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Authors

Le, Catherine N
Britto, Paula
Brummel, Sean S
et al.

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Time to Viral Rebound and Safety after Antiretroviral Treatment Interruption in Postpartum Women Compared to Men

Corresponding Author: Catherine N. Le, 1624 Glendon Avenue, Los Angeles, California 90024, catherinele@mednet.ucla.edu.

Description of author roles:

Author Name	Conception and Design	Analysis and interpretation	Writing the article	Critical revision of the article	Final approval of the article	Data collection	Provision of materials, patients, or resources	Statistical expertise	Obtaining funding	Literature search	Administrative, technical, or logistic support
Catherine Le	x	x	x	x	x					x	
Judith Currier	x	x	x	x	x				x		x
Sean Brummel	x	x		x	x	x		x			x
Jonathan Li	x	x		x	x						x
Rajesh Gandhi		x		x	x						
Risa Hoffman		x		x	x						
Pat Flynn	x			x	x						
Paula Britto	x	x		x	x	x		x			x
Ron Bosch	x	x		x				x			
Karin Klingman				x	x						
Mary Glenn Fowler	x	x		x	x				x		
Taha Taha	x	x		x	x				x		
James McIntyre	x			x	x				x		x
Anne Coletti	x			x	x		x				x

List of Supplemental Digital Content

- Supplemental Digital Content 1. Figure illustrating schematic of original PROMISE study, including BF, FF, and HS components. jpg
- Supplemental Digital Content 2. Table listing baseline characteristics for all PROMISE participants, regardless of availability of baseline viral load. pdf
- Supplemental Digital Content 3. Table listing baseline characteristics for PROMISE participants included in analysis by region. Pdf

Catherine N. LE[1], **Paula BRITTO**[2], **Sean S. BRUMMEL**[2], **Risa M. HOFFMAN**[1], **Jonathan Z. LI**[3], **Patricia M. FLYNN**[4], **Taha E. TAHA**[5], **Anne COLETTI**[6], **Mary Glenn FOWLER**[7], **Ronald J. BOSCH**[2], **Rajesh T. GANDHI**[8], **Karin L. KLINGMAN**[9], **James A. MCINTYRE**[10,11], **Judith S. CURRIER**[1]

[1]University of California Los Angeles, Los Angeles, CA, USA,

[2]Harvard T.H. Chan School of Public Health, Boston, MA, USA,

[3]Brigham and Women's Hospital, Boston, MA, USA,

[4]St. Jude Children's Research Hospital, Memphis, TN, USA,

[5]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA,

[6]FHI 360, Durham, NC, USA,

[7]Johns Hopkins U. School of Medicine, Baltimore, MD, USA,

[8]Massachusetts General Hospital and Ragon Institute, Harvard Medical School, Boston, MA, USA,

[9]DAIDS, NIAID, Bethesda, MD, USA,

[10]Anova Health Institute, Johannesburg, South Africa,

[11]School of Public Health & Family Medicine, University of Cape Town, Cape Town, South Africa

Abstract

Objective(s): The short-term safety of treatment interruptions, a necessary part of cure studies, is not well-established, particularly in women. We explored viral rebound kinetics and safety in a group of postpartum women discontinuing ART and compared results to males in historical interruption trials.

Design: Prospective evaluation of time to virologic rebound.

Methods: 1,076 asymptomatic, virally suppressed, postpartum women living with HIV enrolled in the PROMISE trial with baseline $CD4^+$ cell counts $\geq 350/mm^3$ underwent antiretroviral treatment (ART) discontinuation. Proportion with virologic suppression at weeks 4 and 12 were compared to participants in ACTG treatment interruption trials (91% male population).

Results: In PROMISE, using interval censored methods, the estimated median time to HIV viral rebound was two weeks. An estimated 6% of women would remain virally suppressed at 30 weeks. Of those who had viral rebound by 30 weeks (N=993), <4% experienced grade 3 or higher laboratory events, and 1% experienced WHO stage 2 or higher clinical events. Overall, <1% of participants progressed from WHO Stage 1 to Stage 2 or higher after discontinuation of ART, and 3.9% experienced a decline in $CD4^+$ cell count to $< 350/mm^3$ or local treatment guidelines. A significantly higher proportion of women in PROMISE (25.4%) were virologically suppressed (<400 copies/mL) at 12 weeks compared to ACTG NWCS 371 participants (6.4%).

