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Evaluation of Inflammation and Atherogenesis Biomarkers Through 148 Weeks Postswitch to Dolutegravir and Rilpivirine in SWORD-1/SWORD-2

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Background: Switching to the 2-drug regimen dolutegravir + rilpivirine demonstrated noninferiority vs continuing a 3-drug or 4-drug current antiretroviral regimen (CAR) at week 48 and maintained high levels of virologic suppression to week 148 in the SWORD studies. We report inflammation and atherogenesis biomarkers postswitch to dolutegravir + rilpivirine.

Setting: SWORD-1: 65 centers, 13 countries; SWORD-2: 60 centers, 11 countries.

Methods: Virologically suppressed adults were randomized to switch to dolutegravir + rilpivirine (early-switch group; n = 513) or continue CAR (n = 511). Participants continuing CAR switched to dolutegravir + rilpivirine at week 52 (late-switch group; n = 477). Biomarkers were evaluated from Baseline to week 48 for dolutegravir + rilpivirine and CAR and noncomparatively for dolutegravir + rilpivirine postswitch through 148 weeks (early-switch) and 96 weeks (late-switch).

Results: Through week 48, changes in biomarkers did not significantly differ between dolutegravir + rilpivirine and CAR groups, except for increases in soluble CD14 and decreases in fatty acid–binding protein-2, which favored dolutegravir + rilpivirine. For inflammation biomarkers through week 148, there was no marked change in C-reactive protein, inconsistent changes in soluble CD14 and interleukin-6, and increases in soluble CD163. For atherogenesis biomarkers through week 148, fatty acid–binding protein-2 and soluble vascular cell adhesion molecule-1 showed sustained reductions; D-dimer showed inconsistent increases between early-switch vs late-switch groups.

Conclusions: No consistent pattern of change in biomarkers postswitch to dolutegravir + rilpivirine was observed through weeks 48 and 148 in SWORD-1/SWORD-2, suggesting no association of increased inflammation or atherogenesis with the 2-drug regimen while maintaining virologic suppression.

Key Words: (limit 3–6): HIV-1, 2-drug regimen, inflammation, dolutegravir + rilpivirine

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Anonymized individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

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INTRODUCTION

The 2-drug regimen dolutegravir + rilpivirine is approved as a switch strategy for virologically suppressed people living with HIV-1 (PLWH) without prior virologic failure or known resistance to either drug.[1,2] The SWORD-1 and SWORD-2 trials demonstrated that switching to dolutegravir + rilpivirine was noninferior to continuing a 3-drug or 4-drug current antiretroviral regimen (CAR) in maintaining HIV-1 RNA <50 copies/mL at week 48 and maintained high levels of virologic suppression through week

148.[3–5] No safety concerns related to long-term dolutegravir + rilpivirine exposure were observed.[4,5]

Despite persistent HIV-1 RNA suppression with effective antiretroviral regimens, chronic inflammation is a hallmark of HIV-1 infection, and non–AIDS-defining illnesses are an ongoing challenge.[6] Biomarkers of inflammation [eg, C-reactive protein (CRP) and interleukin-6 (IL-6)], monocyte and macrophage activation [eg, soluble CD14 (sCD14) and soluble CD163 (sCD163)], hypercoagulation (eg, D-dimer), intestinal barrier dysfunction [eg, fatty acid–binding protein-2 (FABP-2)], and endothelial dysfunction [eg, soluble vascular cell adhesion molecule-1 (sVCAM-1)] are independent predictors of mortality in PLWH.[6–8] We evaluated biomarkers of inflammation and atherogenesis through 148 weeks postswitch from the 3-drug or 4-drug CAR to the 2-drug regimen dolutegravir + rilpivirine in the SWORD-1 and SWORD-2 studies.

METHODS

Study Design

SWORD-1 (NCT02429791) and SWORD-2 (NCT02422797) are identically designed, randomized, open-label, phase III studies conducted at 65 centers in 13 countries and 60 centers in 11 countries, respectively. Eligible participants were adults with HIV-1 infection who were virologically suppressed on a 3-drug or 4-drug regimen (HIV-1 RNA $<$50 copies/mL for 6 months and $\leq$200 copies/mL between 6 and 12 months before screening). Participants were randomized (1:1) to switch to once-daily oral dolutegravir 50 mg + rilpivirine 25 mg (ES group) or to continue CAR for 52 weeks before switching to dolutegravir + rilpivirine through week 148 (LS group). Complete study methods have been previously published.[4]

Both studies were approved by national, regional, or investigational center ethics committees or institutional review boards and conducted in accordance with the 2008 Declaration of Helsinki. All participants provided written informed consent.

