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Predictors of Viral Rebound and Clinical Outcomes after Antiretroviral Treatment Interruption in Postpartum Women: An Analysis of the PROMISE Trial

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A dissertation submitted in partial satisfaction

of the requirements for the degree

Master of Science in Clinical Research

by

Catherine Nhu-Nguyen Le

2019

ABSTRACT OF THE THESIS

Predictors of Viral Rebound and Clinical Outcomes after Antiretroviral Treatment Interruption in Postpartum Women: An Analysis of the PROMISE Trial

by

Catherine Nhu-Nguyen Le

Master of Science in Clinical Research

University of California, Los Angeles, 2019

Professor Jamie O Lloyd-Smith, Chair

Background: A cure for HIV requires the interruption of antiretroviral therapy (ART) to assess the efficacy of curative interventions. Study designs using time to virologic rebound (TTR) as the primary endpoint aim to improve patient safety compared to strategies that expose participants to prolonged periods of viremia, but the safety of treatment interruption (TI) in women and ethnically diverse populations remains poorly characterized. We took advantage of a completed randomized trial in order to describe adverse events (AEs) during the aviremic period preceding TTR in women stopping ART compared to women who continued ART postpartum and clinical predictors of time to rebound.

Methods: 1,691 asymptomatic women living with HIV with baseline $CD4^+$ counts ≥ 350 cells/mm^3 and undetectable viral loads were randomized to stop or continue triple ART postpartum in the

PROMISE trial. Primary outcomes included comparison of time to first composite AE prior to viral rebound between the two study arms, as well as clinical predictors of TTR in women stopping therapy. Secondary outcomes included comparison of baseline characteristics between post-treatment controllers (PTCs) and non-controllers and rates of acute retroviral syndrome (ARS). Follow up time was 48 ± 2 weeks.

Results: After adjusting for $CD4^+$ nadir, duration of ART, and pre-treatment viral load, women in the stop arm had a lower risk of early events compared to women who continued ART (HR 3.56 (95% CI 1.81, 7.02), $p<0.001$). There were no serious adverse events observed. Being from African regions was also protective of early events compared to other regions. AEs after stopping therapy were characterized mostly by mild neutropenia, anemia, headache, and diarrhea, with a combined incidence of 8 per 1000 person-years in the first 2 weeks after stopping therapy. Events beyond 6 weeks were rare. Estimated TTR was 1.86 weeks, with the projected proportion remaining virally suppressed at 12, 24, and 48 weeks 5.5% (4.3, 5.9%), 2.0% (1.4, 2.7%), and 0.7% (0.4, 1.1%), respectively. Higher $CD4^+$ nadir (HR 0.4 (0.28, 0.57), $p<0.001$) and older age (HR 0.97 (0.96, 0.99), $p=0.001$) were predictive of delayed TTR; however, in a subgroup analysis (N=412) that included pre-treatment viral load, low pre-treatment HIV-1 RNA was the only predictor of delayed TTR (HR 1.7 (1.48, 1.95), $p<0.001$). PTCs made up 16.7% of the study population, were slightly older with higher BMI at baseline, and had significantly lower pre-ART viral loads compared to non-controllers. Incidence of ARS was <5%.

Conclusion: In young, healthy, postpartum women living with HIV with high $CD4^+$ counts, adverse events were rare in the period after TI preceding viral rebound. Pre-treatment viral load was the strongest predictor of TTR, and TTR was similar to historical cohorts despite brief ART duration

and chronic infection. Future cure studies with brief TIs using TTR as the primary endpoint may be considered safe in low-risk populations, and inclusion of diverse participant populations is necessary to characterize the impact of race/ethnicity and sex hormones on the viral reservoir.

The thesis of Catherine Nhu-Nguyen Le is approved.

Judith Silverstein Currier

Chi-Hong Tseng

Mary Elizabeth Sehl

Jamie O Lloyd-Smith, Committee Chair

University of California, Los Angeles

2019

In dedication to my husband, Terrence,

my daughter, Lennon,

and to the memory of my grandfather, Dai Cong Ky,

who closed doors in his own life in order to open doors in mine.

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Introduction

A cure for HIV will inevitably involve the withdrawal of antiretroviral therapy (ART) in hopes of a sustained period of aviremia. As such, temporary treatment interruptions (TIs) are a necessary aspect of current cure studies, but studies such as the Strategies for Management of Antiretroviral Therapy (SMART) trial, a large randomized control trial that assigned participants to continuous or episodic ART, have raised concerns regarding the safety of TIs due to poor outcomes and increased mortality.[1,2] However, the SMART trial included some participants with low $CD4^+$ nadirs, involved prolonged monitoring intervals off ART (TI duration), and used a low $CD4^+$ threshold to restart ART, thereby exposing high-risk individuals to long periods of viremia that likely contributed to poor outcomes. On the other hand, cure studies with analytic TIs using fixed TI duration, set viral load thresholds for re-initiation of ART , or higher $CD4^+$counts as primary endpoints in highly selected, low-risk populations have demonstrated good safety,[3–7] but the prolonged exposure to viremia has still raised concerns regarding long-term patient safety, immunologic adverse effects, expansion of the viral reservoir, emergence of resistance mutations, and disease transmission.[8–12]

In response, a novel study design approach using time to viral rebound (TTR) as the primary endpoint has been proposed.[13] Also known as a monitored antiretroviral pause (MAP), this approach is characterized by intense monitoring during periods preceding viral rebound and re-initiation of ART with the first detectable viral load in hopes of minimizing potential risks to participants by limiting the duration of viremia. There have been small studies using this approach that have had promising safety results, but more studies are needed.[14–20] It is also helpful for investigators and participants involved in MAP strategies to know if adverse events (AEs) generally occur early, late, or rarely in the aviremic period, and to the best of our knowledge, this data has not been described. Furthermore, understanding the efficacy of future curative interventions requires

characterization of post-interruption viral control in all populations, yet there remains a considerable paucity of data regarding the safety and efficacy of treatment interruption in women, ethnically diverse groups, and among those from resource-poor settings.[21,22] Multiple qualitative studies have highlighted safety and ethical concerns surrounding TIs from both patients and providers, demonstrating that these considerations remain a significant barrier to enrollment. Clearly, there is a continued need for more inclusive research in order to inform study designs that will maximize patient safety across all populations.

To address these gaps in knowledge, we use data from the Promoting Maternal and Infant Survival Everywhere (PROMISE) trial, an international, multicenter, randomized control trial that investigated outcomes of ART strategies for the prevention of mother-to-child HIV transmission (PMTCT) and postpartum maternal health.[23,24] The study began enrollment prior to World Health Organization (WHO) recommendations for initiation of ART in all persons living with HIV (PLWH) regardless of $CD4^+$ count,[25] and thus included randomization of women to continue or discontinue ART after delivery. We describe the temporal relationship of adverse events and viral recrudescence by opportunistically using the trial as a model for MAP strategies. We also identify clinical variables that may be associated with TTR in women in order to help prioritize promising treatment strategies and identify likely responders for future cure trials.

Methods

Data from 1,691 participants of the "HAART standard (HS)", "breastfeeding (BF)", and "formula feeding (FF)" components of the PROMISE trial who initiated triple ART during pregnancy and were randomized to receive or discontinue postpartum ART were screened for this analysis. An outline of the original study schematic is shown in the appendix, Supplemental Figure S1. In addition to those from the parent study,[23] participants met the following inclusion criteria for

this analysis: had a screening $CD4^+$ count ≥ 350 cells/mm^3 (1077BF/FF) or ≥ 400 cells/mm^3 (1077HS); were ART-naïve except for prior PMTCT use; were randomized to continue or discontinue ART within 0-42 days after delivery; received continuous triple ART before delivery for ≥ 4 weeks (defined as no breaks in therapy > 7 days); had a documented ART regimen during the study; had a known (BF component) or estimated (HS component) delivery date; and had a plasma HIV-1 RNA that was below the lower limits of detection within 0-30 days prior to postpartum randomization to continue or stop ART. A higher $CD4^+$ count criterion was used in 1077HS, where women entered the study while already receiving ART, in order to avoid immediate re-initiation of ART (at $CD4^+ \leq 350$ cells/mm^3 per country-specific guidelines at the time) in those who stopped therapy. Exclusion criteria included detectable HIV-1 RNA (defined as above the lower limit of quantification as determined by site-specific assay; see Appendix, Supplementary Table S1) within 0-30 days before randomization to stop ART; clinical indication for ART which included WHO Stage 3 or higher defining condition, prior or current tuberculosis disease, or country-specific treatment guidelines for treatment initiation; or if ART was started on the day of randomization to stop therapy.

All ART regimens recorded by site investigators were reviewed. Triple ART was defined as three antiretroviral agents from at least two different classes including nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and integrase inhibitors (INSTIs). Participants with regimens not meeting these criteria, listed as unknown, or listed as including single-class agents were excluded from this analysis. The study supplied ART regimen was emtricitabine/tenofovir disoproxil fumarate plus lopinavir/ritonavir in BF and emtricitabine/tenofovir disoproxil fumarate plus lopinavir/ritonavir or zidovudine/lamivudine plus lopinavir/ritonavir in FF. In HS, antepartum ART regimens were self-reported (Appendix, Supplementary Table S2). Viral load measurements through the end of 50

weeks (48 week visit ± 2 weeks) after discontinuation of ART were included in this analysis. Measurements were obtained at weeks 0, 4, 8 (FF only), 12, 24, 36 and 48 for PROMISE components HS/FF and at weeks 0/1, 6, 14, 26, 38 and 50 for the postpartum component of BF, but could be less frequent for those who discontinued ART. Baseline viral load was defined as the last measurement within 30 days prior to or at the time of postpartum randomization. Events occurring after 48 ± 2 weeks were censored.

The primary outcome measure was time to first composite endpoint, defined by any one of the following events: grade 2 or higher clinical sign or symptom, grade 2 or higher laboratory abnormality, WHO Stage 2 or higher clinical event, or HIV/AIDS related event (WHO Stage 4 illness, pulmonary tuberculosis, other serious bacterial infections including single episode bacterial pneumonia, grade 4 severity bacterial infection, bacterial infection requiring hospitalization within three days of infection, or bacterial infection resulting in death) compared between women who discontinued ART and women who continued ART postpartum. Times to each individual endpoint were evaluated as secondary outcomes. Other primary outcome measures included clinical predictors of time to viral rebound, defined as the time to first detectable HIV-1 RNA by site-specific assay. Secondary outcomes included rates of targeted events in each arm, rates of signs/symptoms consistent with acute retroviral syndrome (ARS) in women who stopped ART and experienced viral recrudescence during the course of study follow up, and baseline comparison between women identified as post-treatment controllers (PTCs) and non-controllers. PTCs were defined as women who did not have documented viremia above the lower limit of detection at or beyond 12 weeks after discontinuing ART.

Statistical Methods

All data analyses were performed in R version 3.5.1.[26]

Survival Analyses

For the primary outcome, a Cox proportional hazard model was used to compare the two arms. In order to determine survival estimates relative to viremia and ART use, time of viral rebound and time of restarting ART were treated as time-dependent covariates, effectively dividing participants into discrete groups based on whether or not they remained virally suppressed and whether or not they had restarted ART. Although all groups are accounted for in the model, for clarity, only the comparison between the two groups of interest (Stop and Continue arms, before viral rebound and before restarting ART) are shown. Univariate analyses for each clinical predictor were performed to determine which variables were individually associated with time to event and included: age, body mass index (BMI), region (Africa, Asia, North America, and South America/Caribbean), hepatitis B coinfection, duration of ART, WHO Stage at time of randomization, ART regimen (PI-use, NNRTI-use, or INSTI-use, defined as the last regimen used before discontinuation of ART or the last regimen used during the study follow-up period), $CD4^+$ nadir (defined as documented nadir for HS participants, who were enrolled 0-42 days post-delivery, or the lowest of either the screening or baseline $CD4^+$ count for BF/FF participants), and infant feeding strategy (breastfeeding versus formula-feeding). Covariates with a p-value ≥ 0.20 were included in the final multivariate model. Time to first laboratory and clinical endpoints, time to first HIV/AIDS defining event, and time to first WHO stage 2 or higher event in each arm were evaluated as secondary endpoints using Kaplan-Meier estimates.

Ultimately, a multivariate Cox proportional hazard model adjusting for age, BMI, $CD4^+$ nadir, duration of ART, region, infant feeding strategy, and ART regimen (PI- vs. NNRTI- use) was performed. INSTI-use was not included due to small sample size. Parity and pre-treatment HIV-1 RNA level were only available BF/FF participants and thus were not included in the full multivariate

model but were tested in a subgroup analysis. This analysis excluded ART regimen as a covariate due to small cell sizes.

Median $CD4^+$ trajectory over the study follow up period was analyzed using linear mixed model effects, censoring participants in the stop arm at the time of restarting ART. Due to interval censoring, pre- and post-rebound $CD4^+$ counts were only available for 204 of the participants in the stop arm.

Sensitivity Analyses

Two sensitivity analyses were performed. First, a modified intention-to-treat (mITT, Model 1) analysis for the multivariable Cox proportional hazard model was performed to account for women randomized to continue ART postpartum but were known to discontinue therapy for other reasons. In this analysis, events occurring in women in the continue ART arm were censored at the time of stopping ART. A second sensitivity analysis (Model 2) attempted to account for infrequent viral load sampling in participants who were randomized to stop ART, which limited our ability to determine precisely when an event occurred relative to viral rebound (Appendix, Supplementary Figure S2). In this analysis, the following adjustments were made: for those with events occurring between an undetectable viral load measurement and a detectable viral load measurement, time of viral rebound was estimated as occurring at the mean time between the last undetectable viral load and the time of the targeted event; for those who did not experience a targeted endpoint, time of viral rebound was adjusted to the mean between the last undetectable viral load measurement and the next detectable viral load measurement; if the last viral load measurement was done before the end of follow up and was undetectable *and* the participant did not experience a targeted endpoint, time of rebound was estimated as the mean between the last measurement and the end of follow up. AICs are reported and used to determine model fit.

Rates of Clinical and Laboratory Events

Occurrences of targeted laboratory and clinical events per total follow-up time (person-weeks) were summarized for each study arm. Events occurring after viral rebound were censored. Because more participants experienced viral rebound in the discontinue ART arm and the number at risk changed dramatically over the study period in this group, events are summarized by approximately 12-week intervals in order to more accurately reflect rates of events. Each participant was counted once for any specific event and once for the overall total. To avoid counting events that occurred longitudinally over multiple study visits as discrete events in any one category, each participant was counted once for the event category overall using the highest grade event.

Viral kinetics and predictors of time to rebound: Interval censored analysis

Due to large gaps in viral load monitoring particularly in women who discontinued ART, TTR was estimated using interval censoring methods[27] defining intervals as the time between the last known undetectable viral load and the first known detectable viral load. Events were censored after time of restarting ART. Semi-parametric, nonparametric, and parametric models were tested, and the estimated TTRs were all similar. Parametric models using both Weibull and log-logistic distributions were fitted and compared to the semi-parametric model, and the log-logistic model was deemed to be a good fit by visual comparison and AIC. For simplicity, this model is used to report results.

