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MAJOR ARTICLE

Determinants of Antiretroviral Treatment Success and Adherence in People With Human Immunodeficiency Virus Treated for Tuberculosis

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Background. In people with human immunodeficiency virus [HIV] presenting with advanced disease, rates of virologic success may be lower than expected. The Reflate TB2 trial did not show non-inferiority of raltegravir versus efavirenz in people with HIV (PWH) treated for tuberculosis. We aimed to identify factors associated with virologic success and higher adherence in the trial.

Methods. In this analysis, we included participants enrolled in the Reflate TB2 trial with adherence data available. The primary outcome was virologic success (HIV-1 ribonucleic acid [RNA] <50 copies/mL) at week 48, and the secondary outcome was adherence as assessed by the pill count adherence ratio. We used logistic regression to study determinants of virologic success and optimal adherence in 2 separate analyses.

Results. Four hundred forty-four participants were included in the present analysis. Over the 48-week follow-up period, 290 of 444 (65%) participants had a pill count adherence ratio ≥95%. At week 48, 288 of 444 (65%) participants were in virologic success. In the multivariate analysis, female sex (adjusted odds ratio [aOR], 1.77; 95% confidence interval [CI], 1.16–2.72; $P = .0084$), lower baseline HIV-1 RNA levels (<100 000; aOR, 2.29; 95% CI, 1.33–3.96; $P = .0087$), and pill count adherence ratio ≥95% (aOR, 2.38; 95% CI, 1.56–3.62; $P < .0001$) were independently associated with virologic success. Antiretroviral pill burden was the only factor associated with pill count adherence ratio ≥95% (OR, 0.81; 95% CI, .71–.92; $P = .0018$).

Conclusions. In PWH with tuberculosis receiving raltegravir or efavirenz-based regimens, female sex, optimal adherence, and baseline HIV-1 RNA <100 000 copies/mL were associated with virologic success, and the number of antiretroviral tablets taken daily was a strong predictor of adherence.

Keywords. adherence; HIV viral load; raltegravir; tuberculosis.

Tuberculosis remains a major cause of morbidity and the leading cause of death in people with human immunodeficiency virus (PWH). In 2020, 214 000 of the 680 000 deaths reported in PWH were due to tuberculosis [1]. Better access to tuberculosis diagnosis, appropriate tuberculosis treatment, and early initiation of antiretroviral therapy (ART) are key to reduce tuberculosis-related mortality [2–4]. Antiretroviral therapy options are limited in PWH with tuberculosis due to drug-drug interactions with rifampicin, which lead to reduced plasma drug levels for most antiretrovirals.

Until recently, efavirenz, a nonnucleoside reverse-transcriptase inhibitor, was the preferred first-line ART recommended by the World Health Organization (WHO) in (1) PWH overall and in (2) those with tuberculosis due to less potential drug-drug interactions with rifampicin requiring no dose adaptation [5]. In 2017, the WHO recommended the second-generation integrase inhibitor dolutegravir at the standard dose of 50 mg in association with tenofovir disoproxil fumarate (TDF) and lamivudine (3TC) for all adults as first-line

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ART [5]. Due to drug-drug interactions with rifampicin, standard dose dolutegravir cannot be used in PWH with tuberculosis, and the WHO recommended double-dose dolutegravir (50 mg twice daily) as the first-line option to treat patients coinfected with tuberculosis and human immunodeficiency virus (HIV), based on the moderate certainty of evidence from a noncomparative randomized study [5–7].

The ANRS 12300 Reflate TB2 trial was a large, phase 3 trial that evaluated the use of another integrase inhibitor, raltegravir, in PWH with tuberculosis. This trial did not show the noninferiority at week 48 of twice-daily raltegravir 400 mg compared with once-daily efavirenz 600 mg, whereas a similar proportion of patients achieved HIV-1 RNA-1 <50 copies/mL at week 24 in the 2 arms [8]. Rates of virologic success at week 48 were lower in patients with baseline viral load ≥100 000 copies/mL and when adherence to ART was suboptimal, which may have contributed to the results observed in trial, with significantly lower adherence in the raltegravir arm compared with the efavirenz arm throughout the study [8].

