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Clinical Infectious Diseases

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Safety and Pharmacokinetics of Double-Dose Lopinavir/Ritonavir + Rifampin Versus Lopinavir/Ritonavir + Daily Rifabutin for Treatment of Human Immunodeficiency Virus–Tuberculosis Coinfection

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Background. Protease inhibitor-based antiretroviral therapy may be used in resource-limited settings in persons with human immunodeficiency virus and tuberculosis (HIV-TB). Data on safety, pharmacokinetics/pharmacodynamics (PK/PD), and HIV-TB outcomes for lopinavir/ritonavir (LPV/r) used with rifampin (RIF) or rifabutin (RBT) are limited.

Methods. We randomized adults with HIV-TB from July 2013 to February 2016 to arm A, LPV/r 400 mg/100 mg twice daily + RBT 150 mg/day; arm B, LPV/r 800 mg/200 mg twice daily + RIF 600 mg/day; or arm C, LPV/r 400 mg/100 mg twice daily + raltegravir (RAL) 400 mg twice daily + RBT 150 mg/day. All received two nucleoside reverse transcriptase inhibitors and other TB drugs. PK visits occurred on day 12 ± 2. Within-arm HIV-TB outcomes were summarized using proportions and 95% CIs; PK were compared using Wilcoxon tests.

Results. Among 71 participants, 52% were women; 72% Black; 46% Hispanic; median age, 37 years; median CD4+ count, 130 cells/mm^3; median HIV-1 RNA, 4.6 $\log_{10}$ copies/mL; 46% had confirmed TB. LPV concentrations were similar across arms. Pooled LPV AUC12 (157 203 hours × ng/mL) and C_{trough} (9876 ng/mL) were similar to historical controls; RBT AUC_{24} (7374 hours × ng/mL) and C_{trough} (208 ng/mL) were higher, although 3 participants in arm C had RBT C_{max} <250 ng/mL. Proportions with week 48 HIV-1 RNA <400 copies/mL were 58%, 67%, and 61%, respectively, in arms A, B, and C.

Conclusions. Double-dose LPV/r+RIF and LPV/r+RBT 150mg/day had acceptable safety, PK and TB outcomes; HIV suppression was suboptimal but unrelated to PK. Faster RBT clearance and low C_{max} in 3 participants on RBT+RAL requires further study.

Keywords. HIV; tuberculosis; lopinavir; rifampin; rifabutin.

Tuberculosis (TB) is the most common opportunistic infection among people with human immunodeficiency virus (PWH) [1]. Current guidelines indicate that PWH and TB (PWH-TB) receive antiretroviral therapy (ART) to reduce the risk of human immunodeficiency virus (HIV) disease progression or death and improve TB outcomes [1–11]. One preferred regimen for the treatment of drug-susceptible HIV-TB in high-burden countries is isoniazid (INH), rifampin (RIF), pyrazinamide (PZA) and ethambutol (EMB) with efavirenz (EFV)-based ART [12–14]. However, not all PWH-TB can be treated with EFV due to toxicity, prior ART failure, or drug resistance. Although integrase strand transfer inhibitor (INSTI)–based ART regimens have been implemented in many resource-limited settings, some PWH-TB still require protease inhibitor (PI)–based ART.

Rifampin and rifapentine markedly decrease plasma concentrations of PIs, particularly atazanavir/ritonavir (ATV/r) and lopinavir/ritonavir (LPV/r), often used in high-TB-burden countries. Doubling ritonavir (RTV) doses (200–400 mg twice daily [BID]) can overcome the effect of RIF on selected PIs [15–19]. However, adults with TB but without HIV have poorly tolerated double-dose RTV with a PI and RIF [17–19]. Despite limited TB or HIV outcomes data, these combinations continue to be used in adult PWH-TB [15–20] in high-TB-burden countries.

While rifabutin (RBT) may be an effective alternative to RIF for treating pulmonary TB, data are limited in PWH-TB receiving ART [21–29]. Rifabutin, on the World Health Organization Essential Medicines list, may not be

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readily available in high-TB-burden countries and has minimal effects on PI plasma concentrations [25–29]. In some small studies, RBT-based TB regimens with PI-based ART have been well tolerated and effective [29]. Protease inhibitors markedly increase RBT and its main metabolite plasma concentrations, increasing the risk of adverse reactions, including uveitis, neutropenia, and nausea. A study of ATV/r with RBT 150 mg twice weekly in healthy adult volunteers was stopped prematurely due to excess neutropenia [26]. Based on this and other pharmacokinetic (PK) studies in healthy adults, RBT 150 mg administered 3 times weekly (TIW) has been recommended when coadministered with PIs. However, in studies in PWH treated with this dose and LPV/r-based ART, the unbound RBT maximum plasma concentration (C_{max}) was below the minimum inhibitory concentrations for drug-susceptible *Mycobacterium tuberculosis* (MTB; range, 0.03–0.25 μg/mL); values for the area-under-the-plasma concentration-time curve (AUC) were below those associated with TB treatment failure or relapse [29, 30]. Others reported relapse of TB with an RIF-resistant isolate after treatment with RTV-boosted PI-based ART coupled with RBT 150 mg TIW [31]. A South African study randomized 16 PWH-TB to RBT 150 mg daily for 4 weeks, followed by 150 mg TIW, or to the converse after starting a standard-dose LPV/r-based ART regimen [32]. One participant developed uveitis before starting LPV/r and 1 participant each developed transaminitis and neutropenia. Daily RBT 150 mg approximated PK parameters observed with standard 300 mg daily without a boosted PI. These data and others suggest the current recommended RBT dose (150 mg TIW) may be insufficient with PI-based ART [32, 33].

