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Response to de Bruin

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We thank Dr. de Bruin for his thoughtful comments. First, we agree that non-use of electronic monitors (EMs) despite taking the medication can introduce bias [1]. In Dr. de Bruin's scenario, monitor non-use would be more common in controls, biasing adherence results in favor of the intervention. We attempted to avoid this bias at each visit by emphasizing the importance of using the EMs, querying about their use, and reiterating their importance, if participants reported non-use. Fewer than 5% of reports from all visits included taking unmonitored doses more than weekly. Of course, these self-reports themselves may have been biased. Yet, importantly, differential monitor use would have had no effect on virologic differences between the study arms; only the differences in adherence would have been affected. We therefore agree with Dr. de Bruin that demonstrating that adherence mediated the effect on virologic outcome would further support the trial results [2], and have performed the additional analysis he suggested. The association between our intervention and virologic suppression decreased from 1.48 (95% confidence interval (CI) 0.94–2.31) in unadjusted models to 1.04 (95% CI 0.64–1.70) in models adjusted for EM-measured adherence. Moreover, for every 1% increase in EM-measured adherence, the probability of undetectable viral load increased by 2.8% (95% CI 2.0%–3.6%, $p < 0.001$). We interpret these findings to mean that the EMs captured important true adherence differences, and the adherence improvement increased virologic response rates.

Second, dropouts were indeed more common in the intervention than the control arm. In analyses assuming all dropouts had virologic suppression, the intervention's effect on treatment success was even stronger with an odds ratio of 1.99 (95% CI 1.20–3.31). The approach dictated by our *a priori* analysis plan was of course more conservative, and yet still supported an intervention effect.

Finally, we believe Dr. deBruin has created a useful tool for measuring adherence practices across sites, but it was not available when our study started. This study was conducted at three sites of one academic clinical HIV group with the same adherence standard-of-care at

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each. It included patients meeting with an HIV-specialist pharmacist who instructed patients about the medication schedule and major adverse effects, and provided pill boxes upon request. All patients also had the opportunity for referral to mental health treatment, addictions treatment, and social work services, whenever deemed necessary by providers. Facilitating use of the available support is a component of our intervention. Therefore, the results of our trial should be interpreted to have its protective effect in settings where these services can be accessed [3]. Further testing of the intervention in settings where fewer resources are available is warranted to assess its wider generalizability.

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