Adherence to ART is a main driver of virologic efficacy and suboptimal adherence is associated to virologic failure [9–12]. Various indirect measures of adherence have been used, including patients' self-reports, pill count adherence or medication possession ratio, pharmacy refill, physician evaluation, or electronic measures [13–17]. There is no gold standard measure of adherence; thus, addition of different measures may be more robust than 1 single evaluation (for example, self-reported adherence or pill-count) to correlate with virologic failure [18–22]. The threshold to define optimal adherence has been largely debated, but it is accepted that an adherence equal to or above 95% can be considered an optimal adherence level enabling to achieve virologic control [22, 23]. A further understanding of the determinants of adherence and measuring their influence on virologic efficacy is challenging because socio-demographic and economic factors are also involved [9–12].

Adherence issues at ART initiation might have been underestimated recently with better tolerated, convenient, and more robust once-daily fixed-dose ART combinations accessible. Those regimens may allow for more flexibility and nonoptimal adherence, notably in patients with less advanced disease starting ART at low HIV-1 ribonucleic acid (RNA) levels. Reflate TB2 and other recent studies conducted in Africa suggest that in patients with very high HIV-1 RNA at ART initiation, suboptimal adherence may be more of an issue and that lower adherence is a good predictor of virologic failure, even in patients receiving integrase inhibitors [8, 24, 25].

We hypothesized that high baseline HIV-1 RNA and suboptimal adherence in the context of twice-daily raltegravir might explain the negative results of the Reflate TB2 trial. We sought to further identify factors associated with virologic success and optimal adherence to ART.

METHODS

Study Design and Population

We conducted a secondary analysis of the ANRS 12.300 Reflate TB2. The trial design and study results have been reported previously [8]. Between September 2015 and January 2018, ART-naive HIV-1-infected adults age ≥18 years with tuberculosis initiated on antituberculosis treatment within the prior 8 weeks were randomized to initiate ART with either raltegravir 400 mg 1 pill twice daily or efavirenz 600 mg once daily, both in association with TDF 300 mg once daily and 3TC 300 mg once daily. Tenofovir disoproxil fumarate/3TC/efavirenz or TDF/3TC were available as single pill fixed-dose combinations depending on countries and stock. Stock outs in some countries of fixed-dose combination for once-daily TDF/3TC led to temporarily use TDF 1 tablet per day once daily and 3TC 150 mg 1 tablet twice daily in association with raltegravir 1 tablet twice daily (total of 5 tablets daily).

In the present study, we included all patients enrolled in the Reflate TB2 trial in Brazil, Côte d'Ivoire, Mozambique, and Vietnam, excluding those with HIV-1 RNA <50 copies/mL at baseline ($n = 3$) and those with missing data on ART accountability ($n = 9$). We excluded patients enrolled in France ($n = 4$) because we wished to restrict the analysis to low- and middle-income countries and because the low number of French participants would not allow for comparisons.

Patient Consent Statement

The Reflate TB2 study protocol was approved by relevant National and Local Ethics Committees in all participating countries and registered with ClinicalTrials.gov (NCT02273765). All participants provided signed informed consent before enrollment in the main trial.

Study Procedures

We performed clinical and laboratory assessments for all patients at all study visits. We monitored adherence to ART in patients using pill count; patients were thus requested to return their remaining pills to the pharmacy at all study visits from week 2 to week 48 (weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, and 48). In addition, we evaluated self-reported adherence to ART with 4 days and 1 month recall periods at all study visits after week 2 (Supplementary Appendix) [14]. Adherence to tuberculosis treatment was also monitored using the Taxo INH Test Strips (Becton Dickinson, Franklin Lakes, NJ) to detect isoniazid metabolites in urines at weeks 0 and at study visits closest to months 2 and 5 of tuberculosis treatment [26]. Isoniazid (INH) metabolites are detected in urine up to 36 hours postdrug intake. The production of Taxo INH Test Strips was interrupted during the trial, and isoniazid urine strips were no longer used after March 3, 2017. Treatments were reported in the case report form for all participants, at

each study visit, including the number of pills prescribed for antiretrovirals, antituberculosis drugs, and oral concomitant treatments, which allowed for computing treatments durations and pill burden.

Outcomes and Definitions

The primary outcome of the present study was virologic success at week 48, defined as plasma HIV-1 RNA <50 copies/mL on allocated study drugs per the US Food and Drug Administration Snapshot algorithm [27]. Our secondary outcome was adherence to ART as assessed by pill count adherence ratio (Supplementary Appendix). We defined high or optimal adherence as a pill count adherence ratio ≥95% and low or suboptimal adherence as a pill count adherence ratio <95% [22]. Self-reported nonoptimal adherence was defined as missing at least 1 dose of treatment during the recall time (4 days and/or 1 month self-reported nonadherence). We also calculated treatment related pill burden for ART, tuberculosis treatment, and other concomitant treatments (full definitions in Supplementary Appendix).