Persons with HIV who fail a prior nonnucleoside reverse transcriptase inhibitor (NNRTI) regimen have a high risk of resistance to NNRTIs and nucleoside RTIs used in the regimen. When coupled with RIF or RBT, a PI combined with a compromised nucleoside reverse transcriptase inhibitor (NRTI) backbone may be further compromised by drug interactions with rifamycins. Adding an INSTI may increase activity of the regimen. Raltegravir (RAL) is metabolized by glucuronidation; RIF induces UDP-glucuronosyltransferase 1A1, resulting in a 50% reduction in RAL concentrations when given with RIF [34, 35]. The RAL dose is 800 mg BID given with RIF; however, RAL can be used with RBT without dose adjustment [34, 36].

Few studies have evaluated PK and pharmacodynamics (PD) of TB drugs combined with PI-based ART in PWH-TB. Thus, we evaluated PK/PD interactions and HIV and TB outcomes when comparing double-dose LPV/r-based ART combined with RIF to standard-dose LPV/r with RBT anti–TB therapy with or without RAL in PWH-TB.

METHODS

Study Design

A5290 was a prospective, randomized, open-label, phase 2b study conducted at 9 AIDS Clinical Trials Group sites in Brazil, Peru, Haiti, Kenya, and South Africa to compare 3 LPV/r-based ART regimens combined with TB treatment with either RIF or RBT. Institutional review boards at all sites approved the study. All participants provided written informed consent. An independent study monitoring committee reviewed the safety data and interim results.

Study Population

Eligible participants were men or women aged 18 years or older with HIV-1 infection, a Karnofsky score higher than 40, confirmed (sputum/tissue culture or nucleic acid amplification test positive for MTB) or probable TB, and who required a PI-based ART regimen due to first-line ART failure or resistance/intolerance to NNRTIs. Probable TB was defined as at least 1 of the following: sputum smear positive for acid fast bacilli (AFB), abnormal chest radiograph, tissue histopathology with AFB-positive organisms, positive tuberculin skin test (≥5 mm) or interferon-γ release assay, MTB cultures negative or not available, no other concurrent diagnosis, and initiation of TB treatment. Eligible participants had absolute neutrophil counts of 750 cells/mm^3 or greater, hemoglobin of 8.5 g/dL or greater, platelet counts 50 000 cells/mm^3 or greater, alanine aminotransferase (ALT) 2 or fewer times the upper limit of normal (ULN), aspartate aminotransferase (AST) 5 or fewer times the ULN, and total bilirubin 2.5 or fewer times the ULN 14 days or less before entry. Exclusions included the following: history of completed TB treatment less than 1 year before the current episode; incomplete prior TB treatment; rifamycin monoresistance; multidrug-resistant (MDR) or extensively drug-resistant (XDR) TB; history of close contact with patients with known MDR or XDR TB before study entry; more than 28 cumulative days of TB treatment for the current episode; pregnancy or breastfeeding; or any drug, alcohol, concomitant medication use, or systemic illness that would hinder study participation.

Accrual and Study Treatment

Accrual period 1 assessed LPV/r and RBT PK and safety of each regimen. After PK and safety criteria were met at interim analysis (described below), the study planned to proceed to accrual period 2 to evaluate longer-term PK, safety, and TB and HIV outcomes in a larger cohort. Accrual ended after period 1 due to low accrual. This report addresses accrual period 1 results.

Participants were randomized 1:1:1 to the following groups—arm A: LPV/r 400 mg/100 mg BID plus 2 NRTIs coupled with INH, EMB, PZA, and RBT 300 mg daily then decreased to 150 mg/day when ART was started; arm B: LPV/r

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800 mg/200 mg BID plus 2 NRTIs coupled with INH, RIF, EMB, and PZA; and arm C: the same regimen as arm A plus RAL 400 mg BID. All participants received pyridoxine 25 mg/day. Tuberculosis treatment was started within 72 hours of randomization and ART within 14 days. After 8 weeks of TB treatment, EMB and PZA were stopped; continuation-phase TB treatment included INH and pyridoxine with either RIF or RBT at assigned doses until 24 weeks. At TB treatment completion, all participants reverted to LPV/r 400 mg/100 mg BID. For those receiving RBT, if LPV/r was stopped during TB treatment, RBT was increased to 300 mg/day.