There were a small number of participants who did not experience viral rebound during the course of the study follow up period (N=39). In the primary interval censoring analysis (Model A), TTR was analyzed as observed without adjustment, censoring participants at the last known undetectable viral load. A sensitivity analysis was also performed where the participant was presumed to have experienced viral rebound at some point during follow up that was not captured,

and TTR was estimated as the mean difference between the last known undetectable viral load measurement and the end of follow up (Model B).

Age, BMI, duration of ART during pregnancy, $CD4^+$ nadir, region, infant feeding strategy, hepatitis B coinfection, WHO stage at randomization, and ART regimen (PI- and NNRTI- use) were univariately evaluated as independent predictors of TTR. Covariates with p-value ≥ 0.20 were included in the multivariate models. Due to programming constraints of the interval censored model, the number at risk for each time point is reported using Kaplan-Meier estimates from observed data. Again, a subgroup analysis using parity and pre-treatment HIV-1 RNA as covariates was performed using 1077BF/FF participants. ART regimen was not included in this multivariable sub-analysis due to small cell sizes. HIV-1 RNA was $\log_{10}$-transformed.

Post-treatment Controllers

Women who had an undetectable viral load measurement at or beyond 12 weeks after stopping ART were identified as post-treatment controllers (PTCs, N=130). This excluded women who were known to restart ART prior to recorded viral rebound. Baseline characteristics of PTCs were compared to non-PTCs using Wilcoxon rank sum tests and Chi-square tests for continuous and categorical variables, respectively. P-values ≥ 0.05 were considered statistically significant. A sensitivity analysis using multivariable logistic regression was also performed to determine predictors of controller phenotype, treating TTR as a dichotomous outcome (less than 12 weeks or greater than or equal to 12 weeks).

Acute Retroviral Syndrome

In women who discontinued ART, we described rates of signs/symptoms occurring on the day of viral rebound that were consistent with possible acute retroviral syndrome (ARS). To be

conservative, ARS was defined as the occurrence of any of the following symptoms on the day of first detectable HIV-1 RNA: fever, fatigue/malaise, anorexia, weight loss, joint pain/arthralgias, headache, nausea/vomiting, rash or other skin lesions, night sweats, lymphadenopathy, diarrhea, oral ulcers, or myalgias.

Participants who experienced viral rebound during the study follow up period were identified. Those who restarted ART prior to viral rebound were excluded. Signs/symptoms reported on the day of first detectable viremia were reviewed and summarized.

Results

Baseline characteristics

1,691 women meeting the inclusion and exclusion criteria were included in this analysis (778 women randomized to stop ART postpartum and 913 women randomized to continue ART postpartum). Baseline characteristics of these participants are shown in Table 1. Mean overall age was 28.1 years. There were 702 women from the BF component, 64 from the FF component, and 925 from the HS component of PROMISE. The majority of women were from African countries (N=1,041 [61.6%], represented by Botswana, Malawi, South Africa, Tanzania, Uganda, Zambia, and Zimbabwe) and South American/Caribbean countries (N=379 [22.4%], represented by Argentina, Brazil, Peru, and Haiti), followed by 210 (12.4%) from Asian countries (including China, India, and Thailand). The mean $CD4^+$ nadir was 679 cells/mm^3. Only 4% of participants had hepatitis B-coinfection. 58.5% used formula-feeding (N=989) as the infant feeding strategy. The majority of participants (97.8%) were classified as WHO Stage 1 at the time of postpartum randomization. Median duration of ART was 17.7 (IQR 13-22) weeks in the discontinue ART arm and 68.9 (63.1-74.1) weeks in the continue ART arm. Most participants used PI-containing regimens, consistent with the parent study protocol (N=1,498 [88.6%]). INSTI-containing regimens were rare (N=6

[0.4%]). Apart from duration of ART and regimen, as expected, characteristics were similar between the two arms. Parity and pre-treatment HIV-1 RNA were only available for BF/FF participants (N=766).

Survival analysis

In univariate analyses, age, BMI, region, duration of ART, $CD4^+$ nadir, ART regimen (specifically NNRTI-use), and infant feeding strategy were found to be independently associated with the composite safety endpoint with p-values of ≤ 0.20 (Appendix, Supplementary Table S3). In the full multivariate model adjusted for these covariates (AIC=4226, not including INSTI-use due to small sample size), aviremic participants in the discontinue ART group did not have a higher risk of meeting the composite endpoint (Table 2). In fact, women who were randomized to continue ART experienced earlier adverse events in the period before viral rebound with a hazard ratio of over 3.5-fold (HR 3.56 (95% CI 1.81, 7.02), p<0.001). These differences were primarily driven by earlier grade 2 or higher laboratory abnormalities in the continue ART arm, as demonstrated by Kaplan-Meier plots (Figure 1). Women from Asia (HR 2.1 (1.49-2.97), p<0.001), N. America (HR 2.77 (1.64-4.68), p<0.001), and S. America/Caribbean regions (HR 2.03 (1.47-2.81), p<0.001) had an increased risk of experiencing an early adverse event compared to women from African regions. Age, BMI, $CD4^+$ nadir, duration of ART, infant feeding strategy, and ART regimen were not found to be predictive of time to first event. By linear mixed model regression, the mean $CD4^+$ decline over the follow up period in women who stopped ART (regardless of rebound status) was -116 cells/μL (-131, -102), from 790.6 (771, 809) to 674 (656, 692) (Appendix, Supplementary Figure S3). For women stopping ART who had pre- and post-rebound $CD4^+$ counts available, 47 participants (23%) experienced a decline in $CD4^+$ count to less than 500 cells/uL, occurring at a median 89 days (84, 173) after ART discontinuation. The earliest drop to less than 500 cells/uL in the stop arm

occurred at 74 days. In contrast, $CD4^+$ count generally increased over time in the continue arm, as expected (Appendix, Supplementary Figure S4).

Sensitivity analyses

In the mITT analysis (Model 1, AIC=4140), women in the continue ART arm were censored at the time of stopping ART (Table 3). The adjusted hazard of continuing ART compared to stopping ART increased to 4.03 (2.5, 6.49) ($p<0.001$). In this model, region remained significantly associated with increased risk of early adverse events in Asian (HR 2.16 (1.51, 3.07), $p<0.001$), N. American (HR 2.87 (1.66, 4.96), $p<0.001$), and S. American/Caribbean (HR 2.18 (1.56, 3.03), $p<0.001$) countries compared to Africa. While women continuing ART had a higher risk of developing an adverse event, longer duration of ART was found to be protective (HR 0.56 (0.39, 0.81), $p=0.002$), possibly reflecting the time-dependent influence of ART: those who experienced events experienced them early on but then would go on to fare better than those who were on shorter durations of ART, possibly due to tolerance of drug side effects over time.

In Model 2 (adjusting for potential viral rebound occurring in between study visits or before targeted events, AIC=4349), results were similar except ART duration was no longer predictive of time to event (Table 4).

BF/FF subgroup analysis

Overall results of the subgroup survival analysis were similar to the full analysis (Appendix, Supplementary Tables S4-5). In the generalized model, stopping ART was not associated with earlier time to composite endpoint during the period of aviremia. Higher baseline BMI was borderline protective (HR 0.96 (0.92, 1), $p=0.05$). Only African and Asian countries were represented, but again, African participants had delayed time to composite endpoint relative to Asian participants.

Neither parity nor pre-treatment HIV-1 RNA level was associated with time to event. Results were similar for both sensitivity models.

Rates of laboratory and clinical events

Occurrences of grade 2 or higher laboratory abnormality per total participant follow-up time broken into approximately 12-week intervals are shown for women in the discontinue ART group (Table 5) and continue ART group (Table 6, Figure 2). The initial six weeks are shown in more granular detail as most participants in the discontinue ART group experienced early viral rebound by 4 weeks. The total follow-up time was 8,269 person-weeks for the discontinue ART arm and 37,063 person-weeks in the continue ART arm. Similarly, rates of grade 2 or higher clinical sign/symptom per total participant follow-up time for both groups are summarized in Tables 7-8 and Figure 3.

Overall, rates of adverse laboratory events were low with a rate of 4 events per 1000 person-weeks in both the stop and continue ART arms in the first 2 weeks post-randomization and were characterized by mostly benign neutropenia and anemia (Appendix, Supplementary Figure S5). Peak rates of laboratory abnormalities were 6 per 1000 person-years and 11 per 1000 person-years in stop and continue arms, respectively, occurring between 2 and 6 weeks post-randomization. In general, women who continued ART had higher rates of liver enzyme abnormalities throughout the follow up period compared to those who stopped therapy. In the stop arm, there were no events past 36 weeks in women who had prolonged suppression. There were no grade 4 lab abnormalities in the stop arm.

Women stopping therapy experienced very low rates of grade 2 or higher clinical sign/symptoms, with a peak event rate of 6 events per 1000 person-weeks between weeks 2-6 and very few symptoms reported beyond 12 weeks. Most events reported were low-grade headaches, vertigo, diarrhea, abdominal pain, musculoskeletal complaints, and symptoms related to labor and

breastfeeding (Appendix, Supplementary Figure S6). In women who continued ART, the peak rate was similar at 9 per 1000 person-weeks also occurring between weeks 2-6. Symptom profiles included a greater variety of complaints compared to women who stopped therapy, though early reported symptoms were mostly gastrointestinal and musculoskeletal complaints and were mild in nature. Most symptoms were resolved by 24-36 weeks post-randomization.

Viral kinetics and predictors of time to rebound: Interval censored analysis

Univariate analyses identified age, $CD4^+$ nadir, duration of ART, region, infant feeding strategy, and ART regimen as independent predictors of time to viral rebound and were included in the final multivariate models (Appendix, Supplementary Table S6). In Model A (AIC=1018), younger age (HR 0.97 (0.96, 0.99), p=0.001) modestly predicted more rapid rebound, and higher $CD4^+$ nadir (HR 0.40 (0.28, 0.57), p<0.001) was strongly associated with delayed rebound. Duration of ART, infant feeding strategy, region, and ART regimen were not predictive of TTR (Table 9). In further analysis, age and $CD4^+$ nadir were negatively correlated by Spearman's rank test (rho -0.06, p=0.01). However both were found to be inversely correlated to pre-treatment viral loads in the subgroup analysis. Based on parametric interval censoring methods, Model A estimated a median time to viral rebound in those who stopped ART of 1.86 weeks (Figure 4). The numbers estimated to be virally suppressed at 8, 12, 24, and 48 weeks were 9.7% (95% CI 7.9, 11.7%), 5.5% (4.3, 5.9%), 2.0% (1.4, 2.7%), and 0.7% (0.4, 1.1%) respectively.

A sensitivity analysis adjusting the presumed time of viral rebound for women who did not experience viral rebound during the follow-up period was a better fit model (AIC=932) but had similar results. Older age (HR 0.98 (0.96, 0.995), p=0.01) and higher $CD4^+$ nadir (HR 0.56 (0.40, 0.60), p=0.001) were associated with delayed rebound after ART discontinuation (Table 10). Median time to viral rebound in this model was 2.06 weeks (Figure 5). The estimated mean proportions

(95% CI) of participants remaining virally suppressed at 8, 12, 24, and 48 weeks were more conservative, consistent with model assumptions: 7.6% (6.0, 9.4%), 3.8% (2.7, 5.0%), 1.1% (0.7, 1.6%), and 0.3% (0.2, 0.5%) respectively.

In the BF/FF subgroup analysis including parity and pre-treatment HIV-1 RNA as covariates, only pre-treatment RNA was predictive of viral rebound in both models (HR 1.86 (1.61, 2.14), $p<0.001$; HR 1.70 (1.48, 1.95), $p<0.001$ for Models A and B, respectively), with higher pre-treatment values associated with more rapid viral rebound (Appendix, Supplementary Tables S7 and S8). Age and $CD4^+$ nadir were no longer predictive of TTR and, as mentioned, were both significantly correlated with pre-treatment HIV-1 RNA (rho -0.13, $p=0.01$ and rho -0.12, $p=0.02$ for age and $CD4^+$ nadir, respectively).

Post-treatment controllers

We identified 130 women (16.7%) who were randomized to discontinue ART postpartum and experienced viral rebound at or beyond 12 weeks. Baseline characteristics compared to non-PTCs are shown in Table 11. PTCs were slightly older with a mean age of 29.3 years compared to 28.0 years ($p=0.009$) and had lower median BMIs (25.0 kg/m^2 compared to 25.3 kg/m^2, $p=0.009$), but most importantly, had significantly lower pre-treatment viral loads (mean difference 3.5 log copies/ml (95% 3.4-3.6), $p<0.001$), consistent with findings from the primary interval censored analysis. A sensitivity analysis treating TTR as a dichotomous outcome (rebound before or after 12 weeks) was performed using multivariable logistic regression and also found similar results to the interval censored analysis (Appendix, Supplementary Tables S9-S10).

<u>Acute Retroviral Syndrome</u>

In women who stopped ART (N=739), 36 (4.9%) experienced signs/symptoms on day of viral rebound that were attributable to possible ARS. These participants and their clinical signs/symptoms are summarized in Table 12. All were less than grade 3 in severity. On day of viral rebound, 12 participants reported headache, 9 reported cough, 5 reported diarrhea, 4 reported skin lesions/rash, 3 had lymphadenopathy, 3 had fever, 2 reported pharyngitis, 1 reported generalized weakness, 1 reported fatigue, and 1 reported anorexia. Median viral load at rebound in participants experiencing possible ARS was 3,860 copies/ml (IQR 718, 9884).

Discussion

Survival analysis: Safety of MAP strategies

In this analysis, we describe and compare rates of adverse events during the period of aviremia following ART discontinuation in a group of young, postpartum women with high $CD4^+$ counts to women who continued ART. We found that in general, events were rare and characterized primarily by grade 2 neutropenia and anemia. Stopping ART was associated with lower rates of targeted and composite events, likely attributable to fewer ART-related side effects. Women from African countries had a significantly lower risk of experiencing early adverse events compared to other regions. There were very few events beyond six weeks in those who experienced more delayed rebound. Finally, $CD4^+$ decline over 48 ± 2 weeks in women stopping ART (not accounting for rebound status) was -116 cells/μL compared to an increase in $CD4^+$ count in the continue arm. For those with available data, 23% (N=47) had a decline in $CD4^+$ count to less than 500 cells/uL, but this occurred approximately two to three months after ART discontinuation, likely long after the threshold to restart ART in contemporary ATI models.