Conclusion: Temporary treatment interruptions in healthy, HIV-infected women with high $CD4^+$ cell counts can be safe. Potential sex differences need to be considered in cure studies examining time to virologic rebound.

Keywords

HIV-1; postpartum period; women; viral latency; reservoir; cure; sex differences

Introduction

Antiretroviral therapy (ART) interruptions are a necessary aspect of cure studies, but prolonged treatment interruptions, especially among those low $CD4^+$ cell nadirs, have been associated with poor outcomes and increased mortality associated with prolonged viremia and persistent inflammation.[1–4] Many clinical trials evaluating cure strategies employ antiretroviral treatment interruptions (ATIs) that use various HIV viral load and $CD4^+$ cell count criteria to restart ART. These criteria for re-initiation of therapy are specifically designed to minimize potential risks to participants. Recent data show that short-term ATIs are generally safe.[5,6] However, these data are derived from studies primarily of male participants from resource-rich settings, raising questions about the applicability of these safety results in women and resource-limited settings.[7–10]

The Promoting Maternal and Infant Survival Everywhere (PROMISE) trial was an international, multicenter, randomized control trial studying outcomes of ART strategies for prevention of mother-to-child HIV transmission (MTCT) and postpartum maternal health.[11,12] The study began enrollment prior to World Health Organization (WHO) recommendations for initiation of ART in all persons with HIV regardless of $CD4^+$ cell count,[13] and thus included randomization of women to continue or discontinue ART either post-delivery or post-breastfeeding cessation. The study therefore represents a unique opportunity to model treatment interruption in a large and diverse female population. In addition, The AIDS Clinical Trials Group (ACTG) NWCS 371 study is a combination of six U.S. clinical trials involving ATIs in persons living with HIV and described time to viral rebound and viral load set points among virologically-suppressed participants who underwent ATI without any preceding immunologic interventions.[14]

Here, we describe clinical and laboratory events and viral rebound kinetics in asymptomatic, virologically suppressed, HIV-infected women from PROMISE with $CD4^+$ cell counts ≥ 350 cells/mm^3 who were randomized to discontinue ART in the postpartum period. We also compare rates of viral rebound between these women to predominantly male participants from ACTG NWCS 371 who underwent ATI.

Methods

Data from participants from the “HAART standard” (HS, n=439), “breastfeeding” (BF), n=603), and “formula feeding” (FF, n=34) components of the PROMISE trial were included in this analysis. Methods from the PROMISE trial have been previously reported (see Figure, Supplemental Digital Content 1, which illustrates the schematic of the parent study).[11] HIV-infected women with screening $CD4^+$ cell count ≥ 350 cells/mm^3 for PROMISE-BF/FF and ≥ 400 cells/mm^3 for PROMISE-HS were randomized up to 42 days after delivery or breastfeeding cessation to continue or discontinue ART. Women entered PROMISE-HS while on ART which may have been initiated at a $CD4^+$ cell count < 350 cells/mm^3. Per

country-specific guidelines, these women would not have been allowed to discontinue ART; therefore, a higher screening $CD4^+$ cell count of 400 cells/mm^3 was used for these participants. The ART regimen used was emtricitabine/tenofovir disoproxil fumarate plus lopinavir/ritonavir in PROMISE-BF and emtricitabine/tenofovir disoproxil fumarate plus lopinavir/ritonavir or zidovudine/lamivudine plus lopinavir/ritonavir in PROMISE-FF. In PROMISE-HS, 286 participants were on PI-containing regimens (of which 244 included lopinavir/ritonavir), 149 were on NNRTI-containing regimens (of which 136 included efavirenz), and one participant was on a rilpivirine-containing regimen. Antepartum ART regimen was largely self-reported in HS. In addition to those defined by the primary study, participants were selected for this analysis if they met the following criteria: baseline HIV-1 RNA below the limit of quantification which varied by site (please refer to Table 1), ART naïve prior to enrollment except for prior use for prevention of MTCT, at least four weeks of continuous ART while enrolled in the study, and had a post-entry viral load measurement within 30 weeks. Exclusion criteria included detectable HIV-1 RNA above the lower limit of quantification at the time of randomization, clinical indication for ART (except for one HS participant who was enrolled one week after clinical stage 3 bacterial infection), prior or current tuberculosis disease, or country-specific treatment guidelines for treatment initiation, or if ART was started on the day of randomization.

