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Response to: the relationship of physical performance with HIV disease and mortality: a cohort study

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Dear Editor

We appreciate the comments of Dr. Trevisol and colleagues regarding the significance of our recent manuscript in *AIDS* on the relationship of physical performance with HIV infection and with mortality. Below, we provide additional information in response to their specific inquiries regarding other potential confounding exposures (e.g., injection drug use, HIV duration and treatment), the outcome measure of physical performance used, and the potential effects of physical activity and body composition on our observed association between HIV and reduced physical performance.

The AIDS Linked to the IntraVenous Experience (ALIVE) cohort follows injection drug users (IDUs) both with and without HIV infection collecting detailed risk behavior data at each six month follow-up visit. During 27 years of observation in our cohort, the prevalence of active injection drug use has notably declined from 81% at cohort entry to only 23% of current participants. Table 1 in the manuscript provides the proportion of participants who had recently injected drugs both at the baseline physical performance assessment and across all study visits included in this analysis. As illustrated in the Supplemental Table, recent injection drug use was associated with better rather than reduced physical performance in univariate analysis. Previously, we have noted a “healthy drug user effect” [1] whereby individuals that are able to maintain active illicit drug use are often free of debilitating disease with lower prevalence of multimorbidity and relatively better physical function. Given this known effect in our cohort, we decided *a priori* not to include injection drug use as a variable in our multivariable analyses and hence did not provide more details in the manuscript. However, it should be noted that this ‘healthy drug user effect’ reflects our internal comparison of current injectors to former injectors. It is plausible that in an analysis performed in other settings, IDUs will actually have reduced physical performance compared to other non-IDU populations. Finally, even when active injection status was incorporated into our models, our findings were not substantially altered. For example, the association of HIV infection with reduced physical performance was identical with an odds

ratio of 1.30 irrespective of whether current infection was included in models (95% CI, 1.11–1.51) or not (95% CI, 1.12–1.52).

Although we collect data on when HIV infection was originally diagnosed among our participants, we consider this estimate to be unreliable and did not include in our analysis. Estimated duration of HIV infection is wholly dependent on when an HIV diagnosis is made; substantial variability exists in how and when individuals seek HIV testing or enter care in response to symptoms. Alternatively, we incorporated CD4 nadir as a measure of the severity of HIV disease progression prior to treatment and reported an increased likelihood of reduced physical performance associated with lower CD4 cell count nadir. By performing routine HIV testing on HIV-uninfected participants, we do have estimated dates of seroconversion for 131 individuals. In analysis of this subset, we failed to observe a dose-response increase in the likelihood of reduced physical performance with increasing years since seroconversion compared to HIV-uninfected participants. An estimated 15 years or more since seroconversion was associated with reduced physical performance (OR 1.41; 95% CI, 1.01–1.96); associations with age, gender, education, depressive symptoms and comorbidities persisted in this model.

Table 1 in the manuscript also includes the proportion of participants on antiretroviral therapy (ART) at baseline (56.2%) and across all visits (65.6%). As further context, the distribution of ART regimens by class reported across study visits included 62% protease inhibitors (PI), 22% non-nucleoside reverse transcriptase inhibitors (NNRTI), 10% combination of PI/NNRTI and 6% other classes; nucleoside analogs were used almost uniformly. The median duration of ART for participants during the study period analyzed was 2.7 years. Compared to other ‘in-care’ clinic-based cohorts, we follow participants in and out of care and have observed frequent treatment interruptions and inability to maintain viral suppression [2, 3]. However, our limitation in comparison to clinic-based cohorts is that we do not prescribe ART and rely on participant self-report of ART usage. Instead, we emphasize examination of effective ART as measured by viral suppression. We observed a strong association of detectable HIV RNA levels with reduced physical performance.

As Dr. Trevisol and colleagues point out, the Short Physical Performance Battery (SPPB) was originally developed and validated in populations substantially older than our study population. Physical function has been assessed using varying approaches relying on both subjective and objective measurements. To date, there remains considerable debate on what approach constitutes the ‘gold’ standard. In the absence of a clear gold standard, we sought to apply the SPPB as a standardized, objective measure of physical performance. Our findings do demonstrate strong criterion validity of SPPB in our younger population with the observation of expected associations of lower SPPB scores with factors previously associated with reduced physical function (age, female gender, comorbidities) and independent, dose-response increases in mortality risk associated with lower SPPB scores.

We strongly agree that physical activity is an important construct that merits further investigation in HIV-infected populations. In terms of evaluating physical activity in ALIVE, we did not have any standardized measures available during this study period. As a surrogate, we evaluated health-related limitations in physical activity from the Medical

Outcomes Survey-HIV (“Does your health now limit the kinds or amounts of vigorous activities you do, like lifting heavy objects, running, or participating in strenuous sports?” [4]), which has previously been incorporated as a marker of limited physical activity in frailty phenotype assessments [5, 6]. As illustrated in the Venn diagram, there was only limited overlap in the proportion of study visits where persons were characterized both with low physical activity (defined as severe limitation to above question) and with reduced physical performance.

When this measure of low physical activity was included in multivariable models, it was significantly associated with reduced physical performance but this did not impact the association of other covariates (e.g., HIV, age, gender) with reduced physical performance. Recent studies from the general population have shown that the physical performance-to-mortality relationship in mid-life is robust to adjustment for physical activity [7]. Similarly, in our study including low physical activity in the survival analysis did not substantially attenuate the associations of reduced physical performance or of HIV infection with mortality; low physical activity was not associated with increased mortality in multivariable analysis.

While abnormalities in fat distribution would be interesting to examine in relation to physical performance, we currently do not have these data available in ALIVE. Lipodystrophy is a particularly difficult construct to reliably and efficiently measure in our observational cohort setting.

Sincerely,

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