An ongoing challenge in HIV cure clinical research is having to face the paradigm of strict medication adherence, long ingrained in patients, when the nature of the current stage of cure

science still requires treatment interruption in order to evaluate the safety and efficacy of potential treatment modalities and characterize disease progression. In addition, because these studies are unlikely to offer much personal benefit to the individual, particularly the virally suppressed individual, special attention must be paid to the risks versus the benefits of cure research, as the potential ethical issues surrounding analytical TIs remain active obstacles to patient accrual.[28–32]

Our results are reassuring and add to the growing body of literature suggesting that brief ATIs used in cure studies should be considered safe in low-risk populations with careful and frequent monitoring,[4–7,33–36] particularly in MAP strategies where viral rebound is used as criteria to restart therapy. In addition, these data provide some insight into a considerable knowledge gap in cure research regarding the potential impact of sex and race/ethnicity on the viral reservoir. In a systematic review of 151 cure studies, only 30% of studies provided information on race, and only 23.6% of participants overall were non-white.[21,22] A survey exploring attitudes toward cure research studies revealed that women, African American/black, Hispanic, and low-income PLWH were significantly less willing to participate in HIV cure studies.[37] Much of the data we have on viral kinetics, the latent reservoir, and implementation of cure strategies therefore has unclear relevance in more diverse populations. Our analysis includes an international, mostly non-white population, and we found differences in the risk of adverse events during aviremia by region favoring African participants. Mechanisms driving these differences are most certainly multifactorial, including behavioral and socioeconomic considerations as well as biological factors.[38] For example, simple cultural differences that drive the likelihood of reporting symptoms would drastically affect these results. HLA alleles are known to cluster according to race and ethnicity, which may contribute to racial differences in immune response to natural infection and therapeutic vaccines.[39,40] The geographic distribution of HIV-1 subtypes may also account for the racial differences seen in our analysis.[9,41,42] Finally, transmission of HIV in African countries is primarily from unprotected

heterosexual intercourse, whereas in many other countries, the HIV epidemic affects primarily men who have sex with men and intravenous drug users. Behavioral differences between these populations may play a role in increasing or mitigating one's risk of developing secondary complications. It was not possible to account for these details in this analysis, and studies designed to explore the impact of these characteristics would be necessary to answer such questions.

Our study also lends support for greater inclusion of women in HIV cure studies. Women represent half of the world's HIV burden yet make up only 17% of cure study participants, and over a quarter of cure studies did not include women at all.[21,43] Pregnancy is generally an exclusion criterion for clinical trials, so this analysis of PROMISE represents a unique opportunity to define cure-related outcomes in peripartum women. We demonstrate that short TIs can be deployed safely in a diverse population of young, healthy, postpartum, treatment-naïve women with high $CD4^+$ counts. Our results provide insight into ways in which sex hormones might influence HIV disease and clinical outcomes. We hope that these results can inform future study designs exploring sex-specific viral targets and host immune pathways, leading to the discovery of novel therapeutic targets.

Sex differences in the viral reservoir and time to rebound

In this study, we use TTR as a surrogate marker for the size of the latent reservoir since smaller reservoirs should theoretically lead to delayed rebound following TI,[16,44–46] as has been observed in 'near-cure' cases following allogeneic stem cell transplantation[14,15] or very early treatment initiation.[47,48] The median estimated TTR in our study is on the order of two weeks, similar to other studies with primarily white male cohorts.[7,18,19,46,49–55] This finding is intriguing when considering the PROMISE population has several characteristics that should favor more rapid rebound, including a

median duration of ART of only 17.7 weeks (IQR 13-22)[19] and initiation of treatment during chronic infection.[53,56–58]

We postulate that this relatively delayed rebound in briefly treated, chronically-infected women may be partially due to effects of sex hormones on the viral reservoir. It was observed in early studies that women living with HIV have significantly lower initial HIV viral loads than men,[59–64] and while this effect is attenuated later in the disease course, they continue to exhibit higher markers of inflammation and immune activation and have accelerated disease progression when adjusted for viral load.[65–70] X-linked immune target loci, $CD4^+$ T cell fluctuations in response to hormonal changes, and estrogen-mediated modulation of immune responses have all been shown to contribute to the sex-specific phenotypes in HIV.[65–69,71] However, less is known about the role of sex on dynamics of the HIV reservoir. Women have been observed to make up a higher proportion of PTCs[48] and are more likely to be spontaneous controllers of HIV.[9,72–75] These observations suggest that women may have smaller reservoirs compared to men; in fact, HIV-1 DNA levels from PBMCs have been found to be lower in women.[76–78] The reasons for this are mechanistically not yet clear. One potential pathway may involve greater HIV-1 specific immune response during acute infection resulting in a lower HIV-1 viral set point. Interferon-α responses from plasmacytoid dendritic cells following Toll-like receptor-7 stimulation by HIV have been shown to be elevated in women[65,68] and is exaggerated *in vitro* with estradiol exposure via estrogen receptor-1 (ER-1) activation.[66,67,69] Increased immune activation may also affect quality of the viral reservoir, as Scully *et al.* demonstrated lower levels of cell-associated and plasma HIV-1 RNA levels in women.[79] On the other hand, exposure to estrogen in vivo may promote viral latency and maintain the reservoir by directly suppressing HIV-1 transcription.[78,80]

We previously reported that PROMISE participants had higher estimated rates of viral suppression at 12 weeks compared to the 91% male cohort from ACTG ATI studies.[81] Using more

longitudinal data, this analysis estimated approximately 1.1-2% of participants would remain virally suppressed at 24 weeks. The estimated proportion of PTCs in PROMISE was 17%, but this did not exclude women with a limited number of post-randomization viral load measurements and is likely a gross overestimation. The proportion of controllers in other ATI studies ranges widely from 6% to 25%, with variable definitions of post-treatment control.[17,19,53,82] Strict comparisons between the PROMISE population and historical studies is difficult, as the majority of ATI studies were conducted in highly selected, low-risk populations, often with years of viral suppression on ART, early treatment initiation, and low HIV-1 DNA levels. The retrospective nature of many of these studies also prohibits firm conclusions. In addition, PROMISE was not specifically designed to assess viral dynamics and TIs, and while interval censoring methods were employed to account for infrequent viral load sampling, much of our data is based on modeling and, as such, multiple assumptions. For these reasons and without a direct comparative analysis, it is difficult to conclude if there would be a significant difference in the proportion of virally suppressed female participants beyond 12 weeks. It is also important to note that there are TI studies involving very early-treated individuals[18,83] or participants with low total HIV-1 DNA levels[17] that did *not* find substantially shorter TTR, emphasizing the complexity of host and viral responses governing viral dynamics and signal that factors other than reservoir size must be taken into account. Considering these and our results, sex differences in curative aspects must be further characterized in order to ensure equal efficacy of future interventions.

Predictors of viral rebound in postpartum women after ART cessation

In the large subgroup analysis (N=412), a low pre-treatment HIV-1 RNA level was the only predictor of delayed TTR. The addition of pre-ART RNA in the subgroup analysis attenuated the predictive value of higher $CD4^+$ nadir and older age on slowing TTR. Even so, it is notable that in

our primary analysis, differences in $CD4^+$ count remained predictive of viral rebound, even at the higher $CD4^+$ counts seen in this otherwise healthy population.

Our results are consistent with analyses from the Swiss-Spanish intermittent treatment trial correlating pre-ART viral loads and proviral HIV-1 DNA levels, with low pre-treatment viremia being predictive of maintaining viral loads <5000 copies/ml at 52 weeks post-TI.[84,85] Currently, low $CD4^+$ nadir is consistently used as part of exclusion criteria for cure studies involving TIs, but our data suggest that pre-treatment viral load, if available, may also be useful in identifying ideal patients for future functional cure trials.

There is controversy regarding the ability of long-term ART to decrease the size of the reservoir.[86,87] We know that in most PLWH, cessation of ART results in rapid viral rebound, usually within days. While there are data supporting lower levels of HIV-1 DNA in individuals with long-term viral suppression on ART,[19] we did not find that duration of ART had a substantial impact on TTR, but our results are limited by the very short duration of antepartum ART in PROMISE. In addition, some prior studies have found an association between NNRTI-use and delayed rebound possibly due to longer drug half-life,[53,83] but the small number of patients on NNRTI-based regimens precludes us from making any conclusions regarding the impact of specific drug classes on the viral reservoir. In addition, these results, derived from participants using mostly PI-based regimens, is arguably of questionable relevance in an age where INSTI-based regimens are considered first-line therapy. Future studies utilizing more contemporary regimens are crucial to characterizing the potential intersection between sex and ART effects on the viral reservoir.

Rate of acute retroviral syndrome

The development of ARS following treatment interruption is not theoretical and remains a potential barrier to study participation from both participants and providers.[88,89] We found the rate

of possible ARS in PROMISE women stopping ART to be less than 5% in participants randomized to stop ART, similar to the rate reported in a small, retrospective cohort study.[90] Symptoms were also mild; all were grade 2 or less in severity. The definition for ARS used in our study was very conservative, and most cases counted as possible ARS were characterized by headache (N=12) and cough (N=9). Therefore our results are likely a gross overestimation of the true ARS incidence in PROMISE. Participants of future cure studies should be cautioned about the development of ARS, but overall rates are most likely low and may not represent significant risk.

Limitations

We acknowledge that our analysis has several limitations. As mentioned, while we attempt to correct for infrequent viral load measurements using interval censoring methods, the model relies on multiple assumptions. We attempted to perform several sensitivity analyses to account for different scenarios surrounding viral rebound, but nonetheless, considerable data manipulation was required. Therefore, our findings should be interpreted with some caution, and future studies designed to closely examine the effect of TIs in this population are warranted.

Furthermore, while the PROMISE population offers a valuable opportunity to study TIs in a diverse, young, female population, the peripartum period is a unique immunological and hormonal environment, both of which may directly affect HIV-1 persistence as we have previously discussed. Breastfeeding is also associated with hormonal shifts. While infant feeding strategy was considered in the multivariable model, it is difficult to truly account for fluctuating sex-hormone levels and other, many unknown, peripartum immunological changes.

An important consideration in the interpretation of our results is the fact that sustained viral rebound was not verified; therefore our definition of viral rebound may in actuality represent viral 'blips' of unclear clinical significance. We do not know the outcome for participants who may have

experienced transient detectable viremia but subsequent control off ART, and it is possible that our results may be an underestimation of time to rebound. Conversely, due to the fact that ART adherence was not confirmed with drug level testing or other means, we cannot verify that the women who experienced prolonged suppression did not receive ART from non-study sources, thereby leading to an overestimation of time to rebound.

Finally, PROMISE did not include direct measures of viral persistence. While we demonstrate that clinical and laboratory adverse events were rare, we cannot comment on potential expansion of the reservoir while off therapy or during the follow up period of this analysis, though prior studies have shown that brief TIs do not alter the size or composition of the viral reservoir.[17,91–93]

Conclusion

In our study, the rate of adverse clinical or laboratory events after treatment interruption was low, peaking at 6 per 1000 person-years between two and six weeks and dropping significantly thereafter. $CD4^+$ cell decline is minimal over this time period, and the development of ARS is rare. Despite brief exposure to ART and initiation during chronic infection, time to viral rebound in PROMISE women is similar to male-predominant populations on prolonged ART with early therapy initiation, potentially a reflection of sex differences in immune phenotype and HIV-1 pathogenesis. Pre-treatment HIV-1 RNA level was highly predictive of time to rebound. These data demonstrate that short treatment interruption using viral recrudescence as therapy reinitiation criteria can be safe in young, postpartum women living with HIV who have high $CD4^+$ counts and undetectable viral loads. Inclusion of women and people of color is crucial to fully characterizing viral control, both spontaneous and post-curative therapies, in order to better inform the design and

measurement of investigational interventions and the evaluation and implementation of future cure strategies.

Tables

Table 1. Baseline characteristics

	Continue ART (n=913)	Stop ART (n=778)	Overall (n=1691)
Age at randomization (years)			
Mean (SD)	28.0 (5.62)	28.2 (5.39)	28.1 (5.52)
Median (IQR)	27.5 (23.7, 32.0)	27.9 (24.1, 32.0)	27.7 (23.9, 32.0)
BMI prior to randomization (kg/m^2)			
Median (IQR)	25.7 (22.3, 28.2)	25.2 (22.5, 29.0)	25.0 (22.3, 28.6)
Missing	17 (1.9%)	14 (1.8%)	31 (1.8%)
PROMISE component			
1077BF	324 (35.5%)	378 (48.6%)	702 (41.5%)
1077FF	30 (3.3%)	34 (4.4%)	64 (3.8%)
1077HS	559 (61.2%)	366 (47.0%)	925 (54.7%)
Region			
Africa	515 (56.4%)	526 (67.6%)	1041 (61.6%)
Asia	142 (15.6%)	68 (8.7%)	210 (12.4%)
N. America	40 (4.4%)	21 (2.7%)	61 (3.6%)
S. America/Caribbean	216 (23.7%)	163 (21.0%)	379 (22.4%)
CD4$^+$ nadir (cells/μL)*			
Mean (SD)	662 (238)	699 (264)	679 (251)
Median (IQR)	606 (484, 770)	640 (501, 830)	622 (493, 797)
Missing	0 (0%)	1 (0.1%)	1 (0.1%)
Hepatitis B coinfection			
Hepatitis B negative	877 (96.1%)	747 (96.0%)	1624 (96.0%)
Hepatitis B positive	36 (3.9%)	31 (4.0%)	67 (4.0%)
WHO Stage at randomization			
WHO Stage 1	891 (97.6%)	765 (98.3%)	1656 (97.9%)
WHO Stage 2	22 (2.4%)	12 (1.5%)	34 (2.0%)
Missing	0 (0%)	1 (0.1%)	1 (0.1%)
Infant feeding strategy			
Breastfeeding	324 (35.5%)	378 (48.6%)	702 (41.5%)
Formula feeding	589 (64.5%)	400 (51.4%)	989 (58.5%)
Duration of ART (weeks)			
Mean (SD)	67.3 (10.6)	17.4 (6.08)	44.4 (26.4)
Median (IQR)	68.9 (63.1, 74.1)	17.7 (13.0, 22.0)	55.1 (18.4, 69.6)
ART regimen**			
PI-containing regimen	844 (92.4%)	654 (84.1%)	1498 (88.6%)
NNRTI-containing regimen	65 (7.1%)	122 (15.7%)	187 (11.1%)
INSTI-containing regimen	5 (0.5%)	1 (0.1%)	6 (0.4%)
Parity prior to PROMISE pregnancy$^{\pm}$			
Mean (SD)	1.56 (1.20)	1.58 (1.24)	1.57 (1.22)
Median (IQR)	1.00 (1.00, 2.00)	1.00 (1.00, 2.00)	1.00 (1.00, 2.00)
Pre-treatment HIV-1 RNA (log copies/ml)$^{\pm}$			
Mean (SD)	3.71 (0.80)	3.66 (0.78)	3.68 (0.79)
Median (IQR)	3.59 (2.95, 3.0)	3.63 (4.18, 4.15)	3.61 (2.97, 4.18)

* For 1077HS participants, used documented CD4$^+$ cell nadir. For 1077BF/FF participants, used lowest of either screening CD4$^+$ cell count or baseline CD4$^+$ cell count

** last regimen used in follow-up period

$^{\pm}$ 1077BF/FF participants only (N=766)

Table 2. Multivariate Cox proportional hazard model for time to composite safety endpoint
Adjusted for age, BMI, nadir CD4 cell count, duration of ART, region, infant feeding strategy, and PI/NNRTI use for composite endpoint. Did not include INSTI-use as sample size was very small (N=6). AIC 4226.

