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BRIEF REPORT

Changes in Body Mass Index with Longer-term Integrase Inhibitor Use: A Longitudinal Analysis of Data from the Randomized Trial to Prevent Vascular Events in Human Immunodeficiency Virus (REPRIEVE)

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Over 2-years of follow-up, integrase strand transfer inhibitor (INSTI)-use was associated with weight gain among those on an INSTI <2 years at entry (+0.27 kg/m^2/year; 95% confidence interval [CI], .22 to .33 vs +0.17 kg/m^2/year; 95% CI, .12 to .23; $P = .01$), but not those on an entry INSTI >2 years.

Keywords. integrase strand transfer inhibitors (INSTIs); weight; body mass index (BMI); HIV.

Weight gain has been seen with integrase strand transfer inhibitor (INSTI) use in numerous trials of antiretroviral therapy (ART)–naive patients and may relate to a return to health phenomena [1]. Though some of the trials that have assessed specific regimens have been carried out for longer periods of time [2], little is known regarding the overall effects of longer-term INSTI use (>2 years) in clinical practice. The Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE; NCT02344290) cohort offers an ideal setting to investigate the association between INSTI use and body mass index (BMI) among a diverse, international cohort of people with human immunodeficiency virus (HIV; PWH) eligible for primary prevention of cardiovascular disease with well-controlled HIV on ART as determined by primary care providers. Here, we assess changes in BMI over 2 years of follow-up in REPRIEVE among participants with 0–2, 2–5, and 5+ years of INSTI experience at study entry. These data extend our understanding of the longer-term effects of INSTI use in the clinical setting.

METHODS

REPRIEVE enrolled a global population of PWH aged ≥40 and ≤75 years on a stable ART regimen with a CD4$^+$ T-cell count >100 cells/mm^3 [3, 4]. Here, we assess weight change over 2 years among enrolled participants in high-income or Latin America/Caribbean global burden of disease regions (Supplementary Figure 1). Participants who had been on their ART regimen for >15 years at study entry were excluded. We assessed BMI measured at year 1 and year 2 by INSTI status and duration of INSTI use at study entry.

Using an intent-to-treat approach, we evaluated the effect of INSTI use on BMI using mixed-effect models with and without adjustment for baseline BMI centered on mean BMI at study entry (27.5 kg/m^2). Time on study was modeled as a continuous covariate in years. We performed a stratified analysis to evaluate the 2-year change in BMI among participants who had been on their entry ART regimen for 0–2 years, 2–5 years, and 5–15 years. We evaluated interaction terms of year × INSTI use to determine if change per year was significantly different between INSTI users and nonusers. Interaction terms for regimen duration were also included to determine whether INSTI-associated changes differed by time on regimen. We further evaluated the effect stratified by sex at birth and race. All *P* values presented represent *P* values for interactions. All models used inverse probability treatment (IPT) weights to account for potential confounding in choice of regimen at study entry, as previously described [5], and inverse probability censoring weights to account for potential selection bias (see Supplementary Methods and Supplementary Figure 2).

In supplemental analyses, we restricted our analyses to those who continued on their INSTI strategy for the duration of the follow-up period, rebalanced IPT weights to account for NRTI status, and conducted analyses among tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (TDF) users (see Supplementary Methods).

Ethics Statement

Each clinical research site obtained institutional review board/ethics committee approval and any other applicable regulatory

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entity approvals. Participants were provided with study information, including discussion of risks and benefits, and signed the approved declaration of informed consent.

RESULTS

This analysis included 5475 of 7769 REPRIEVE participants, of whom 2492 were on an INSTI-based regimen at study entry (Supplementary Figure 1). Median age was 51 years (Q1, 46; Q3, 55), and the majority of participants (77%) were male (Supplementary Table 1). Over the follow-up period, 418 participants (8%) discontinued follow-up and 882 (16%) switched their INSTI status. Among INSTI users at baseline, 90% continued on an INSTI-based regimen over the follow-up period; 65% of non-INSTI users continued on a non–INSTI-based regimen. At study entry, the mean duration of current INSTI use was 1.6 years (standard deviation, ± 1.7); 74% of INSTI users had been on their regimen for <2 years and 6% had been on for >5 years. Dolutegravir was used most frequently (Supplementary Table 1).

