Impact of Raltegravir or Efavirenz on Cell-Associated Human Immunodeficiency Virus-1 (HIV-1) Deoxyribonucleic Acid and Systemic Inflammation in HIV-1/Tuberculosis Coinfected Adults Initiating Antiretroviral Therapy


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Impact of Raltegravir or Efavirenz on Cell-Associated Human Immunodeficiency Virus-1 (HIV-1) Deoxyribonucleic Acid and Systemic Inflammation in HIV-1/Tuberculosis Coinfected Adults Initiating Antiretroviral Therapy

Héloïse M. Delaugerre, Claire Bauduin, Nathalie De Castro, Beatriz Grinsztejn, Marc Cherrier, Fanélie Jouenne, Samia Mourah, Issa Kalidi, Jose Henrique Pilotto, Carlos Brites, Nemora Tregnago Barcellos, Ali Amara, Linda Wittkop, Jean-Michel Molina, and Constance Delaugerre


Background. In view of the fast viremia decline obtained with integrase inhibitors, we studied the respective effects of initiating efavirenz (EFV) or raltegravir (RAL)-based antiretroviral therapy (ART) regimens on human immunodeficiency virus (HIV)-1 deoxyribonucleic acid (DNA) levels and inflammation biomarkers in the highly inflammatory setting of advanced HIV-1 disease with tuberculosis (TB) coinfection.

Methods. We followed cell-associated HIV-1 DNA, high-sensitivity C-reactive protein (hsCRP), interleukin 6 (IL-6), soluble CD14 and D-Dimer levels for 48 weeks after ART initiation in the participants to the ANRS12-180 REFLATE-TB study. This phase II open-label randomized study included ART-naive people with HIV and TB treated with rifampicin to receive RAL 400 mg twice daily (RAL400), RAL 800 mg twice daily (RAL800) or EFV 600 mg QD with tenofovir and lamivudine.

Results. In 146 participants, the median (interquartile range [IQR]) week (W)0 HIV-1 DNA level was 4.7 (IQR, 4.3–5.1) log10 copies/106 CD4+, and the reduction by W48 was −0.8 log10 copies/106 CD4+ on EFV, −0.9 on RAL400, and −1.0 on RAL800 (P = .74). Baseline median (IQR) hsCRP, IL-6, sCD14, and D-Dimer levels were 6.9 (IQR, 3.3–15.6) mg/L, 7.3 (IQR, 3.5–12.3) pg/mL, 3221 (IQR, 2383–4130) ng/mL, and 975 (IQR, 535–1970) ng/mL. All biomarker levels decreased over the study: the overall W0–W48 mean (95% confidence interval) fold-change on ART was 0.37 (IQR, 0.28–0.48) for hsCRP, 0.42 (IQR, 0.35–0.51) for IL-6, 0.51 (IQR, 0.47–0.56) for sCD14, and 0.39 (IQR, 0.32–0.47) for D-Dimers. There were no differences in biomarker reduction across treatment arms.

Conclusions. In participants with HIV and TB, EFV, RAL400, or RAL800 effectively and equally reduced inflammation and HIV-1 DNA levels.

Keywords. HIV-1 DNA; HIV integrase inhibitors; inflammation; raltegravir; tuberculosis.
coinfected with HIV-1 and TB. Safety and efficacy were similar between treatment arms at week (W)48, and, as expected, viral suppression was achieved faster with RAL between W0 and W24 [3]. In the pharmacokinetics (PK) study, the trough concentration of RAL and other PK parameters were modestly altered by rifampicin coadministration [4].

People with HIV/TB coinfected typically present with low nadir CD4+ T-cell count and high HIV viral load. These characteristics are associated with marked systemic inflammation [5–8] and a greater viral reservoir [9, 10]. In addition to drug interactions and toxicities, ART initiation during TB infection is at high risk of immune reconstitution inflammatory syndrome (IRIS) [11]. In view of the fast decrease of HIV viral load with INSTI-based ART, these drugs raised high expectations regarding HIV reservoir reduction and immune activation/inflammation recovery but also concern regarding the risk of IRIS [12, 13].