Statistical Analysis

We described baseline characteristics in each group for the 2 main analysis on virologic success, and optimal adherence using frequency and proportions for qualitative variables, and median and interquartile range (IQR) for quantitative variables. We compared characteristics across groups using Wilcoxon tests (comparison of medians) for quantitative variables, and we used the χ^2 or the Fisher's exact test for qualitative variables as appropriate.

We used logistic regression to study determinants of virologic success and optimal adherence in 2 separate analyses (Supplementary Appendix). We selected variables based on previous evidence from the literature and clinical relevance. We derived a final model that resulted from a stepwise descending selection retaining all variables with a level of significance $P = .05$. We analyzed data with the SAS software (version 9.4M3).

RESULTS

Of 460 participants enrolled in the Reflate TB2 trial, we included 444 in the present analysis (Supplementary Figure 1). The study participants had advanced HIV disease with median $CD4^+$ T-cell count of 102 (IQR, 38–242) cells per cubic millimeter, and median plasma HIV-1 RNA was 5.5 (IQR, 5.0–5.8) $\log_{10}$ copies/mL, with 330 of 444 (74%) participants with HIV-1 RNA above 100 000 copies/mL (Table 1). Participants were started on ART at a median of 20 (IQR, 15–27) days after tuberculosis treatment initiation.

Overall, 222 of 444 (50%) patients received a raltegravir-based regimen for a median of 48 months and 222 of 444 (50%) received an efavirenz-based regimen for a median of 48 months ($P = .3103$). The median ART pill burden was 1.0 (IQR, 1.0–3.0) tablets per day, 1 (IQR, 1–1) tablet per day for patients on efavirenz, and 3.0 (IQR, 3.0–5.0) tablets per day for patients on raltegravir. Patients received tuberculosis treatment for a median duration of 26 (IQR, 26–27) weeks from randomization. During the trial, the median tuberculosis treatment pill burden was 4.0 (IQR, 3.0–4.2) tablets per day and concomitant treatment pill burden was 0.5 tablets per day (IQR, 0.1–1.5).

Over the 48-week follow-up period, the median ART pill count adherence ratio was 98.6% (IQR, 91.6%–101.6%); 290 (65%) of the participants had optimal adherence with a pill count adherence ratio ≥95%. The proportion of optimal adherent participants decreased after week 24, from 72% during the first 24 weeks of the study to 66% during the last 24 weeks of the study.

At week 48, 288 (65%) participants had HIV-1 RNA <50 copies/mL on allocated therapy. Of the 156 (35%) participants who did not achieve virologic success, 20 (5%) died, 75 (17%) had HIV-1 RNA ≥50 copies/mL at week 48, and 39 (9%) had discontinued raltegravir or efavirenz treatment before week 48, including 22 (5%) who had been switched to second-line ART for lack of efficacy (9 on efavirenz and 13 on raltegravir-based ART). Considering other thresholds for virologic success at week 48, 319 of 444 (72%) and 326 of 444 (73%) participants had HIV-1 RNA of <200 copies/mL and <1000 copies/mL, respectively (Supplementary Table 1).

Patients with virologic success differed from those who did not achieve virologic success on 3 major characteristics: (1) the proportion of female participants was higher in the group achieving virologic success (44% vs 31%; $P = .0091$) (Table 1), (2) the median baseline HIV-1 RNA before ART was lower in those who achieved virologic success (5.4 $\log_{10}$ copies/mL vs 5.6 $\log_{10}$ copies/mL; $P = .0009$), and (3) the proportion of participants with optimal adherence and a pill count adherence ≥95% over the 48 weeks of the study was higher in those in virologic success (72% vs 53%; $P < .0001$) (Table 1). Hemoglobin levels and CD4 cell counts differed statistically between the 2 groups, but the differences were not clinically relevant. In the multivariate analysis, optimal adherence measured by pill count adherence ratio ≥95% (adjusted odds ratio [aOR], 2.38; 95% confidence interval [CI], 1.56–3.62; $P = .0084$), lower baseline HIV-1 RNA levels (HIV-1 RNA < 100 000; aOR, 2.29; 95% CI, 1.33–3.96; $P = .009$), and female sex (aOR, 1.77; 95% CI, 1.16–2.72; $P \leq .0001$) were independently associated with virologic success (Table 2).