Assessments and Data Analyses

End points for this analysis were change from Baseline in biomarkers of inflammation (CRP, sCD14, IL-6, and sCD163) and atherogenesis (D-dimer, FABP-2, and sVCAM-1) at week 48 in the ES and CAR groups (secondary end point) and at weeks 100 and 148 in the ES and LS groups (exploratory end points).

Methodology for sample collection and biomarker analyses is described in Supplemental Digital Content 1, http://links.lww.com/QAI/B903. Biomarkers were analyzed as change from Baseline to week 48 for the ES and CAR groups. Median difference (dolutegravir + rilpivirine group–CAR group) in change from Baseline to week 48 was calculated using the Hodges–Lehmann estimate, and associated P values were obtained in a post hoc analysis using the Wilcoxon rank sum test.[9] Absolute values were measured to determine longitudinal changes from Baseline or LS Baseline (ie, the last assessment before switch, usually week 48) for the ES and LS groups, respectively. Biomarker assays were performed on all samples from each group after each time point; hence, data from weeks 48, 100, and 148 were not collected at the same time.

RESULTS

Study Population

Across SWORD-1 and SWORD-2, participant demographics were well-balanced between the ES (n = 513) and CAR (n = 511) or LS groups (n = 477).[3,4] Overall, most participants were male (78%), White (80%), and younger than 50 years (72%).[3] In the ES and LS groups, respectively, 85% of participants who switched to dolutegravir + rilpivirine at Baseline and 90% who switched at LS Baseline completed through week 148.[5]

Inflammation Biomarkers

CRP

In the comparative ES phase, no marked differences were observed from Baseline to week 48 in median CRP between the dolutegravir + rilpivirine and CAR groups (see, Supplemental Digital Content 2, http://links.lww.com/QAI/B904, table summarizing change from Baseline to week 48 in biomarkers). Longitudinally through week 148 in the noncomparative analyses, minor fluctuations around Baseline or LS Baseline values were consistently observed in median CRP in the ES and LS groups across the SWORD studies (Figs. 1A, B; see, Supplemental Digital Content 3, http://links.lww.com/QAI/B905, figure showing inflammation biomarkers in SWORD-1/SWORD-2).

sCD14

From Baseline to week 48, sCD14 increased in both the dolutegravir + rilpivirine and CAR groups, with a greater increase observed with CAR (median difference, −374.42; $P < 0.0001$; see, Supplemental Digital Content 2, http://links.lww.com/QAI/B904). Longitudinally, mean sCD14 consistently decreased from Baseline to week 148 in the LS group and transiently increased at weeks 48 and 100, before markedly decreasing at week 148 in the ES group in both SWORD studies (Figs. 1C, D; see, Supplemental Digital Content 3, http://links.lww.com/QAI/B905).

IL-6

At week 48, small decreases in median IL-6 were observed in both the dolutegravir + rilpivirine and CAR groups, with no differences between groups (see, Supplemental Digital Content 2, http://links.lww.com/QAI/B904). Longitudinally, fluctuations around Baseline values were observed in the ES group for both SWORD studies, with a single increase observed only in SWORD-2 at week 100 (Fig. 1E; see, Supplemental Digital Content 3, http://links.lww.com/QAI/B905). In the LS group, the results across SWORD studies were inconsistent, with increases from LS Baseline observed at week 100 in SWORD-1 and week 148 in