Study Procedures and Pharmacokinetic Evaluations

Assessments occurred at entry; at weeks 2, 8, 16, 24, 48, and 72; at premature discontinuation of study medication; and at time of virologic failure, or TB treatment failure/recurrence. Plasma HIV-1 RNA was assessed at entry; at weeks 8, 16, 24, 48, and 72; and at time of virologic failure using the Abbott RealTime HIV-1 assay (lower limit of detection [LLOD]: 40 copies/mL) or the Roche COBAS AmpliPrep/TaqMan HIV-1 assay (LLOD: 20 copies/mL). Tuberculosis diagnostic tests were performed at weeks 8, 12, and 16 and at time of TB treatment failure/recurrence; TB outcome was assessed at TB treatment completion, weeks 48 and 72, and at time of TB treatment failure/recurrence or premature TB treatment or study discontinuation.

Plasma samples for day 12 steady-state PK were obtained predose and 2, 4, 5, 6, and 12 (arm B, LPV) or 24 (arm A, LPV and RBT; arm C, LPV, RBT, and RAL) hours after the morning dose. This sampling strategy required that RBT (and RAL for arm C) be given with the morning dose of LPV/r for arms A and C. Timing of TB and HIV medications dosed the day before the PK study day was recorded. Participants reporting missing doses or not following the dosing schedule on the day before the PK visit returned for repeat PK sampling within 5–12 days. If the participant again failed dosing criteria, PK samples were not obtained and participants were replaced until sample size requirements were met.

Plasma was frozen and shipped every 2 weeks to the Clinical Laboratory Improvement Amendments (CLIA)–certified Antiviral Pharmacology Laboratory at the University of Nebraska Medical Center. Plasma concentrations of LPV, RBT, 25-*O*-desacetyl-RBT (desRBT), and RAL were quantified by validated, quality-controlled, liquid chromatography–tandem mass spectroscopy methods [37, 38]. Lower limits of quantification were 20 (LPV), 75 (RBT), 35.5 (desRBT), and 5 (RAL) ng/mL. The coefficient of variation (CV) was less than 15% at all standard and quality-control levels tested; each assay met Food and Drug Administration guidance on bioanalytical method validation criteria [39].

The primary PK outcome measures were C_{max}, trough plasma concentration (C_{trough}; either 12 hours post-dose [C_{12}] for LPV and RAL or 24 hours [C_{24}] for RBT), AUC12 (area under the plasma concentration-time curve between 0 and 12 hours) or AUC24 (area under the plasma concentration-time curve between 0 and 24 hours), and apparent oral clearance (CL/F). Standard noncompartmental techniques using the trapezoidal rule (WinNonLin; Certara, Princeton, NJ, USA) were used to calculate AUC; C_{max}, time of C_{max} (T_{max}), minimum plasma concentration (C_{min}), and C_{trough} were directly observed; and CL/F was calculated (dose/AUC). Pharmacokinetic targets were defined for RBT and LPV. A low RBT C_{max} was less than 250 ng/mL and a high RBT C_{max} was greater than 900 ng/mL. A low LPV C_{12} was less than 1 mg/L and a high LPV C_{max} was greater than 12 mg/L. Dose adjustment based on PK criteria was allowed but none was required (see Supplementary Data).

Statistical Considerations

The sample size for the interim PK analysis was calculated using the RBT AUC_{24} for historical controls [32, 40]. Assuming a 32% CV in the RBT AUC_{24}, 18 participants/arm provided 90% power to have the 90% confidence interval (CI) around the geometric mean ratio fall within the prespecified no-effect boundary of 67–150%.

Pharmacokinetic parameters were compared between arms and with historical controls [32, 40, 41] using Wilcoxon tests. Historical PK data were taken from Naiker et al [32] for RBT 150 mg/day plus LPV/r 400 mg/100 mg. From Sekar et al [40], we used PK data for RBT 300 mg/day. We used PK data for LPV/r 400 mg/100 mg from Schöller-Gyüre et al [41].

The sample size for efficacy and safety analyses was 471 participants, assuming a 20% difference in virologic response at week 48 (90% [arm A] – 70% [arm B]), 90% power, and a 2-sided 0.025-level asymptotically normal binomial test. Because the study closed after accrual period 1 with a sample size of 71, formal statistical comparisons were not done. Within-arm proportions with 95% CIs were calculated using Wilson's score method. The primary HIV outcome measure was viral suppression (<400 copies/mL) at week 48; participants who died (1), were lost to follow-up (LFU; 4) by week 48 or missed the week 48 visit (3) were considered virologic failures. Virologic failure was defined as 2 consecutive HIV-1 RNA levels of 1000 or more copies/mL at or after week 16 or 2 consecutive HIV-1 RNA levels of 400 or more copies/mL at or after week 24. Time-to-virologic failure was summarized using Kaplan-Meier plots of cumulative proportions based on weeks from randomization to virologic failure. Sputum conversion was defined as culture or smear negative at week 8 in participants who were baseline culture, smear, or Cepheid Xpert MTB/RIF assay (Xpert) positive; inability to produce sputum even with induction was considered sputum converted. Tuberculosis treatment failure was defined as an MTB-positive culture from any site after week 16. Tuberculosis recurrence was suspected if, after 2 MTB-negative cultures post–TB treatment initiation, clinical or radiological

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deterioration consistent with active TB occurred at any time at or after week 24. All statistical analyses were performed using SAS version 9.4 and SAS/STAT version 14.1 (SAS Institute, Inc, Cary, NC, USA).