In the analysis on factors associated with optimal ART adherence, a strong predictor of virologic success, we found no difference in terms of demographic characteristic and tobacco, alcohol or other substances use, baseline body mass index, and CD4 counts between participants with optimal adherence compared to those with non-optimal adherence (Table 3). The

Table 1. Patients Characteristics by HIV-1 RNA at Week 48[a]

	N*	Virologic Success (N = 288)	N*	Not in Virologic Success (N = 156)	N*	Total (N = 444)	P Value
Antiretroviral Treatment	…	…	…	…	…	…	
Efavirenz	…	150 (52%)	…	49 (31%)	…	199 (45%)	
Raltegravir	…	138 (48%)	…	65 (42%)	…	203 (46%)	
Country	…	…	…	…	…	…	
Ivory Coast	…	98 (34%)	…	66 (42%)	…	164 (37%)	P = .2646 (K)
Brazil	…	32 (11%)	…	11 (7%)	…	43 (10%)	
Vietnam		74 (26%)	…	36 (23%)	…	110 (25%)	…
Mozambique	…	84 (29%)	…	43 (28%)	…	127 (29%)	
Age (years)	…	35 (29–43)	…	35 (29–44)	…	35 (29–43)	P = .9456 (W)
Female sex	…	127 (44%)	…	49 (31%)	…	176 (40%)	P = .0091 (K)
Body mass index (kg/m^2)	287	19.1 (17.6–21.1)	…	18.9 (17.3–20.6)	443	19.1 (17.5–21.0)	P = .2055 (W)
Hemoglobin (g/dL)	…	9.8 (8.6–11.4)	…	9.8 (8.4–11.1)	…	9.8 (8.5–11.3)	P = .4260 (W)
CD4$^+$ T-cell count (cells per mm^3)	287	117 (47–245)	…	80 (26–212)	443	102 (38–242)	P = .0259 (W)
≤200 cells per mm^3	287	186 (65%)	…	116 (74%)	443	302 (68%)	
≤50 cells per mm^3	287	89 (31%)	…	57 (37%)	443	146 (33%)	
Plasma HIV-1 viral load (log$_{10}$ copies per mL)	287	5.4 (4.9–5.8)	154	5.6 (5.2–5.9)	441	5.5 (5.0–5.8)	P = .0009 (W)
< 100 000 copies per mL	287	82 (29%)	154	29 (19%)	441	111 (25%)	
[100 000; 500 000]	287	122 (43%)	154	58 (38%)	441	180 (41%)	
≥500 000 copies per mL	287	83 (29%)	154	67 (44%)	441	150 (34%)	
On cotrimoxazole prophylaxis	…	258 (90%)	…	134 (86%)	…	392 (88%)	P = .2489 (K)
Current anatomical site of tuberculosis disease	…	…	…	…	…	…	
Pulmonary only	…	196 (68%)	…	113 (72%)	…	309 (70%)	P = .5733 (K)
Extrapulmonary only	…	54 (19%)	…	27 (17%)	…	81 (18%)	
Pulmonary and extrapulmonary	…	38 (13%)	…	16 (10%)	…	54 (12%)	
Bacteriologically confirmed tuberculosis	286	197 (69%)	154	106 (69%)	440	303 (69%)	P = .9914 (K)
Time on tuberculosis treatment at enrollment (days)	…	20 (15–27)	…	20 (15–27)	…	20 (15–27)	P = .7075 (W)
Alanine aminotransferase level (UI/L)	287	25 (16–41)	154	22 (14–33)	441	24 (15–38)	P = .0409 (W)
Creatinine clearance (mL/min/1.73 m^2)		99.1 (81.8–122.8)	…	100.7 (78.4–125.6)	…	99.6 (80.7–123.1)	P = .9410 (W)
Pill count adherence ratio week 0–week 48	…	99.2% (94.4%–101.4%)	…	95.8% (85.1%–102.3%)	…	98.6% (91.6%–101.6%)	P = .0075 (W)
≥95%	…	208 (72%)	…	82 (53%)	…	290 (65%)	P < .0001 (K)
[80%–95%]	…	62 (22%)	…	45 (29%)	…	107 (24%)	
<80%	…	18 (6%)	…	29 (19%)	…	47 (11%)	
Pill count adherence ratio week 0–week 24	…	99.7% (96.1%–101.5%)	155	98.9% (86.9%–102.4%)	443	99.4% (94.1%–101.8%)	P = .0211 (W)
≥95%	…	228 (79%)	155	93 (60%)	…	321 (72%)	P < .0001 (K)
[80%–95%]	…	49 (17%)	155	33 (21%)	…	82 (18%)	
<80%	…	11 (4%)	155	30 (19%)	…	41 (9%)	
Pill count adherence ratio week 24–week 48	…	99.4% (93.6%–103.0%)	119	95.2% (73.6%–103.9%)	407	99.1% (88.8%–103.3%)	P = .0064 (W)
≥95%	…	207 (72%)	119	60 (50%)	407	267 (66%)	P < .0001 (K)
[80%–95%]	…	51 (18%)	119	22 (18%)	407	73 (18%)	
<80%	…	30 (10%)	119	37 (31%)	407	67 (16%)	