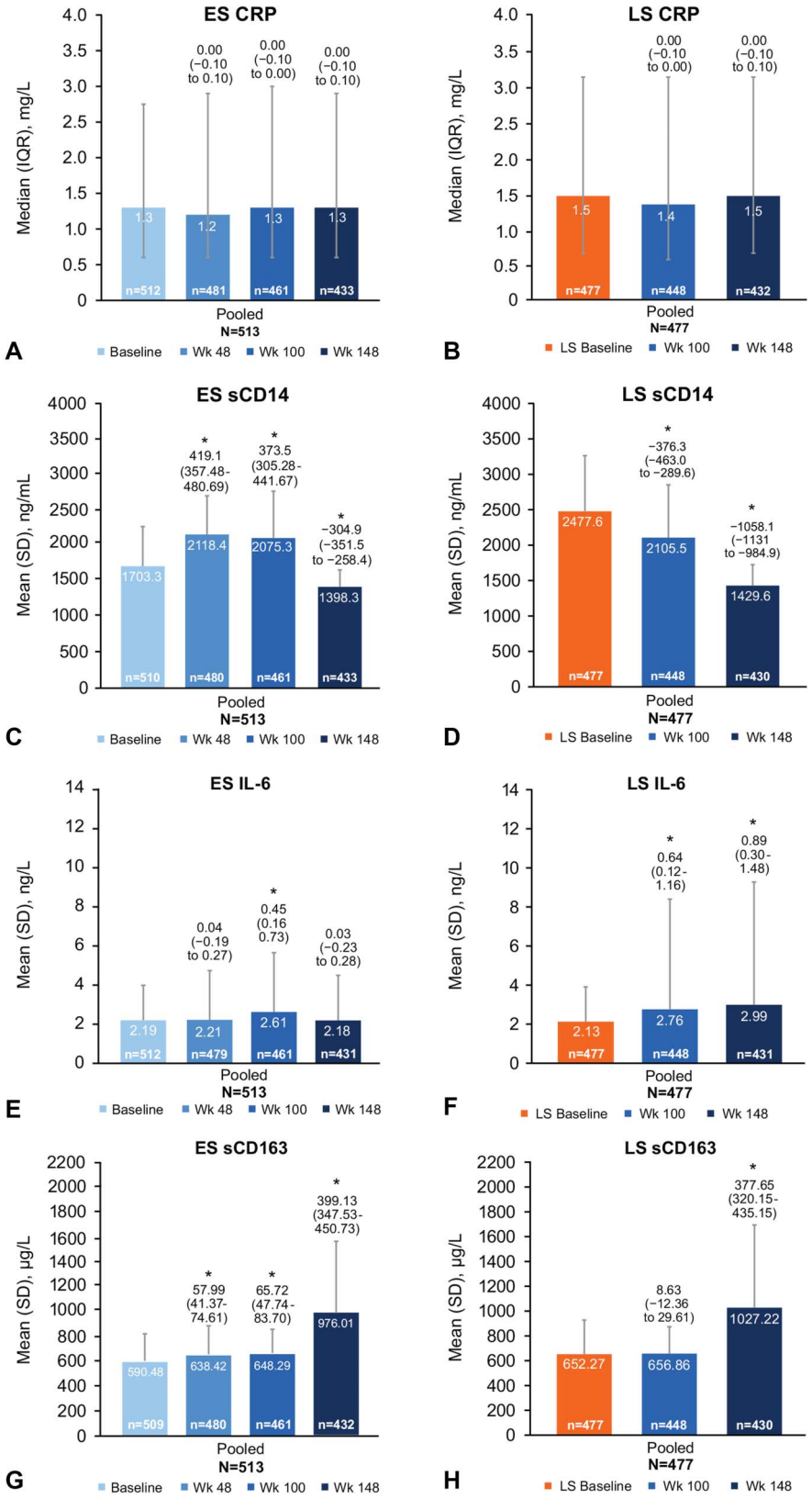

FIGURE 1. Biomarkers of inflammation in the SWORD-1 and SWORD-2 studies postswitch to dolutegravir + rilpivirine. Absolute values as median (interquartile range) or mean (SD) for biomarkers of inflammation in the pooled SWORD studies. Estimated median or mean change from Baseline or LS Baseline (95% confidence interval) at each time point is listed above the interquartile range or SD bars. For CRP, *P* values and 95% confidence intervals for longitudinal change from (A) Baseline or (B) LS Baseline were derived from median values using a 1-sample Wilcoxon signed rank test because the data distribution was skewed. For sCD14, IL-6, and sCD163, *P* values and 95% confidence intervals for longitudinal change from (C, E, and G) Baseline or (D, F, and H) LS Baseline were derived from mean values using a 1-sample 2-sided *t* test. If the *P* value for longitudinal change from Baseline or LS Baseline reached $P < 0.05$, this is indicated by * above the median or mean value at that time point (week 48, 100, or 148). The n value represents the number of participants with data at each time point. The n value for change from Baseline or LS Baseline may be lower because participants required a result at both Baseline or LS Baseline and the time point of interest. CRP, C-reactive protein; ES, early switch; IL-6, interleukin-6; LS, late switch; s, soluble.