RESULTS

Accrual and Baseline Characteristics

Between July 2013 and February 2016, 71 participants enrolled: the median age was 37 years, 52% were women, 72% were Black/African, 17% were White, and 46% were Hispanic (Table 1). Median CD4+ count was 130 cells/mm^3, median HIV-1 RNA was 4.6 $\log_{10}$ copies/mL in the 62 participants with quantifiable HIV-1 RNA; 75% had NNRTI resistance; 46% had confirmed TB and 2 had INH resistance.

Study Disposition

Figure 1 provides a CONSORT (Consolidated Standards of Reporting Trials) diagram of study disposition. Among 10 participants (14%) who prematurely discontinued follow-up, the study follow-up was 36.5 (8.9, 47.1) weeks.

Antiretroviral and Tuberculosis Treatment

Fourteen participants (20%) interrupted (12) and/or discontinued (6) at least 1 antiretroviral due to toxicity: 5 in arm A, 4 in arm B, and 5 in arm C. Ten participants (14%) interrupted (6) and/or discontinued (8) at least 1 anti-TB medication due to toxicity: 5 in arm A, 2 in arm B, and 3 in arm C (see Supplementary Data for details).

HIV Outcomes

Median (Q1, Q3) CD4+ increases from baseline to week 48 were 99 (1, 159) cells/mm^3 in arm A, 119 (57, 263) in arm B, and 74 (16, 115) in arm C. One new AIDS-defining illness (esophagitis; week 4) occurred in arm B. Viral suppression to less than 400 copies/mL at week 48 occurred in 58% in arm A (14/24; 95% CI, 39–76%), 67% in arm B (16/24; 95% CI, 47–82%), and 61% in arm C (14/23; 95% CI, 41–78%); week 48 viral suppression to less than 50 copies/mL was observed in 46% (11/24; 95% CI, 28–65%), 54% (13/24; 95% CI, 35–72%), and 57% (13/23; 95% CI, 37–4%) in arms A, B, and C, respectively. Virologic failure occurred in 29% (7/24; 95% CI, 15–49%), 50% (12/24; 95% CI, 31–69%), and 30% (7/23; 95% CI, 16–51%) in arms A, B, and C, respectively (Figure 2). Pooled results for RBT-containing arms A and C and results of sensitivity analyses excluding deaths and those LFU were similar.

Tuberculosis Outcomes

Tuberculosis outcome measures included sputum conversion, treatment failure, and recurrence. Sputum conversion was observed in 88% in arm A (14/16; 95% CI, 64–97%), 82% in arm B (9/11; 95% CI, 52–95%), and 70% in arm C (7/10; 95% CI, 40–89%). Tuberculosis treatment failure was not observed. Two recurrences were reported at 45 weeks: 1 probable pulmonary TB in arm B and 1 probable extrapulmonary TB in arm C.

Adverse Events

Fifteen participants (21%) had grade 3 or 4 clinically significant adverse events: 7 (29%) in arm A, 3 (13%) in arm B, and 5 (22%) in arm C (Table 2). One participant in arm A experienced grade 4 anemia and acute hepatitis B requiring hospitalization and died. Three participants in arm A experienced grade 3 uveitis due to RBT (RBT C_{max}: 346, 422, and 727 ng/mL; for arm A, median [Q1, Q3] RBT C_{max} was 461 [361, 625] ng/mL) (Table 3; see Supplementary Data for details). There were 3 deaths (bacterial sepsis, anemia, and congestive heart failure); none were attributed to study medications.

Pharmacokinetic Outcomes

No participant required an RBT or LPV dose adjustment based on PK criteria. There were no differences in LPV PK parameters for AUC_{12}, C_{max}, or C_{trough} among the arms (Table 3). Pooling arms A and C, median CL/F was higher in arm B when double-dose LPV was used with RIF. Pooling all arms, median LPV AUC_{12}, C_{trough}, and C_{max} were comparable to historical control PWH-TB receiving LPV/r with RBT 150 mg/day [32] (Table 4) [42]. Median LPV AUC_{12}, C_{max}, and C_{min} were higher than in adults without HIV-TB [41].