Abbreviations: F, Fisher's exact test; HIV, human immunodeficiency virus; K, χ^2 test; RNA, ribonucleic acid; W, Wilcoxon test.

[a]Data are *n* (%) or median (interquartile range).

median ART pill burden differed significantly between participants with optimal adherence (1.0 [IQR, 1.0–3.0] tablet per day) and participants with lower adherence (3.0 [IQR, 1.0–3.0] tablets per day; P = .0005), but there was no difference in median tuberculosis treatment pill burden and concomitant treatment pill burden between the 2 groups (Table 3). In the multivariate analysis, only higher ART pill burden was associated with lower adherence (OR, 0.81; 95% CI, .71–.92; P = .0018) (Table 4).

Patients with pill count adherence ratio ≥95% also had better self-reported adherence (Table 5). The proportion of participants with 4-day, self-reported nonadherence throughout the 48 weeks of the study was lower in participants with pill count adherence ratio ≥95%: 51 of 290 (18%) compared to 51 of 154 (33%) for participants with pill count adherence ratio <95% (P = .0002) (Table 5). One-month, self-reported nonadherence was also higher in participants with pill count adherence ratio <95%: 55 of 154 (36%) compared to 62 of 290 (21%) for participants with optimal adherence (P = .0011) (Table 5). Reported adherence to tuberculosis treatment was also higher in patient with optimal adherence to ART; 4-day, self-reported nonadherence to tuberculosis treatment was 4% and 10% in participants with optimal adherence and those with suboptimal adherence, respectively (P = .0187). There was no difference

Table 2. Factors Associated to Virologic Success

…	Total	Virologic Success *N* (%*N*) or Median (q1, q3)	Univariate Analysis				Multivariate Analysis			
…	*N*		OR	Lower 95% CI	Upper 95% CI	Pr > χ^2	OR	Lower 95% CI	Upper 95% CI	Pr > χ^2
Treatment	…	…	…	…	…	…	…	…	…	…
Efavirenz	222	150 (68%)	1	…	…	0.2332	…	…	…	…
Raltegravir	222	138 (62%)	0.79	0.53	1.17	…	…	…	…	…
Country	…	…	…	…	…	…	…	…	…	…
Brazil	43	32 (74%)	1	…	…	0.2694	…	…	…	…
Ivory Coast	164	98 (60%)	0.51	0.24	1.08	…	…	…	…	…
Mozambique	127	84 (66%)	0.67	0.31	1.46	…	…	…	…	…
Vietnam	110	74 (67%)	0.71	0.32	1.56	…	…	…	…	…
Sex	…	…	…	…	…	…	…	…	…	…
Male	268	161 (60%)	1	…	…	0.0094	…	…	…	…
Female	176	127 (72%)	1.72	1.14	2.60	…	1.77	1.16	2.72	0.0084
Age (Years)	…	…	…	…	…	…	…	…	…	…
Age >35	223	149 (67%)	1	…	…	0.3871	…	…	…	…
Age ≤35	221	139 (63%)	0.84	0.57	1.24	…	…	…	…	…
BMI (kg/m^2)	…	…	…	…	…	…	…	…	…	…
BMI > 18.5	259	172 (66%)	1	…	…	0.3961	…	…	…	…
BMI ≤ 18.5	184	115 (63%)	0.84	0.57	1.25	…	…	…	…	…
CD4 counts (/mm^3)	…	…	…	…	…	…	…	…	…	…
CD4 < 50	142	87 (61%)	1	…	…	0.1208	…	…	…	…
CD4: [50 to 200]	160	99 (62%)	0.97	0.61	1.55	…	…	…	…	…
CD4 ≥ 200	141	101 (72%)	0.63	0.38	1.03	…	…	…	…	…
Viral Load at Baseline	…	…	…	…	…	…	…	…	…	…
HIV-1 VL ≥500 000	150	83 (55%)	1	…	…	0.0054	…	…	…	…
<100 000	111	82 (74%)	2.28	1.34	3.88	…	2.29	1.33	3.96	0.0087
100 000 to 500 000	180	122 (68%)	1.70	1.08	2.66	…	1.62	1.02	2.57	0.0087
Pill count ratio	…	…	…	…	…	…	…	…	…	…
Pill count ratio <95%	154	80 (52%)	1	…	…	…	…	…	…	…
Pill count ratio ≥95%	290	208 (72%)	2.35	1.56	3.52	<.00001	2.38	1.56	3.62	0

Abbreviations: BMI, body mass index; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; VL, viral load.

between participants with optimal and suboptimal adherence regarding baseline detection of isoniazid metabolites in urines (Table 5).