Primary outcome measures included clinical adverse events including grade 2 or higher sign/symptoms, grade 2 or higher laboratory events, HIV/AIDS related events (WHO stage 4 illness, pulmonary tuberculosis, and other serious bacterial infections including single episode bacterial pneumonia or any bacterial infection that was grade 4 severity, resulted in unscheduled hospitalization within 3 days of infection, or resulted in death), and WHO stage 2 or higher clinical events. Time-to-viral rebound was estimated as time of randomization to the first HIV-1 RNA above the lower limit of quantification. Viral load measurements through 30 weeks (24 week visit ± 6 weeks) after discontinuation of ART were included in this analysis and were obtained at weeks 0, 4, 8, 12, and every 12 weeks for PROMISE components HS/BF/FF, and at weeks 0, 6, 12, and 25 for the postpartum component of BF. Baseline viral load was defined as the measurement 30 days prior to or at the time of randomization to discontinue ART. All HS participants had measurements at week 0; 328 BF and 29 FF participants had a viral load measurement within 30 days prior to time of randomization to discontinue ART. Follow-up was censored at the time of ART re-initiation.

ACTG NWCS 371[14] was a pooled analysis of participants from six U.S. ACTG studies involving ATIs to identify predictors of viral rebound: ACTG 371[15], A5024[16], A5068[17], A5170[18], A5187[19], and A5197[20]. All participants included in this analysis were on suppressive ART, had not received immunologic interventions such as therapeutic vaccinations or IL-2 therapy, and had HIV-1 RNA < 50 copies/mL at the time of ATI. Participants in ACTG 371 and A5187 included participants who initiated ART within six months of HIV infection. ACTG 371 participants were treated for 52 weeks with ART prior to the ATI. A5187 also included participants with early HIV Infection and included both those with acute HIV infection, defined as having a positive HIV-1 RNA with either a negative or indeterminate Western blot, and early HIV infection, defined as a positive ELISA or Western blot with a non-reactive detuned ELISA *and* less than six months between reported symptoms consistent with acute retroviral syndrome and ART initiation.

The remaining four studies involved participants with chronic HIV infection. All participants were on stable ART with suppressed HIV-1 RNA < 50 copies/mL for at least six months prior to enrollment. For A371, A5024, A5068, and A5197, participants had viral load measurements at weeks 1, 2, 3, 4, 6, 8, 10, 12, and 16 weeks after stopping ART. In A5187, viral load measurements were at weeks 2, 4, 6, 8, 10, 12, and 16 post-ATI; in A5170, measurements were less frequent at weeks 4, 8, 12, and 16 post-ATI.

Primary outcome measures for the comparison between PROMISE and ACTG NWCS 371 were time to HIV-1 RNA viral load above 400 copies/mL, and time to HIV-RNA viral load above 1000 copies/mL.

Statistical Methods

Due to infrequent sampling of viral load in PROMISE participants, it is impossible to provide an accurate estimate of time to rebound; thus, survival estimates and standard errors were obtained through parametric interval censoring methods[21] using a piecewise exponential distribution with 5 evenly spaced constant hazards[22]. Because HIV-1 RNA was frequently measured as part of the ACTG ATI studies, such modeling or other imputation methods were not necessary for ACTG NWCS 371. Survival estimates from PROMISE were compared to the percentages of viral suppression with a binomial variance for ACTG NWCS 371. In addition, five women who were randomized to antepartum ART and postpartum discontinuation of ART stopped therapy prematurely (received < 4 weeks of ART) and six women who received non-HAART regimens were incorrectly included in the analysis. These participants were excluded in subsequent sensitivity analyses, and results remained unchanged. P-values were computed by normal approximation. Clinical and laboratory safety outcomes in PROMISE were summarized in women who experienced viral rebound within 30 study weeks; women who did not experience viral rebound by 30 weeks were excluded in order to estimate effects of viral rebound. Summary statistics for targeted events included only the highest grade for each participant, but individual events were also reported in the respective body-system category. P-values less than 0.05 were considered to be statistically significant. All analyses were performed using SAS v9.4.

Ethics Statement

Written informed consent was provided by all study participants in the ACTG NWCS 371 and PROMISE trials, and both studies were approved by local and collaborating institutional review boards.