Median RBT AUC_{24}, C_{max}, and C_{trough} were lower and CL/F was higher when RBT was combined with RAL (arm C) than without RAL (arm A). No differences were observed in desRBT PK parameters by treatment arm. In arm A, median RBT AUC_{24}, C_{trough}, and C_{max} were higher than historical control PWH-TB receiving LPV/r with RBT 150 mg/day [32]. Median RBT AUC_{24} and C_{trough} were also higher than in adults without HIV-TB receiving RBT 300 mg/day [40].

DISCUSSION

We demonstrated that TB treatment with an RIF- or RBT-containing regimen coupled with LPV/r ART in the doses evaluated in this study were generally safe and tolerable in PWH-TB. However, 3 participants who received RBT 150 mg/day with standard LPV/r doses (arm A) developed treatment-limiting uveitis after 28 days or more of treatment. Those randomized to the same RBT dose and LPV/r, but combined with RAL (arm C), had lower RBT AUC_{24} and C_{max} and none experienced uveitis, suggesting uveitis in arm A was due to higher RBT concentrations. Higher RBT concentrations and slower CL/F in arm A compared with arm C suggest a drug–drug interaction. While the effect of RBT on RAL PK has been evaluated, no study has evaluated the effect of RAL (or dolutegravir [DTG]) on RBT concentrations. Rifabutin is metabolized by CYP3A4 (and

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Table 1. Baseline Demographic Characteristics

Characteristics	Arm A (n = 24)	Arm B (n = 24)	Arm C (n = 23)	Total (N = 71)
Age, median (Q1, Q3), years	42 (33, 49)	35 (29, 41)	38 (32, 47)	37 (32, 46)
Female sex, n (%)	13 (54)	9 (38)	15 (65)	37 (52)
Country, n (%)				
Brazil	8 (33)	10 (42)	10 (43)	28 (40)
Haiti	6 (25)	6 (25)	6 (26)	18 (25)
South Africa	4 (17)	3 (13)	3 (13)	10 (14)
Kenya	4 (17)	3 (13)	2 (9)	9 (13)
Peru	2 (9)	2 (9)	2 (8)	6 (8)
Race/ethnicity, n (%)				
Black/African	15 (63)	14 (58)	10 (43)	39 (55)
Mixed Black	3 (13)	5 (21)	4 (17)	12 (17)
White	4 (17)	2 (8)	6 (26)	12 (17)
Hispanic/Latino	10 (42)	11 (46)	12 (52)	33 (46)
Body mass index, median (Q1, Q3), kg/m^2	19.9 (18.3, 22.1)	20.4 (17.9, 21.5)	18.9 (17.9, 21.5)	19.6 (17.9, 21.5)
CD4+, median (Q1, Q3), $cells/mm^3$	128 (60, 234)	117 (51, 246)	158 (73, 202)	130 (55, 231)
HIV-1 RNA below lower limit of quantification, n (%)	4 (17)	2 (8)	3 (13)	9 (13)
HIV-1 RNA,[a] median (Q1, Q3), log_{10} copies/mL	4.7 (3.4, 5.6) (n = 20)	4.8 (4.2, 5.3) (n = 22)	4.2 (3.2, 5.0) (n = 20)	4.6 (3.5, 5.3) (N = 62)
Site-provided reason for PI regimen, n (%)				
NNRTI resistance	17 (71)	16 (67)	20 (87)	53 (75)
Adverse reaction/contraindication to NNRTIs	4 (17)	7 (29)	2 (9)	13 (18)
Pre-entry PI use	3 (12)	1 (4)	1 (4)	5 (7)
Confirmed TB,[b] n (%)	15 (63)	9 (38)	9 (39)	33 (46)
Abnormal chest radiography,[c] n (%)	21 (88)	20 (83)	21 (91)	62 (87)
Bilateral infiltrates	5 (24)	8 (40)	12 (57)	25 (40)
Cavitary disease	2 (10)	3 (15)	3 (14)	7 (11)
Duration of anti–TB treatment before randomization, median (Q1, Q3), days	14 (7, 23)	15 (10, 19)	14 (7, 22)	14 (7, 22)

Abbreviations: HIV, human immunodeficiency virus; MTB, *Mycobacterium tuberculosis*; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; Q, quartile; TB, tuberculosis.

[a]Within the 62 participants with HIV-1 RNA above the lower limit of quantification (40 copies/mL).

[b]Confirmed TB required culture or nucleic acid amplification test positive for MTB or MTB complex.

[c]Within the 62 participants with abnormal chest radiography.