SWORD-2 (Fig. 1F; see, Supplemental Digital Content 3, http://links.lww.com/QAI/B905).

sCD163

At week 48, sCD163 values increased from Baseline in both the dolutegravir + rilpivirine and CAR groups, with no difference observed between groups (see, Supplemental Digital Content 2, http://links.lww.com/QAI/B904). Longitudinally, mean sCD163 increased from Baseline in the ES group of both SWORD studies at weeks 48, 100, and 148, with the largest increase at week 148 (Fig. 1G; see, Supplemental Digital Content 3, http://links.lww.com/QAI/B905). In the LS group, mean sCD163 showed a marked increase only at week 148 (Fig. 1H).

Atherogenesis Biomarkers

D-Dimer

In the comparative ES phase, no changes from Baseline to week 48 were observed in median D-dimer in the dolutegravir + rilpivirine or CAR groups (see, Supplemental Digital Content 2, http://links.lww.com/QAI/B904). Longitudinally, in the noncomparative analyses, increases from Baseline D-dimer values were observed at weeks 48, 100, and 148 in the ES group in SWORD-1 and only at week 148 in SWORD-2 (Fig. 2A; see, Supplemental Digital Content 4, http://links.lww.com/QAI/B906, figure showing atherogenesis biomarkers in SWORD-1/SWORD-2). Inconsistent changes from LS Baseline were observed in median D-dimer values in the LS group, with no numeric increase at week 100 in either SWORD study and a marked increase at week 148 in both studies (Fig. 2B). All postswitch increases were below the normal range for D-dimer in healthy individuals (clinical cutoff of 0.50 mg/L fibrinogen-equivalent units or 2.74 nmol/L fibrinogen-equivalent units).[10]

FABP-2

At week 48, FABP-2 decreased in both the dolutegravir + rilpivirine and CAR groups, with a greater decrease observed with dolutegravir + rilpivirine (median difference, −0.47; $P < 0.0001$; see, Supplemental Digital Content 2, http://links.lww.com/QAI/B904). Longitudinally, sustained reductions from Baseline and LS Baseline in mean FABP-2 were observed at each time point in both the ES and LS groups, respectively, across SWORD studies (Figs. 2C, D; see, Supplemental Digital Content 4, http://links.lww.com/QAI/B906).

sVCAM-1

At week 48, a small decrease from Baseline in median sVCAM-1 was observed in the dolutegravir + rilpivirine group and a small increase was observed in the CAR group (see, Supplemental Digital Content 2, http://links.lww.com/QAI/B904). Longitudinally, sVCAM-1 remained close to Baseline values at week 48 in the ES group, with marked reductions from Baseline observed at weeks 100 and 148 in both SWORD studies (Fig. 2E; see, Supplemental Digital Content 4, http://links.lww.com/QAI/B906). In the LS group in both SWORD studies, marked reductions from LS Baseline were observed at weeks 100 and 148 (Fig. 2F).

DISCUSSION

In the comparative, randomized phase of the SWORD studies through week 48, changes from Baseline in inflammation and atherogenesis biomarkers were minimal and similar for the dolutegravir + rilpivirine and CAR groups, except for increases in sCD14 and decreases in FABP-2, which favored dolutegravir + rilpivirine.

Longitudinally, in the noncomparative analyses through week 148, with all participants receiving dolutegravir + rilpivirine, changes from Baseline or LS Baseline varied across inflammation biomarkers, and the patterns of change observed were not consistent across SWORD studies and/or between the ES and LS groups. This lack of concordance contrasted with the reproducibility observed for clinical efficacy, adverse event data (irrespective of causality), and bone and kidney tubular function biomarker improvements.[4,5] There was also no consistent pattern of change observed across atherogenesis biomarkers. Overall, these inconsistent observations across biomarkers, including multiple inflammation biomarkers involving the same physiologic processes, limit data interpretation yet do not indicate an increase in inflammation after switching to the 2-drug regimen of dolutegravir + rilpivirine. Although the lack of a control group after week 48 limits the interpretation of the longitudinal changes observed through week 148, these results do not provide evidence for any meaningful changes because the data demonstrate a lack of robust or consistent increases in biomarkers postswitch to dolutegravir + rilpivirine. In fact, decreases were observed in multiple biomarkers, including FABP-2, sVCAM-1, and sCD14. Finally, while both increases and decreases in biomarkers were observed through 148 weeks, these differences were small in magnitude and unlikely to be associated with clinical changes.

