#337

HIV-1 VIRAL REBOUND AND SAFETY OUTCOMES OF POSTPARTUM TREATMENT INTERRUPTION IN WOMEN

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Introduction

Structured, temporary treatment interruptions are a necessary aspect of cure studies and eventually, cure therapies. However, CD4-guided analytic treatment interruptions (ATIs) have been associated with poor outcomes and increased mortality.[1,2]

In contrast, short-term ART interruptions with intense viral load monitoring are designed to minimize potential risks by using time to first detectable viremia as the primary outcome, but safety data are limited.[3,4] Such data are very limited in women, who make up greater than 50% of the global HIV burden yet are included in only 18% of current cure studies.[5,6]

Here, we describe safety events and viral rebound kinetics data from asymptomatic, virologically suppressed, HIV-infected women with CD4 counts >350 cells/mm^3 in the PROMISE trial who were randomized to discontinue ART postpartum.[7]

Methods

This study included 1,076 HIV-infected women who participated in the PROMISE Study (1077BF/1077FF/ 1077HS). Women were included in this analysis if they were randomized to discontinue ART at the end of risk for perinatal transmission, had an HIV-1 viral load below the limit of detection on the day of randomization, met the inclusion/exclusion criteria as described below, and had post-randomization viral load measurements. Follow-up time was censored at the time of ART re-initiation. Baseline was defined as the last measurement 30 days prior to or at the time of randomization.

Viral load and safety events through week 24 (± 6 weeks) after time of randomization were included in this analysis. Viral load and safety events were collected at weeks 0, 4, 8, 12 and q12 for 1077BF/FF/HS, and at weeks 0, 1, 6, 15, 26, 38, and 50 for the postpartum component of 1077BF.

Primary outcome measures

1. **Safety data** including grade 2+ signs/symptoms and laboratory safety events, HIV/AIDS related events, and WHO stage 2 and 3 clinical events. Safety events were summarized counting the highest grade for each participant.
2. **Time-to-viral rebound** estimated as time of randomization to first positive HIV-1 RNA above the limit of detection. Survival probability estimates were calculated using interval censored methods.

Inclusion criteria

- HIV-1 infected women age ≥ 18 years
- HIV-1 RNA below the limit of detection (varied by assay, max limit ≤ 400 copies/ml)
- Known hepatitis B status
- ART-naïve except for prior use for prevention of mother-to-child HIV transmission
- At least 4 weeks of ART prior to study entry
- CD4+ cell count ≥ 350 cells/mm^3
- Absolute neutrophil count ≥ 750/mm^3
- Hemoglobin ≥ 7.0 g/dL
- Platelet count ≥ 50,000/mm^3
- AST, ALT, alk phos ≤ 2.5x ULN
- Estimated creatinine clearance ≥ 60 ml/min

Exclusion criteria

- HIV-1 RNA above limit of detection at time of randomization (>400 copies/ml)
- Clinical indication for ART (any WHO clinical stage 3 or 4 condition, prior or current TB disease, other country-specific treatment guidelines)
- Clinically significant illness or condition requiring systemic treatment or hospitalization within 30 days prior to entry
- Documented conduction heart defect
- HBV co-infection meeting criteria for treatment

Results

Women were recruited from Argentina, Botswana, Brazil, China, Haiti, India, Malawi, Peru, South Africa, Tanzania, Thailand, USA, Uganda, Zambia and Zimbabwe. Median age was 28 years, CD4 count 766 cells/mm^3 (IQR 618, 957). Median duration on ART before discontinuation was 17 weeks (IQR 11-12). At baseline, 97.6% of participants were classified as WHO Stage I. (Table 1.)

Overall, <1% of patients progressed from WHO Stage I to Stage 2 or higher after discontinuing ART. 3.6% of participants experienced a decline in CD4-count to levels meeting country-specific treatment criteria. While off ART, 1% of participants experienced any HIV/AIDS-related or WHO Stage II/III clinical event (Table 2). 10% experienced grade 2 or higher sign/symptom or laboratory event (Figure 2, Table 3).

Median time to detectable viremia was 2 weeks by interval censoring methods. In the absence of ART re-initiation, we estimated that 6% of women who discontinued ART would remain virally suppressed through 24 weeks (Figure 1).

CHARACTERISTICS	
N (%)	1076 (100)
N. America	49 (4.5)
S. America	191 (17.8)
Africa	758 (70.4)
Asia	78 (7.2)
Age at randomization (years)	
Median (IQR)	28 (24-32)
Range	16-44
Pre-randomization CD4 cell count (cells/mm^3)	
Median (IQR)	766 (613-957)
Range	355-2353
Median (IQR) duration on ART (weeks)	17 (11-22)
WHO Clinical Stage (%)	
I	97.6%
II	2%
III	<1%

Table 1. Participant baseline characteristics.