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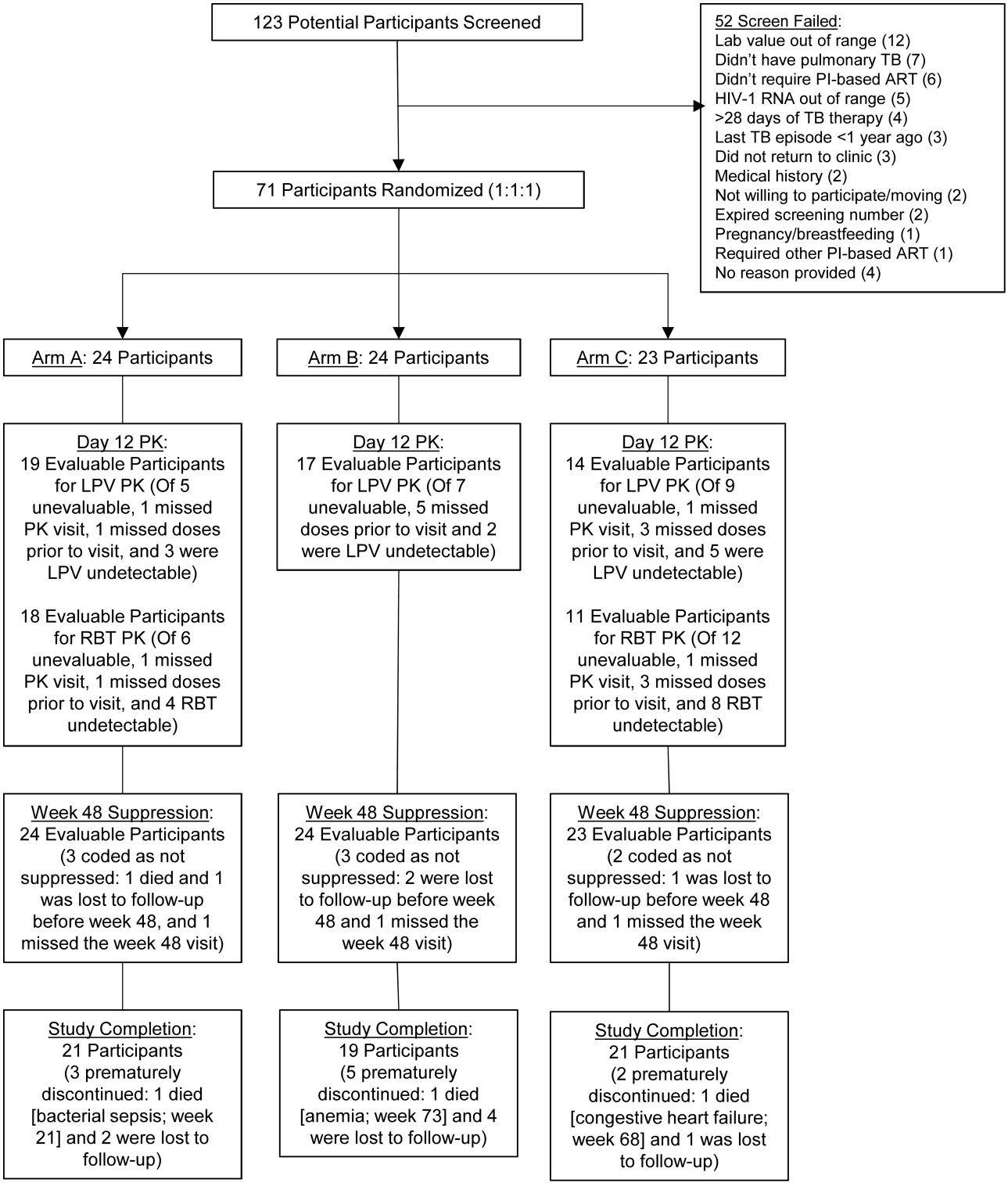


Figure 1. Study disposition. Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; LPV, lopinavir; PI, protease inhibitor; PK, pharmacokinetics; RBT, rifabutin; TB, tuberculosis.

cholinesterase) and RAL and DTG are not known to induce or inhibit CYP3A4 [36, 43]. There is no obvious mechanism for an effect of RAL on RBT PK; the equivalent (25%) decreases in RBT C_{max} and C_{trough} point to a decrease in drug absorption rather than an induction in drug metabolism. The concordant findings of higher RBT concentrations in arm A associated with treatment-limiting uveitis in 3 participants, compared with none in arm C, suggest that these