Multiple uncontrolled factors may affect inflammation, including concomitant infections, obesity, diabetes, tobacco use, alcohol or drug use, residual structural immune damage, and lifestyle factors.[6,7,11] Hence, one or more factors, other than the switch to dolutegravir + rilpivirine, could contribute to the observed changes in biomarkers. However, the SWORD studies were not designed to evaluate these aspects of the study population.

Other recent studies have assessed changes in biomarkers of inflammation and atherogenesis after switching to the 2-drug regimen dolutegravir/lamivudine. At week 48, switching from a 3-drug or 4-drug regimen to the 2-drug regimen dolutegravir/lamivudine resulted in greater decreases from Baseline in sCD14 in the TANGO and SALSA studies and a significantly lower decrease from Baseline in IL-6 in TANGO vs continuing 3-drug or 4-drug antiretroviral therapy (ART).[12,13] In the SWORD studies, sCD14 levels were increased from Baseline at week 48 in the ES group but decreased by week 148 and were decreased from LS Baseline at 48 and 96 weeks postswitch in the LS group. These observed differences and inconsistencies through week 96 in the ES group vs the LS group in the SWORD studies and the different patterns noted in participants in TANGO and SALSA suggest that inflammation is likely affected by several factors beyond a change in successful ART regimen because all studies reported similarly high rates of HIV-1 suppression in the 2-drug and 3-drug regimen treatment