In this substudy of ANRS 12-180 REFLATE-TB, we investigated the impact of ART initiation with 2 doses of RAL compared with EFV on the size of the total cell-associated HIV-1 deoxyribonucleic acid (DNA) reservoir, the levels of inflammation and coagulation markers (high-sensitivity C-reactive protein (hsCRP), interleukin 6 (IL-6), soluble CD14 (sCD14) and D-Dimers) and IRIS rate. This is the first report of a large randomized study of reservoir and inflammation reduction after INSTI-based ART initiation in people with HIV and TB coinfection and high baseline inflammation.

METHODS

Study
ANRS12-180 REFLATE-TB is registered in www.ClinicalTrials.gov (NCT00822315). Adult participants with untreated chronic HIV-1 infection and plasma viral load >1000 copies/mL were recruited in Brazil and France from July, 2009 to June, 2011 and randomized into 3 treatment arms: RAL (Merck, Philadelphia, PA) 400 mg BID (RAL400), RAL 800 mg BID (RAL800), or EFV (Bristol Myers Squibb, Rueil Malmaison, France) 600 mg once daily associated with tenofovir (Gilead Sciences, Foster City, CA) (245 mg once daily) and lamivudine (ViiV HealthCare, Marly le Roi, France) (300 mg once daily). Participants in the RAL800 arm switched to the standard 400 mg dose of RAL 1 month after rifampin discontinuation, but not before W24. Tuberculosis treatment was initiated 2–8 weeks before ART initiation (W0). All participants with available W0 samples were included in the reservoir and inflammation study.

Ethics Statement
The study was carried out in accordance with the ANRS Ethical Chart for Research in Developing Countries, the Brazilian regulatory requirements for clinical trials, and the Declaration of Helsinki. The protocol was approved by national and local ethics committees in Brazil (Comissao Nacional de Etica em Pesquisa and Comite de Etica em Pesquisa at Instituto de Pesquisa Clinica Evandro Chagas–Fundacao Oswaldo Cruz [IPEC–FIOCRUZ]) and France (Comité de Protection des Personnes de Paris Ile-de-France I). The experiments were conducted with the understanding and the written consent of each participant.

Samples
Ethylendiaminetetraacetic acid (EDTA) blood samples were collected at W0, W24, and W48 for cell-associated HIV-1 DNA quantification. Inflammation and coagulation biomarkers were measured in EDTA plasma samples collected at W0, W4, W12, W24, and W48. Samples were banked at −80°C.

Total Cell-Associated Human Immunodeficiency Virus-1 Deoxyribonucleic Acid Quantification
Total DNA was extracted from thawed EDTA whole blood samples using the DSP DNA Mini Kit with a QiaSymphony instrument (QIAGEN, Courtaboeuf, France). Human immunodeficiency virus-1 DNA copy numbers were quantified by real-time polymerase chain reaction (PCR) using the Generic HIV-1 DNA Cell kit ([Biocentric, Bandol, France] variability coefficient 3.9% [14]) and normalized by the total cell input into the PCR (by µg DNA) and the frequency of CD4+ T cells in peripheral blood (by flow cytometry).

Inflammation Biomarkers
High-sensitivity CRP and IL-6 levels were measured with the high-sensitivity Tina-Quant CRP Gen3 (limit of quantification [LOQ] 0.1 mg/L, interassay variability coefficient at LOQ 6.2%) and the IL-6 Elecsys Immunoassay (LOQ 1.5 pg/mL, variability coefficient 3.1%) kits with an automated COBAS Modular platform (Roche Diagnostics, Meylan, France). D-Dimers were quantified using the LIATEST DdiPlus STA kit (LOQ 270 ng/mL, variability coefficient 7.31%) with a STA-R coagulation analyzer (Stago Diagnostica, Asnières-sur-Seine, France). Human sCD14 was measured with the hCD14 Quantikine ELISA Kit (LOQ 250 pg/mL, variability coefficient 7.4%; R&D Systems, Minneapolis, MN). Biomarkers were quantified using consistent reagent lots to eliminate lot-to-lot variability.

