SUPPLEMENTAL DIGITAL CONTENT

A more detailed description of the statistical model for CD4 count trajectories and the simulation study is provided here. Specifically, for subject i with a CD4 count measurement at time t years after their first seropositive HIV test result, $CD4_i(t)$, the model is specified as:

$$\sqrt{CD4_i(t)} = \eta_{it} + \varepsilon_{it}.$$

The model describing how the latent square root CD4 count, η_{it}, changes with time is:

$$\eta_{it} = \beta_0 + \beta_1 t + b_{i0} + b_{i1} t + W_i(t).$$

In this model, β_0 is the estimated population mean square root CD4 count at time = 0 (the time of the first seropositive HIV test result) and β_1 describes the population mean rate of change over time in square root CD4 count. The estimates (standard errors) of β_0 and β_1 were 27.03 (0.29) and -2.08 (0.13), respectively. b_{i0} is patient i's deviation from the population mean square root CD4 count at time t=0, and b_{i1} is patient i's deviation from the population mean rate of change in square root CD4 count. The random effects, b_{i0} and b_{i1}, are assumed to arise from a mean zero bivariate normal distribution providing for variability in the intercept and rate of change in CD4 count among patients in the study population. The estimated variances of the b_{i0} and b_{i1} were 17.30 and 2.23, and the estimated covariance was -0.35. The term $W_i(t)$ is a stochastic process which allows for both periods of slower and periods of faster change in latent CD4 count about the subject's general linear trajectory; these changes are assumed to occur over periods of weeks or months as distinct from the very short-term variability described by ε_{it}. We found, as in other studies [12; 14], that the best-fitting stochastic process was a scaled Brownian motion process with estimated variance 1.10. The estimated variance of ε_{it} was 10.09.

The goodness of fit of the model used in the simulation study is illustrated in Figure 1 by showing that the cumulative proportions of patients starting ART for different CD4 thresholds are similar to the Kaplan-Meier estimates of these proportions obtained directly from the MACS data (i.e. without assuming a model). In producing the Kaplan-Meier estimates, if a patient had a missing CD4 measurement, follow-up was censored prior to their first missing measurement, thereby avoiding any assumption about whether it was above or below a threshold. This censoring explains why some Kaplan-Meier curves terminate before 60 months.

Having estimated the model parameters, we then used the model with these estimates to generate monthly latent square root CD4 counts, η_{it}, and monthly square root observed CD4 counts, $\sqrt{CD4_i(t)}$, for times through to 61 months after the first seropositive HIV test result. Squaring each of these two quantities gave a sequence of monthly latent CD4 counts and a sequence of monthly observed CD4 counts over a 61 month period for each of the 50,000 patients. This simulation assumes that the statistical model is appropriate for monthly measurements and hence that the term ε_{it} in the model includes very short-term biological

variation over a few days while the model for η_{it} captures longer-term variation over months and years.

Next, the sequence of latent CD4 counts was used to identify when a patient first had a latent CD4 count below each of the thresholds 500, 350, 200 and 100 cells/μl. These were then used to estimate the proportion of patients with latent CD4 counts below one of these thresholds who would be treated "late" or "very late" according to the monitoring threshold of interest. For example, for a monitoring threshold of 350 cells/μl, the proportion starting "late" during the 60 months simulated was defined as:

$$\frac{\#\ who\ start\ ART\ at\ any\ time\ after\ their\ latent\ CD4\ count\ was\ \ first < 350}{\#\ with\ latent\ CD4\ count < 350\ during\ the\ 60\ months\ simulated}.$$

The very late thresholds for ART initiation thresholds of 500, 350 and 200 cells/μl were defined as 350, 200 and 100 cells/μl, respectively. The percentage starting ART very late was then calculated as the number who start ART at any time after their latent CD4 count is first below the very late threshold divided by the number who have a latent CD4 count below the very late threshold at any time during the 60 months simulated

To evaluate the effects of decreased or increased precision of a novel technology, reflected by a change in the standard deviation, σ_ε, by a factor δ, we generated a different ε_{it} (from a normal distribution with mean zero and standard deviation $\delta\sigma_\varepsilon$) for the novel technology than the ε_{it} generated for the same measurement time for flow cytometry, but used the same value of η_{it} for both technologies. When considering bias in a novel technology, we applied the -10% or +10% change to each latent CD4 count generated (i.e. each $(\eta_{it})^2$), square-rooted the result to give a biased value η_{it} and then added the appropriate ε_{it}.

Further details can be found in the biostatistical literature [8].