Results

Baseline characteristics of both PROMISE and ACTG NWCS 371 participants are represented in Table 1. 1,076 women from countries representing Africa (N=758), Asia (N=78), North America (N=29), and Caribbean/South America (N=211) in the PROMISE trials met the inclusion criteria to be included in this analysis. The median age was 28 years, screening $CD4^+$ count was 766 cells/mm^3 (interquartile range 618–957), and median duration on ART before discontinuation was 20 weeks (IQR 15–26). At baseline, 97.6% of participants were classified as WHO clinical stage 1. These characteristics are similar to all

PROMISE participants, including those excluded from this analysis (see Table, Supplementary Digital Content 2, which lists baseline characteristics for all PROMISE participants) and also similar across the represented continents (see Table, Supplementary Digital Content 3, which lists baseline characteristics of PROMISE participants included in analysis by region). In contrast to PROMISE, 91% (N=213) of ACTG NWCS 371 participants were male. Median age was older at 41 years, median $CD4^+$ cell count was 829 cells/mm^3, and median duration on ART was 177 weeks (IQR 57–296), expectedly much longer than PROMISE participants. Seven percent of participants had nadir $CD4^+$ cell counts ≤ 200/mm^3 and 59% had nadir $CD4^+$ cell counts ≤ 500/mm^3, though it is important to note that not every ACTG NWCS 371 participant had these data available, and some of the included ACTG studies had exclusion criteria related to nadir $CD4^+$ cell count. Participants were primarily White non-Hispanic (71%) and Black non-Hispanic (13%). WHO stage information at baseline was not summarized.

Based on interval censoring modeling, the median time to detectable viremia in PROMISE women was estimated to be 2 weeks (95% CI 1.60, 2.46) (Figure 1). The proportion estimated to remain undetectable off ART at 8, 12, and 24 weeks was 11% (95% CI 4.9%, 24.9%), 7% (95% CI 5.3%, 8.4%) and 6% (95%CI 4.1%, 7.6%) respectively; the number of women observed to be virally suppressed at the end of the designated follow-up period was 7.7% (N=83). Of the 993 participants who experienced viral rebound by week 30, 1% of participants progressed from WHO stage 1 to 2 or higher after discontinuing ART and 3.9% of participants experienced a decline in $CD4^+$ count to levels meeting country-specific treatment criteria. While off ART, 99% remained WHO stage I throughout follow up, and 1% of participants experienced a clinical HIV/AIDS-related or WHO stage 2 or higher event. Of these, three participants developed a serious bacterial infection (one probable bacterial pneumonia, one presumed bacterial pneumonia, and one presumed pyelonephritis). Nine participants developed a WHO stage 2–3 clinical event: herpes zoster infection (N=4), moderate weight loss (N=3), fungal nail infection (N=1), and seborrheic dermatitis (N=1). Over 30 weeks, 10% of participants (N=100) experienced a grade 2 or higher laboratory event (Table 2). The majority (7%) of these events were comprised of grade 2 hematologic white blood cell abnormality.

For ACTG NWCS 371, there were 235 participants who were on ART and virologically suppressed at the time of ATI. Table 3 compares the observed proportion of participants from PROMISE and ACTG NWCS 371 who remained virally suppressed at week 4 and week 12 using thresholds of HIV-1 RNA <1000 copies/mL and <400 copies/mL, respectively. A higher proportion of women from PROMISE had virologic suppression at week 12 compared to participants in ACTG NWCS 371 at threshold of both 1000 copies/mL (25.4% vs 6.44%, $p<0.0001$) and 400 copies/mL (16.8% vs 5.11%, $p<0.0001$) as thresholds. We repeated this analysis using only female participants from ACTG NWCS 371 (N=22, Table 3) compared to PROMISE women. While more women in PROMISE remained virologically suppressed at week 12 using the 1000 copies/mL threshold (25.4% vs. 13.6%, $p=0.11$), this comparison was limited by small sample size and did not reach statistical significance. However, using the 400 copies/mL threshold, a significantly greater proportion of women in PROMISE remained suppressed at week 12 compared to ACTG NWCS 371 (16.8% vs. 4.55%, $p<0.01$).