Statistical Analysis
Qualitative variables were described in terms of frequency and proportion. Quantitative variables were described in terms of median, interquartile range, minimum, and maximum. Overall comparisons between the 3 arms were made by using a Kruskal-Wallis test. Two-by-two comparisons were performed using a Student’s t test or a Wilcoxon test as appropriate. Transformations to normalize distributions were performed when necessary. Within each treatment arm, 2-sided Wilcoxon signed-rank tests were used to assess significant changes from W0 to W4 and from W0 to W48 for biomarkers levels. Correlations between 2 quantitative variables were calculated using the Spearman correlation.
coefficient. Tests were 2-sided with the risk $\alpha$ set at 5%. Fold-changes of each biomarker level from W0 to W4 (early fold-change) and from W0 to W48 (late fold-change) were calculated as the mean differences of the biomarker level at W4 (early fold-change) and at W48 (late fold-change) compared with baseline on the log$_{10}$ scale and backtransformed to represent mean fold-change from baseline. Fold-changes were described with mean and 2-sided 95% confidence interval (CI) of the mean, with 1 indicating no change. Separate linear mixed models including random effects on intercept and slope were adjusted on sex and age and used to study factors associated with the evolution of HIV-DNA, hsCRP, IL-6, D-Dimer, and sCD14 to account for intrapatient correlation. An unstructured variance-covariance matrix was used, and biomarkers were log$_{10}$ transformed to respect model assumptions, ie, normality and homoscedasticity of residuals. Analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC).

RESULTS

Participant Characteristics at Baseline

Of the 155 participants randomized into ANRS12-180 REFLATE-TB, 146 participants were included in this study: 50 in the EFV arm, 48 in the RAL400 arm, and 48 in the RAL800 arm (Figure 1). Blood and plasma samples were not available for all participants at W0; therefore, HIV-1 DNA blood levels and systemic inflammation markers were analyzed in 126 and 139 participants, respectively.

Baseline characteristics were similar across treatment arms (Table 1) and to those of the overall participants initially included in the trial [3]. A total of 72.6% of the participants were men, the median age was 37 years, and the median body mass index was 21 kg/m$^2$ (below 18.5 kg/m$^2$ in 23% of the participants). Participants had received TB treatment for a median of 5.8 weeks (interquartile range [IQR], 4.9–7.0), the median CD4$^+$ T-cell count was 140 cells/mm$^3$ (IQR, 57–297), and the median plasma HIV-1 ribonucleic acid (RNA) viral load was 4.9 log$_{10}$ copies/mL (IQR, 4.4–5.4), with no differences between arms.

The overall median HIV-1 DNA level was 4.7 (IQR, 4.3–5.1) log$_{10}$ copies/10$^6$ CD4$^+$ T cells at W0: 4.9 (IQR, 4.4–5.1) in the EFV arm, 4.7 (IQR, 4.2–5.1) in the RAL400 arm, and 4.6 (IQR, 4.2–5.0) in the RAL800 arm ($P = .28$).

The median plasma levels of all 4 biomarkers at W0 in the EFV, RAL400, and RAL800 arms, respectively, were as follows: hsCRP levels were 5.4 mg/L (IQR, 3.5–13.3), 8.5 mg/L (IQR, 3.2–19.9), and 10.6 mg/L (IQR, 3.3–20.8), respectively ($P = .19$); IL-6 levels were 6.3 pg/mL (IQR, 3.1–11.4), 7.3 pg/mL (IQR, 3.9–13.7), and 8.3 pg/mL (IQR, 3.5–14.1), respectively ($P = .39$); sCD14 levels were 3490 ng/mL (IQR, 2800–4126), 3025 ng/mL (IQR, 2163–4203), and 3137 ng/mL (IQR, 2300–4049), respectively ($P = .37$); and D-Dimer levels were 890 ng/mL (IQR, 460–1570), 1200 ng/mL (IQR, 620–2980), and 985 ng/mL (IQR, 555–1840), respectively ($P = .24$).
After ART initiation, the suppression of HIV-1 viremia was faster with RAL: by W4, the median (IQR) viremia was significantly higher on EFV (2.2 [IQR, 1.8–2.7] log_{10} copies/mL) than on RAL (RAL400 1.7 [IQR, 1.7–2.0] and RAL800 1.7 [IQR, 1.7–1.9] log_{10} copies/mL) (P < .0001). At W12, W24, and W48, median HIV-1 RNA was suppressed below the LOQ of 1.7 log_{10} copies/mL in all treatment arms.

