Appendix

An idealized clinical trial would randomize individuals to either boosted PI or NNRTI regimens and maintain this regimen for 24 months. In such a trial, individuals may not necessarily remain on their initial therapy regimen over follow-up and may discontinue for numerous reasons, including treatment failure, drug toxicity or side-effects. Intention-to-treat analyses to compare randomization arms are a mainstay that capitalize on the benefits of randomization. When adherence to the protocol is poor, however, as-treated analyses better reflect the causal effect of NNRTIs versus boosted PIs (1).

Non-dynamic marginal structural models (MSM) with inverse probability of censoring weights were used to correct for discontinuation of, or change from, initial ART regimen class (hereafter “discontinuation”) to estimate the average causal effect of initial ART regimen on immunologic and virologic response. The following description applies equally to both our immunologic and virologic outcomes of interest. The following description applies equally to both our immunologic and virologic outcomes of interest.

MSM models were created using pooled logistic regression models and a combined weight for the inverse probability of discontinuation censoring as well as “regular” censoring (i.e. lost to follow-up or death). If an individual had the outcome of interest and discontinued or change from their initial HAART regimen class in the same month, the outcome of interest was used for that person-month. In the formulas below, let subscript \( i \) represent the unique participant and \( j \) represent the month from ART initiation, logit \( (p) = \ln \left[ \frac{p}{1-p} \right] \) and \( \epsilon \) the indicator variable for censored (1 = censored, 0 = uncensored).

The first component of the weights was calculated as the probability of remaining uncensored due to discontinuation. These weights were set equal to 0 at and after an individual discontinued their initial ART regimen class thereby censoring any contributions of the individual after discontinuation. We estimated these weights using logistic regression models for remaining uncensored due to discontinuation and then computing the probability from the odds output from the model (2). These weights were stabilized as a ratio (3) to improve efficiency (4).

Numerator: The logistic regression model to estimate the numerator was:

\[
\text{logit} \, P(C_{ij} = 0|X_i) = \alpha_{0j} + \alpha_1 X_i
\]

where \( \alpha_{0j} \) is the month-specific intercept (fit using a linear term for month from ART initiation) and \( \alpha_1 X_i \) is the transpose of the column vector of the log odds ratio for the components of the covariate baseline matrix \( X_i \).

Baseline covariates included: initial ART regimen, pre-HAART CD4 (centered on 200 cells/mm\(^3\)) and HIV RNA (centered on log\(_{10} \) 2.0 copies/mL), race, HIV transmission risk, sex, cohort, year of HAART initiation, a clinical AIDS diagnosis before HAART initiation and a linear term for the month from HAART initiation.

Denominator: The denominator of the weights is the probability of remaining uncensored conditional on a collection of baseline and time-varying covariates, estimated using the following logistic regression model:

\[
\text{logit} \, P(C_{ij} = 0|X_i, Z_{ij-1}) = \beta_{0j} + \beta_1 X_i + \beta_2 Z_{ij-1}
\]

where \( \beta_{0j} \) is the month-specific intercept (fit using a linear term for month from ART initiation) and \( \beta_1 X_i \) is the transpose of the column vector of the log odds ratio for the components of the covariate baseline matrix \( X_i \) and \( \beta_2 Z_{ij-1} \) is the transpose of the column vector of the log odds ratio for the components of the time-varying covariates matrix \( Z_{ij-1} \). The covariates used to estimate the denominator included the same baseline covariates used in the numerator as well as time-varying CD4 count and HIV RNA.

Next, within each individual, the stabilized weight was multiplied over time as follows:

\[
W_{ij} = \begin{cases} 
\prod_{k=0}^{j} \frac{P(C_{ik} = 0|X_i, V_k)}{P(C_{ik} = 0|X_i, Z_{ik-1})}, & C_{ij} = 0 \\
1, & C_{ij} = 1
\end{cases}
\]

Thus, each individual at each person-month had a stabilized weight to account for censoring due to discontinuation that was equivalent to the inverse of the probability of remaining uncensored due to discontinuation.

The second component of the weights was calculated as the probability of remaining uncensored from regular censoring. We estimated these weights using the outcome of regular censoring and utilizing the exact same methodology above with the same baseline and time-varying covariates (3). Each individual at each person-month had a stabilized weight to account for regular censoring that was equivalent to the inverse of the probability of remaining uncensored.

Finally, the two weights are multiplied at each personmonth to create one combined weight. The 1st and 99th percentiles of the weights were then truncated; sensitivity analyses were conducted to evaluate other percentiles for truncation (5). These weights were used in the pooled logistic regression models used to estimate the hazard odds ratio of our immunologic or virologic outcome of interest. In our analysis using weighted with pooled logistic regression models, the mean of the stabilized weights for changing regimen was 0.9920 (med-
ian = 1.0010, IQR = 0.9940–1.0040) for virologic response and 1.0026 (median = 1.0020, IQR = 0.9860–1.0190) for an immunologic response.

Interactions of age and initial HAART regimen class were tested with a $X^2$ test statistic with 4 degrees of freedom calculated as the difference of the quasilikelihood (QICu) for a full model as compared with a nested model with only age and initial HAART regimen main effects.

References


