Tenofovir Hair Levels Rise Over the Postpartum Period and Highly Predict Viral Loads

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BACKGROUND

- Adherence to ART in pregnant and breastfeeding women living with HIV is essential for maternal health and prevention of perinatal transmission
- Self-reported adherence has limitations due to recall bias and "social desirability" bias
- ARV concentrations in hair reflect long-term exposure (weeks-months) and several ARVs measured in hair have been shown to strongly predict virologic outcomes
- Tenofovir (**TFV**) disoproxil fumarate (**TDF**) is one of the most widely used ARVs globally and has been looked at in PrEP; the association between TFV and virologic outcomes in persons living with HIV has not yet been examined.
- We examined hair TFV levels as a predictor of concurrent and future virologic outcomes, and explored patterns and predictors of hair levels throughout breastfeeding.

METHODS

Study sample

- The *Promoting Maternal and Infant Survival Everywhere* (PROMISE) studies examined optimal strategies for prevention of perinatal transmission and preservation of maternal health among pregnant and postpartum women
- PROMISE 1077BF conducted at 14 sites in sub-Saharan Africa and India where breastfeeding is standard.
- Women not ART eligible enrolled between 2011 and 2014 (n=3490 antepartum; n=2431 postpartum, 95% from the antepartum study)
- In a hair sub-study (n=790 mothers), hair was collected at all postpartum visits to measure antiretroviral concentrations.
- This analysis includes 71 women from sub-Saharan Africa who:
  - were on ART during both pregnancy and breastfeeding
  - consented to the hair substudy
  - had hair samples collected through the end of breastfeeding

Hair analysis

- Hair samples were analyzed in the UCSF Hair Analytical Laboratory (HAL),
- Samples were cut to 1 or 1.5 cm for those on TDF for 30-80 days or >80 days, respectively
- TFV levels were analyzed using liquid chromatography/tandem mass spectrometry

Statistical analysis

TFV levels were $\log_2$ transformed for all analyses.

1. Do hair TFV levels predict viral suppression (HIV RNA <400 copies/mL)?
   - Only included viral loads after 90 days on ART
   - Used logistic regression with generalized estimating equations (GEE)
   - Outcome: concurrent viral suppression (same day as hair sample)
   - Outcome: future viral suppression (1-6 months after hair sample)
     - Among those previously known to be suppressed
2. What are the predictors of hair TFV levels?
   - Used linear regression with GEE
   - Back-transformed coefficients to report fold-effects

RESULTS

Table 1. Participant characteristics, N=71

Characteristics at enrollment (at ART initiation in pregnancy)	
	median (IQR)
Maternal age	26 (22-30)
Weeks of gestation	27 (21-30)
CD4 count	552 (472-703)
Viral load	7,097 (1,317-26,794)
	n (%)
Country	
Malawi	13 (18)
South Africa	10 (14)
Tanzania	3 (4)
Uganda	30 (42)
Zambia	4 (6)
Zimbabwe	11 (15)
ART Regimen	
3TC-ZDV/LPV-RTV*	47 (66)
FTC-TDF/LPV-RTV	24 (34)
Education (6 missing)	
None/less than primary	14 (22)
Finished primary	35 (54)
Finished high school	13 (20)
College or other after HS	3 (5)
Follow-up characteristics	
	median (IQR)
Weeks on ART at delivery	12 (7-17)
Total breastfeeding duration, months	14 (12-15)

* Participants on 3TC-ZDV during pregnancy were switched to TDF/FTC at 1-week postpartum

Hair TFV levels (ng/mg)

Throughout breastfeeding (N=370 samples)
Among women on TDF ≥ 30 days

- **Geometric mean (95% CI)** 0.047 (0.043-0.052)
- **Median (IQR) [Range]** 0.052 (0.030-0.086) [0.002-1.067]

Figure 1. Hair TFV levels over time since delivery

- geometric means and 95% CI
- among women on TDF ≥ 30 days (n=23 at 1 week postpartum)

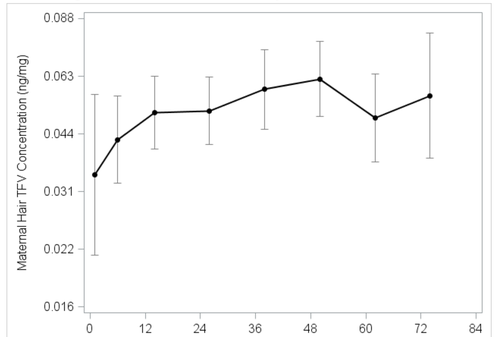

Table 2. Predictors of hair TFV levels

	Unadjusted			Multivariable		
	Fold effect	95% CI	p-value	Fold effect	95% CI	p-value
Characteristics at ART initiation						
Maternal age, per year	0.99	0.97 1.02	0.67			
CD4 count, per 100 cells/mm3	0.98	0.93 1.03	0.44			
HIV RNA, per log10 copies/mL	1.05	0.92 1.20	0.45			
Completed high school (vs. less)	1.06	0.80 1.39	0.68			
Country						
Uganda (reference)			Overall: 0.07			Overall: 0.06
Malawi	0.76	0.48 1.19	0.23	0.77	0.47 1.25	0.28
South Africa	0.73	0.49 1.09	0.12	0.69	0.46 1.02	0.06
Tanzania	0.51	0.38 0.69	<.0001	0.54	0.38 0.76	0.0004
Zambia	0.61	0.39 0.97	0.03	0.63	0.38 1.04	0.07
Zimbabwe	1.26	0.88 1.81	0.21	1.26	0.86 1.84	0.23
Time varying characteristics						
Time since delivery						
0-90 days (reference)			Overall: 0.02			Overall: 0.04
91-180 days	1.27	0.99 1.63	0.06	1.22	0.94 1.58	0.13
181-365 days	1.50	1.18 1.91	0.001	1.41	1.08 1.84	0.01
>365 days	1.28	0.97 1.69	0.09	1.18	0.88 1.59	0.26
No longer breastfeeding (vs still)	0.90	0.73 1.12	0.34			
Disclosed to husband/partner	0.99	0.73 1.34	0.92			
Disclosed to someone else in home	1.12	0.88 1.42	0.36	1.09	0.85 1.40	0.50
Food insecurity						
None			Overall: 0.22			Overall: 0.61
Moderate	0.90	0.69 1.18	0.44	0.90	0.68 1.19	0.47
Severe	0.74	0.51 1.07	0.11	0.84	0.54 1.31	0.45

RESULTS

Viral load outcomes

- N=69 women had 1 viral load (median 5 measures)
- 18 (26%) experienced viremia (HIV RNA > 400) at least once

Table 3. Increased odds of viral suppression (VS) per doubling of hair TFV level

	OR	95% CI	p-value
Outcome: **concurrent** VS	2.35	1.44-3.84	0.0006
Outcome: **future** VS*	1.43	0.75-2.73	0.28

* n=100 included in analysis of future VS, with 4 viremic events

CONCLUSIONS

- Hair TFV levels strongly associated with viral suppression in breastfeeding women on TDF based ART
- For prediction of future viral suppression, hair TFV levels had a wide confidence interval (few events) but suggest substantial association with future viremia among previously-suppressed
- Adherence, as measured with hair TFV levels, lowest in the early postpartum period, a time of major transition which could benefit from enhanced adherence support
- Objectively measuring adherence with concurrent viremia could help distinguish between virologic failure due to non-adherence versus resistance, avoid switches to more expensive 2nd and 3rd line ART regimens, and facilitate adherence support.
- Further work to expand cost-effective real-time objective ART adherence monitoring could inform timely intervention

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