Group	Estimate (95% CI)	Hazard (95% CI)	p-value
Stop ART, pre-rebound±	ref		
Continue ART, pre-rebound	1.27 (0.59, 1.95)	3.56 (1.81, 7.02)	<0.001
Age (years)	-0.02 (-0.03, 0.002)	0.98 (0.97, 1.002)	0.09
BMI (kg/m²)	-0.02 (-0.04, 0.002)	0.98 (0.96, 1.002)	0.08
CD4⁺ nadir (cells/μL)*	-0.27 (-0.74, 0.2)	0.77 (0.48, 1.23)	0.27
Duration of ART (years)	-0.36 (-0.95, 0.24)	0.70 (0.38, 1.27)	0.24
Region			
Africa	ref		
Asia	0.82 (0.49, 1.15)	2.28 (1.64, 3.17)	<0.001
N. America	0.97 (0.46, 1.49)	2.65 (1.58, 4.45)	<0.001
S. America/Caribbean	0.76 (0.44, 1.07)	2.13 (1.56, 2.92)	<0.001
Infant feeding strategy			
Breastfeeding	ref		
Formula feeding	0.07 (-0.26, 0.4)	1.07 (0.77, 1.49)	0.67
PI-use**	-0.34 (-1.43, 0.75)	0.71 (0.24, 2.12)	0.54
NNRTI-use**	-0.62 (-1.75, 0.51)	0.54 (0.17, 1.66)	0.28

± prior to restarting ART
* For 1077HS participants, used documented CD4⁺ cell nadir. For 1077BF/FF participants, used lowest of either screening CD4⁺ cell count or baseline CD4⁺ cell count

Table 3. Sensitivity analysis: Multivariate Cox proportional hazard model, Model 1 (modified intention-to-treat)
Adjusted for age, BMI, nadir CD4 cell count, duration of ART, region, infant feeding strategy, and PI/NNRTI use for composite endpoint, censoring women in Continue ART arm at the time of stopping ART. AIC 4140.

Group	Estimate (95% CI)	Hazard (95% CI)	p-value
Stop ART, pre-rebound±	ref		
Continue ART, pre-rebound	1.39 (0.92, 1.87)	4.03 (2.5, 6.49)	<0.001
Age (years)	-0.01 (-0.03, 0.01)	0.99 (0.97, 1.01)	0.20
BMI (kg/m²)	-0.02 (-0.04, 0)	0.98 (0.96, 1.001)	0.06
CD4⁺ nadir (cells/μL)*	-0.2 (-0.69, 0.29)	0.82 (0.5, 1.34)	0.43
Duration of ART (years)	-0.58 (-0.94, -0.21)	0.56 (0.39, 0.81)	0.002
Region			
Africa	ref		
Asia	0.77 (0.41, 1.12)	2.16 (1.51, 3.07)	<0.001
N. America	1.05 (0.51, 1.6)	2.87 (1.66, 4.96)	<0.001
S. America/Caribbean	0.78 (0.45, 1.11)	2.18 (1.56, 3.03)	<0.001
Infant feeding strategy			
Breastfeeding	ref		
Formula feeding	0.02 (-0.32, 0.36)	1.02 (0.73, 1.44)	0.90
PI-use**	-0.18 (-1.42, 1.06)	0.83 (0.24, 2.88)	0.77
NNRTI-use**	-0.23 (-1.49, 1.03)	0.8 (0.23, 2.81)	0.72

± prior to restarting ART
* For 1077HS participants, used documented CD4⁺ cell nadir. For 1077BF/FF participants, used lowest of either screening CD4⁺ cell count or baseline CD4⁺ cell count
** last regimen used in study follow up period

Table 4. Sensitivity analysis: Multivariate Cox proportional hazard model, Model 2 (adjusted viral rebound times)

Adjusted for age, BMI, nadir CD4 cell count, duration of ART, region, infant feeding strategy, and PI/NNRTI use for composite endpoint, using adjusted rebound times for women in Stop ART group. AIC 4349.

Group	Estimate (95% CI)	Hazard (95% CI)	p-value
Stop ART, pre-rebound±	ref		
Continue ART, pre-rebound	1.51 (0.77, 2.25)	4.51 (2.16, 9.44)	<0.001
Age (years)	-0.01 (-0.03, 0.004)	0.99 (0.97, 1.004)	0.12
BMI (kg/m²)	-0.02 (-0.04, 0.002)	0.98 (0.96, 1.002)	0.08
CD4⁺ nadir (cells/μL)*	-0.27 (-0.75, 0.2)	0.76 (0.47, 1.23)	0.26
Duration of ART (years)	-0.5 (-1.1, 0.11)	0.61 (0.33, 1.11)	0.11
Region			
Africa	ref		
Asia	0.74 (0.4, 1.09)	2.1 (1.49, 2.97)	<0.001
N. America	1.02 (0.5, 1.54)	2.77 (1.64, 4.68)	<0.001
S. America/Caribbean	0.71 (0.38, 1.03)	2.03 (1.47, 2.81)	<0.001
Infant feeding strategy			
Breastfeeding	ref		
Formula feeding	0.08 (-0.26, 0.41)	1.08 (0.77, 1.51)	0.65
PI-use**	-0.39 (-1.51, 0.72)	0.68 (0.22, 2.06)	0.49
NNRTI-use**	-0.64 (-1.8, 0.51)	0.52 (0.17, 1.66)	0.27

± prior to restarting ART

* For 1077HS participants, used documented CD4⁺ cell nadir. For 1077BF/FF participants, used lowest of either screening CD4⁺ cell count or baseline CD4⁺ cell count

** last regimen used in study follow up period

Table 5. Rates of targeted laboratory events per person-week in women randomized to stop ART

Events censored after viral rebound. The highest grade of each event category is counted once per participant. Total follow up time was 8,269 person-weeks.

	0-2 weeks N=778 (1,555 person-weeks [pw])				2-6 weeks N=778 (3,781 pw)				6-12 weeks N=241 (2,845 pw)			
Grade	**2**	**3**	**4**	**Total**	**2**	**3**	**4**	**Total**	**2**	**3**	**4**	**Total**
Any Laboratory event	5 (0.3%)	1 (0.1%)	0 (0%)	6 (0.4%)	19 (0.5%)	5 (0.1%)	0 (0%)	24 (0.6%)	1 (0%)	0 (0%)	0 (0%)	1 (0%)
Any Hematology, General	4 (0.3%)	1 (0.1%)	0 (0%)	5 (0.3%)	17 (0.4%)	4 (0.1%)	0 (0%)	21 (0.6%)	1 (0%)	0 (0%)	0 (0%)	1 (0%)
Any Hematology, RBC	1 (0.1%)	0 (0%)	0 (0%)	1 (0.1%)	3 (0.1%)	1 (0%)	0 (0%)	4 (0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Hematology, WBC	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)	0 (0%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Hematology, ANC	3 (0.2%)	1 (0.1%)	0 (0%)	4 (0.3%)	13 (0.3%)	2 (0.1%)	0 (0%)	15 (0.4%)	1 (0%)	0 (0%)	0 (0%)	1 (0%)
Any Chemistry, General	1 (0.1%)	0 (0%)	0 (0%)	1 (0.1%)	2 (0.1%)	1 (0%)	0 (0%)	3 (0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Chemistry, Liver/Hepatic	1 (0.1%)	0 (0%)	0 (0%)	1 (0.1%)	2 (0.1%)	1 (0%)	0 (0%)	3 (0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Chemistry, Electrolyte/Creatinine	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

	12-24 weeks N=216 (3,697 pw)				24-36 weeks N=89 (3,048 pw)			
Grade	**2**	**3**	**4**	**Total**	**2**	**3**	**4**	**Total**
Any Laboratory event	2 (0%)	1 (0%)	0 (0%)	3 (0%)	1 (0%)	0 (0%)	0 (0%)	1 (0%)
Any Hematology, General	2 (0%)	1 (0%)	0 (0%)	3 (0%)	1 (0%)	0 (0%)	0 (0%)	1 (0%)
Any Hematology, RBC	0 (0%)	1 (0%)	0 (0%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Hematology, WBC	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Hematology, ANC	2 (0%)	0 (0%)	0 (0%)	2 (0%)	1 (0%)	0 (0%)	0 (0%)	1 (0%)
Any Chemistry, General	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Chemistry, Liver/Hepatic	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Chemistry, Electrolyte/Creatinine	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

	36-48 weeks N=80 (3,721 pw)				48-52 weeks N=70 (3,409 pw)			
Grade	**2**	**3**	**4**	**Total**	**2**	**3**	**4**	**Total**
Any Laboratory event	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Hematology, General	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Hematology, RBC	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Hematology, WBC	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Hematology, ANC	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Chemistry, General	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Chemistry, Liver/Hepatic	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Chemistry, Electrolyte/Creatinine	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 6. Rates of targeted laboratory events per person-week in women randomized to continue ART

Events censored after viral rebound. The highest grade of each event category is counted once per participant. Total follow up time was 37,063.3 person-weeks.

	0-2 weeks N=913 (1,826 person-weeks [pw])				2-6 weeks N=913 (5,350 pw)				6-12 weeks N=842 (10,078 pw)			
Grade	**2**	**3**	**4**	**Total**	**2**	**3**	**4**	**Total**	**2**	**3**	**4**	**Total**
Any Laboratory event	3 (0.2%)	4 (0.2%)	1 (0.1%)	8 (0.4%)	45 (0.8%)	12 (0.2%)	3 (0.1%)	60 (1.1%)	18 (0.2%)	16 (0.2%)	4 (0%)	38 (0.4%)
Any Hematology, General	2 (0.1%)	4 (0.2%)	1 (0.1%)	7 (0.4%)	25 (0.5%)	4 (0.1%)	2 (0%)	31 (0.6%)	8 (0.1%)	6 (0.1%)	1 (0%)	15 (0.1%)
Any Hematology, RBC	0 (0%)	2 (0.1%)	1 (0.1%)	3 (0.2%)	4 (0.1%)	1 (0%)	1 (0%)	6 (0.1%)	0 (0%)	1 (0%)	1 (0%)	2 (0%)
Any Hematology, WBC	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Hematology, ANC	2 (0.1%)	2 (0.1%)	0 (0%)	4 (0.2%)	17 (0.3%)	3 (0.1%)	1 (0%)	21 (0.4%)	6 (0.1%)	5 (0%)	0 (0%)	11 (0.1%)
Any Chemistry, General	1 (0.1%)	0 (0%)	0 (0%)	1 (0.1%)	20 (0.4%)	8 (0.1%)	1 (0%)	29 (0.5%)	10 (0.1%)	10 (0.1%)	3 (0%)	23 (0.2%)
Any Chemistry, Liver/Hepatic	1 (0.1%)	0 (0%)	0 (0%)	1 (0.1%)	19 (0.4%)	8 (0.1%)	1 (0%)	28 (0.5%)	10 (0.1%)	10 (0.1%)	3 (0%)	23 (0.2%)
Any Chemistry, Electrolyte/Creatinine	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)	0 (0%)	0 (0%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

	12-24 weeks N=824 (19,004 pw)				24-36 weeks N=742 (26,047 pw)			
Grade	**2**	**3**	**4**	**Total**	**2**	**3**	**4**	**Total**
Any Laboratory event	33 (0.2%)	16 (0.1%)	1 (0%)	50 (0.3%)	29 (0.1%)	8 (0%)	3 (0%)	40 (0.1%)
Any Hematology, General	28 (0.1%)	16 (0.1%)	6 (0%)	50 (0.3%)	23 (0.1%)	16 (0.1%)	1 (0%)	40 (0.1%)
Any Hematology, RBC	1 (0%)	1 (0%)	2 (0%)	4 (0%)	1 (0%)	1 (0%)	0 (0%)	2 (0%)
Any Hematology, WBC	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Hematology, ANC	14 (0.1%)	3 (0%)	0 (0%)	17 (0.1%)	13 (0%)	0 (0%)	0 (0%)	13 (0%)
Any Chemistry, General	17 (0.1%)	10 (0.1%)	1 (0%)	28 (0.1%)	13 (0%)	7 (0%)	3 (0%)	23 (0.1%)
Any Chemistry, Liver/Hepatic	17 (0.1%)	10 (0.1%)	1 (0%)	28 (0.1%)	13 (0%)	7 (0%)	3 (0%)	23 (0.1%)
Any Chemistry, Electrolyte/Creatinine	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

	36-48 weeks N=682 (32,024 pw)				48-52 weeks N=639 (32,107 pw)			
Grade	**2**	**3**	**4**	**Total**	**2**	**3**	**4**	**Total**
Any Laboratory event	31 (0.1%)	7 (0%)	31 (0.1%)	7 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Hematology, General	11 (0%)	2 (0%)	11 (0%)	2 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Hematology, RBC	1 (0%)	1 (0%)	1 (0%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Hematology, WBC	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Hematology, ANC	11 (0%)	1 (0%)	11 (0%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Chemistry, General	20 (0.1%)	5 (0%)	20 (0.1%)	5 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Chemistry, Liver/Hepatic	20 (0.1%)	5 (0%)	20 (0.1%)	5 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Chemistry, Electrolyte/Creatinine	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 7. Rates of targeted clinical sign/symptoms per person-week in women randomized to stop ART

Events censored after viral rebound. The highest grade of each event category is counted once per participant. Total follow up time was 8,268.9 person-weeks.

	0-2 weeks N=778 (1,555 pw)				2-6 weeks N=778 (3,781 pw)				6-12 weeks N=241 (2,845 pw)			
Grade	**2**	**3**	**4**	**Total**	**2**	**3**	**4**	**Total**	**2**	**3**	**4**	**Total**
Any Sign/symptom	4 (0.3%)	2 (0.1%)	0 (0%)	6 (0.4%)	20 (0.5%)	3 (0.1%)	0 (0%)	23 (0.6%)	3 (0.1%)	0 (0%)	0 (0%)	3 (0.1%)
Any Cardiovascular	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)	2 (0.1%)	0 (0%)	3 (0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Dermatologic	1 (0.1%)	0 (0%)	0 (0%)	1 (0.1%)	3 (0.1%)	0 (0%)	0 (0%)	3 (0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Genitourinary/Gastrointestinal	0 (0%)	1 (0.1%)	0 (0%)	1 (0.1%)	4 (0.1%)	0 (0%)	0 (0%)	4 (0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Respiratory	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)	0 (0%)	0 (0%)	1 (0%)
Any Neurologic	2 (0.1%)	0 (0%)	0 (0%)	2 (0.1%)	6 (0.2%)	0 (0%)	0 (0%)	6 (0.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Musculoskeletal	1 (0.1%)	1 (0.1%)	0 (0%)	2 (0.1%)	5 (0.1%)	1 (0%)	0 (0%)	6 (0.2%)	1 (0%)	0 (0%)	0 (0%)	1 (0%)
Any Systemic	1 (0.1%)	0 (0%)	0 (0%)	1 (0.1%)	3 (0.1%)	0 (0%)	0 (0%)	3 (0.1%)	1 (0%)	0 (0%)	0 (0%)	1 (0%)
Any Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (0.1%)	0 (0%)	0 (0%)	3 (0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

	12-24 weeks N=216 (3,697 pw)				24-36 weeks N=89 (3,048 pw)			
Grade	**2**	**3**	**4**	**Total**	**2**	**3**	**4**	**Total**
Any Sign/symptom	1 (0%)	0 (0%)	0 (0%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Cardiovascular	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Dermatologic	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Genitourinary/Gastrointestinal	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Respiratory	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Neurologic	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Musculoskeletal	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Systemic	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Other	1 (0%)	0 (0%)	0 (0%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

	36-48 weeks N=80 (3,721 pw)				48-52 weeks N=70 (3,409 pw)			
Grade	**2**	**3**	**4**	**Total**	**2**	**3**	**4**	**Total**
Any Sign/symptom	0 (0%)	1 (0%)	0 (0%)	1 (0%)	0 (0%)	1 (0%)	0 (0%)	1 (0%)
Any Cardiovascular	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Dermatologic	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Genitourinary/Gastrointestinal	1 (0%)	0 (0%)	1 (0%)	0 (0%)	1 (0%)	0 (0%)	1 (0%)	0 (0%)
Any Respiratory	0 (0%)	1 (0%)	0 (0%)	1 (0%)	0 (0%)	1 (0%)	0 (0%)	1 (0%)
Any Neurologic	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Musculoskeletal	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Any Systemic	1 (0%)	0 (0%)	1 (0%)	0 (0%)	1 (0%)	0 (0%)	1 (0%)	0 (0%)
Any Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 8. Rates of targeted clinical sign/symptoms per person-week in women randomized to continue ART

Events censored after viral rebound. The highest grade of each event category is counted once per participant. Total follow up time was 37,063.3 person-weeks.