**Viral Suppression on Antiretroviral Therapy**

Overall, HIV-1 DNA levels declined to 4.1 (3.5–13.3) log_{10} copies/10^6 CD4+ by W24 (W0–W24 variation: −0.8 [−0.7 to −0.3]) and to 3.8 (3.5–4.1) log_{10} copies/10^6 CD4+ by W48 (W24–W48 variation: −0.3 [−0.4 to 0.0]). In the EFV, RAL400, and RAL800 arms, HIV-1 DNA levels decreased by −0.8, −0.9, and −1.0 log_{10} copies/10^6 CD4+ T cells over the 48 weeks of the study, reaching 3.9 (3.6–4.2), 3.9 (3.5–4.1), and 3.8 (3.5–4.0) log_{10} copies/10^6 CD4+ at W48, respectively (P = .74) (Figure 2). The reduction in HIV-1 DNA was similar in the 3 treatment arms, both in the earlier W0–W24 period (median, −0.6, −0.6, and −0.5 log_{10} copies/10^6 CD4+, respectively; P = .47) and in the later W24–W48 period (median, −0.2, −0.4, and −0.3 log_{10} copies/10^6 CD4+, respectively; P = .32).

**Inflammation and Coagulation Biomarkers Reduction on Antiretroviral Therapy**

The evolution of W0, W4, W12, W24, and W48 inflammation and coagulation biomarkers levels by treatment arm is shown in Figure 3 (see Table: Supplementary Digital Content 2 for detailed values and ranges). Overall median hsCRP levels first increased by +3.3 mg/L (IQR, −1.3 to +9.4) by W4 before subsiding through W48. This increase was significant in the EFV arm (+6.4 mg/L [IQR, +2.0 to +12.1], within-arm change; Table 1. Participant Characteristics at W0

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>EFV n = 50</th>
<th>RAL400 n = 48</th>
<th>RAL800 n = 48</th>
<th>Total n = 146</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Individual Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>36.5 (29.0–45.0)</td>
<td>36.5 (30.5–45.0)</td>
<td>37.5 (32.5–42.0)</td>
<td>37.0 (30.0–44.0)</td>
</tr>
<tr>
<td>Gender: male</td>
<td>39 (78.0%)</td>
<td>32 (66.7%)</td>
<td>35 (72.9%)</td>
<td>106 (72.6%)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21 (19–23)</td>
<td>21 (19–22)</td>
<td>21 (18–23)</td>
<td>21 (19–23)</td>
</tr>
<tr>
<td><strong>TB Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary-only/other</td>
<td>19 (38%)/31 (62%)</td>
<td>23 (48%)/25 (52%)</td>
<td>21 (44%)/27 (56%)</td>
<td>63 (43%)/83 (57%)</td>
</tr>
<tr>
<td>Bacteriologically confirmed</td>
<td>23 (46%)</td>
<td>26 (54%)</td>
<td>23 (48%)</td>
<td>72 (49%)</td>
</tr>
<tr>
<td><strong>Virological Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of TB treatment before W0 (weeks)</td>
<td>5.7 (4.9–7.0)</td>
<td>6.1 (4.9–7.1)</td>
<td>5.7 (5.0–6.7)</td>
<td>5.8 (4.9–7.0)</td>
</tr>
<tr>
<td>CD4+ T cell count/mm³</td>
<td>129 (45–306)</td>
<td>115 (51–209)</td>
<td>170 (80–387)</td>
<td>140 (57–297)</td>
</tr>
<tr>
<td>CD4+ T cells &lt;50/mm³</td>
<td>14 (28.0%)</td>
<td>12 (25.0%)</td>
<td>10 (18.9%)</td>
<td>36 (24.7%)</td>
</tr>
<tr>
<td>HIV-1 RNA (log_{10} copies/mL)</td>
<td>5.0 (4.6–5.5)</td>
<td>4.9 (4.4–5.4)</td>
<td>4.9 (4.2–5.4)</td>
<td>4.9 (4.4–5.4)</td>
</tr>
<tr>
<td>HIV-1 RNA &gt;5 log_{10} copies/mL</td>
<td>26 (52.0%)</td>
<td>20 (41.7%)</td>
<td>23 (47.9%)</td>
<td>69 (47.3%)</td>
</tr>
<tr>
<td>HBV or HCV coinfection</td>
<td>1 (2.0%)</td>
<td>1 (2.1%)</td>
<td>2 (4.2%)</td>
<td>2 (2.7%)</td>
</tr>
<tr>
<td>HIV-1 DNA (log_{10} copies/10^6 CD4+ T)</td>
<td>4.9 (4.4–5.1)</td>
<td>4.7 (4.2–5.1)</td>
<td>4.6 (4.2–5.0)</td>
<td>4.7 (4.3–5.1)</td>
</tr>
<tr>
<td><strong>Inflammation Biomarkers</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>5.4 (3.5–13.3)</td>
<td>8.5 (3.2–19.9)</td>
<td>10.6 (3.3–20.8)</td>
<td>6.9 (3.3–15.8)</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>6.3 (2.1–11.4)</td>
<td>7.3 (3.9–13.7)</td>
<td>8.3 (3.5–14.1)</td>
<td>7.3 (3.5–12.3)</td>
</tr>
<tr>
<td>sCD14 (ng/mL)</td>
<td>3490 (2800–4126)</td>
<td>3025 (2163–4203)</td>
<td>3137 (2300–4049)</td>
<td>3221 (2383–4130)</td>
</tr>
<tr>
<td>D-Dimer (ng/mL)</td>
<td>890 (460–1570)</td>
<td>1200 (620–2980)</td>
<td>985 (555–1840)</td>
<td>975 (535–1970)</td>
</tr>
</tbody>
</table>

