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Journal

J AIDS Journal of Acquired Immune Deficiency Syndromes, 91(3)

ISSN

1525-4135

Authors

Nematadzira, Teacler G
Murnane, Pamela M
Odiase, Osamuedeme J
[et al.](#)

Publication Date

2022-11-01

DOI

10.1097/qai.0000000000003076

Peer reviewed

Antiretroviral Therapy Adherence During and Postbreastfeeding Cessation Measured by Tenofovir Levels in Hair

Teacler G. Nematadzira, MBChB, MCE,^a Pamela M. Murnane, PhD, MPH,^{b,c}
 Osamuedeme J. Odiase, MS,^d Peter Bacchetti, PhD,^c Hideaki Okochi, PhD,^d Regina Tallerico, BA,^d
 Vongai M. Chanaiwa, BPharm, MCE,^a Tichaona Vhembo, MBChB, MPH,^a
 Mercy T. Mutambanengwe-Jacob, BPharm,^a Alexander Louie, BS,^d
 Tsungai Chipato, MBChB, MMed, MCE,^{a,e} Monica Gandhi, MD, MPH,^d and
 Lynda Stranix-Chibanda, MBChB, MMed,^{a,e} for the IMPAACT PROMISE Study Team

Background: We examined change in antiretroviral treatment (ART) adherence after breastfeeding (BF) cessation using hair tenofovir (TFV) concentrations as an objective metric of medication consumption.

Methods: A subset of postpartum women in Zimbabwe randomized in IMPAACT PROMISE to take ART while BF and post-BF cessation had hair TFV measured longitudinally. Using linear mixed-effect models, we estimated differences in hair TFV levels after BF cessation, accounting for trends in levels over time regardless of BF status and change in slope after breastfeeding cessation. We also estimated the relative risk of viremia (>50 copies/mL) per doubling of hair TFV concentration.

Results: Among 55 women (median age 26, interquartile range 24–29 years), hair TFV levels (n = 305) were available for a median of 9 visits per woman between 3 and 29 months postpartum. Hair TFV levels ranged from undetected to 0.25 ng/mg (median 0.04 ng/mg). Controlling for trends since delivery [decline of 2.2% per month, 95% confidence interval (CI): –5.3 to 1.0], TFV levels averaged 24.4% higher (95% CI: –5.1 to 63.1) post-BF cessation than during BF, with no change in slope (0.0% per month, 95% CI: –3.8 to 3.9). Postpartum, 42% of women were ever viremic. Higher TFV levels were strongly protective; relative risk of viremia per doubling of TFV was 0.52 (95% CI: 0.43 to 0.63; $P < 0.0001$).

Conclusions: Leveraging an objective metric of ART use, we observed modestly declining adherence across the postpartum period, but no additional decline associated with breastfeeding cessation. High viremia frequency and varying postpartum TFV levels observed highlight the importance of enhanced adherence support with viral load monitoring among postpartum women.

Key Words: HIV, ART, adherence, breastfeeding, TFV hair levels, viremia

(*J Acquir Immune Defic Syndr* 2022;91:237–241)

From the ^aUniversity of Zimbabwe-Clinical Trials Research Centre, Harare, Zimbabwe; ^bInstitute for Global Health Sciences, University of California-San Francisco, San Francisco, CA; ^cDepartment of Epidemiology and Biostatistics, University of California-San Francisco, San Francisco, CA; ^dHair Analytical Laboratory, University of California-San Francisco, San Francisco, CA; and ^eFaculty of Medicine and Health Sciences, University of Zimbabwe, Harare, Zimbabwe.

Parts of the data were presented at the 2021 Conference on Retroviruses and Opportunistic Infection (vCROI 2021) which was held virtually from March 6, 2021–March 10, 2021.

Overall support for the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) was provided by the National Institute of Allergy and Infectious Diseases (NIAID) 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), all components of the National Institutes of Health (NIH), under Award Numbers UM1AI068632-15 (IMPAACT LOC), UM1AI068616-15 (IMPAACT SDMC) and UM1AI106716-15 (IMPAACT LC), and by NICHD Contract Number HHSN2752018000011.