	0-2 weeks N=913 (1,826 pw)				**2-6 weeks** N=913 (5,350 pw)				**6-12 weeks** N=842 (10,078 pw)			
Grade	**2**	**3**	**4**	**Total**	**2**	**3**	**4**	**Total**	**2**	**3**	**4**	**Total**
Any Sign/symptom	9 (0.5%)	3 (0.2%)	0 (0%)	12 (0.7%)	39 (0.7%)	7 (0.1%)	0 (0%)	46 (0.9%)	10 (0.1%)	4 (0%)	0 (0%)	14 (0.1%)
Any Cardiovascular	0 (0%)	1 (0.1%)	0 (0%)	1 (0.1%)	5 (0.1%)	4 (0.1%)	0 (0%)	9 (0.2%)	1 (0%)	0 (0%)	0 (0%)	1 (0%)
Any Dermatologic	4 (0.2%)	1 (0.1%)	0 (0%)	5 (0.3%)	5 (0.1%)	1 (0%)	0 (0%)	6 (0.1%)	1 (0%)	0 (0%)	0 (0%)	1 (0%)
Any Genitourinary/Gastrointestinal	5 (0.3%)	2 (0.1%)	0 (0%)	7 (0.4%)	21 (0.4%)	0 (0%)	0 (0%)	21 (0.4%)	7 (0.1%)	1 (0%)	0 (0%)	8 (0.1%)
Any Respiratory	1 (0.1%)	0 (0%)	0 (0%)	1 (0.1%)	1 (0%)	0 (0%)	0 (0%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Neurologic	2 (0.1%)	0 (0%)	0 (0%)	2 (0.1%)	7 (0.1%)	0 (0%)	0 (0%)	7 (0.1%)	0 (0%)	1 (0%)	0 (0%)	1 (0%)
Any Musculoskeletal	3 (0.2%)	0 (0%)	0 (0%)	3 (0.2%)	14 (0.3%)	0 (0%)	0 (0%)	14 (0.3%)	2 (0%)	0 (0%)	0 (0%)	2 (0%)
Any Systemic	3 (0.2%)	0 (0%)	0 (0%)	3 (0.2%)	3 (0.1%)	1 (0%)	0 (0%)	4 (0.1%)	2 (0%)	2 (0%)	0 (0%)	4 (0%)
Any Other	1 (0.1%)	0 (0%)	0 (0%)	1 (0.1%)	3 (0.1%)	1 (0%)	0 (0%)	4 (0.1%)	1 (0%)	0 (0%)	0 (0%)	1 (0%)

	12-24 weeks N=824 (19,004 pw)				**24-36 weeks** N=742 (26,047 pw)			
Grade	**2**	**3**	**4**	**Total**	**2**	**3**	**4**	**Total**
Any Sign/symptom	17 (0.1%)	8 (0%)	0 (0%)	25 (0.1%)	10 (0%)	7 (0%)	0 (0%)	17 (0.1%)
Any Cardiovascular	1 (0%)	1 (0%)	0 (0%)	2 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Dermatologic	1 (0%)	1 (0%)	0 (0%)	2 (0%)	4 (0%)	0 (0%)	0 (0%)	4 (0%)
Any Genitourinary/Gastrointestinal	13 (0.1%)	2 (0%)	0 (0%)	15 (0.1%)	6 (0%)	2 (0%)	0 (0%)	8 (0%)
Any Respiratory	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)	0 (0%)	1 (0%)
Any Neurologic	1 (0%)	0 (0%)	0 (0%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Musculoskeletal	5 (0%)	1 (0%)	0 (0%)	6 (0%)	1 (0%)	0 (0%)	0 (0%)	1 (0%)
Any Systemic	2 (0%)	4 (0%)	0 (0%)	6 (0%)	1 (0%)	5 (0%)	0 (0%)	6 (0%)
Any Other	2 (0%)	0 (0%)	0 (0%)	2 (0%)	2 (0%)	0 (0%)	0 (0%)	2 (0%)

	36-48 weeks N=682 (32,024 pw)				**48-52 weeks** N=639 (32,107 pw)			
Grade	**2**	**3**	**4**	**Total**	**2**	**3**	**4**	**Total**
Any Sign/symptom	4 (0%)	5 (0%)	4 (0%)	5 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Cardiovascular	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Dermatologic	1 (0%)	0 (0%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Genitourinary/Gastrointestinal	3 (0%)	1 (0%)	3 (0%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Any Respiratory	0 (0%)	1 (0%)	0 (0%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Neurologic	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Musculoskeletal	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Systemic	1 (0%)	3 (0%)	1 (0%)	3 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any Other	0 (0%)	1 (0%)	0 (0%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 9. Multivariate interval censoring model for predictors of time to viral rebound, Model A (censoring at last known undetectable viral load)

Multivariable model using parametric interval censoring with log logistic distribution estimating predictors of time-to-viral rebound in participants who stopped ART (N=778). Participants were censored at the time of restarting ART (n=6). AIC 1018.

	Estimate (95% CI)	**Hazard (95% CI)**	**p-value**
Age (years)	-0.03 (-0.04, -0.01)	0.97 (0.96, 0.99)	0.001
Duration of ART (years)	0.04 (-0.73, 0.80)	1.04 (0.48, 2.23)	0.92
CD4+ nadir (cells/μL)*	-0.92 (-1.27, -0.91)	0.4 (0.28, 0.57)	<0.001
Region			
Africa	ref		
Asia	0.1 (-0.27, 0.47)	1.11 (0.77, 1.6)	0.59
N. America	-0.18 (-0.78, 0.43)	0.84 (0.46, 1.54)	0.57
S. America/Caribbean	0.23 (-0.07, 0.54)	1.26 (0.93, 1.71)	0.14
Infant feeding strategy			
Breastfeeding	ref		
Formula feeding	-0.23 (-0.51, 0.05)	0.8 (0.6, 1.05)	0.11
PI-use**	-1.66 (-6.34, 3.02)	0.19 (0.002, 20.4)	0.49
NNRTI-use**	-2.5 (-7.18, 2.19)	0.08 (0.001, 8.96)	0.3

* For 1077HS participants, used documented CD4+ cell nadir. For 1077BF/FF participants, used lowest of either screening CD4+ cell count or baseline CD4+ cell count

** last regimen used in study follow up period

Table 10. Sensitivity analysis: Multivariate interval censoring model for predictors of time to viral rebound, Model B (adjusted viral rebound times)

Multivariable model using parametric interval censoring with log logistic distribution estimating predictors of time-to-viral rebound in participants who stopped ART (N=778). Participants were censored at the time of restarting ART (n=6). AIC 932.

	Estimate (95% CI)	**Hazard (95% CI)**	**p-value**
Age (weeks)	-0.02 (-0.04, -0.005)	0.98 (0.96, 0.995)	0.01
Duration of ART (years)	0.02 (-0.71, 0.74)	1.02 (0.49, 2.10)	0.96
CD4+ nadir (cells/μL)*	-0.58 (-0.93, -0.23)	0.56 (0.4, 0.8)	0.001
Region			
Africa	ref		
Asia	0.22 (-0.16, 0.59)	1.24 (0.85, 1.81)	0.26
N. America	-0.16 (-0.79, 0.46)	0.85 (0.46, 1.58)	0.61
S. America/Caribbean	0.29 (-0.02, 0.59)	1.33 (0.98, 1.81)	0.07
Infant feeding strategy			
Breastfeeding	ref		
Formula feeding	0.13 (-0.15, 0.41)	1.14 (0.86, 1.5)	0.37
PI-use**	-1.77 (-8.22, 4.68)	0.17 (0, 108.02)	0.59
NNRTI-use**	-2.6 (-9.05, 3.86)	0.07 (0, 47.62)	0.43

* For 1077HS participants, used documented CD4+ cell nadir. For 1077BF/FF participants, used lowest of either screening CD4+ cell count or baseline CD4+ cell count

** last regimen used in study follow up period

Table 11. Baseline characteristics of post-treatment controllers (PTCs) vs. non-PTCs

	Non-PTCs (n=648)	PTCs (n=130)	p-value
Age at randomization (years)			0.009
Mean (SD)	28.0 (5.39)	29.3 (5.27)	
Median (IQR)	27.7 (24.0, 31.6)	29.2 (26.2, 33.3)	
BMI prior to randomization (kg/m^2)			0.009
Median (IQR)	25.3 (22.3, 28.9)	25.0 (22.8, 29.7)	
Missing	12 (1.9%)	2 (1.5%)	
PROMISE component			0.14
1077BF	306 (47.2%)	72 (55.4%)	
1077FF	27 (4.2%)	7 (5.4%)	
1077HS	315 (48.6%)	51 (39.2%)	
Region			0.38
Africa	430 (66.4%)	96 (73.8%)	
Asia	59 (9.1%)	9 (6.9%)	
N. America	19 (2.9%)	2 (1.5%)	
S. America/Caribbean	140 (21.6%)	23 (17.7%)	
CD4$^+$ nadir (cells/μL)*			0.12
Mean (SD)	693 (262)	729 (269)	
Median (IQR)	632 (500, 820)	682 (515, 861)	
Missing	1 (0.2%)	0 (0%)	
Hepatitis B coinfection			0.41
Hepatitis B negative	620 (95.7%)	127 (97.7%)	
Hepatitis B positive	28 (4.3%)	3 (2.3%)	
WHO Stage at randomization			0.69
WHO Stage 1	636 (98.1%)	129 (99.2%)	
WHO Stage 2	11 (1.7%)	1 (0.8%)	
Missing	1 (0.2%)	0 (0%)	
Infant feeding strategy			0.11
Breastfeeding	306 (47.2%)	72 (55.4%)	
Formula feeding	342 (52.8%)	58 (44.6%)	
HIV-1 RNA assay lower limit of quantification used at the time of rebound (copies/ml)			0.12
< 20	67 (10.3%)	4 (3.1%)	
< 40	530 (81.8%)	87 (66.9%)	
< 50	5 (0.8%)	0 (0%)	
< 400	2 (0.3%)	1 (0.8%)	
Duration of ART (weeks)			0.38
Mean (SD)	17.4 (6.08)	17.9 (6.08)	
Median (IQR)	17.5 (12.9, 22.0)	17.9 (14.5, 21.9)	
PI-containing regimen**	545 (84.1%)	109 (83.8%)	0.37
NNRTI-containing regimen**	102 (15.7%)	20 (15.4%)	1
INSTI-containing regimen**	0 (0%)	1 (0.8%)	0.37
Parity prior to PROMISE pregnancy±			0.59
Mean (SD)	1.53 (1.23)	1.76 (1.25)	
Median (IQR)	1.0 (1.0, 2.0)	2.0 (1.0, 2.5)	
Pre-treatment HIV-1 RNA± (log copies/ml)			<0.001
Mean (SD)	3.64 (0.830)	3.02 (1.09)	
Median (IQR)	3.7 (3.1, 4.2)	3.0 (2.1, 4.1)	

* For 1077HS participants, used documented CD4$^+$ cell nadir. For 1077BF/FF participants, used lowest of either screening CD4$^+$ cell count or baseline CD4$^+$ cell count

** last regimen used in study follow up period

± 1077BF/FF participants only (N=766)

Table 12. List of participants with signs/symptoms associated with possible ARS occurring on day of first known detectable HIV-1 RNA.

Participant	Sign/symptom	Grade	Time of viral rebound (days)	HIV-1 RNA at time of viral rebound (copies/ml)
1	Diarrhea	1	27	367
2	Anorexia	1	29	564
3	Headache	1	84	5443
4	Headache	1	28	195
5	Diarrhea	1	28	7458
6	Skin lesions, vulva	1	86	8435
7	Diarrhea	1	31	15900
8	Weakness	1	166	3910
9	Cough	1	28	162
10	Headache	1	93	1259
11	Fever	1	34	3811
12	Headache	1	33	17857
13	Skin lesions, vulva	1	27	1091
14	Cough	1	35	545
15	Skin lesions, hand	1	89	1355
	Pharyngitis	1		
16	Headache	1	90	48
17	Cough	1	34	25208
18	Cough	1	21	2892
19	Cough	1	91	1952
20	Fever	1	125	18392
	Lymphadenopathy, axillary	1		
	Cough	1		
21	Headache	2	14	123
22	Headache	2	26	5961
23	Headache	2	27	5117
24	Fever	1	28	1394
25	Diarrhea	1	28	2022
26	Headache	1	30	11944
27	Headache	2	35	6647
28	Headache	2	28	11333
29	Cough	1	39	5564
30	Lymphadenopathy, cervical/submandibular	1	28	333
31	Pharyngitis	1	28	68248
32	Cough	1	28	11363
33	Diarrhea	1	28	871
34	Skin lesions, back/abdomen/ arms	2	30	437
35	Fatigue	1	28	40695
36	Cough	2	24	5129
	Headache	2		

Figures

Figure 1. Kaplan-Meier plots for time to first adverse event

Using Model 2 estimates, censoring participants at the time of rebound or time of restarting ART (stop arm)/stopping ART (**Panel A.** Survival estimates for time to first composite endpoint. **Panel B.** Survival estimates for time to first grade ≥ 2 laboratory abnormality. **Panel C.** Survival estimates for time to first grade ≥ 2 clinical sign/symptom. **Panel D.** Survival estimates for time to first HIV/AIDS-related event. **Panel E.** Survival estimates for time to first WHO stage 2 or higher event.

