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Authors

Murnane, Pamela M
Bacchetti, Peter
Currier, Judith S
et al.

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Tenofovir concentrations in hair strongly predict virologic suppression in breastfeeding women

Pamela M. Murnane[1], **Peter Bacchetti**[2], **Judith S. Currier**[3], **Sean Brummel**[4], **Hideaki Okochi**[5], **Nhi Phung**[6], **Alexander Louie**[6], **Karen Kuncze**[6], **Risa M. Hoffman**[3], **Teacler Nematadzira**[7], **Dean K. Soko**[8], **Maxensia Owor**[9], **Friday Saidi**[10], **Patricia M. Flynn**[11], **Mary Glenn Fowler**[12], and **Monica Gandhi**[6]

[1]Center for AIDS Prevention Studies, Department of Medicine, University of California, San Francisco, San Francisco, California, USA [2]Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, California, USA [3]Division of Infectious Diseases, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California, USA [4]Center for Biostatistics in AIDS Research, T.H. Chan School of Public Health, Harvard University, Cambridge, Massachusetts, USA [5]Department of Bioengineering and Therapeutic Sciences, Schools of Pharmacy and Medicine, University of California, San Francisco, California, USA [6]Division of HIV, Infectious Diseases, and Global Medicine, Department of Medicine, University of California, San Francisco, California, USA [7]University of Zimbabwe College of Health Sciences, Clinical Trials Research Centre, Harare, Zimbabwe [8]College of Medicine-Johns Hopkins Research Project, Blantyre, Malawi [9]Makerere University-Johns Hopkins University Research Collaboration, Kampala, Uganda [10]University of North Carolina-Lilongwe, Lilongwe, Malawi [11]Department of Infectious Diseases, St. Jude Children's Research Hospital, Memphis, Tennessee, USA [12]Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

Abstract

Background: Antiretroviral treatment (ART) adherence is often suboptimal in the perinatal period. We measured hair tenofovir (TFV) concentrations as a metric of adherence in postpartum women to understand patterns and predictors of adherence throughout this critical period. Additionally, we examined the association between hair TFV concentrations and virologic outcomes.

Methods: Between 12/2012–09/2016, hair samples were collected longitudinally from delivery through breastfeeding from women on ART in the PROMISE study (NCT01061151) in sub-Saharan Africa. Hair TFV levels were measured using validated methods. Using generalized estimating equations, we estimated the association between hair TFV levels and virologic suppression (<400 copies/mL) over time and assessed predictors of hair TFV levels.

Results: Hair TFV levels were measured at 370 visits in 71 women from delivery through a median of 14 months (IQR 12–15) of breastfeeding. Levels ranged from below detection (0.002) to 1.067 nanograms/milligram (geometric mean: 0.047). After 90 days on ART, 69 women had at least one viral load measured (median 5 measures, range 1–9); 18 (26%) experienced viremia at least once. Each doubling of TFV level more than doubled odds of concurrent virologic

suppression (OR 2.35, 95%CI: 1.44–3.84, p=0.0006) and was associated with 1.43 times the odds of future suppression (95%CI: 0.75–2.73, p=0.28). Relative to the first 3 months after delivery, hair levels were highest in months 6–12 (1.42 fold higher, 95%CI: 1.09–1.85, p=0.01).

Conclusion: Hair TFV levels strongly predicted concurrent virologic suppression among breastfeeding women. Objective adherence metrics can supplement virologic monitoring to optimize treatment outcomes in this important transition period.

Keywords

HIV; adherence; pregnancy; breastfeeding; viral load; hair

INTRODUCTION

Among pregnant and breastfeeding women living with HIV, antiretroviral treatment (ART) optimizes maternal health [1–3] and virtually eliminates the risk of perinatal transmission [4–6]. Realization of these benefits requires satisfactory adherence to ART [7–9], which can be challenging. Identifying suboptimal adherence through self-report is often limited by over-reporting [10], and while viral load testing is increasingly available in sub-Saharan Africa, objective methods to detect suboptimal adherence could facilitate timely intervention to avert virologic failure.