**Abbreviations**: BMI, body mass index; CRP, high sensitivity C-reactive protein; DNA, deoxyribonucleic acid; EFV, efavirenz; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IL-6, interleukin 6; RAL, raltegravir; RNA, ribonucleic acid; sCD14, soluble CD14; TB, tuberculosis; W, week.

aData are n (%) or median (interquartile range).
Biomarker variations were confirmed by multivariable linear mixed models including random effects on intercept and slope.

\[
P < .001 \text{ and in the RAL800 arm (+2.1 mg/L [IQR, −1.3 to +7.9], within-arm change; } P = .04). \text{ Interleukin-6 levels did not vary significantly from W0 to W4 but decreased after W4 in all arms. Soluble CD14 and D-Dimer levels started decreasing as soon as the W0–W4 period.}
\]

All 4 markers were significantly reduced over the study period in the 3 treatment arms. By W48, median hsCRP levels had decreased to 3.2 (IQR, 1.1–9.3) mg/L, 2.1 (IQR, 0.8–4.0) mg/L, and 2.6 (IQR, 0.7–3.9) mg/L in the EFV, RAL400, and RAL800 arms, respectively (\(P = .30\)); IL-6 levels decreased to 2.0 (IQR, 1.5–4.5) pg/mL, 2.1 (IQR, 1.5–3.9) pg/mL, and 2.6 (IQR, 1.5–3.8) pg/mL, respectively (\(P = .78\)); sCD14 levels decreased to 1775 (IQR, 1392–2565) ng/mL, 1549 (IQR, 1204–1775) ng/mL, and 1475 (IQR, 1182–1779) ng/mL, respectively (\(P = .01\), with EFV levels higher than in the RAL arms); and D-Dimer levels decreased to 405 (IQR, 270–570) ng/mL, 290 (IQR, 270–420) ng/mL, and 350 (IQR, 270–410) ng/mL, respectively (\(P = .26\)).

The mean overall fold-change from W0 to W48 was 0.37 (95% CI, 0.28–0.48) for hsCRP, 0.42 (95% CI, 0.35–0.51) for IL-6, 0.51 (95% CI, 0.47–0.56) for sCD14, and 0.39 (95% CI, 0.32–0.47) for D-Dimers. By W48, the respective mean fold-change from baseline in the EFV, RAL400, and RAL800 arms was as follows: 0.58 (95% CI, 0.41–0.82), 0.30 (95% CI, 0.17–0.51), and 0.26 (95% CI, 0.16–0.42), respectively, for hsCRP; 0.47 (95% CI, 0.35–0.63), 0.40 (95% CI, 0.28–0.56), and 0.39 (95% CI, 0.27–0.56), respectively, for IL-6; 0.54 (95% CI, 0.46–0.62), 0.52 (95% CI, 0.44–0.60), and 0.48 (95% CI, 0.41–0.56), respectively, for sCD14; and 0.51 (95% CI, 0.37–0.71), 0.30 (95% CI, 0.21–0.43), and 0.37 (95% CI, 0.26–0.52), respectively, for D-Dimers. Biomarker variations were confirmed by multivariable linear mixed models including random effects on intercept and slope.

