development of treatment-emergent resistance; this is in contrast with the INSPIRING results, which are in line with the recognized high barrier to resistance of DTG.

To use DTG-based ART with rifampicin-containing TB treatment will require resources and coordination. DTG dosing should be increased to 50 mg twice daily during TB treatment (and for 2 weeks following TB treatment completion), so an additional (non-fixed-dose combination) dose of DTG must be available. Additionally, coordination between HIV and TB providers is critical to ensure that dose adjustments are made

Table 4. Geometric Mean Plasma Concentrations for Dolutegravir and Efavirenz

	Dolutegravir at 50 mg Twice Daily		Dolutegravir at 50 mg Once Daily		Efavirenz at 600 mg 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

Treatments were during concurrent tuberculosis treatment (Weeks 8 and 24) versus during treatment for human immunodeficiency virus alone (Weeks 36 and 48). Data are for the dolutegravir treatment troughs (C12h or C24h; ng/mL) and the efavirenz mid-dose interval (10–14h; mcg/mL). The LLQ was 20 ng/mL.

Abbreviations: CI, confidence interval; LLQ, lower limit of quantification; SD, standard deviation.

Table 5. Number (%) of Participants With Adverse Events, 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 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)
Grades 1–2	5 (7)	6 (14)
Grades 3–4	0	0
SAE	0	1 (2)[d]

Abbreviations: AE, adverse event; DTG, dolutegravir; EFV, efavirenz; IRIS, immune reconstitution inflammatory syndrome; SAE, serious adverse event; TB, tuberculosis.

[a]The SAEs in the DTG arm were TB-associated IRIS, gastrointestinal tuberculosis, a ruptured ectopic pregnancy, bronchospasm, cellulitis, and a skin abrasion, with the latter 2 both experienced by 1 participant. The SAEs in the EFV arm were pneumonia, a patella fracture, a spontaneous abortion, suicidal ideation, IRIS, and an acute kidney injury, with the latter 2 both experienced by 1 participant.

[b]The drug-related SAEs in the DTG arm were TB-associated IRIS, on Day 15, and a ruptured ectopic pregnancy. The drug-related SAE in the EFV arm was IRIS, on Day 8.

[c]The AEs leading to withdrawal were drug hypersensitivity and gamma-glutamyltransferase elevation.

[d]The psychiatric SAE was suicidal ideation, which was considered unrelated to the study drug and was resolved the same day.

(at the beginning and end of cotreatment and in situations of prolonged treatment interruption). However, the logistics of different dosing for patients are less complicated than the logistics of providing different regimens and requiring ART regimen switches upon TB diagnoses in patients that are stable and suppressed on their current regimens. Whether giving DTG at a dose of 50 mg or 100 mg once daily (rather than 50 mg twice daily) will be efficacious requires further study [33]. In addition, children are a subpopulation with few treatment options for HIV/TB cotreatment, especially since EFV cannot be given to children under the age of 3 years and pediatric formulations are lacking [34]; the further study of DTG-containing regimens in children is a priority.

In conclusion, our trial provides efficacy, safety, and pharmacokinetic evidence that DTG is effective and well tolerated in HIV treatment-naive patients who have drug-susceptible TB and are taking rifampicin-containing TB treatments, provided the DTG dose is increased to 50 mg twice daily during (and for 2 weeks after) TB treatment. More work is needed to characterize the safety and tolerability of DTG-based ART regimens in children and in patients with low CD4 counts.

Notes

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Potential conflicts of interest. M. A.-K., M. A., R. S., C. L. T., K. A., A. R. T., D. B., and M. R. K. are employed by and own shares in GlaxoSmithKline. K. E. D. received salary support through her university for research efforts devoted to this study. O. S. has received advisory board payments from Alere. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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