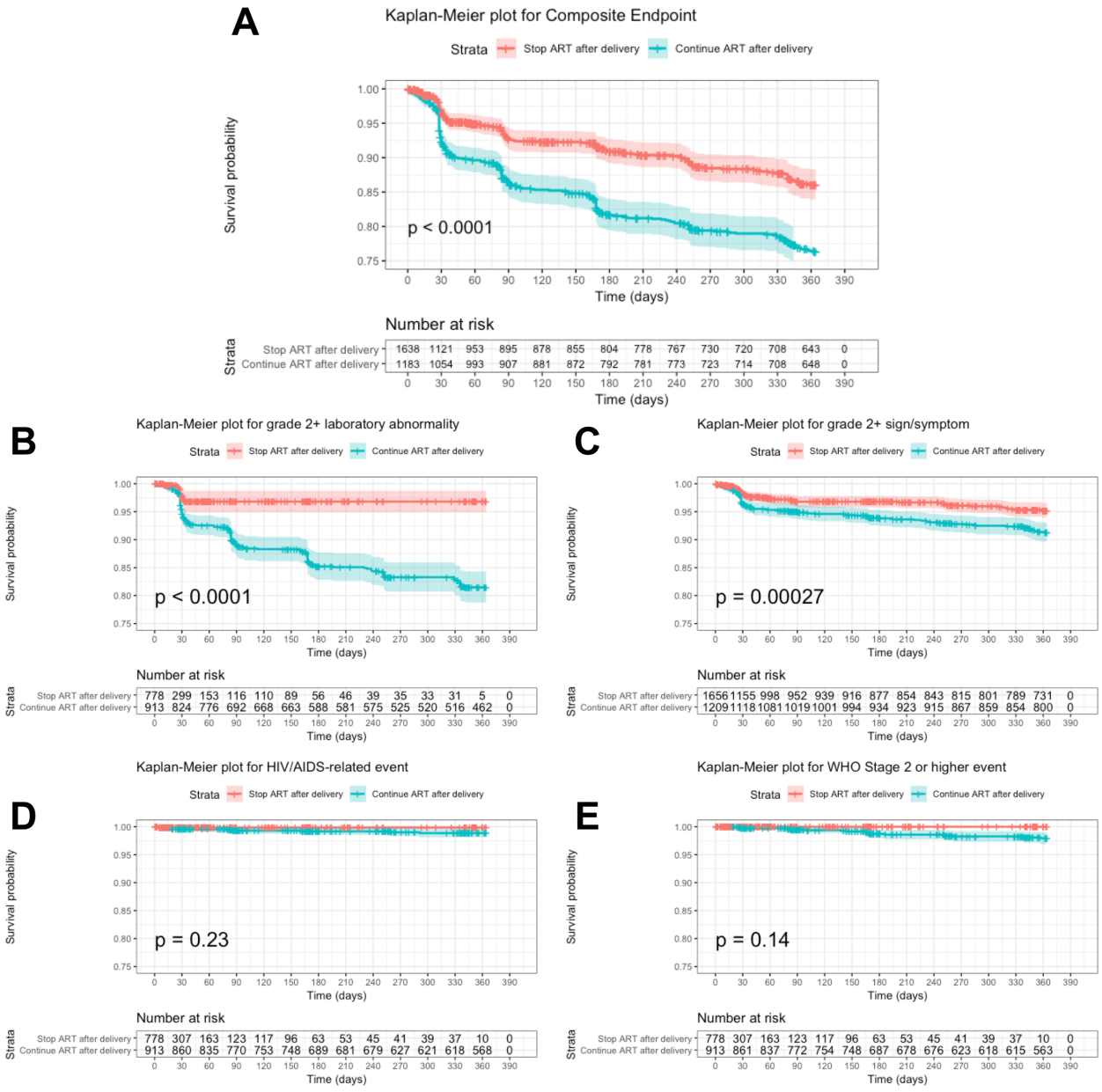


Figure 2. Total occurrences of targeted laboratory events by treatment group, per total person-follow up time by time interval since randomization

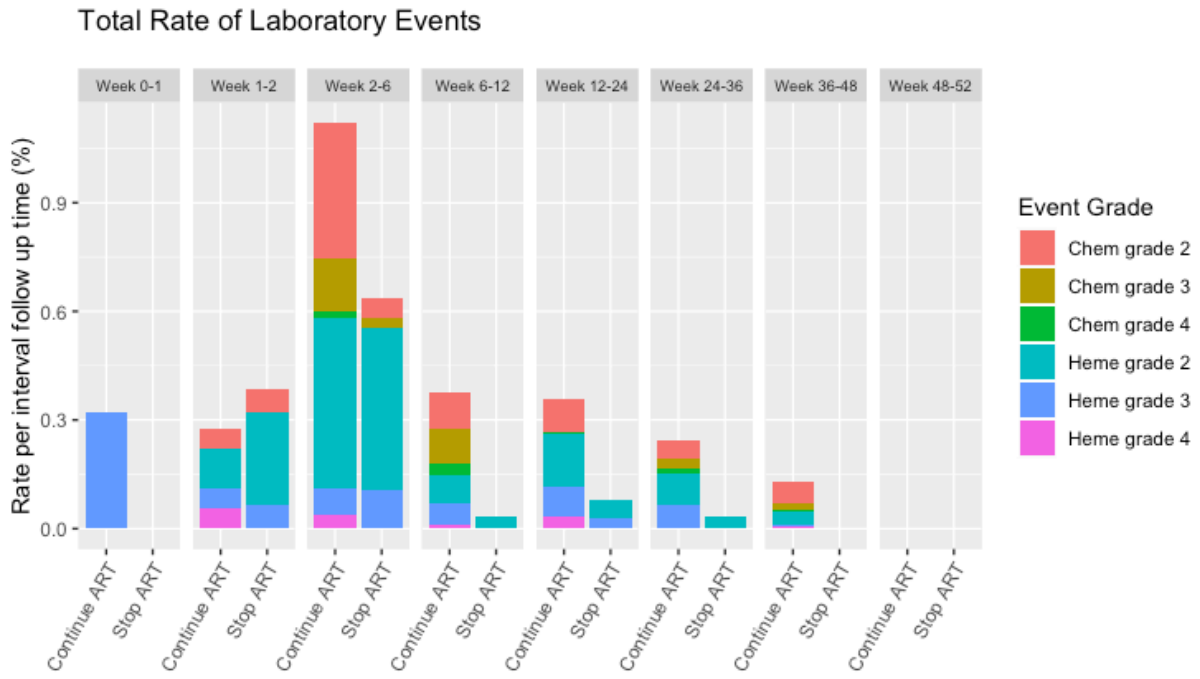


Figure 3. Total occurrences of targeted clinical events by treatment group, per total person-follow up time by time interval since randomization

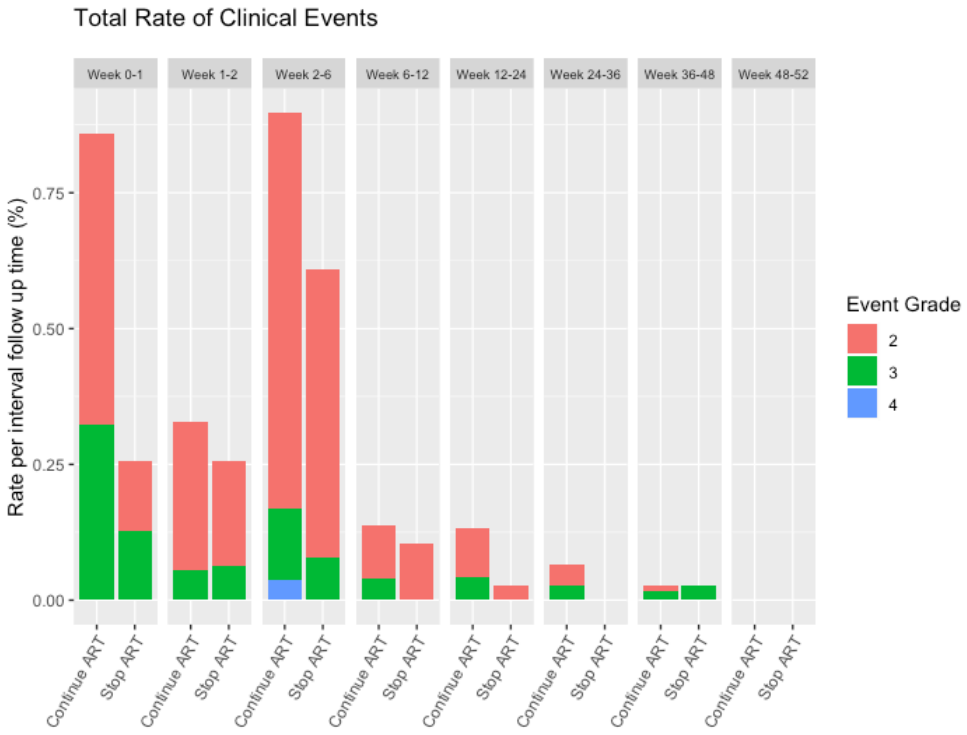


Figure 4. Estimated time to viral rebound, Model A (censoring at last known undetectable viral load)
Estimated survival curve using parametric interval censoring model with log logistic distribution. Participants who did not rebound during the study follow up period were censored at the time of last known undetectable viral load (N=39, Model 1). Median time to rebound was 1.86 weeks. Estimated mean proportion (95% CI) without rebound at 8, 12, 24, and 48 weeks was 9.7% (7.9-11.7%), 5.5% (4.3-5.9%), 2.0% (1.4-2.7%), and 0.7% (0.4-1.1%) respectively. Number at risk for each time point is calculated from observed data using a Kaplan-Meier model.

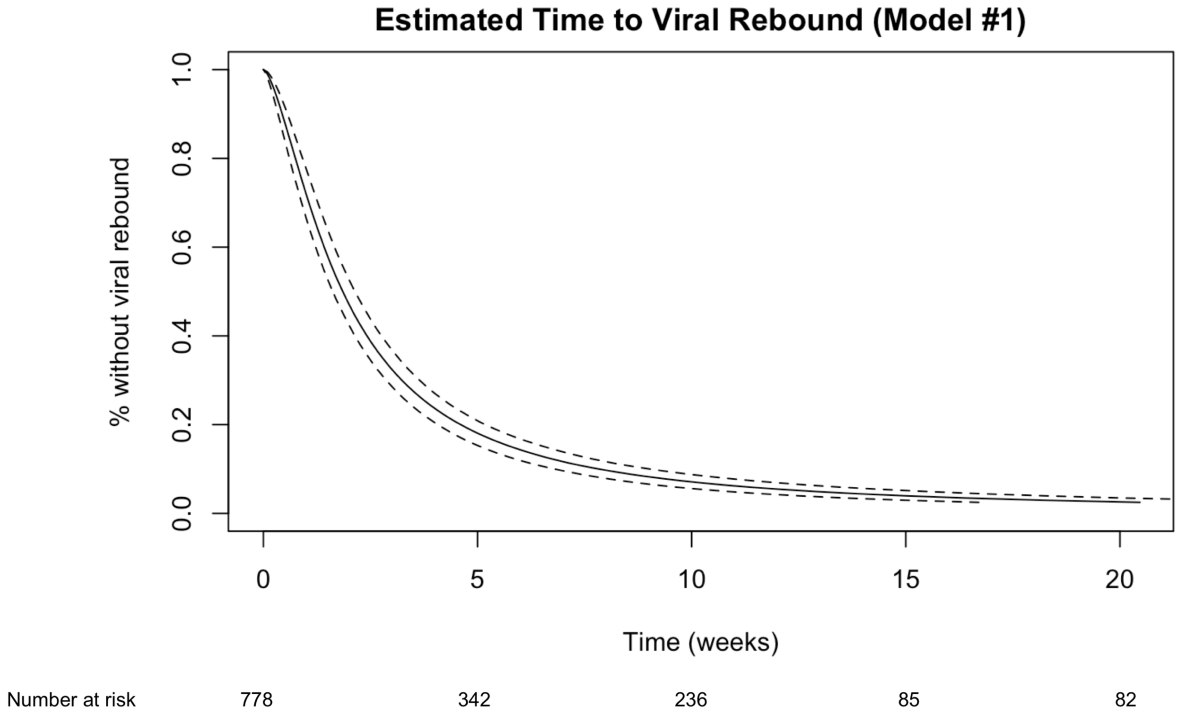
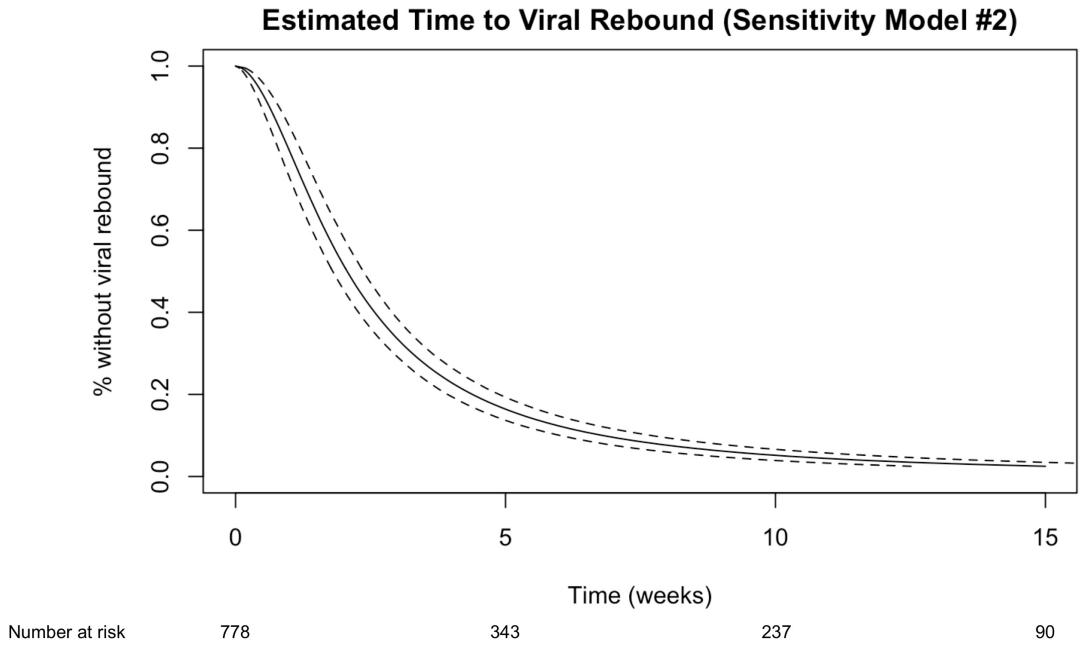


Figure 5. Estimated time to viral rebound, Model B (adjusted viral rebound times)

Estimated survival curve using parametric interval censoring model with log logistic distribution. Participants who did not rebound during the study follow up period had adjusted viral rebound estimated to be the mean difference between last known undetectable viral load and end of follow up (Model 2). Median time to rebound was 2.06 weeks. Estimated mean proportion (95% CI) without rebound at 8, 12, 24, and 48 weeks was 7.6% (6.0-9.4%), 3.8% (2.7-5.0%), 1.1% (0.7-1.6%), 0.3% (0.2-0.5%) respectively. Number at risk for each time point is calculated from observed data using a Kaplan-Meier model.