Self-reported adherence according to ART is shown in Supplementary Figure S2.

DISCUSSION

In this secondary analysis of the Reflate TB2 trial, we showed that optimal adherence to ART as well as lower baseline HIV-1 RNA and female sex were associated with virologic success. We also showed that the main determinant of optimal adherence was ART pill burden, hence hampering success in the raltegravir-based regimen that requires twice-daily intake of 3 tablets.

Virologic success was achieved in 65% of the patients, which was lower than expected 1 year after ART initiation in HIV-1-infected naive patients receiving efavirenz or raltegravir, and it contrasts with pivotal studies in which more than 80% of the participants achieved virologic suppression on both regimens [28, 29]. We found that 73% of the patients had HIV-1 RNA below 1000 copies/mL at week 48, much lower than the UNAIDS/WHO 90-90-90 third target to have globally 90% of PWH with viral load below 1000 copies per mL 1 year after initiation of ART. One explanatory factor was that a high proportion of patients had baseline viral load above 100 000 copies/mL including 34% with baseline HIV-1 RNA above 500 000 copies/mL, and indeed in the multivariate model, HIV-1 RNA of less than 100 000 copies/mL was associated to virologic success. The impact of high baseline HIV-1 viral load on virologic success rates was also found in previous studies [25, 30].

It is interesting to note that our analysis showed that female sex was associated with better virologic outcomes but not with higher adherence. It was also reported previously that men were more likely to experience virologic failure than women, without clear explanation. Tuberculosis coinfection has been reported to be a factor associated with virologic failure in some studies [31–34]. The reasons for these associations remain unclear.

We found that only 65% of the participants had optimal adherence to ART, which was one other factor associated to virologic success. This finding is consistent with previous reports

Table 3. Patient Characteristics by Pill Count Adherence Ratio

	*N**	Pill Count Ratio ≥95% (*N* = 290)	*N**	Pill Count Ratio <95% (*N* = 154)	
Antiretroviral Treatment	…	…	…	…	
Efavirenz	…	162 (56%)	…	60 (39%)	*P* = .0007 (K)
Raltegravir	…	128 (44%)	…	94 (61%)	
Country	…	…	…	…	
Ivory Coast	…	99 (34%)	…	65 (42%)	*P* = .2372 (K)
Brazil	…	30 (10%)	…	13 (8%)	
Vietnam	…	79 (27%)	…	31 (20%)	
Mozambique	…	82 (28%)	…	45 (29%)	
Sex	…	…	…	…	
Male	…	176 (61%)	…	92 (60%)	*P* = .8457 (K)
Female	…	114 (39%)	…	62 (40%)	
Age (years)	…	35 (29–43)	…	36 (30–43)	*P* = .3087 (W)
BMI (kg/m^2)	289	19.2 (17.4–20.8)	…	18.8 (17.7–21.0)	*P* = .8783 (W)
Tobacco smoking	…	…	…	…	
Never	289	208 (72%)	153	114 (75%)	*P* = .3835 (F)
Yes, but stopped	289	70 (24%)	153	37 (24%)	
Yes, ongoing	289	11 (4%)	153	2 (1%)	
Alcohol Consumption	…	…	…	…	
Never	…	132 (46%)	153	56 (37%)	*P* = .0710 (K)
Yes, past or ongoing	…	158 (55%)	153	97 (63%)	
Drug use	…	…	…	…	
Never	…	265 (91%)	153	134 (88%)	*P* = .2038 (K)
Yes, past or ongoing	…	25 (9%)	153	19 (12%)	
CD4 (/mm^3) at PI	289	111 (39–248)	…	89 (35–215)	*P* = .1505 (W)
ART pill burden[a]	…	1.0 (1.0–3.0)	…	3.0 (1.0–3.0)	*P* = .0005 (W)
…	…	1.0–5.0	…	1.0–5.0	
TB pill burden[b]	289	4.0 (3.0–4.4)	…	3.9 (3.0–4.0)	*P* = .1534 (W)
Min-max	…	2.0–9.9	…	2.0–8.7	
CT pill burden[c]	…	0.5 (0.1–1.5)	…	0.5 (0.1–1 .7)	*P* = .5713 (W)
min-max	…	0.0–14.5	…	0.0–8.4	

Abbreviations: ART, antiretroviral treatment; BMI, body mass index; CT, concomitant treatment; F, Fisher's exact test; K, χ^2 test; max, maximum; min, minimum; PI, protease inhibitor; TB, tuberculosis; W, Wilcoxon test.