Discussion

In this large, international trial which enrolled young, postpartum women with HIV and high $CD4^+$ cell counts, we estimated that approximately 6% of participants would maintain viral loads below the lower limit of quantification through 30 weeks in the absence of ART re-initiation. Treatment interruption was safe with less than 1% of participants progressing from WHO clinical stage 1 to stage 2 or higher, and less than 4% experiencing a decline in $CD4^+$ count to country-specific guidelines for ART initiation at the time of study conduct. In women who experienced viral rebound, serious adverse events were very rare. The majority of targeted events noted were mild hematologic abnormalities, namely leukopenia and anemia. Such abnormalities are not uncommon in HIV-infected adults and postpartum women, respectively, and benign neutropenia is known to occur in certain ethnic populations.[23] Primary safety analysis of the PROMISE trial demonstrated similar outcomes in women with HIV who continued therapy compared to those who stopped therapy.[24,25]

Our analysis also showed higher rates of viral suppression up to week 12 in women from PROMISE compared to the male-predominant ACTG NWCS 371 cohort and that PROMISE women remained suppressed longer compared to women in ACTG NWCS 371, though the number of women included in the ACTG studies was small. These results give valuable insight into sex differences and potential regional differences in viral rebound kinetics. Sex-based differences in HIV infection are well-described, with early studies showing that HIV-infected women have consistently lower HIV-1 RNA levels at matched stages of infection compared to men yet still progress to AIDS at similar rates.[26–28] Results from the SPARTAC trial identified female sex as independently associated with maintaining viral suppression.[29,30] In our study, we estimated that approximately 6% of PROMISE women would remain aviremic at 24 week follow up. In comparison to the male-predominant cohort in ACTG NWCS 371, a significantly higher proportion of PROMISE participants were virologically suppressed at week 12 using both 400 copies/mL and 1000 copies/mL as thresholds.

While limited by differences in study design and far less frequent viral load monitoring in PROMISE, these results are interesting and surprising considering that participants of ACTG NWCS 371 were on ART for a median duration of 3.4 years (IQR 1.1–5.7) and one-third of ACTG NWCS 371 participants were started on ART during acute or early infection. This is compared to only 17 weeks of ART in PROMISE participants, who were also more likely to have chronic HIV infection at baseline. Because both shorter duration of ART and initiation of therapy during chronic illness have been associated with shorter time to viral rebound, [29,31,32] our findings that PROMISE women had *longer* times to viral rebound are striking and suggest important differences that may be, at least in part, driven by sex. Recently, estrogen receptor-1 has been identified as a key cellular factor for HIV-1 latency reversal and may partially explain observed sex differences in the viral reservoir and impact viral rebound kinetics after ART discontinuation.[14,33–36] Identifying clinically relevant parameters related to cure research that may differ between men and women or by regional population is critical in the search for safe and efficacious therapeutic interventions for all persons with HIV.

Our study has several limitations. We are unable to confirm that women who remained suppressed off therapy were not receiving ART that they failed to report. Drug levels were not performed to confirm ART use in women from either treatment arm. Other potentially confounding factors such as pre-treatment viral load, nadir $CD4^+$ cell count, and parity (and thus prior potential exposure to ART) were not available for most participants and were not accounted for in this analysis. The peri- and postpartum (and breastfeeding) immunologic milieu might differ substantially from other women, so somewhat cautious generalization of these results is warranted. Compared to other ATI studies where viral loads are measured weekly or biweekly, we did not have frequent time points for estimating time to viral rebound, and this, in addition to differences in study design, limit the interpretations of our comparison between PROMISE and ACTG NWCS 371 cohorts. Key baseline differences between the participant populations must also be considered for their potential effects on viral kinetics in our comparison of these two studies. Indeed, differences in the proportion of participants remaining virally suppressed were persistent when analyses were restricted to only women participants of ACTG NWCS 371, a signal that factors other than sex—such as age, race/ethnicity, HIV subtype, ART regimen, and nadir $CD4^+$ cell count—may influence the viral reservoir and rebound. Strengths of this analysis include the large sample size and the diverse female population, in whom there are few data on safety of temporary ART discontinuation.

