PREDICTORS OF VIROLOGIC FAILURE IN POSTPARTUM WOMEN ON ART IN PROMISE 1077HS

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ABSTRACT

BACKGROUND

Antiretroviral (ART) adherence can be challenging for postpartum women and may result in virologic failure (VF). We examined predictors of VF and viral re-suppression in postpartum women randomized to continue ART in PROMISE 1077HS.

METHODS

Asymptomatic HIV+, non-breastfeeding women with pre-ART CD4 cell counts ≥400 cells/mm³ who started ART during pregnancy were randomized up to 42 days after delivery to continue or discontinue treatment. Women were enrolled from 12/2011-11/2014. The preferred regimen was LPV/RTV with TDF/FTC. Viral load and self-reported adherence were collected every 12 weeks. VF was defined as 2 consecutive viral loads >1,000 copies/mL after 24 weeks on ART. Viral re-suppression was defined as 2 consecutive viral loads ≤1,000 copies/mL after VF. For this analysis, self-reported adherence was dichotomized as missing versus not missing ART doses in the prior 4 weeks. Predictors of VF and re-suppression were examined using Cox proportional hazards univariable and multivariable regression, with adherence as a time-varying covariate. Other predictors were values at baseline.

RESULTS

Among the 802 women randomized to continue ART, median age at entry was 27 years (IQR 23-32) and median CD4 T-cell count 696 cells/mm³ (IQR 576-860). Participants were enrolled from South America/Caribbean (39%), Africa (28%), Asia (25%), and the United States (8%). Of 175 women with VF, 139 had resistance data available. Of these, 17(139 (12%) failed with resistance to their current regimen. The rate was an estimated 0.12 probability of VF by week 48, 0.20 by week 96, and 0.25 by week 144. In univariable regressions, self-report of any missed ART doses in the prior 4 weeks, younger age, region, and shorter duration of pre-entry ART were predictive of VF. In the final multivariable model for VF, significant predictors included missed ART doses within the prior 4 weeks, younger age, shorter duration of pre-entry ART, and region (South America/Caribbean). Among the 175 women with VF, the probability of re-suppression was 0.37 by 48 weeks, 0.48 by 96 weeks, and 0.57 by 144 weeks. There were no statistically significant predictors of re-suppression.

CONCLUSION

A simple 4-week ART recall question predicted first VF among women in PROMISE 1077HS. Postpartum women who have VF are high risk for continued viremia, and further research should explore strategies that can successfully support ART adherence for this vulnerable population.

BACKGROUND

More than 1 ½ million HIV-infected women become pregnant and deliver babies annually, and the majority of these women now receive antiretroviral therapy (ART) antepartum and are expected to continue lifelong ART after delivery[1]. The benefits of postpartum ART were recently reported from PROMISE 1077HS; however, high rates of virologic failure (VF) were seen in this study[2].

Previous studies have shown high rates of nonadherence and VF among postpartum HIV-infected women[3,4]. Predictors of poor adherence and VF have included younger age[4,5], nondisclosure/stigma[6], and low levels of HIV, ART and prevention knowledge[6].

The PROMISE 1077HS study design provides a unique opportunity to explore predictors of virologic failure among women randomized to continue ART postpartum, including whether self-report about missed doses of ART is an accurate measure of adherence and risk for VF.

METHODS

PROMISE 1077HS was an open-label, randomized clinical trial evaluating two strategies for the management of ART among postpartum women with high CD4 T-cell counts (>400 cells/mm³): continuing ART or discontinuing ART and restarting when clinically indicated (Figure 1). The preferred ART regimen supplied by the study was Lopinavir/Ritonavir (LPV/RTV) plus fixed dose combination Emtricitabine/Tenofovir (FTC/TDF) and was chosen because it was the preferred regimen for use in pregnancy according to DHHS guidelines at the time the study was designed. Women were required to enter within 42 days of delivery.

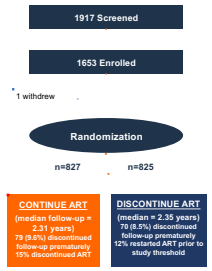
Participants randomized to the discontinue ART arm re-started ART if they met any of the following criteria:

1) Developed an AIDS-defining/WHO Stage 4 illness,
2) Had a confirmed CD4+ T-cell count <350 cells/mm³,
3) Developed a clinical condition (other than pregnancy) considered an indication for ART by country-specific guidelines or otherwise required ART as determined by the clinical management committee.