NOTE: Data are *n* (%) or median (interquartile range).

[a]Number of pills per day during allocated therapy treatment.

[b]Number of pills per day during TB treatment.

[c]Number of pills per day during the study.

showing that lower ART adherence contributes to virologic failure [18, 31, 35, 36]. In our study, lower ART pill burden was the only factor associated to optimal adherence, hence disadvantaging the raltegravir-based regimen. Importantly, 28% of the patients on raltegravir received 5 pills per day because of stock outs of the coformulated 3TC/TDF pill, possibly further hampering adherence to the combination. We could not separately evaluate the effect of ART pill burden and daily dosing of ART regimen because the number of pills taken daily was de facto different according to the ART regimen prescribed. However, other studies showed that twice-daily dosing ART rather than pill burden was associated to lower adherence [37–41]. Lower patient satisfaction with the twice-daily regimen seems to explain this finding [41]. Although we did not evaluate participants' satisfaction about ART, our data also suggest the same impact of the twice-daily dosing of raltegravir regimen.

Optimal adherence defined as pill count adherence ratio ≥95% was concordant with other markers of adherence, especially with reporting at least 1 lapse in ART or tuberculosis treatment intake over the past 4 days or month. Also of note, we found that adherence decreased after week 24 when most patients were off tuberculosis treatment, which is difficult to interpret because we did not evaluate patients' motivations. For PWH presenting with advanced disease, the WHO now strongly recommends intensified adherence interventions during the first months of ART, including home- or community-based follow-up and early tracing in case of missed visits, in addition to initial counseling at ART initiation [24, 42–45]. Our results, along with previous recent studies, show that using pill count adherence ratio and self-adherence questionnaires at each visit could help to target such interventions by identifying patients who may benefit the most from adherence support [16, 21, 42].

Table 4. Factors Associated to Pill Count Ratio ≥95%

…	Total	Pill Count ≥95% *N* (%*N*) or Median (q1, q3)	Univariate Analysis				Multivariate Analysis			
…	*N*		OR	Lower 95% CI	Upper 95% CI	Pr > χ^2	OR	Lower 95% CI	Upper 95% CI	Pr > χ^2
ART pill burden[a]	290	1.0 (1.0–3.0)	0.81	0.71	0.92	0.0018	0.81	0.71	0.92	0.0018
Country	…	…	…	…	…	…	…	…	…	…
Brazil	43	30 (70%)	1	…	…	…	…	…	…	…
Ivory Coast	164	99 (60%)	0.69	0.34	1.43	0.2806	…	…	…	…
Mozambique	127	82 (65%)	0.82	0.39	1.73	0.2806	…	…	…	…
Vietnam	110	79 (72%)	1.14	0.53	2.48	0.2806	…	…	…	…
Sex	…	…	…	…	…	…	…	…	…	…
Male	268	176 (66%)	1	…	…	…	…	…	…	…
Female	176	114 (65%)	0.98	0.66	1.47	0.9310	…	…	…	…
Age (years)	…	…	…	…	…	…	…	…	…	…
Age >35	223	141 (63%)	1	…	…	…	…	…	…	…
Age ≤35	221	149 (67%)	1.18	0.80	1.75	0.4064	…	…	…	…
BMI (kg/m^2)	…	…	…	…	…	…	…	…	…	…
BMI >18.5	259	170 (66%)	1	…	…	…	…	…	…	…
BMI ≤18.5	184	119 (65%)	0.95	0.64	1.41	0.7906	…	…	…	…
Alcohol Consumption	…	…	…	…	…	…	…	…	…	…
Alcohol: yes (stopped or ongoing)	188	158 (62%)	1	…	…	…	…	…	…	…
Alcohol: never	255	132 (70%)	1.44	0.96	2.15	0.0778	…	…	…	…

Abbreviations: ART, antiretroviral treatment; BMI, body mass index; CI, confidence interval; OR, odds ratio.