Human immunodeficiency virus-1 DNA quantification did not appear to be correlated with inflammation biomarkers levels at W0, W24, or W48 (r values from −0.15 to +0.14). Baseline median HIV-1 DNA levels were 4.8 log_{10} copies/10^6 CD4+ (IQR, 4.4–5.1) in the subgroup of participants with an initial increase in hsCRP on ART and 4.8 log_{10} copies/10^6 CD4+ (IQR, 4.4–5.1) and 4.9 log_{10} copies/10^6 CD4+ (IQR, 4.4–5.1) in those with ≥1 inflammation biomarker in the highest quartile of the distribution by W24 and W48 of ART, similarly to the levels in the total population. The changes in inflammation biomarker levels were not notably correlated with RNA viral load or with CD4+ T-cell counts at W0, W24, or W48 (r values from −0.20 to +0.14) (see Table: Supplementary Digital Content 3 for detailed values).

**DISCUSSION**

Faster viremia control is obtained on INSTI-based regimens compared with nonnucleoside reverse-transcriptase inhibitor regimens. Consequently, INSTI-based ART raised high expectations regarding HIV reservoir reduction and immune activation/inflammation recovery, but also concern regarding the risk of IRIS.

Raltegravir may be an option in the context of HIV/TB coinfection with concurrent rifampin administration. The ANRS 12180 REFLATE-TB phase II trial has demonstrated a similar safety and efficacy of RAL 400 mg BID, RAL 800 mg BID, and EFV 600 mg QD based-regimens [3].

In this substudy, we focused on the evolution of HIV-1 DNA and systemic inflammation after ART initiation in randomized participants with HIV and TB. Antiretroviral therapy initiation with EFV, RAL400, or RAL800 consistently decreased blood HIV-1 DNA levels. There were no differences across treatment arms: EFV decreased HIV-1 DNA as effectively as RAL, and the standard dose of RAL was as effective as the double dose. The overall reduction was estimated as −0.9 log_{10} copies/10^6 CD4+ T cells over 48 weeks, in accordance with previous studies of HIV-1 reservoir decay on RAL and EFV [15, 16]. In REFLATE-TB participants, changes in HIV-1 DNA levels from W0 to W48 were associated with baseline HIV-1 RNA levels and CD4+ T-cell counts, independently from the ART regimen and from inflammation biomarkers. Indeed, baseline HIV-1 RNA and HSV-1 DNA levels have been widely reported to be correlated and to associate with their decay slope and setpoint on ART [17–19]. Inflammation has also been often reported...
to drive HIV reservoir persistence through CD4+ T-cell activation and proliferation [10, 20, 21], but a study by Gandhi et al [7] reported that levels of cell-associated HIV-1 DNA and RNA depend on pre-ART levels, independently from persistent on-ART inflammation.

The impact of INSTI-based regimens on the viral reservoir size has been investigated mostly in ART switch and intensification trials so far, with conflicting results regarding HIV-1 DNA levels that were either unchanged or decreased [22–27]. Little data are available regarding the evolution of the viral reservoir after ART initiation with INSTI. In an observational nonrandomized study of 8 chronically infected participants initiating RAL, HIV-1 DNA levels decreased by −0.61 log_{10} copies/10^6 CD4+ over 1 year [15]. The overall reduction in HIV-1 DNA levels was greater in our study, possibly because we included a larger number of participants (81 vs 8) with advanced HIV disease and low CD4+ T-cell counts and where baseline HIV-1 DNA levels were higher than in the study by Koelsch et al [15].