The authors have no conflicts of interest to disclose.
 Correspondence to: Teacler G. Nematadzira, MBChB, MCE, University of Zimbabwe Clinical Trials Research Centre, 15 Phillips Avenue, Belgravia, Harare, Zimbabwe (e-mail: tnatadzira@uz-ctrc.org).

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INTRODUCTION

In sub-Saharan Africa, where breastfeeding is the norm, approximately 1.1 million women living with HIV became pregnant in 2020.¹ Adherence to antiretroviral treatment (ART) can reduce the risk of perinatal transmission to almost zero and benefit maternal health.^{2–4} Despite accessing universal ART, women can experience significant challenges to adherence and engagement to HIV care,^{5–8} with 20%–40% of women experiencing elevated viral loads postpartum.^{9–11} Breastfeeding cessation may be critical juncture when intense contact with the health care system ends.^{12–14} Moreover, when risk of transmission of HIV to the infant passes, women's capacity to adhere to ART could change. Declining

adherence after pregnancy has been attributed to declining concern about in utero transmission and failure to optimize women's own health outcomes.^{15,16} Few studies measure adherence among healthy women, no longer at risk of transmitting HIV to their infant after breastfeeding cessation.¹⁷ In addition, breastfeeding cessation is often followed by a subsequent conception (within 2 years) in settings with high fertility rates, underscoring the importance of sustained viral suppression to maximally reduce the risk of HIV transmission.^{18,19} UNAIDS estimates for 2020 showed that 37% of infants who acquired HIV were born to women who had initiated ART before the pregnancy, signaling the need to better understand adherence in this period.¹

Measuring adherence to antiretroviral drugs (ARVs) is vital for monitoring response to treatment. Suboptimal adherence leads to virologic failure, development of resistance, and onward transmission, including transmission of resistant mutations.^{20–22} Commonly used adherence measures such as pill counts may inadequately predict virologic outcomes.^{23–25} Drug concentrations in hair provide an objective measure of cumulative adherence.^{26,27}

We assessed how ART adherence changed with breastfeeding cessation by longitudinally measuring hair TFV levels in a subset of postpartum women enrolled in the IMPAACT PROMISE randomized trial in Zimbabwe. In addition, we estimated the association between hair TFV levels and virologic suppression.

METHODS

Study Sample and Procedures

Data are from the International Maternal Pediatric Adolescents AIDS Clinical Trials Network (IMPAACT) Promoting Maternal and Infant Survival Everywhere Breastfeeding Study (PROMISE 1077BF; NCT01061151), conducted between 2011 and 2015 in 7 countries to examine optimal strategies for prevention of perinatal transmission of HIV and improving maternal health among women not yet eligible for treatment at the time. It included a series of open-label, parallel randomization components. In the postpartum component (within 14 days postdelivery), women not requiring ART for their own health were randomized to either maternal ART (TDF/FTC+LPV/r) or daily infant nevirapine prophylaxis during breastfeeding.³ Women on ART in the postpartum component at BF cessation were randomized to continue or stop ART (maternal health component) (consistent with the country guidelines at that time).²⁸ This analysis includes participants in Zimbabwe who were randomized to ART in both the postpartum and maternal health components and participated in a hair substudy throughout these 2 components at the 3 study clinics. Participants attended study visits at least quarterly, with more frequent visits in the first 3 months of each component. Hair samples and detailed breastfeeding questionnaires were collected at all visits, and HIV viral load was assessed at least every 6 months. All participants provided written informed consent before participation. This study was reviewed and approved by local and collaborating institutional review boards, relevant regulatory

authorities, and reviewed for safety and efficacy by an independent Data and Safety Monitoring Board.