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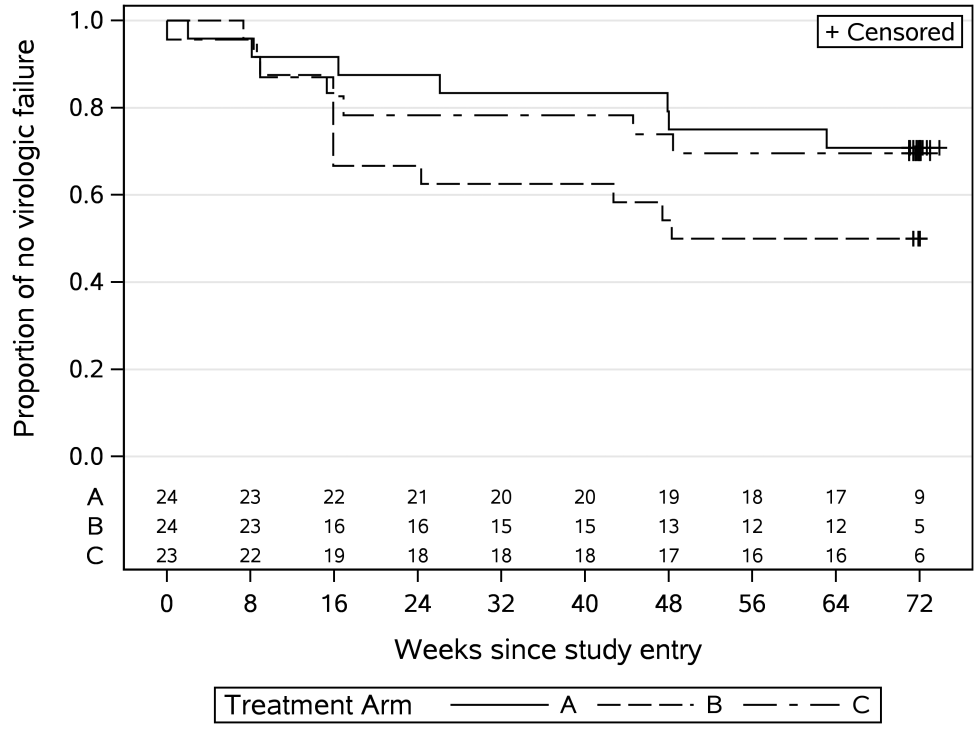


Figure 2. Cumulative proportions of participants without HIV-1 virologic failure. Abbreviation: HIV, human immunodeficiency virus.

PK differences had clinical significance and argue for further PK/PD study.

Double-dose LPV/r with RIF achieved LPV AUC_{12}, C_{max}, and C_{trough} not different from those of standard-dose LPV/r with RBT 150 mg/day. Three participants receiving double-dose LPV/r with RIF (arm B) had an LPV C_{trough} of less than 1 mg/L, which met our predetermined criterion for proportion with adequate LPV concentrations when combined with RIF. Rifabutin concentrations were generally higher than in historical controls, similarly suggesting that higher RBT concentrations led to a higher risk of adverse events.

Raltegravir concentrations in this study were similar to those in a trial in PWH-TB that evaluated RAL PK with or without RIF [44]. A comparison with RAL PK given without RIF, however, does show that RBT increased RAL AUC (≈14%) and decreased RAL C_{trough} (≈26%), similar to changes in healthy male volunteers where RAL AUC increased by 19% while C_{trough} decreased by 20% [36]. Inclusion of RAL in arm C did not lead to improved HIV or TB outcomes. Week 8 sputum conversion was lower (70%) than for arm A (88%), although this difference was not statistically significant; HIV-1 suppression to less than 400 copies/mL at 48 weeks was similar.

Study accrual prematurely ended due to low recruitment, yet we had sufficient data to reach several key conclusions. Double-dose LPV/r-based ART coupled with standard RIF-based TB therapy was associated with acceptable PK, safety, and TB

Table 2. Clinically Significant Grade 3 and 4 Adverse Events Generally Associated With the Study Medications (Lopinavir/Ritonavir, Rifabutin, Rifampin, Raltegravir) of Interest

Adverse Event	Arm A (n = 24)	Arm B (n = 24)	Arm C (n = 23)
Uveitis	3	0	0
Neutropenia	2	0	1
Anemia	1	0	0
Thrombocytopenia	1	1	0
Pancytopenia	0	0	1
Elevated AST	3	0	1
Elevated ALT	1	1	2
Diarrhea	1	1	0
Abdominal pain/weight loss[a]	0	0	1

Data are presented as number of adverse events.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

[a]These grade 3 or 4 adverse events occurred in the same participant who developed an ileal mucous fistula.

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Table 3. Pharmacokinetic Parameters for Lopinavir, Rifabutin, and Raltegravir

	Parameter Median (Q1, Q3)					
	Arm A	Arm B	Arm C	Wilcoxon Test *P* Value[a]	Arms A and C Pooled	Wilcoxon Test *P* Value[b]
Lopinavir, n	19	17	14		33	
AUC_{12}, h × ng/mL	159 796 (113 493, 222 251)	161 772 (102 118, 209 509)	149 247 (122 324, 243 273)	.91	150 967 (122 324, 222 251)	.73
C_{max}, ng/mL	18 531 (12 978, 21 627)	18 138 (11 366, 22 807)	16 802(12 609, 24 924)	.96	16 819 (12 978, 21 627)	.98
C_{trough},[c] ng/mL	12 143 (3248, 19 932)	8,788 (4363, 14 089)	9903 (5602, 17 467)	.59	11 212 (5603, 18 356)	.20
T_{max}, h	5.0 (3.5, 6.0)	4.0 (2.0, 4.0)	4.0 (2.1, 4.0)	.011	4.0 (2.1, 5.0)	.20
CL/F, L/h	2.5 (1.8, 3.5)	4.9 (3.8, 7.8)	2.7 (1.6, 3.3)	<.001	2.6 (1.8, 3.3)	<.001
Rifabutin, n	18		11			
AUC_{24}, h × ng/mL	7374 (5909, 11 785)	…	5516 (4147, 7060)	.023	…	
C_{max},[d] ng/mL	461 (361, 625)	…	349 (249, 505)	.045	…	
C_{trough}, ng/mL	208 (160, 367)	…	157 (115, 192)	.029	…	
T_{max}, h	5.0 (4.0, 5.5)	…	4.0 (3.1, 5.1)	.24	…	
CL/F, L/h	20.3 (12.7, 25.4)	…	27.2 (21.2, 36.2)	.023	…	
Raltegravir, n			16			
AUC_{12}, h × ng/mL	…	…	11 338 (2618, 15 363)	…	…	
C_{max}, ng/mL	…	…	2830 (469, 4560)	…	…	
C_{trough}, ng/mL	…	…	148 (68, 415)	…	…	
T_{max}, h	…	…	4.1 (2.6, 5.5)	…	…	
CL/F, L/h	…	…	35.8 (26.1, 157.4)	…	…	