DIAGNOSIS	N	Total %
Any event	12	(1%)
Serious Bacterial Infections	3	(<1%)
Bacterial pneumonia, probable	1	
Presumed pyelonephritis	1	
Presumed bacterial pneumonia	1	
WHO Stage II/III Clinical Event	9	(<1%)
Herpes Zoster	4	
Moderate weight loss	3	
Fungal nail infection	1	
Seborrheic dermatitis	1	

Table 2. HIV/AIDS-related or WHO Stage II/III clinical events.

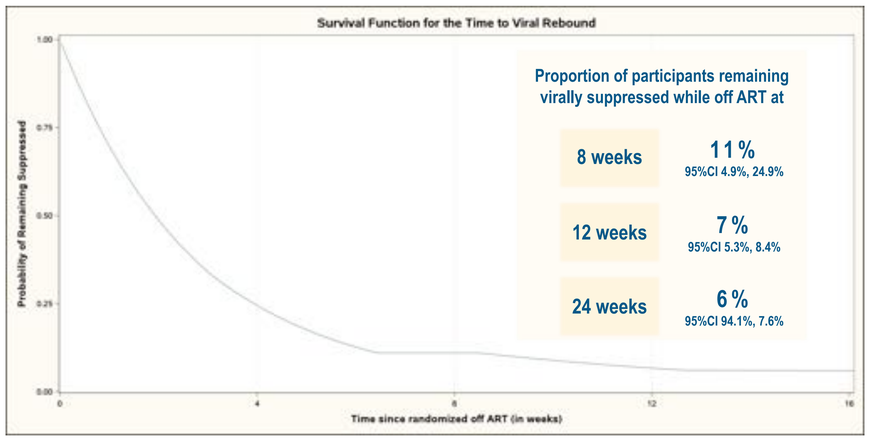
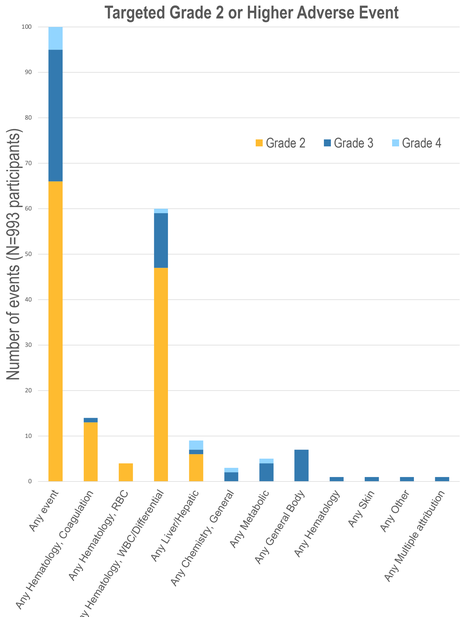


Figure 1. Survival curve of proportion of participants with viral suppression while off ART versus time from randomization. Estimates were calculated using interval censored methods.

Results (cont'd)



TOXICITIES	Grade (N, %) 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%)

Figure 2, Table 3. Targeted Grade 2 or higher adverse event.
Includes women who experienced viral rebound by week 24 ± 6 weeks (N=993); data after resuming ART is censored. 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.

Conclusions

In this large, international cohort of young, postpartum women with high CD4 cell counts, we estimated that 6% of participants would remain virally suppressed through 24 weeks in the absence of ART re-initiation. Overall, less than 1% of participants progressed from WHO Clinical Stage 1 to Stage 2 or higher, and approximately 4% of participants experienced a decline in CD4-count to country-specific treatment criteria during this study. In women who experienced viral rebound, serious adverse events during the first 24 weeks off ART were rare.

These data suggest that short treatment interruptions in HIV-cure related studies can be done safely in young women with nadir CD4 cell counts above 350 cells/mm^3. Such strategies need to be explored further in other populations but should be considered for use in cure-related study protocols.

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Acknowledgements

The authors would like to thank the women participating in the PROMISE trial as well as the staff at the PROMISE clinical trial sites. Funding for this study was provided by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH) under Award Numbers UM1AI068632 (IMPAACT LOC), UM1AI068616 (IMPAACT SDMC) and UM1AI106716 (IMPAACT LC), with co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH). Study drugs were provided by AbbVie, Boehringer-Ingelheim, Gilead Sciences, and ViiV/GlaxoSmithKline. This analyses was also supported in part by the UCLA AIDS Institute and UCLA CFAR grant AI028697, ACTG grant UM1AI068636 (ACTG LOC), as well as funding from training grant 2T32MH080634-11.

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