Antiretroviral concentrations in hair reflect exposure to the medication over the prior weeks to months. Several antiretroviral classes (e.g. protease inhibitors, NNRTIs), when measured in hair, strongly predict virologic outcomes among persons living with HIV [11–19]. Tenofovir (TFV) disoproxil fumarate/emtricitabine (TDF/FTC) is used globally for both HIV treatment (in a multicomponent regimen) and prevention (as pre-exposure prophylaxis, PrEP). For persons on PrEP, hair TFV levels predict adherence [20–24] and toxicities [24, 25] but the relationship between hair TFV levels and virologic outcomes in persons living with HIV has not been evaluated.

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 living with HIV [1, 4, 6, 26]. In a sample of women enrolled in PROMISE taking TDF/FTC, 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 Population and Procedures

Data are from the antepartum [4] and postpartum [6] components of PROMISE 1077BF, which was conducted at 14 sites in sub-Saharan Africa and India, where breastfeeding is standard. Both components enrolled women between 2011 and 2014 who were not yet ART-eligible (by CD4 cell count per contemporaneous country guidelines). In the antepartum component, 3490 pregnant women were randomized to either zidovudine alone or one of two three-drug ART regimens, one of which contained TDF/FTC. In the postpartum

component, 2431 women (95% from the antepartum component) were randomized 6–14 days postpartum to daily infant nevirapine or maternal combination ART (primarily ritonavir-boosted lopinavir with TDF/FTC) over the duration of breastfeeding, up to 18 months. Mothers were followed postpartum at weeks 1, 6, 14, then every 12 weeks. HIV status disclosure and food insecurity [27] were assessed at least every 24 weeks. Viral load was measured at weeks 1, 6, 14, 26, and every 24 weeks thereafter. Hair samples were collected at all visits in a sub-study within the postpartum component.

This analysis includes an initial subset of women with hair samples collected through the end of breastfeeding, selected among the 363 women in the Hair sub-study who were from sub-Saharan Africa, initiated ART in pregnancy, and continued postpartum. All study components were approved by site-specific institutional review boards; all participants provided written informed consent.

Hair collection and analyses

Hair samples of ~20–50 strands were cut from the scalp following published methods [28]. Hair grows approximately one centimeter per month and medications are incorporated from the systemic circulation into hair as it grows [29]. Thus, the centimeter of hair most proximal to the scalp reflects exposures in the month prior to collection, the next centimeter reflects the next prior month, and so on. Hair samples were shipped to and analyzed in the UCSF Hair Analytical Laboratory, where they were cut to 1 or 1.5 cm for those on TDF/FTC for 30–80 days or >80 days, respectively; a few samples had longer lengths assayed when the lab could not determine the proximal end. If samples included any portion unexposed to TDF/FTC, we adjusted concentrations with the following ratio: hair growth period (centimeters*30 days)/days of growth with exposure to TDF/FTC (assumed to start 6 days after initiation to allow TFV levels to build up in the systemic circulation and hair to grow out of the scalp). TFV levels were analyzed using validated liquid chromatography/ tandem mass spectrometry (LC-MS/MS)-based methods as described previously [20, 30].

Statistical analysis

For all analyses, TFV levels were $\log_2$ transformed. Prior to transformation, those below the limit of detection (0.002 nanograms/milligrams (ng/mg)) were set to the lower limit, and a small constant (0.002) was added to all values to reduce the potential for undue influence from differences between very small values.

Hair TFV levels and viral suppression.—We defined viral suppression as HIV RNA <400 copies/mL, and only included virologic outcomes measured after 90 days on ART. The association between hair TFV levels and viral suppression over time was estimated with logistic regression using generalized estimating equations (GEE). Because $\log_2$ was used, the estimated odds ratios represent the relative odds of virologic suppression per 2-fold increase in TFV levels. In our primary analysis, we examined hair TFV levels as a predictor of concurrent viral suppression. In a secondary analysis, we examined hair TFV levels as a predictor of future suppression, including all hair samples from participants 1) known to be suppressed prior to hair collection, 2) without a viral load measured 14 days prior through

30 days after hair collection, and 3) with a viral load measured 31–180 days after hair collection. We adjusted for maternal age and time since delivery as potential confounders.

