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Real-time electronic adherence monitoring plus follow-up improves adherence compared with standard electronic adherence monitoring

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The impact of real-time electronic monitoring on antiretroviral therapy adherence warrants further study. We conducted an analysis of cohort participants that initially involved standard electronic adherence monitoring (EAM), followed by real-time EAM and home visits for sustained at least 48-h adherence interruptions. Immediately after switching between the two types of EAM, mean adherence among 112 participants increased from 84% to 93% and remained elevated for 6 months ($P < 0.001$). Real-time EAM is a promising approach for improving adherence.

In electronic adherence monitoring (EAM), a device records each opening with a date-and-time stamp as a proxy for medication ingestion. Standard EAM devices store these data for later transfer to a computer; wireless devices are been increasingly used and transmit these data over cellular networks in real time [1].

Recent randomized trials have generally shown improvement in adherence when real-time EAM are coupled with text message reminders [2–4]; however, it is unclear how EAM monitoring itself or other types of associated interventions influence adherence behavior.

We present an ad-hoc analysis of a cohort study of adults taking antiretroviral therapy (ART) in Uganda that initially involved a standard EAM device, followed subsequently by a real-time EAM device and home visits for sustained adherence interruptions. We assessed differences in overall adherence and sustained adherence interruptions between these two periods.

Participants were drawn from a observational cohort (NCT01596322) [5,6] in which ART adherence was monitored by standard EAM (medication event monitoring system; WestRock, Sion, Switzerland) from 2005 to 2011, followed by real-time EAM (Wisepill; Wisepill Technologies, Cape Town, South Africa) from 2011 to 2015. During real-time EAM, sustained (at least 48-h) interruptions triggered home visits to characterize the cause and to assess HIV RNA levels (real-time EAM plus follow-up). Cohort enrollment occurred through 2012. Some participants were therefore monitored with both types of EAM; others were monitored only with real-time EAM.

We analyzed data from participants whose ART adherence was monitored for 6 months with standard EAM and who were switched within 1 day to monitoring with real-time EAM plus follow-up for 6 additional months. We used regression modeling (linear, logistic, or Poisson) with fixed effects and robust standard errors to compare participant characteristics, weekly average adherence, and at least 48-h adherence interruptions between the 6-month periods. Next, we used least squares regression modeling to project estimated standard EAM adherence per participant as if he/she had not switched to real-time EAM plus follow-up, and compare projected and observed adherence during real-time EAM plus follow-up. We estimated the total difference between projected and observed adherence per participant and tested the null hypothesis of no difference between the two variables, stratifying by tertiles of time on ART. We used generalized estimating equations to compare adherence data during real-time EAM plus follow-up for participants initiating ART versus participants who had 6 months of prior ART with standard EAM.

Ethical approval was received from Mbarara University of Science and Technology, the Uganda National Council for Science and Technology, Partners Healthcare, and the University of San Francisco, California.

One hundred and twelve participants had standard EAM for 6 months, followed by 6 months of real-time EAM plus follow-up. Median age was 36 years, 68% were female, 82% were literate, and pre-ART $CD4^+$ cell count was 141 cells/ml (similar to the clinic from which participants were recruited) [7,8]. No change was seen in household size, household income, time to clinic, alcohol use [9], depression [10], social support [11], food insecurity [12], or ART regimen between the two monitoring periods (all $P > 0.05$).

Immediately after switching from standard EAM to real-time EAM plus follow-up, mean adherence increased from 84% to 93% (Fig. 1; $P < 0.001$). The increase was similar for participants triggering home visits 30 days or less versus more than 30 days after the device switch. When compared with projected average adherence with standard EAM and adjusting for time on ART, this difference persisted over 6 months. The mean number of at least 48-h interruptions per 6-month monitoring

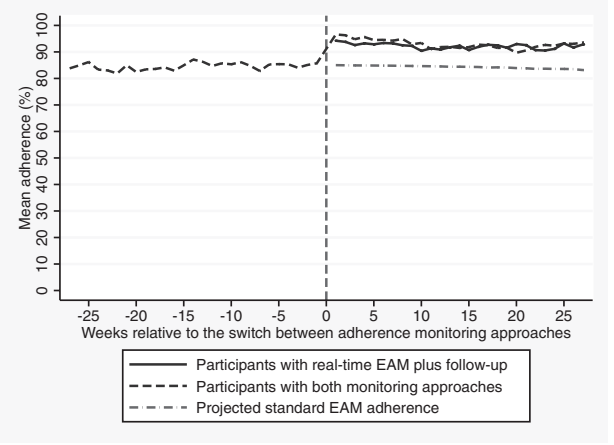

Fig. 1. Comparison of adherence during monitoring with standard electronic adherence monitoring and real-time electronic adherence monitoring plus follow-up.

period decreased from 2.2 (SD 3.1) to 0.7 (SD 1.2) per participant after switching from standard EAM to real-time EAM plus follow-up. No difference was seen in viral suppression (6% versus 7%, $P = 0.48$).