Appendix

Table S1. List of HIV-1 RNA assays used in PROMISE

Assay type	Lower limit of detection (copies/ml)
Roche Amplicor Monitor HIV RT-PCR	400
Roche Ultrasenstiive HIV RT-PCR	20
Roche Amplicor Monitor COBAS	50
Roche Ultra Sensitive COBAS	50
Roche COBAS AmpliPrep/TaqMan HIV-1	48
Abbott RealTime HIV-1	40

Table S2. Breakdown of reported ART regimens in PROMISE HS

ART Regimen	Frequency
3tc,abc,drv,rtv	2
3tc,abc,lpv,rtv	3
3tc,abc,zdv	1
3tc,abc,zdv,lpv,rtv	1
3tc,d4t,atv	1
3tc,d4t,idv,rtv	1
3tc,d4t,lpv,rtv	9
3tc,tdf,atv	1
3tc,tdf,atv,rtv	10
3tc,tdf,efv	26
3tc,tdf,lpv,rtv	17
3tc,zdv,atv	3
3tc,zdv,atv,rtv	14
3tc,zdv,drv,rtv	2
3tc,zdv,drv,rtv,ral	1
3tc,zdv,efv	10
3tc,zdv,fpv,rtv	11
3tc,zdv,idv,rtv	1
3tc,zdv,lpv,rtv	559
3tc,zdv,nfv	8
3tc,zdv,nvp	3
3tc,zdv,ral	3
ftc,tdf,atv,rtv	9
ftc,tdf,drv,rtv	5
ftc,tdf,efv	214
ftc,tdf,lpv,rtv	5
ftc,tdf,lpv,rtv,ral	1
ftc,tdf,ral	1
ftc,tdf,rpv	2
tdf,zdv,atv,rtv	1

3tc: lamivudine; abc: abacavir; atv: atazanavir; drv: darunavir; ftc: efv: efavirenz; emtricitabine; fpv: fosamprenavir; idv: indinavir; lpv: lopinavir; nfv: nefavirenz; nvp: nevirapine; ral: raltegravir; rpv: rilpivirine; rtv: ritonavir; d4t: stavudine; tdf: tenofovir disoproxil fumarate; zdv: zidovudine

Table S3. Univariate survival analyses for composite safety endpoint

Variable	Estimate (95% CI)	Hazard (95% CI)	p-value
Age (years)	-0.02 (-0.04, -0.001)	0.98 (0.96, 0.999)	0.04
Weight (kg)	-0.005 (-0.01, 0.002)	0.995 (0.99, 1.002)	0.20
BMI (kg/m^2)	-0.02 (-0.04, -0.004)	0.98 (0.96, 0.996)	0.02
CD4$^+$ nadir (cells/μL)*	-0.86 (-1.3, -0.41)	0.42 (0.27, 0.66)	<0.001
Region			
Africa	ref		
Asia	0.93 (0.67, 1.19)	2.54 (1.95, 3.3)	<0.001
N. America	0.93 (0.5, 1.37)	2.54 (1.65, 3.92)	<0.001
S. America/Caribbean	0.81 (0.59, 1.04)	2.26 (1.8, 2.83)	<0.001
Hepatitis B coinfection			
Hepatitis B negative	ref		
Hepatitis B positive	0.27 (-0.17, 0.71)	1.31 (0.84, 2.03)	0.23
Duration of ART (weeks)	0.01 (0.01, 0.01)	1.01 (1.01, 1.01)	<0.001
WHO Stage at baseline			
WHO Stage 1	ref		
WHO Stage 2	0.13 (-0.53, 0.79)	1.14 (0.59, 2.2)	0.70
PI-use**	0.18 (-0.14, 0.5)	1.2 (0.87, 1.65)	0.27
NNRTI-use**	-0.24 (-0.57, 0.1)	0.79 (0.56, 1.1)	0.16
INSTI-use**	0.72 (-0.41, 1.86)	2.06 (0.66, 6.43)	0.21
Infant feeding strategy			
Breastfeeding	ref		
Formula feeding	0.65 (0.44, 0.86)	1.91 (1.55, 2.37)	<0.001

* For 1077HS participants, used documented CD4$^+$ cell nadir. For 1077BF/FF participants, used lowest of either screening CD4$^+$ cell count or baseline CD4$^+$ cell count

** last regimen used in study follow up period

Table S4. BF/FF subgroup analysis: Multivariate Cox proportional hazard model, Model 1

Variable	Estimate (95% CI)	Hazard (95% CI)	p-value
Stop ART, pre-rebound$^{\pm}$	ref		
Continue ART, pre-rebound	1.38 (0.39, 2.38)	3.99 (1.48, 10.78)	0.01
Age (years)	-0.02 (-0.07, 0.03)	0.98 (0.94, 1.03)	0.40
BMI (kg/m^2)	-0.04 (-0.08, 0.001)	0.96 (0.92, 1)	0.05
CD4$^+$ nadir (cells/μL)	0.2 (-0.46, 0.87)	1.23 (0.63, 2.39)	0.55
Duration of ART (years)	-0.76 (-1.61, 0.1)	0.47 (0.2, 1.1)	0.08
Region			
Africa	ref		
Asia	1.24 (0.3, 2.19)	3.47 (1.35, 8.94)	0.01
Infant feeding strategy			
Breastfeeding	ref		
Formula feeding	-0.21 (-0.99, 0.57)	0.81 (0.37, 1.77)	0.60
Parity	0.06 (-0.12, 0.24)	1.06 (0.89, 1.27)	0.52
Pre-treatment HIV-1 RNA (log copies/ml)	0.14 (-0.07, 0.35)	1.15 (0.93, 1.42)	0.18

$^{\pm}$ prior to restarting ART

Table S5. BF/FF subgroup analysis: Multivariate Cox proportional hazard model, Model 2

Variable	Estimate (95% CI)	Hazard (95% CI)	p-value
Stop ART, pre-rebound±	ref		
Continue ART, pre-rebound	0.84 (-0.34, 2.03)	2.33 (0.71, 7.6)	0.16
Age (years)	-0.03 (-0.08, 0.02)	0.97 (0.93, 1.02)	0.24
BMI (kg/m²)	-0.04 (-0.09, 0.001)	0.96 (0.91, 1)	0.05
CD4⁺ nadir (cells/μL)*	0.13 (-0.55, 0.81)	1.14 (0.57, 2.25)	0.71
Duration of ART (years)	-0.25 (-1.35, 0.84)	0.78 (0.26, 2.32)	0.65
Region			
Africa	ref		
Asia	0.81 (-0.38, 2)	2.25 (0.68, 7.37)	0.18
Infant feeding strategy			
Breastfeeding	ref		
Formula feeding	-0.34 (-1.18, 0.5)	0.71 (0.31, 1.65)	0.43
Parity	0.06 (-0.13, 0.25)	1.06 (0.88, 1.28)	0.55
Pre-treatment HIV-1 RNA (log copies/ml)	0.11 (-0.11, 0.33)	1.12 (0.9, 1.39)	0.32

± prior to restarting ART

Table S6. Univariate analyses for interval censoring model
Using semi-parametric interval censoring methods with log-logistic distribution

Variable	Estimate (95% CI)	Hazard (95% CI)	p-value
Age (years)	-0.02 (-0.03, 0)	0.98 (0.97, 0.997)	0.02
BMI (kg/m²)	0 (-0.02, 0.01)	0.996 (0.98, 1.01)	0.59
Duration of ART (weeks)	0 (-0.01, 0.01)	1.001 (0.99, 1.02)	0.88
Infant feeding strategy			
Breastfeeding	ref		
Formula feeding	-0.21 (-0.37, -0.05)	0.81 (0.69, 0.96)	0.01
Hepatitis B coinfection			
Hepatitis B negative	ref		
Hepatitis B positive	0.08 (-0.23, 0.39)	1.08 (0.79, 1.48)	0.61
CD4⁺ nadir (cells/μL)*	-0.43 (-0.78, -0.08)	0.65 (0.46, 0.93)	0.02
Region			
Africa	ref		
Asia	0.29 (-0.1, 0.68)	1.34 (0.9, 1.98)	0.14
N. America	-0.05 (-0.83, 0.73)	0.95 (0.43, 2.08)	0.89
S. America/Caribbean	0.35 (0.11, 0.59)	1.42 (1.12, 1.8)	0.004
PI-use	0.77 (0.6, 0.94)	2.16 (1.82, 2.56)	<0.001
NNRTI-use	0.78 (0.61, 0.95)	2.18 (1.85, 2.58)	<0.001
WHO Stage at randomization			
WHO Stage 1	ref		
WHO Stage 2	0.07 (-1.91, 2.05)	1.07 (0.15, 7.73)	0.95

* For 1077HS participants, used documented CD4⁺ cell nadir. For 1077BF/FF participants, used lowest of either screening CD4⁺ cell count or baseline CD4⁺ cell count
** last regimen used in study follow up period

Table S7. BF/FF subgroup analysis: Multivariate interval censoring model for predictors of time to viral rebound, Model A

Multivariable model using parametric interval censoring with log logistic distribution estimating predictors of time-to-viral rebound in 1077BF/FF participants who stopped ART (N=412). Participants were censored at the time of restarting ART. Participants who did not rebound during the study follow up period were censored at the time of last known undetectable viral load (Model A). Due to small sample size, ART regimen (PI- vs NNRTI-use) could not be forced into the model. Regions represented were Africa (N=408) and Asia (N=4). AIC 387.

	Estimate (95% CI)	**Hazard (95% CI)**	**p-value**
Age (years)	-0.02 (-0.05, 0.01)	0.98 (0.95, 1.01)	0.24
Duration of ART (years)	-0.44 (-1.69, 0.81)	0.64 (0.19, 2.24)	0.49
CD4+ nadir (cells/μL)*	-0.24 (-0.71, 0.23)	0.79 (0.49, 1.26)	0.31
Region			
Africa	ref		
Asia	-0.47 (-1.7, 0.76)	0.63 (0.18, 2.15)	0.46
Infant feeding strategy			
Breastfeeding	ref		
Formula feeding	0.01 (-0.46, 0.48)	1.01 (0.63, 1.62)	0.97
Parity	-0.03 (-1.36, 1.31)	0.97 (0.26, 3.69)	0.70
HIV-1 RNA pre-treatment (log copies/ml)	0.62 (0.48, 0.76)	1.86 (1.61, 2.14)	<0.001

* For 1077HS participants, used documented CD4+ cell nadir. For 1077BF/FF participants, used lowest of either screening CD4+ cell count or baseline CD4+ cell count

Table S8. BF/FF subgroup, sensitivity analysis: Multivariate interval censoring model for predictors of time to viral rebound, Model B

Multivariable model using parametric interval censoring with log logistic distribution estimating predictors of time-to-viral rebound in 1077 BF/FF participants who stopped ART (N=412). Participants were censored at the time of restarting ART. Participants who did not rebound during the study follow up period had adjusted viral rebound estimated to be the mean difference between last known undetectable viral load and end of follow up (Model B). Due to small sample size, NNRTI-use could not be forced into the model. Regions represented were Africa (N=408) and Asia (N=4). AIC 388.

	Estimate (95% CI)	**Hazard (95% CI)**	**p-value**
Age (years)	-0.02 (-0.05, 0.01)	0.98 (0.95, 1.01)	0.27
Duration of ART (years)	-0.35 (-1.58, 0.87)	0.70 (0.21, 2.39)	0.57
CD4+ nadir (cells/μL)*	-0.15 (-0.62, 0.32)	0.86 (0.54, 1.38)	0.53
Region			
Africa	ref		
Asia	-0.21 (-1.33, 0.91)	0.81 (0.27, 2.48)	0.72
Infant feeding strategy			
Breastfeeding	ref		
Formula feeding	0.13 (-0.32, 0.58)	1.14 (0.73, 1.79)	0.56
Parity	0 (-0.13, 0.13)	1 (0.88, 1.14)	0.96
HIV-1 RNA pre-treatment (log copies/ml)	0.53 (0.39, 0.67)	1.7 (1.48, 1.95)	<0.001

* For 1077HS participants, used documented CD4+ cell nadir. For 1077BF/FF participants, used lowest of either screening CD4+ cell count or baseline CD4+ cell count

Table S9. Multivariate logistic regression model for controller phenotype

Multivariate logistic regression model of predictors of viral rebound in PTCs (N=130). Variables included from univariate analysis included age, duration of ART, nadir CD4+ count, region, infant feeding strategy, PI-use and NNRTI-use. AIC 694.

Variable	Estimate (95% CI)	OR (95% CI)	p-value
Age (years)	0.05 (0.01, 0.08)	1.05 (1.01, 6.84)	0.01
BMI (kg/m^2)	0.01 (-0.03, 0.05)	1.01 (0.98, 1.09)	0.51
Duration of ART (years)	1.46 (-0.3, 3.22)	4.3 (0.74, 1.05)	0.10
CD4$^+$ nadir (cells/μL)*	0.41 (-0.33, 1.15)	1.51 (0.72, 25.08)	0.27
Region			
Africa	ref		
Asia	-0.31 (-1.24, 0.62)	0.73 (0.29, 3.17)	0.52
N. America	-1.06 (-2.79, 0.67)	0.35 (0.06, 1.86)	0.23
S. America/Caribbean	-0.31 (-1.09, 0.46)	0.73 (0.34, 1.96)	0.43
Infant feeding strategy			
Breastfeeding	ref		
Formula feeding	-0.21 (-0.89, 0.48)	0.81 (0.41, 1.59)	0.56
PI-use**	-2.69 (-5.61, 0.23)	0.07 (0, 1.62)	0.07
NNRTI-use**	-2.56 (-5.56, 0.44)	0.08 (0, 1.26)	0.09

* For 1077HS participants, used documented CD4$^+$ cell nadir. For 1077BF/FF participants, used lowest of either screening CD4$^+$ cell count or baseline CD4$^+$ cell count

** last regimen used in study follow up period

Table S10. BF/FF subgroup analysis: Multivariate logistic regression model for controller phenotype

Multivariate model using logistic regression of predictors of viral rebound in PTCs from 1077BF/FF (N=79). Outcome was PTC status. Used age, duration of ART, nadir CD4+ count, region, parity, and pre-treatment HIV-1 RNA levels. ART regimen and infant feeding strategy could not be forced into the model due to small cell sizes. AIC 378.