Predictors of hair TFV levels.—Predictors of hair TFV levels were assessed with linear regression using GEE. Because the outcome was log-transformed, we back-transformed coefficients to report fold-effects. Food insecurity and HIV status disclosure, which were not measured at every visit, were carried forward from the last visit collected. We built a multivariate model including all predictors with p<0.25 in univariate analysis.

All analyses were done in SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

A total of 71 women from Malawi (n=13), South Africa (n=10), Tanzania (n=3), Uganda (n=30), Zambia (n=4), and Zimbabwe (n=11) who initiated ART in pregnancy and continued throughout breastfeeding were included. Baseline clinical and demographic characteristics in this subgroup were comparable to those in the parent PROMISE study at ART initiation [4] and delivery [6]. At enrollment during pregnancy, the median age was 26 years (interquartile range [IQR] 22–30), median CD4 count was 552 cells/mm^3 (IQR 472–703), and median viral load was 7,097 copies/mL (IQR 1,317–26,794). At delivery, women had been on ART a median of 12 weeks (IQR 7–18), and during follow-up, women breastfed a median of 14 months (IQR 12–15).

Hair TFV levels across visits.

Hair TFV levels were measured at 370 visits (median 6 per woman, range 1–8) postpartum. The geometric mean TFV hair level across all visits was 0.047 (95% CI 0.043–0.052), with values ranging from below the limit of detection (0.002) to 1.067 ng/mg (Table 1). Since most women were switched to TDF/FTC with ritonavir-boosted lopinavir at the one-week postpartum visit, only 23 participants were on TDF/FTC long enough to have hair levels measured one-week postpartum, when levels were lowest (geometric mean 0.032 ng/mg, 95% CI 0.019–0.054; Figure 1). Hair levels were highest at the 50-week visit (geometric mean 0.060 ng/mg, 95% CI 0.047–0.075).

Hair TFV levels and viral suppression.

After 90 days on ART, 69 women had at least one viral load measured (median 5 measures, range 1–9); 18 (26%) experienced viremia at least once (median 8907 copies/mL, range 444–150,122); while 8 (12%) had >1 viral load 400 copies/mL. Each doubling of hair TFV level was associated with 2.35 times the odds of concurrent viral suppression (95% CI 1.44–3.84, p=0.0006). The median TFV hair level was 0.054 ng/mg (IQR 0.033–0.086) in those with concurrent virologic suppression and 0.026 ng/mg (IQR 0.007–0.041) in those without suppression (p=0.0006). Among 100 women suppressed prior to hair collection with no concurrent viral load, 4 experienced viremia 30–180 days after hair collection. As expected given this small number of events, hair TFV levels had a very wide confidence interval for prediction of subsequent viral suppression (OR 1.43 per doubling, 95% CI 0.75–2.73, p=0.28).

Predictors of hair TFV levels.

Compared to the first three months postpartum, hair TFV levels were marginally higher in months 3–6 (1.22 fold, 95% CI 0.95–1.58, p=0.12) and highest in months 6–12 (1.42 fold higher, 95% CI 1.09–1.85, p=0.01) in multivariable analysis (Table 1). Relative to participants from Uganda, we observed lower hair TFV levels in women from South Africa (0.70 fold lower, 95% CI 0.46–1.03), Tanzania (0.51 fold, 95% CI 0.38–0.71) and Zambia (0.62 fold, 95% CI 0.38–1.01), though the number of observations from each country was small. Other characteristics did not have substantial associations with hair levels.