Abbreviations: AUC_{12}, area-under-the-plasma concentration-time curve between 0 and 12 hours; AUC_{24}, area-under-the-plasma concentration-time curve between 0 and 24 hours; CL/F, apparent oral clearance; C_{max}, maximum plasma concentration; C_{trough}, trough plasma concentration; Tmax, time to C_{max}; Q, quartile.

[a]Comparing arms A, B, and C for lopinavir and comparing arms A and C for rifabutin.

[b]Comparing arms A and C pooled and arm B for lopinavir.

[c]Three participants in arm B had lopinavir C_{trough} <1 mg/L, the protocol's definition of an inadequate lopinavir concentration.

[d]Three participants in arm C had rifabutin C_{max} <250 ng/mL, the protocol's definition of an inadequate rifabutin concentration.

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Table 4. Pharmacokinetic Comparisons to Historical Controls

PK Parameters and Data Source	Sample Size	Mean (Standard Deviation)	Median (Q1, Q3)	Wilcoxon Test *P* Value
Lopinavir				
AUC_{12}, h × ng/mL				
A5290[a]	50	171 173 (82 281)	157 203 (110 657, 219 749)	
Naiker et al [32]	14	…	160 100 (129 100, 181 900)	.69
Schöller-Gyüre et al [41]	16	96 790 (21 790)	…	<.001
C_{trough}, ng/mL				
A5290[a]	50	11 358 (7666)	9876 (4363, 17 467)	
Naiker et al [32]	14	…	9400 (7200, 11 600)	.16
C_{max}, ng/mL				
A5290[a]	50	18 208 (7416)	16 870 (12 738, 21 711)	
Naiker et al [32]	14	…	18 100 (14 500, 19 600)	.69
Schöller-Gyüre et al [41]	16	11 170 (2909)	…	<.001
C_{min}, ng/mL				
A5290[a]	50	9573 (7478)	8494 (4217, 13 389)	
Schöller-Gyüre et al [41]	16	5333 (1850)	…	<.001
Rifabutin				
AUC_{24}, h × ng/mL				
A5290[b]	18	8221 (3007)	7374 (5909, 11 785)	
Naiker et al [32]	14	…	4766 (3951, 6,100)	<.001
Sekar et al [40]	15	4659 (969)	…	<.001
C_{trough}, ng/mL				
A5290[b]	18	272 (144)	208 (160, 367)	
Naiker et al [32]	14	…	133 (105, 191)	<.001
Sekar et al [40]	15	62 (14)	…	<.001
C_{max}, ng/mL				
A5290[b]	18	495 (160)	461 (361, 625)	
Naiker et al [32]	14	…	311 (258, 376)	<.001
Sekar et al [40]	15	565 (133)	…	.17

The comparisons to historical controls utilized PK parameter medians from the historical controls. For data without medians, the median was estimated from the mean and standard deviation using $\frac{mean^2}{\sqrt{mean^2+(standard\ \ deviation)^2}}$ (Statistical Rules of Thumb by Gerald van Belle [Table 5.1 on page 105]) [42].

Abbreviations: AUC_{12}, area under the plasma concentration-time curve between 0 and 12 hours; AUC_{24}, area under the plasma concentration-time curve between 0 and 24 hours; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; C_{trough}, trough plasma concentration; PK, pharmacokinetic; Q, quartile.

[a]Arms A, B, and C were pooled.

[b]Arm A.

outcomes. Standard-dose LPV/r coupled with daily RBT-based anti–TB therapy also had acceptable PK and TB outcomes, but RBT-related uveitis and neutropenia were observed. An unexpected drug–drug interaction between RAL and RBT was noted. Viral suppression at 48 weeks was not optimal in any arm, but this outcome did not appear related to adverse PK/PD.

Supplementary Data

Supplementary materials are available at *Clinical 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.

Notes

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