[a]*N*, median (q1, q3) antiretroviral pill burden for pill count <95%: 154, 3.0 (1.0–3.0).

Our study has limitations. First, we did not analyze baseline HIV-1 resistance and its contribution to virologic failure, but in patients who failed we had found in the Reflate TB2 trial that baseline resistance to non-nucleoside reverse-transcriptase inhibitors and integrase inhibitors was 10% and 3%, respectively [8]. Second, adherence measurements in the study may not have been very accurate: (1) pharmacy refills and patients self-reported adherence do not provide an exact measure of the number of pills taken by the patients, (2) we measured adherence over large periods of 6 or 12 months, and (3) we may not identify short treatment interruptions and thus overestimate adherence in some patients. Finally, we did not explore psychosocial determinants of adherence and how they might have contributed to our results.

CONCLUSIONS

Antiretroviral therapy remains challenging in PWH co-infected with tuberculosis, with a risk of reduced exposure to antiretroviral drugs due to drug-drug interactions with rifampicin or tolerance issues. This prompted the search of alternative regimens to efavirenz over the past decade and resulted in the use of better tolerated integrase inhibitor-based regimens. We found that during the first year after tuberculosis diagnosis, patients with optimal adherence and those with lower baseline HIV-1 viral load had higher odds of virologic success. The number of ART tablets taken daily was a strong predictor of adherence and was due to the twice-daily dosing of the raltegravir-based ART regimen. We provide evidence that adherence monitoring using pill count adherence ratio and self-adherence questionnaires may help clinicians to identify patients at risk for virological failure; this group of patients needs targeted adherence counseling within the first months of ART. Despite the fact that dolutegravir is a more robust drug than raltegravir, with higher genetic barrier for resistance, our results raise concerns about adherence to the twice-daily, dolutegravir-based ART now recommended by the WHO for patients treated for tuberculosis. Future studies analyzing data from the national HIV and tuberculosis programs will be important to better describe outcomes in PWH coinfected with tuberculosis and treated with the twice-daily dosage of dolutegravir.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Table 5. Description of Measures of Nonadherence[a]

…	*N**	Pill Count Ratio ≥95% (*N* = 290)	*N**	Pill Count Ratio <95% (*N* = 154)	*N**	Total (*N* = 444)	*P*
Self-reported nonadherence to ART between week 0 and week 48	…	…	…	…	…	…	
In the last 4 d or 1 mo	…	68 (23%)	…	58 (38%)	…	126 (28%)	*P* = .0016 (K)
In the last 4 d	…	51 (18%)	…	51 (33%)	…	102 (23%)	*P* = .0002 (K)
In the last month	…	62 (21%)	…	55 (36%)	…	117 (26%)	*P* = .0011 (K)
Self-reported nonadherence to ART between week 0 and week 24	…	…	…	…	…	…	
In the last 4 d or 1 mo	…	48 (17%)	…	42 (27%)	…	90 (20%)	*P* = .0075 (K)
In the last 4 d	…	35 (12%)	…	33 (21%)	…	68 (15%)	*P* = .0091 (K)
In the last month	…	44 (15%)	…	40 (26%)	…	84 (19%)	*P* = .0057 (K)
Self-reported nonadherence to ART between week 24 and week 48	…	…	…	…	…	…	
In the last 4 d or 1 mo	278	27 (10%)	133	34 (26%)	411	61 (15%)	*P* < .0001 (K)
In the last 4 d	278	17 (6%)	133	31 (23%)	411	48 (12%)	*P* < .0001 (K)
In the last month	278	23 (8%)	133	30 (23%)	411	53 (13%)	*P* < .0001 (K)
Self-reported nonadherence to TB treatment between week 0 and end of TB treatment	…	…	…	…	…	…	
In the last 4 d or 1 mo	…	16 (6%)	…	19 (12%)	…	35 (8%)	*P* = .0111 (K)
In the last 4 d	…	12 (4%)	…	15 (10%)	…	27 (6%)	*P* = .0187 (K)
In the last month	…	14 (5%)	…	18 (12%)	…	32 (7%)	*P* = .0078 (K)
Inclusion: urine INH result, positive (blue)	160	151 (94%)	74	69 (93%)	234	220 (94%)	*P* = .7702 (F)

Abbreviations: ART, antiretroviral therapy; d, days; INH, isoniazid; F, Fisher's exact test; K, χ^2 test; mo, months; TB, tuberculosis; W, Wilcoxon test.

[a]Data are *n* (%).

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