We also studied the plasma levels of 4 major inflammation and coagulation biomarkers, known to associate with mortality rates in people with HIV: hsCRP, IL-6, sCD14, and D-Dimers [28–32]. At W0, all 4 markers were increased to 2- to 4-fold higher levels than is commonly observed in ART-naive people chronically infected with HIV-1 but without TB [33, 34]. We followed the evolution of these markers over 48 weeks after ART initiation. All biomarker levels decreased in all arms, and there were no major differences in the dynamics or amplitude of the reduction according to the ART regimen. Despite this consistent reduction, the levels of inflammation biomarkers at W48 of ART were still higher than those described in ART-treated patients without TB; in fact, they were closer to the numbers generally observed before ART initiation [33, 34]. High levels of systemic inflammation are expected during TB [8, 35, 36] and were likely to account for the higher biomarker levels we observed at W0 compared with TB-free people with HIV. This might also participate in the lack of direct correlation between inflammation levels and HIV-1 RNA reduction on ART in this study. The impact of INSTI-based ART initiation on systemic inflammation has been reported in a number of studies in TB-free participants: ART initiation with RAL decreased IL-6 and D-Dimer levels in a single-arm study [37] and led to a greater reduction in hsCRP and IL-6 levels than protease inhibitor-based regimens did in a comparative trial [33]. Elvitegravir reduced sCD14 and hsCRP levels more than EFV [34]. In the current study, all 4 biomarkers decreased
significantly over 48 weeks, and we did not observe a difference between 2 doses of RAL or EFV. Baseline inflammation levels were high in REFLECT-TB participants, and the combination of TB treatment and ART initiation was presumably favorable to a marked decline in systemic inflammation. In a longer follow-up period, we may have been able to uncover a difference in biomarker setpoints. Nevertheless, in coinfected patients with high baseline values, a longer period on ART with optimal adherence is probably necessary to further decrease residual inflammation, which associates with long-term mortality in HIV infection [28–32]. Long-term clinical and biological monitoring of these vulnerable patients is warranted.

Given the fast virological response elicited by INSTI-based ART regimens, their impact on IRIS rates must be carefully documented. In this substudy of REFLECT-TB, severe IRIS (n = 11 total) was not more frequent in participants randomized to the RAL arms, but numbers are limited. Despite alarming first reports in retrospective observational studies [12, 13], RAL intensification and dolutegravir initiation were indeed found not to increase the frequency of TB-IRIS in large prospective randomized trials [38–40]. In REFLECT-TB participants, hsCRP levels increased at W4 after ART initiation in the EFV and RAL800 arms. Early immune reconstitution on ART may be one explanation for this observation. However, the early increase in hsCRP was not associated with clinical outcomes such as grade III/IV IRIS, death, or TB treatment failure, nor were levels of inflammation biomarkers in the highest quartile of the distribution, perhaps because the numbers of clinical events were limited.

Preliminary results were recently presented at the IAS 2019 conference regarding the phase III ANRS 12-300 REFLECT-TB-2 trial of RAL 400 mg BID versus EFV in participants with HIV-1 and TB from 5 countries [41]. In contrast with the results of ANRS 12-180 where we designed this substudy, RAL was not noninferior to EFV in the ANRS 12-300 trial, with lower rates of virological suppression in all treatment arms. We cannot apply our results to ANRS 12-300 directly, but it can be expected that the viral DNA and inflammation decay may be similar across treatment arms in virologically suppressed participants.

This study has some limitations: first, TB treatment and ART were successful in the majority of participants, and the limited number of major clinical events might hinder the statistical analysis of clinical outcomes. Despite the randomized nature of the study, inflammatory markers may be impacted by a variety of daily life stimuli, and baseline HIV-1 DNA and RNA levels may have impacted the virological outcomes, because they are reported to associate with the time to viral suppression and with their own persistent levels on ART [17–19]. The role of residual viremia could not be assessed. In addition, sample availability prevented a more detailed analysis of the HIV-1 DNA decay kinetics, which may differ across treatment arms between W0 and W24, although all regimens led to a similar HIV-1 DNA reduction by W24. Sample availability also limited the number of reservoir markers tested.

CONCLUSIONS

In conclusion, this randomized study of EFV or RAL initiation in HIV-1/TB coinfection found a similar efficacy of EFV, RAL, and a double dose of RAL in reducing HIV-1 DNA burden in CD4+ T-cells as well as in decreasing systemic inflammation over 48 weeks. Doubling the dose of RAL did not appear beneficial in regard to these 2 parameters. In the context of TB treatment, RAL and EFV had similar effects on reservoir reduction and inflammation biomarkers.

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 coproduced and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Table: Supplementary Digital Content 1. Statistical results of covariate-adjusted linear mixed models adjusted on sex and age.

Table: Supplementary Digital Content 2. Inflammation marker levels and evolution, by randomized treatment arm.

Table: Supplementary Digital Content 3. Spearman rank correlations between participant characteristics and inflammation change and between biomarker levels, from W0 to W48.

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