Two hundred and fifty-five participants initiated ART with real-time EAM plus follow-up. We found no difference in average adherence for the first 6 months of follow-up in these participants compared with the first 6 months of real-time EAM plus follow-up in the 112 participants who had prior experience with standard EAM (92% versus 93%; $P = 0.35$); the mean number of at least 48-h adherence interruptions per participant was significantly higher for those initiating ART with real-time EAM plus follow-up [1.9 (SD 2.8) versus 0.7 (SD 1.2); $P < 0.001$].

Compared with standard EAM, real-time EAM plus home visits for sustained interruptions was associated with increased average adherence and fewer adherence interruptions – both of which are associated with viral suppression [13,14] and reduced immune activation [15]. No differences in common factors affecting adherence were seen between the two monitoring periods.

Adherence with real-time EAM plus follow-up was high regardless of prior experience with standard EAM, suggesting that a real-time approach may effectively promote adherence during early and chronic treatment. Sustained adherence interruptions during real-time EAM plus follow-up were more frequent for those initiating ART compared with those with prior ART experience, possibly reflecting initial challenges in establishing high adherence habits [16].

Our findings strengthen growing evidence that real-time EAM with follow-up triggered by incomplete adherence is an effective intervention. One mechanism may be provision of support precisely when needed. Follow-up visits were not designed as interventions; however, participants likely perceived them as supportive. Given the resource intensity of home visits, cellular phone follow-up may be more feasible, especially if adherence challenges are frequent. In addition, real-time monitoring itself can convey a sense of support [17]. Indeed, the similarity in increased adherence when comparing study participants who triggered home visits early versus later after the device switch suggests that the change in monitoring, not the follow-up, may be responsible for the effect. The impact of anticipated follow-up, including phlebotomy for HIV RNA assessment, however, cannot be excluded.

The current analysis has limitations. First, it is *ad hoc* and compares different adherence measurement devices; differences in technology and/or acceptability may have influenced the measurements. Second, we assume that no other confounding changes occurred concomitantly with the device switch and trends in these other factors were stable throughout the observation period. Third, overall high adherence reduced the ability to show a difference in viral suppression between the monitoring periods. In addition, we did not directly compare standard versus real-time adherence monitoring and cannot estimate relative Hawthorne effects [18].

In conclusion, this analysis provides support for the effectiveness of real-time EAM with follow-up as an ART adherence intervention.

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Conflicts of interest

There are no conflicts of interest.

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Immune activation, smoking, and vaccine response

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Here, we tested the hypothesis that chronic immune activation might fuel interindividual variability in vaccine response in the model of hepatitis B virus vaccine in HIV-1-infected adults. We observed that the marker of inflammation soluble tumour necrosis factor receptor I (sTNFRI) is predictive for vaccine efficiency. We also established that the link between tobacco smoking and impaired vaccine response might be mediated by inflammation. These data are a step forward in personalized vaccination.

Understanding the factors that fuel interindividual variability in vaccine response is important to improve vaccine efficiency. Here, we tested the hypothesis that chronic immune activation might impair vaccine response. To this aim, we studied whether immune activation observed in HIV-1-infected patients [1] might reduce hepatitis B virus vaccine efficiency.

We chose to quantify in peripheral blood soluble CD40L to evaluate platelet, endothelial and T-cell activation, IgG, IgA, and IgM as a sign of B-cell activation, soluble CD14 and CD163 to measure macrophage/monocyte activity, IL-6, sTNFRI, and interferon γ-induced protein 10 to estimate inflammation. We analyzed these markers before vaccination in 124 HIV-1-infected adults who received three intramuscular injections of GenHevac B Pasteur 20 μg in the course of ANRS HB03 trial [2]. In total, 84 (68%) patients were responders, that is, with antihepatitis B surface antigen titers higher or equal to 10 mIU/ml 1 month after the third vaccine injection.

Among the tested markers, sTNFRI was the only one higher in nonresponders than in responders (3.27 ± 1.58 ng/ml and 2.50 ± 1.13 ng/ml, $P = 0.016$, Fig. 1). The antihepatitis B surface antigen titers at week 28 tended to be inversely correlated with baseline sTNFRI levels ($r = -0.168$, $P = 0.061$). A multivariate analysis adjusted on all the factors previously shown to be predictive (female sex, lower age, no active smoking, higher CD4+ cell count, and undetectable HIV-1 RNA