Participants on an INSTI-based regimen had a higher mean BMI at study entry and at year 2 compared with participants on a non–INSTI-based regimen (year 2 BMI, 28.6 kg/m^2; ±6.3 vs 27.3 kg/m^2; ±5.5; Supplementary Table 2). The 2-year mean change in BMI was small in both groups (<0.5 kg/m^2) and greatest among the 848 participants who switched to an INSTI-based regimen over the follow-up period (+0.67 kg/m^2). Unadjusted for baseline BMI, 2-year follow-up BMI was +1.19 kg/m^2 (95% confidence interval [CI], .88 to 1.50) higher on average among INSTI users vs non-INSTI users (Supplementary Table 3). Adjusting for baseline BMI, this effect was attenuated and no longer significant (+0.004 kg/m^2; 95% CI: −.08 to .09).

In stratified analyses, among participants on their regimen strategy for <2 years at study entry, change per year was greater with INSTI use (+0.27 kg/m^2; 95% CI: .22 to .33) vs without INSTI use (+0.17 kg/m^2; 95% CI: .12 to .23; P = .01; Figure 1). Change in BMI per year was not significantly different among participants on their regimen for 2–5 years (P = .67) or 5+ years (P = .33; Figure 1). Among those on an entry INSTI regimen for <2 years, changes in BMI were greatest among female and Black participants (Figure 1). Overall, entry BMI was the strongest predictor of BMI in follow-up, and participants with higher BMI at entry gained less weight over time. Crude change in BMI over the follow-up period was modest in all groups by type of INSTI used (Supplementary Table 4). For additional visualization of study data see Supplementary Figures 3–7.

Supplemental Analyses

Among participants who continued their entry regimen over the follow-up period, change in BMI was comparable to results from the ITT analysis (Supplementary Table 5).

In models that used IPT weights that balanced on NRTI regimen, change in BMI per year remained higher among INSTI users compared with non-INSTI users (Supplementary Table 5). For INSTI effects on BMI among TDF and TAF users, see the Supplementary Results and Supplementary Table 5.

DISCUSSION

Among a diverse, multinational cohort of nearly 5500 PWH, including 2500 INSTI users on a stable ART regimen for at least 6 months at study entry, change in BMI over a 2-year follow-up period associated with INSTI use was minimal among participants with shorter- and longer-term use. Even among key subgroups of the population, including female and Black participants, the 2-year change in BMI associated with INSTI use was <0.5 kg/m^2 overall once participants' entry BMI was accounted for. At study entry, the average BMI of our cohort was 27.5 kg/m^2 and the majority of participants had achieved viral suppression, suggesting that any weight gain over the observation period would not be attributable to a "return to health."

Our findings regarding change in BMI by regimen duration extend the current literature by noting change in BMI among long-term INSTI users. The INSTI-driven accelerated weight increase in the first 2 years of INSTI use has been reported in both ART initiation clinical trials [1] and in switch trials [6]. Our data support prior findings that weight gain with shorter-term use is relatively greater among women and Blacks/African Americans. However, our data extend the current literature by demonstrating that among participants on their regimen for >2 years at study entry, change in BMI did not differ between INSTI users and nonusers, even among key subgroups including female and Black participants. Moreover, changes in weight over the 2-year follow-up period among long-term users were modest and related primarily to weight at the time of study entry. Changes in weight were generally similar among the various INSTIs represented in the study. We saw no significant differences in the primary analyses after accounting for differences in TDF and TAF use; however, these results are limited by relatively small sample sizes.

This analysis incorporated a sophisticated modeling approach that used inverse probability weighting to limit confounding but could not account for unmeasured confounders. Stratified analyses are based on current regimen at time of study entry, rather than lifetime history of ART, which was unavailable. Participants had been on their entry ART regimen for an average of 3 years prior, with a mean duration of INSTI use of 1.6 years. As the most rapid weight gain after ART initiation occurs within the first 6–12 months due in part to a "return to health" effect [1, 2], significant changes in weight could have already occurred in this cohort. Nonetheless, these longer-term surveillance data are valuable as they suggest that any such initial rapid changes are not maintained