For women who continued ART, viral load and self-reported adherence were collected every 12 weeks. For these analyses:

- VF was defined as 2 consecutive viral loads >1,000 copies/mL after 24 weeks on ART.
- Viral re-suppression was defined as 2 consecutive viral loads ≤1,000 copies/mL after first VF.
- Self-reported adherence was dichotomized as missing versus not missing any ART doses in the prior 4 weeks.
- Predictors of VF and re-suppression were examined using Cox proportional hazards regression, with adherence as a time-varying covariate. Other predictors were values at baseline.
- We compared regional differences among the US, Asia (China/Thailand), Africa (Botswana), and South America and the Caribbean (Argentina, Brazil, Haiti, Peru).
- Exploratory analyses were performed comparing the probability of VF using a cut-off of 400 copies/mL.

FIGURE 1. PROMISE 1077HS study design – only women in the Continue ART arm (circled) were included in the analysis of virologic failure



RESULTS

- Of the 827 women randomized to continue ART, 825 had HIV-1 RNA and adherence data, of whom 802 were on ART for at least 24 weeks and were included in the analysis. Complete characteristics of women are included in Table 1.
- Among these 802 women, median age at entry was 27 years (IQR 23-32) and median CD4 T-cell count 696 cells/mm³ (IQR 576-865).
- Participants were from South America/Caribbean (38.8%), Botswana (27.9%), Asia (24.9%), and the United States (8.4%).
- At entry, 13% of women reported using tobacco in the past year, and 3% reported drinking alcohol at least 1-2 times per week in the 30 days prior to entry.
- At entry, 3% of women reported drug use in the past year (cocaine, heroin, amphetamines, and/or marijuana).
- At entry, 9% of women reported missing ART doses over the prior 4 days. This increased to 11% at 48 weeks and 12% at 96 weeks.
- Of 175 women with VF, 139 had resistance data available. Of these, 12% failed with resistance to their current regimen. VF with resistance to current regimen was more common in women on non-nucleoside reverse transcriptase inhibitor-based therapy (86%) compared to protease inhibitor-based therapy (8%).

TABLE 1. Characteristics of women included in the analysis of VF (N=802)

Characteristic	Continued ART arm (N=802)
Region	
Botswana	224 (27.9%)
Argentina/Brazil/Haiti/Peru	311 (38.8%)
Thailand/China	200 (24.9%)
US	67 (8.4%)
Race	
Asian	201 (25.1%)
Black or African American	54 (6.7%)
White	122 (15.2%)
American Indian	1 (0.1%)
Black African	224 (27.9%)
Black of African Origin	75 (9.4%)
Mestizo	5 (0.6%)
Mixed Black	71 (8.9%)
Mixed Native	0 (0.0%)
Native	1 (0.1%)
Other	31 (3.9%)
Subject does not know	4 (0.5%)
Race not available to clinic	13 (1.6%)
Age at entry	
Min-Max	16-47
Median (Q1-Q3)	27 (23-32)
WHO Clinical Stage at entry	
Clinical Stage I	785 (97.9%)
Clinical Stage II	16 (2.0%)
CD4 T-cell count at entry (cells/mm³)	
Min-Max	340-1800
Median (Q1-Q3)	696 (576-860)
# missing	3
Duration on ART at entry (months)	
Min-Max	0.0-8.6
Median (Q1-Q3)	4.0 (2.6-5.3)
Viral load at entry (copies/ml)	
<400	724 (90.3%)
400-1,000	36 (4.5%)
>1,000-100,000	41 (5.1%)
>100,000	1 (0.1%)
Duration of study follow-up (weeks)	
Min-Max	24.7-285.4
Median (Q1-Q3)	128.3 (84.4-181.9)
Self-rated health at entry	
Excellent	156 (19.5%)
Very Good	255 (31.9%)
Good	316 (39.5%)
Fair	70 (8.8%)
Poor	2 (1.5%)
# missing	3 (0.4%)

- The probabilities of VF were (see top panel of Figure 2):
  - **0.12 by week 48**
  - **0.20 by week 96**
  - **0.25 by week 144**
- When using a more stringent definition of VF (400 copies/mL), the estimated probability increases: 0.16 by week 48, 0.25 by week 96, and 0.29 by week 144 (Figure 2, bottom panel).
- There were differences by region, with participants from South America and the Caribbean having the highest estimated probability of VF (Figure 3).
- In univariable regression (Table 2), self-report of any missed ART doses in the prior 4 weeks, younger age, region, and shorter duration of pre-entry ART were predictive of VF.
- In the final multivariable model for VF, significant predictors included missed ART doses within the prior 4 weeks, younger age, shorter duration of pre-entry ART, and region (South America/Caribbean) (Table 2).