Conclusion

We estimated that 6% of postpartum women with HIV with high $CD4^+$ cell counts remained virally undetectable off ART for up to 30 weeks and that treatment interruption in these women was rarely associated with serious adverse events or evidence of immune or clinical disease progression. We also demonstrated that a higher number of women enrolled in PROMISE maintained viral suppression at <400 and <1000 copies/mL at week 12 post ART discontinuation compared to the male-predominant cohort who underwent ATI in ACTG NWCS 371. These data suggest that inclusion of women in future cure studies is safe, and a balanced, racially-diverse representation of both men and women should be considered imperative in order to ensure that both the risks and benefits of cure research are equally shared among all persons living with HIV.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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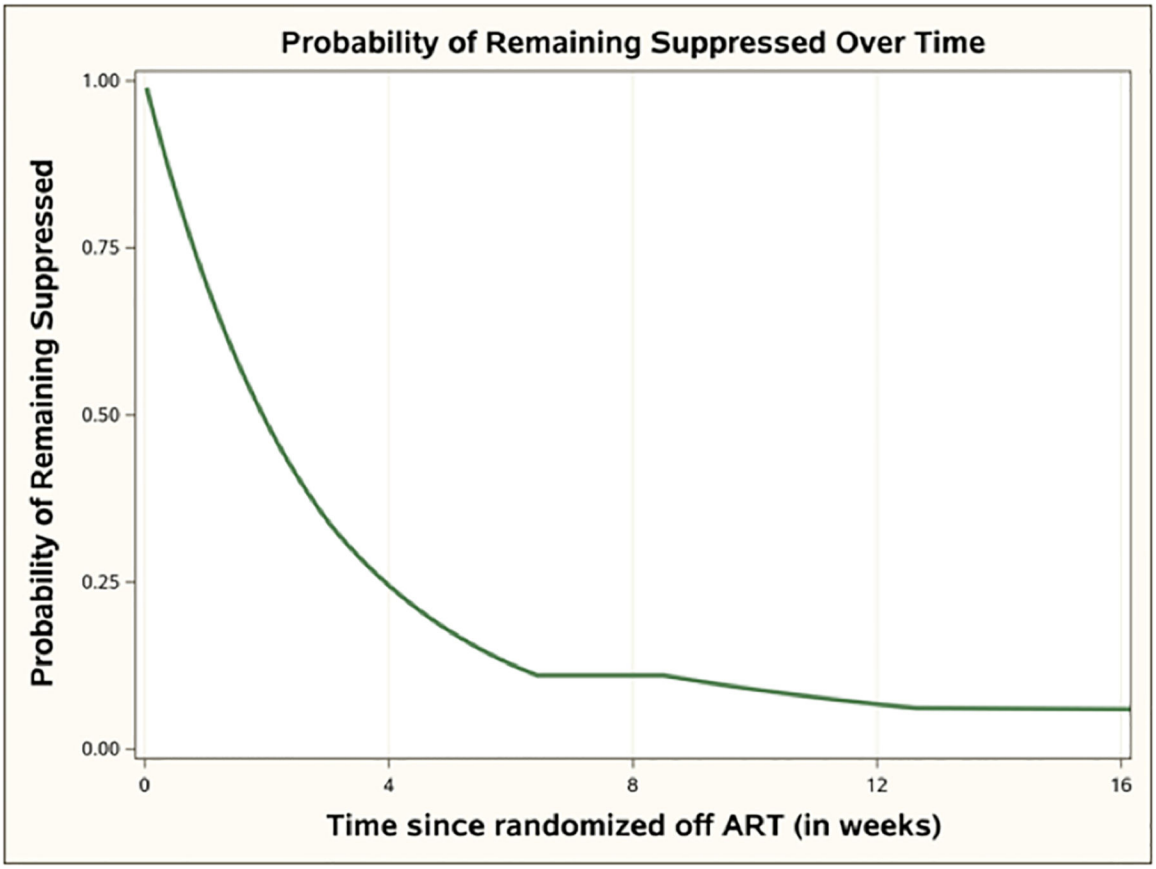

Figure 1.

Estimated proportion of PROMISE participants with viral suppression while off ART versus time from randomization based on interval censoring model. Estimates were obtained using interval censored methods. 989 and 954 viral load measurements were included in the analysis at weeks 4 and 12, respectively.

Table 1.