DISCUSSON

In this longitudinal study nested within a large multi-site clinical trial primarily conducted in sub-Saharan Africa, we found that hair TFV levels were strongly associated with virologic suppression among postpartum breastfeeding women on TDF/FTC-based ART. The median hair TFV level in suppressed participants was twice that among participants with unsuppressed viral loads. This is the first report to examine the association between hair TFV levels and virologic outcomes in persons living with HIV, building on prior evidence that hair TFV levels reflect adherence to PrEP [20–24].

We observed the lowest hair TFV levels in the early postpartum period, with increases over the duration of breastfeeding. This result is consistent with a study from Malawi, which found lower adherence in the first 3 months postpartum based on pharmacy refill data [31]. The event of childbirth and associated life changes could present barriers to adherence, including disruption of routine and post-delivery time spent with family members where fear of disclosure could interfere with pill-taking. Viremia has been observed in a number of cohorts of postpartum women living with HIV across sub-Saharan Africa [1, 32–35], so early identification of suboptimal adherence during this major transition period could facilitate timely adherence support.

Although pharmacologic adherence metrics are often incorporated into PrEP demonstration projects, the most common way to objectively assess inadequate adherence to ART is by diagnosing virologic failure. Objectively measuring adherence with concurrent viremia could help distinguish between virologic failure due to non-adherence versus resistance [36], avoid switches to more expensive 2nd and 3rd line ART regimens, and facilitate adherence support. Of note, although TDF is still widely used worldwide, tenofovir alafenamide (TAF) is replacing TDF in many settings and its use can also be monitored by measuring hair TFV levels [37].

Our analysis of hair levels as a predictor of *future* (not concurrent) virologic suppression was limited by a small number of events but suggest a potential association between hair levels and future viremia among previously-suppressed women, warranting further research on the use of objective metrics to predict future suppression. Hair assays using LC-MS/MS are expensive but lower-cost assays are under development [38], and low-cost point-of-care urine-based immunoassays for TFV are now validated [39–41]. Further research is needed to inform the clinical utility and cost-effectiveness of objective adherence metrics, including

metrics of both recent and long-term medication use, to supplement virologic monitoring in resource-limited settings.

In conclusion, hair TFV levels were strongly associated with virologic suppression in this sample of postpartum women living with HIV on TDF/FTC-based ART in the PROMISE 1077BF trial. Objective adherence metrics can help distinguish virologic failure due to inadequate adherence from failure due to viral resistance. Low-cost approaches to objective adherence monitoring are urgently needed to optimize maternal health and prevent HIV transmission during breastfeeding.

Funding:

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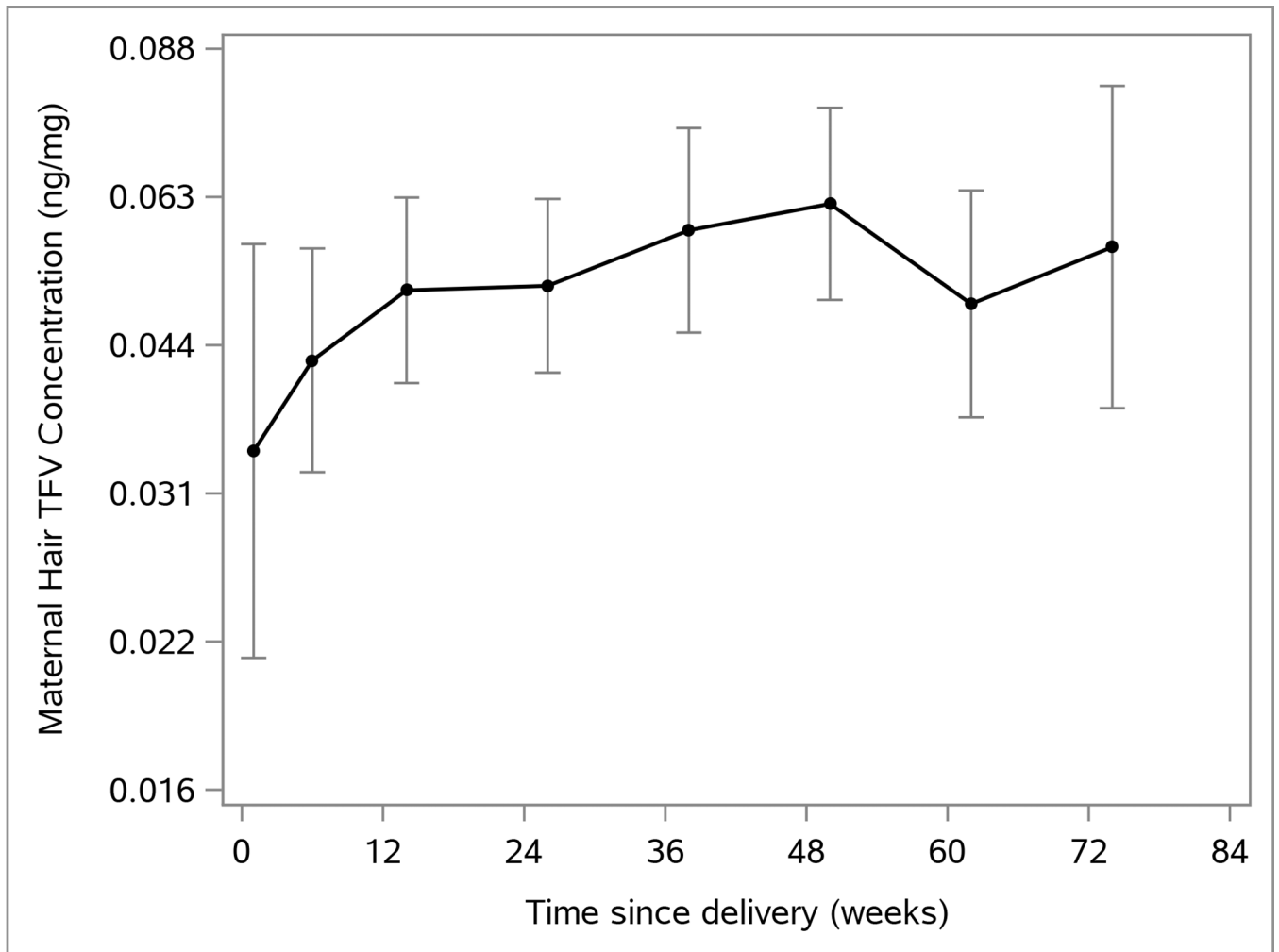
Figure 1.
Maternal hair TFV levels (geometric means and 95% confidence intervals) over time since delivery among 71 postpartum women in the PROMISE Study.

Table 1.

Hair TFV levels and predictors of hair TFV levels throughout breastfeeding in women who initiated ART in pregnancy in the PROMISE Study (N=71).

Hair TFV levels (ng/mg) throughout breastfeeding (N=370 samples)						
Geometric mean (95% CI)	0.047 (0.043–0.052)					
Median (IQR)	0.052 (0.030–0.086)					
Range	0.002–1.067					
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	0.78	0.47 1.25	0.30
South Africa	0.73	0.49 1.09	0.12	0.70	0.46 1.03	0.07
Tanzania	0.51	0.38 0.69	<0.0001	0.51	0.38 0.71	<0.0001
Zambia	0.61	0.39 0.97	0.03	0.62	0.38 1.01	0.05
Zimbabwe	1.26	0.88 1.81	0.21	1.27	0.86 1.85	0.21
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	0.95 1.58	0.12
181–365 days	1.50	1.18 1.91	0.001	1.42	1.09 1.85	0.01
>365 days	1.28	0.97 1.69	0.09	1.30	0.89 1.61	0.24
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			
Food insecurity						
None			Overall: 0.22			Overall: 0.59
Moderate	0.90	0.69 1.18	0.44	0.90	0.69 1.18	0.45
Severe	0.74	0.51 1.07	0.11	0.84	0.54 1.30	0.43