FIGURE 2: Estimated probability of virologic failure after the first 24 weeks on study through 144 weeks of follow-up (top panel for VF cut-off of 1,000 copies/mL and bottom panel for VF cut-off of 400 copies/mL)

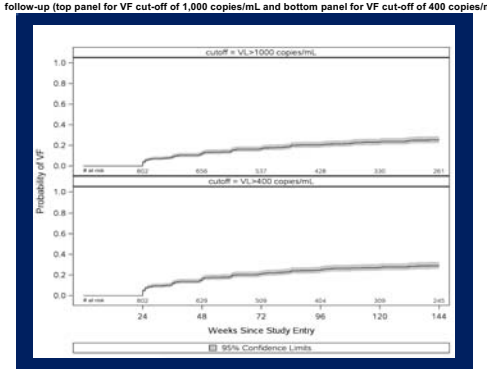
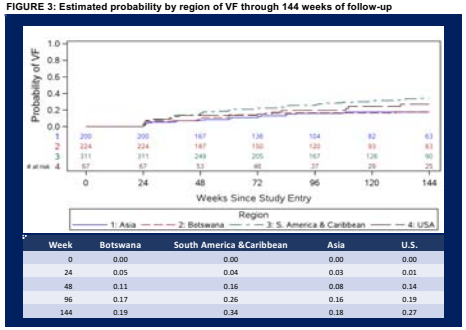


FIGURE 3: Estimated probability by region of VF through 144 weeks of follow-up



Week	Botswana	South America &Caribbean	Asia	U.S.
0	0.00	0.00	0.00	0.00
24	0.05	0.04	0.03	0.01
48	0.11	0.16	0.08	0.14
96	0.17	0.26	0.16	0.19
144	0.19	0.34	0.18	0.27

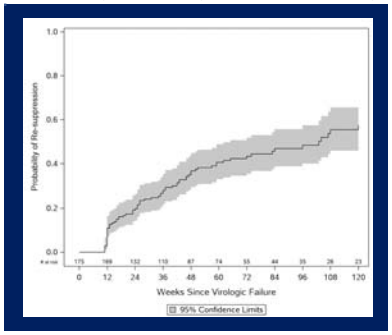
TABLE 2: Univariable and multivariable analyses for virologic failure among women who continued ART in PROMISE 1077HS (N=802)

	Univariable Analysis			Multivariable Model		
Variable	Hazard Ratio	95% Confidence Limits	p-value	Hazard Ratio	95% Confidence Limits	p-value
Missed meds in last 4 weeks*	2.55	(1.89, 3.43)	<0.001	2.05	(1.48, 2.84)	<0.001
Age at entry	0.96	(0.93, 0.98)	0.001	0.97	(0.94, 0.99)	0.01
Pre-entry ART duration (months)	0.92	(0.85, 1.00)	0.05	0.91	(0.83, 0.99)	0.02
Region			<0.001			0.07
• Botswana	1.07	(0.66, 1.74)	0.78	1.06	(0.65, 1.72)	0.82
• Brazil/Haiti/Argentina/Peru	2.06	(1.36, 3.10)	<0.001	1.69	(1.06, 2.52)	0.03
• United States	1.60	(0.87, 2.93)	0.13	1.30	(0.70, 2.43)	0.41
• Thailand/China (reference)	--			--		
Baseline health**	0.98	(0.83, 1.15)	0.78			
ART including PI***	1.22	(0.83, 1.81)	0.31			

*Time-varying co-variate **Using a self-rated health scale (1=excellent, 5=poor) ***PI: Protease Inhibitor-based ART

- Figure 4 shows the probability of viral re-suppression among the 175 women with VF (two consecutive viral loads <1,000 copies/mL):
  - **0.37 by 48 weeks**
  - **0.48 by 96 weeks**
  - **0.57 by 144 weeks**
- When suppression was defined as 2 consecutive VLs <400 copies/mL, the probabilities were 0.33 by 48 weeks, 0.42 by 96 weeks, and 0.51 by 144 weeks.
- There were no statistically significant predictors of re-suppression, although analyses were limited by small sample size.

FIGURE 4: Estimated probability of re-suppression (2 consecutive VL <1,000 copies/mL) after first VF



CONCLUSIONS

- A simple 4-week ART recall question predicted first VF among women in PROMISE 1077HS.
- Regional differences in risk of VF have not been well characterized and require further study in regard to specific drivers of these differences, such as cultural, social, or health systems factors.
- Postpartum women who have VF are high risk for continued viremia; risk factors for persistent viremia require further study.
- Further research should explore strategies that can successfully support ART adherence for postpartum women.

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