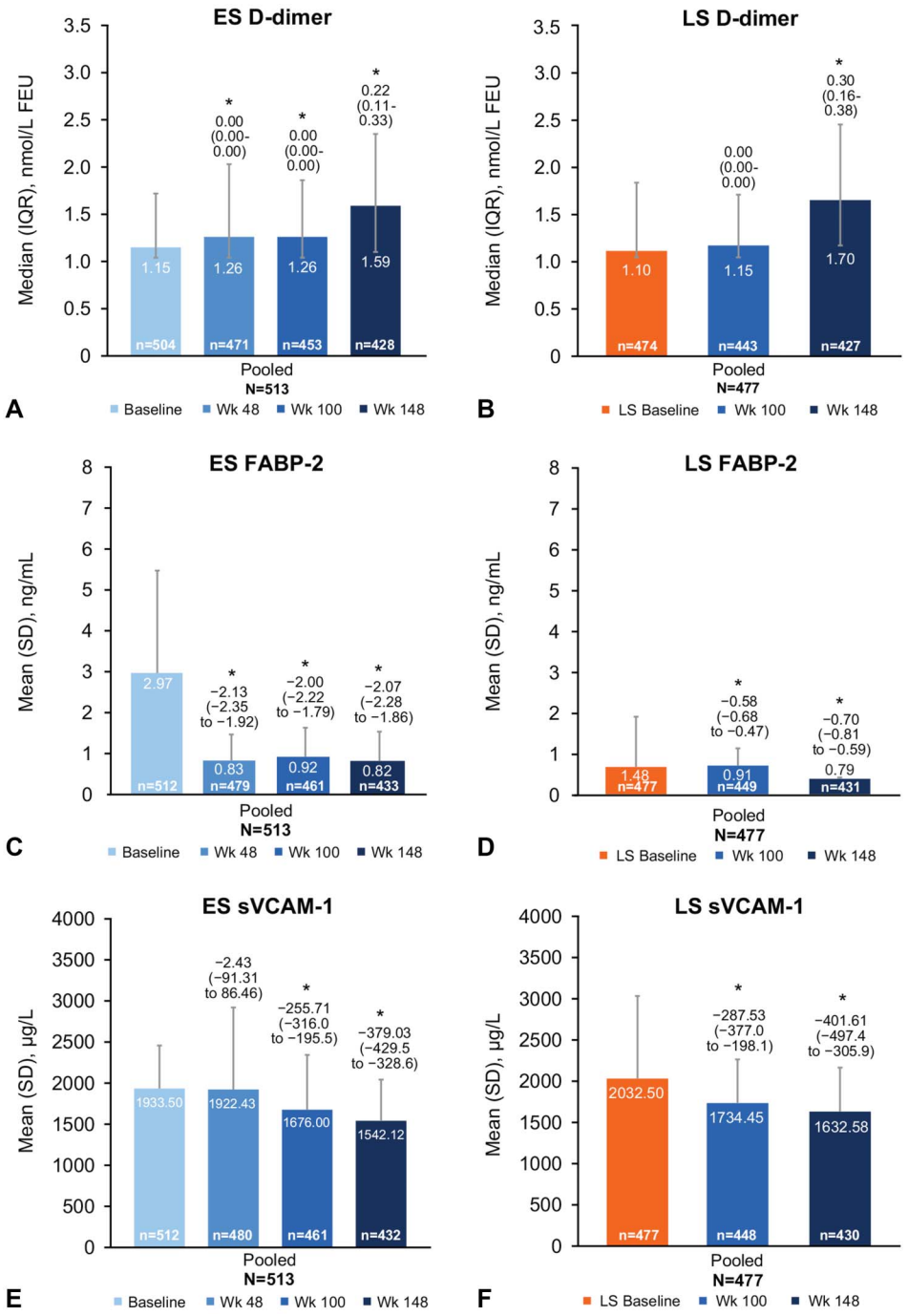

FIGURE 2. Biomarkers of atherogenesis in the SWORD-1 and SWORD-2 studies postswitch to dolutegravir + rilpivirine. Absolute values as median (interquartile range) or mean (SD) for biomarkers of atherogenesis in the pooled SWORD studies. Estimated median or mean change from Baseline or LS Baseline (95% confidence interval) at each time point is listed above the interquartile range or SD bars. For D-dimer, *P* values and 95% confidence intervals for longitudinal change from (A) Baseline or (B) LS Baseline were derived from median values using a 1-sample Wilcoxon signed rank test because the data distribution was skewed. For FABP-2 and sVCAM-1, *P* values and 95% confidence intervals for longitudinal change from (C and E) Baseline or (D and F) LS Baseline were derived from mean values using a 1-sample 2-sided *t* test. If the *P* value for longitudinal change from Baseline or LS Baseline reached $P < 0.05$, this is indicated by * above the median or mean value at that time point (week 48, 100, or 148). The n value represents the number of participants with data at each time point. The n value for change from Baseline or LS Baseline may be lower because participants required a result at both Baseline or LS Baseline and the time point of interest. ES, early switch; FABP-2, fatty acid–binding protein-2; FEU, fibrinogen-equivalent units; LS, late switch; sVCAM-1, soluble vascular cell adhesion molecule-1.

groups.[3,12,13] These observations support the conclusion that merely switching from 3-drug or 4-drug ART to a 2-drug dolutegravir-based regimen is not likely a driver of predictable changes in inflammation or atherogenesis biomarkers.

Our findings in the SWORD studies contrast with the recent report of an increase in CRP and D-dimer, with no change in other inflammation and atherogenesis biomarkers (IL-6, sCD14, sCD163, or FABP-2), in a small cohort of 58 PLWH 3 years postswitch to a 2-drug regimen vs 90 PLWH who remained on 3-drug ART.[14,15] However, it is difficult to interpret the validity of this small study because of several limitations, including small sample size (n = 35 PLWH taking dolutegravir + rilpivirine), potential unreported bias, and unmeasured confounders, such as treatment adherence.

Limitations of this analysis include the inability to analyze all longitudinal samples from each participant in the same biomarker assay because of different frozen sample stability periods (range, 1–24 months); the lack of a diverse study population, which included mostly male

and White participants; and the inherent design of the SWORD studies, which did not include a powered evaluation of any possible impact of other factors affecting inflammation and atherogenesis. Furthermore, in view of the lack of a 3-drug or 4-drug ART control group beyond week 48, the longitudinal changes described at weeks 100 and 148 must be interpreted with caution.

Overall, observations from SWORD-1 and SWORD-2 illustrate the lack of a consistent pattern of change across biomarkers of inflammation and atherogenesis through 2–3 years postswitch to the 2-drug regimen dolutegravir + rilpivirine in a randomized controlled population of 1024 treated SWORD study participants, 833 of whom were evaluated for all 7 biomarkers at Baseline and week 148. Furthermore, any changes reported, whether increases or decreases, were relatively small (ie, any shifts from Baseline medians relative to the ranges of normal values) and unlikely to represent clinically significant effects. Nevertheless, taken together, the data presented provide no evidence for an increase in biomarkers of inflammation or atherogenesis postswitch from a 3-drug or 4-drug ART regimen to the 2-drug dolutegravir + rilpivirine regimen in the presence of virologic suppression through 148 weeks.

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