	Estimate (95% CI)	OR (95% CI)	p-value
Age (years)	0.02 (-0.04, 0.09)	1.02 (0.96, 1.09)	0.51
BMI (kg/m^2)	-0.01 (-0.06, 0.05)	0.99 (0.94, 1.05)	0.79
Duration of ART (years)	3.43 (0.76, 6.1)	30.84 (2.13, 445.43)	0.01
CD4+ nadir (10^3 cells/mm^3)*	-0.97 (-2, 0.07)	0.38 (0.14, 1.07)	0.07
Region			
Africa	ref		
Asia	0.45 (-1.91, 2.8)	1.57 (0.15, 16.52)	0.71
	ref		
	-0.03 (-0.99, 0.93)	0.97 (0.37, 2.54)	0.95
Pre-treatment HIV-1 RNA (log copies/ml)	-0.84 (-1.15, -0.54)	0.43 (0.32, 0.58)	<0.001
Parity	0.14 (-0.13, 0.41)	1.15 (0.88, 1.5)	0.32

* For 1077HS participants, used documented CD4$^+$ cell nadir. For 1077BF/FF participants, used lowest of either screening CD4$^+$ cell count or baseline CD4$^+$ cell count

Figure S1. PROMISE schema

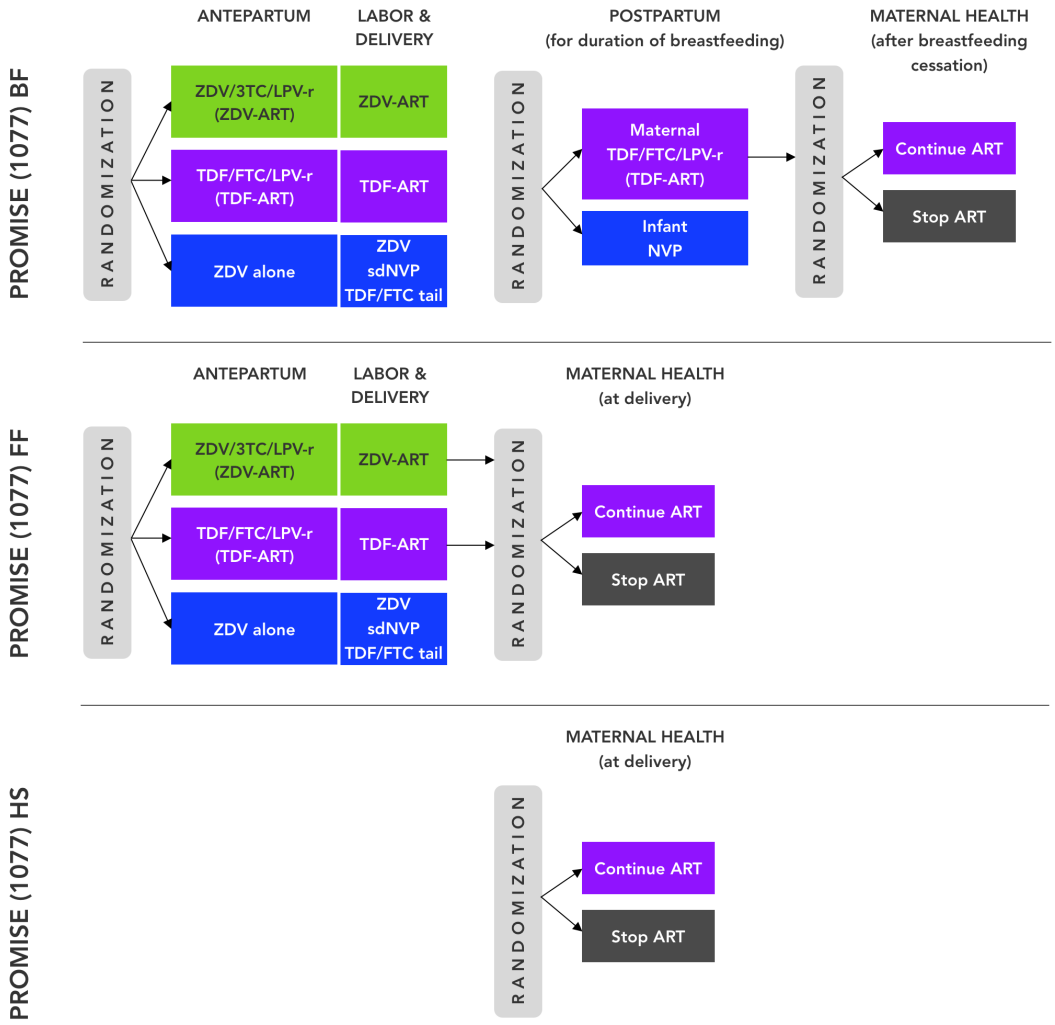


Figure S2. Sensitivity analysis, Model 2 schema

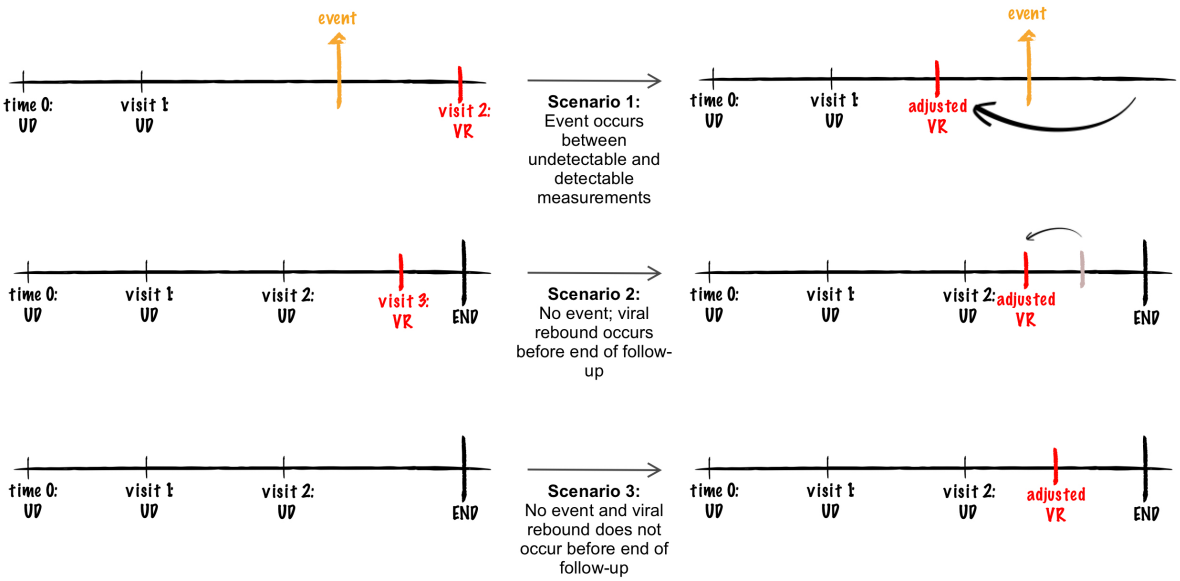


Figure S3. CD4^{+} trajectory over time in women who stopped ART

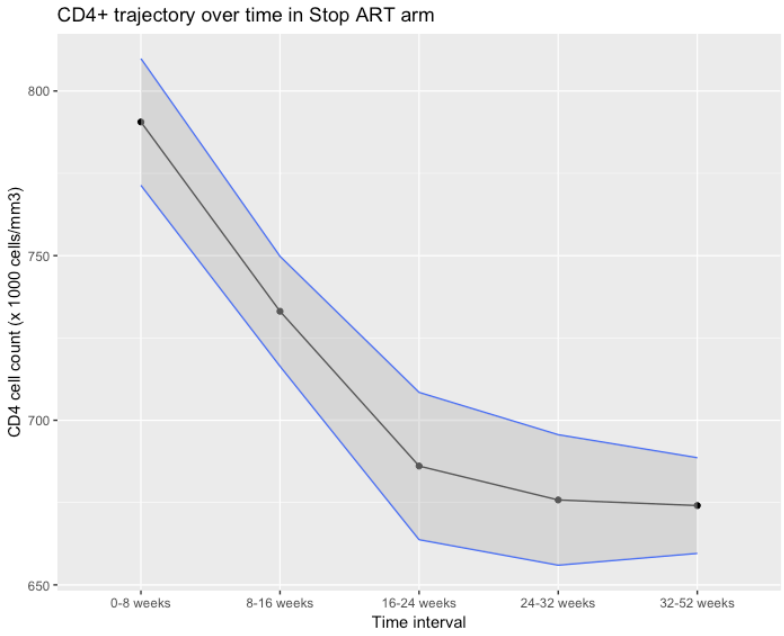


Figure S4. CD4^{+} trajectory over time in women who continued ART

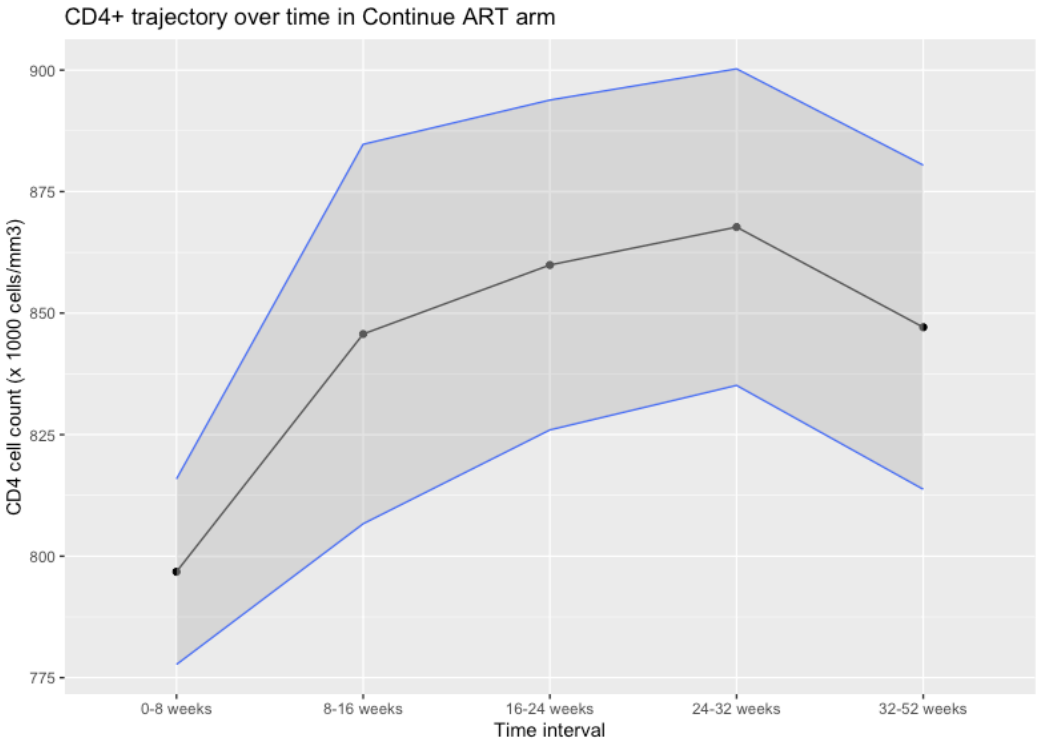


Figure S5. Breakdown of Grade 2+ laboratory abnormalities by treatment group

Each occurrence of grade 2 or higher laboratory finding is counted once. An individual participant may have more than one laboratory abnormality represented per time interval. All laboratory occurrences are recorded even if it represents one abnormal value that persisted over time.

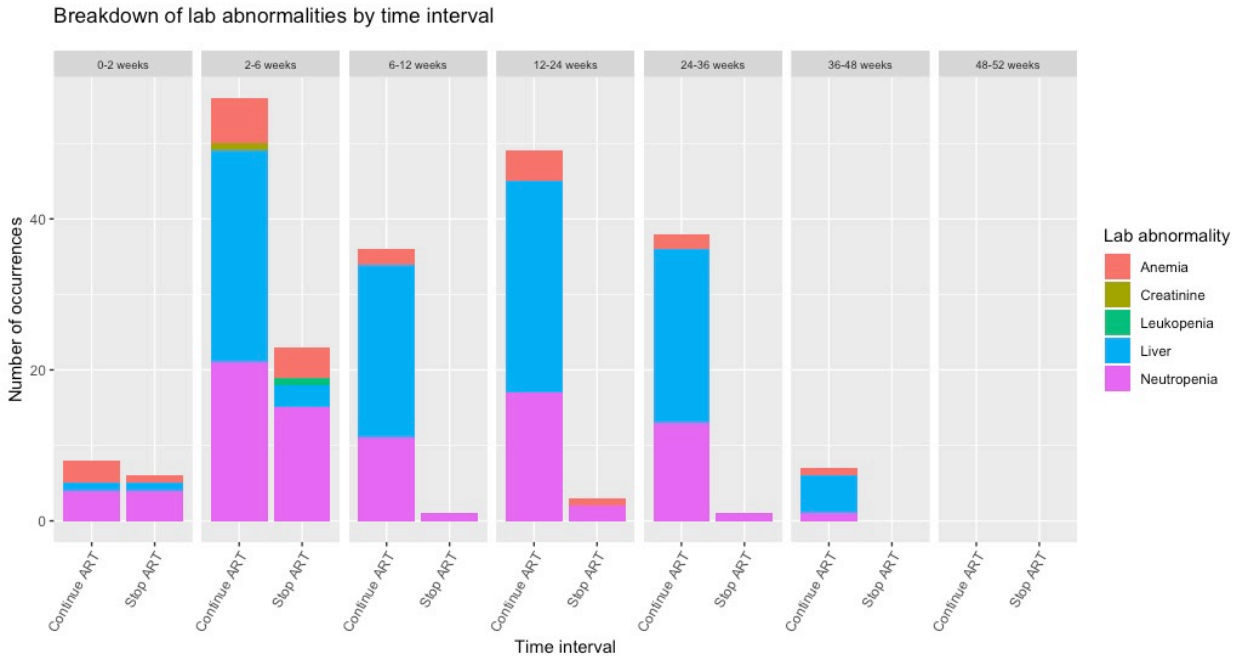
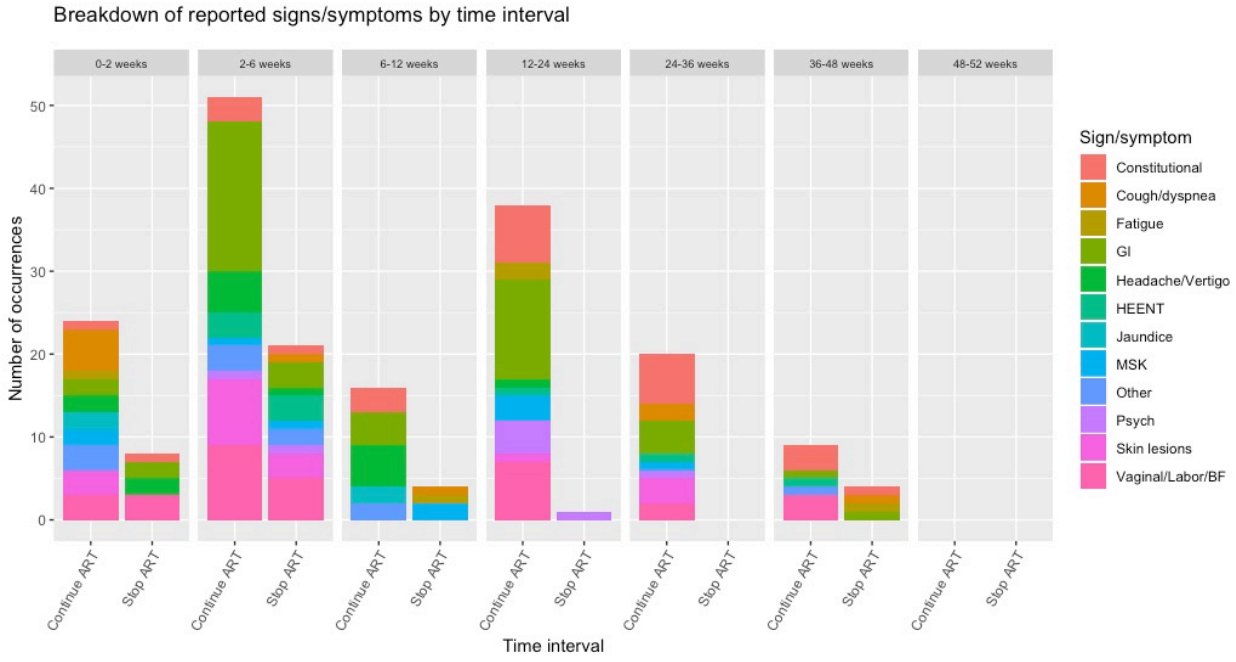


Figure S6. Breakdown of Grade 2+ reported clinical events by treatment group
Each reported occurrence of grade 2 or higher clinical sign or symptom is counted once. An individual participant may have more than one clinical sign/symptom represented per time interval. All occurrences are recorded even if it represents one symptom that persisted over time and was reported over more than one time interval. "Other" is represented by the following complaints: hypertension, pruritis, generalized pallor, palpitations, edema, and alopecia. "Constitutional" includes fever, weight loss, and lymphadenopathy.



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