Baseline characteristics for ACTG NWCS 371 and PROMISE participants

Characteristic		Study	
		PROMISE (N=1076)	ACTG NWCS 371 (N=235)
PROMISE study component	HAART-standard (HS)	439	--
	Breastfeeding (BF)	603	--
	Formula-feeding (FF)	34	--
Age at randomization (years)	Median (IQR)	28 (24–32)	41 (35–46)
	Min-Max	16–44	18–73
Sex	Male	0 (0%)	213 (91%)
	Female	1,076 (100%)	22 (9%)
Screening CD4 cell count (cells/mm^3)	Median (IQR)	766 (618–957)	829 (684–1050)
	Min-Max	355–2353	289–5904
Race/ethnicity	Black/African	882 (82%)	31 (13%)
	White	77 (7%)	NA
	White (non-Hispanic)	NA	166 (71%)
	Asian/Pacific Islander	78 (7%)	5 (2%)
	Hispanic	NA	32 (14%)
	Other	43 (4%)	1 (0%)
Region	Africa	758 (70%)	0 (0%)
	Asia	78 (7%)	0 (0%)
	North America	29 (3%)	235 (100%)
	Caribbean/South America	211 (20%)	0 (0%)
WHO stage at baseline	Clinical stage I	1,053 (98.2%)	--
	Clinical stage II	18 (1.7%)	--
	Clinical stage III	1 (0.1%)	--
	Missing	4	--
Duration on ART (weeks)	Median (IQR)	20 (15–26)	177 (57–296)
	Min-Max	2–102	36–873
	Missing	0	--
ART regimen	PI-containing	911 (85%)	144 (61%)
	NNRTI-containing	158 (15%)	99 (42%)
	INSTI-containing	1 (0%)	0 (0%)
HIV-1 RNA assay lower limit of quantification (copies/ml) *	< 20	80 (7.4%)	--
	< 40	767 (71.3%)	--
	< 50	18 (1.7%)	--
	< 200	29 (2.7%)	--
	< 400	76 (7.1%)	--

Characteristic		Study	
		PROMISE (N=1076)	ACTG NWCS 371 (N=235)
	Missing	103 (9.6%)	--

* HIV-1 RNA assays used in PROMISE include the following: Roche Amplicor Monitor HIV RT-PCR, Roche Ultrasensitive HIV RT-PCR, Roche Amplicor Monitor COBAS, Roche Ultra Sensitive COBAS, Roche COBAS AmpliPrep/TaqMan HIV-1, and Abbott RealTime HIV-1.

Table 2.

Targeted grade 2 or higher adverse event by body system occurring in participants experiencing viral rebound.

	Total (N=993)			
	Grade			
Toxicity	2	3	4	Total
Any event	66 (7%)	29 (3%)	5 (<1%)	100 (10%)
Any Hematology, Coagulation	13 (1%)	1 (<1%)	0 (0%)	14 (1%)
Any Hematology, RBC	4 (<1%)	0 (0%)	0 (0%)	4 (<1%)
Any Hematology, WBC/Differential	47 (5%)	12 (1%)	1 (<1%)	60 (6%)
Any Liver/Hepatic	6 (<1%)	1 (<1%)	2 (<1%)	9 (<1%)
Any Chemistry, General	0 (0%)	2 (<1%)	1 (<1%)	3 (<1%)
Any Metabolic	0 (0%)	4 (<1%)	1 (<1%)	5 (<1%)
Any General Body	0 (0%)	7 (<1%)	0 (0%)	7 (<1%)
Any Hematology	0 (0%)	1 (<1%)	0 (0%)	1 (<1%)
Any Skin	0 (0%)	1 (<1%)	0 (0%)	1 (<1%)
Any Other	0 (0%)	1 (<1%)	0 (0%)	1 (<1%)
Any Multiple attribution *	0 (0%)	1 (<1%)	0 (0%)	1 (<1%)

Each participant is counted once for the specific safety event, once for the safety category total, and once for the overall total. For any given participant, the highest grade for each safety event is counted. Includes women who experienced viral rebound by week 24 ± 6 weeks (N=993). Data after resuming ART are censored.

* Refers to clinic sign or symptom not defined by the previous categories

Table 3.

Proportion of observed participants (total and including ACTG NWCS 371 women only) remaining virologically suppressed at weeks 4 and 12, by HIV-1 RNA threshold.

Week	HIV-1 RNA threshold (copies/mL)	PROMISE % suppressed (SE)	ACTG NWCS 371 % suppressed (SE)	Between-study p-value	ACTG NWCS 371 women only % suppressed (SE)	Between-study p-value
4	< 1000	42.5 (0.02)	37.0 (0.03)	0.12	44.5 (0.11)	0.79
	< 400	35.1 (0.02)	33.6 (0.03)	0.66	40.9 (0.10)	0.59
12	< 1000	25.4 (0.01)	6.4 (0.02)	<0.0001	13.6 (0.10)	0.11
	< 400	16.8 (0.01)	5.1 (0.01)	<0.0001	4.6 (0.07)	0.008