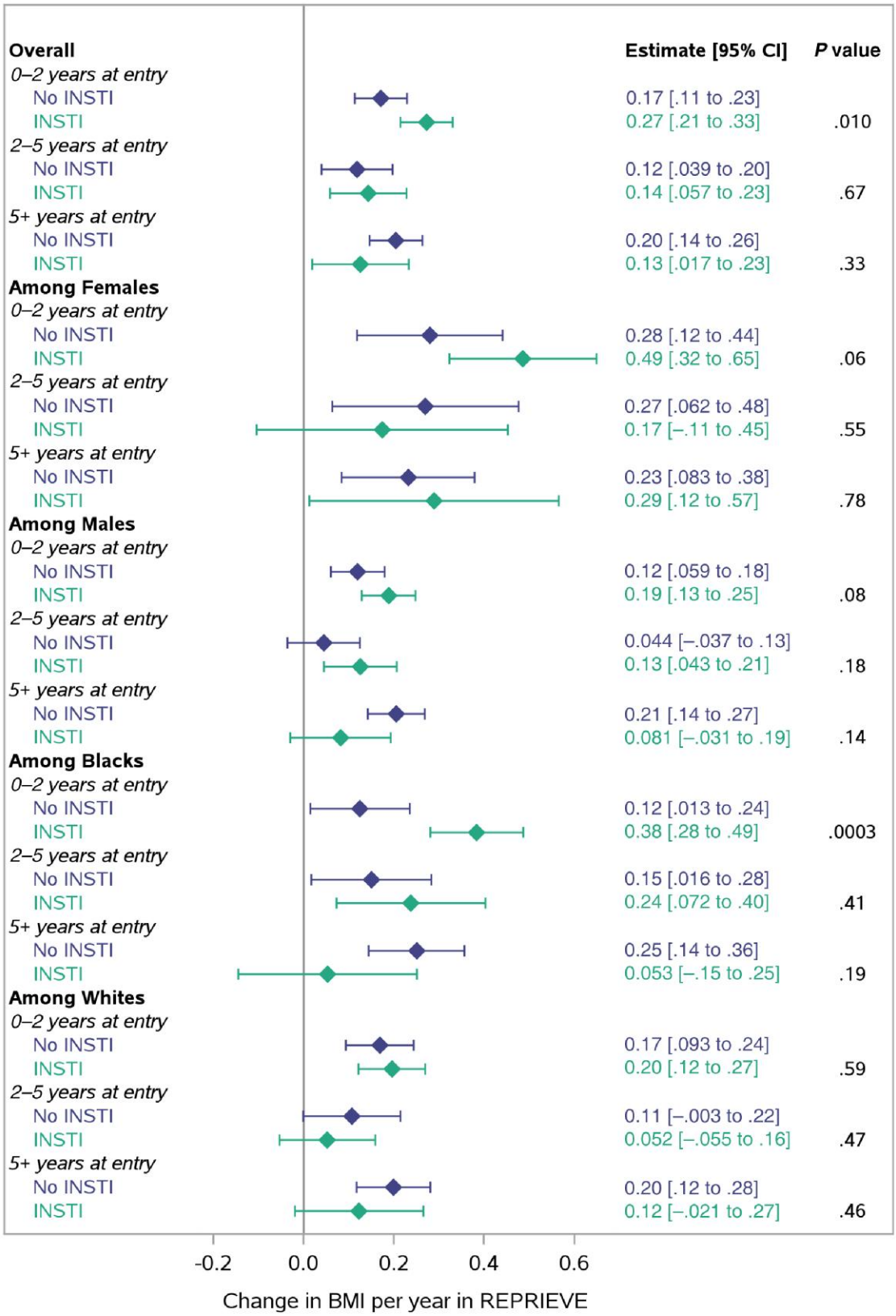

Figure 1. Change in BMI per year over follow-up in REPRIEVE, stratified by duration of entry to ART regimen. Abbreviations: ART, antiretroviral therapy; BMI, body mass index; CI, confidence interval; INSTI, integrase strand transfer inhibitor; REPRIEVE, Randomized Trial to Prevent Vascular Events in HIV. *P values represent P value for 3-way interaction between ART duration, year, and INTSI use.

with chronic use. Furthermore, we do not have BMI measures prior to ART initiation and are therefore unable to evaluate changes in BMI pre- and post-INSTI initiation. However, we assessed weight gain over time among a large group of 848 participants who initiated INSTIs within the first 2 years of starting REPRIEVE and showed that weight gain with INSTI initiation, though larger than seen over time with ongoing INSTI use, was modest on average in this population of relatively healthy PWH. Longitudinal changes in cardiometabolic parameters and events will be assessed in future REPRIEVE studies. Lack of significant weight change with longer-term INSTI use suggests that effects on metabolic end points may be minimal; however, care should be given to assess such changes in particular groups including women and Black/African Americans.

Overall, these data demonstrate that changes in weight associated with INSTI use are modest over the long term. INSTI use >2 years in the clinical setting is not associated with further weight gain over 2 additional years of follow-up.

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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