Study Measures

Objectively Measured Adherence

Small hair samples were collected following established procedures.²⁹ Among women taking tenofovir disoproxil fumarate for at least 60 days, we assayed 1.5 centimeters of hair closest to the scalp for TFV concentrations using validated liquid chromatography/tandem mass spectrometry (LC-MS/MS)-based methods.³⁰ Medications are incorporated from the systemic circulation into hair as it grows, at approximately 1 cm per month; these data reflect cumulative exposure to tenofovir over the prior ~45 days.³¹

Breastfeeding Cessation

The estimated date of breastfeeding cessation is the last date when the baby sucked on the mother's breast for any reason, recorded only after complete breastfeeding cessation for at least 4 weeks. We created an indicator variable to classify breastfeeding status at each visit as follows: visits >45 days after breastfeeding cessation as postbreastfeeding (value = 1), visits during breastfeeding (value = 0), and visits 0–45 days after breastfeeding cessation, before potential changes in adherence would be fully reflected in hair TFV concentrations, were assigned fractional values, for example, 27 days after cessation/45 days = 0.6.

Viremia

We defined viremia as plasma HIV RNA >50 copies/mL following the World Health Organization's recommendation to consider adherence interventions at this threshold in breastfeeding women.³² Only viral loads collected after 90 days on ART were included.

Statistical Analysis

To estimate how much ART adherence changes after breastfeeding cessation, we used mixed linear regression models with a random intercept and assumed an autoregressive covariance structure. The outcome was log₂ transformed hair TFV levels, and we included 3 predictors in the model to assess the impact of breastfeeding cessation on hair levels. First, the indicator variable for breastfeeding status described above: This variable quantifies the differences in hair TFV levels at postbreastfeeding visits vs. still-breastfeeding visits; second, a linear term reflecting months since delivery to account for changes in hair TFV levels over time regardless of breastfeeding status; and third, an additional linear term, measuring time since breastfeeding cessation, to quantify how the slope of TFV levels since delivery changed after breastfeeding cessation. Because quadratic terms for these time trends did not have *P* values <0.10, we only included linear terms in regression models. To facilitate the interpretation of associations between predictor variables and a log-transformed outcome, we back-transformed regression coefficients to reflect percent differences in hair levels associated with a unit change in each predictor.

Potential Confounders

We decided, a priori, to include the following potential confounders in adjusted models estimating the association between breastfeeding cessation and hair TFV levels: maternal age, education, Zimbabwe study clinic, and ART initiation in pregnancy vs at delivery. To ensure a parsimonious model, we screened additional potential confounders, using *P* value <0.25 in bivariate analysis as a threshold for inclusion³³: parity and gravidity at baseline, time-varying (collected at the visit before the hair sample) employment status (any work outside the home vs. none), and food insecurity.³⁴ None achieved this threshold.

Missing Data

Fifteen (27%) participants were missing educational status, and 4 (7%) were missing parity; we used multiple imputation and assumed that data were conditionally missing at random.³⁵ We imputed 50 data sets to minimize sampling variability from the imputation process³⁶ and used multivariate imputation by chained equations.³⁷ We report adjusted regression analyses from multiple imputed data as our primary results for the association between breastfeeding cessation and hair levels.

Hair TFV Levels and Viremia

To quantify the association between hair TFV levels and viral suppression, we used Poisson regression with generalized estimating equations to estimate relative risks.³⁸ Because hair levels were log₂ transformed in this analysis, the risk ratios represent the relative risk of viremia per doubling of hair TFV levels. We report unadjusted models.

RESULTS

Among 55 eligible women, median age was 26 years [interquartile range (IQR) 24–29 years] and 93% were in WHO Clinical Stage I (Table 1). Baseline characteristics were comparable with that of women enrolled in the main PROMISE study.³⁹ The median duration of breastfeeding was 14 months (IQR 12–16 months). Hair samples collected at visits ≥60 days since tenofovir disoproxil fumarate initiation (N = 326) were analyzed for TFV concentrations; 21 (6%) had no results because of technical or sample labeling issues. We include 305 hair TFV results from 55 women for a median of 8 visits per woman, collected between 3 and 29 months postpartum (up to 1 year post-BF cessation).

Hair TFV Levels

Average TFV levels were highly variable over time (Fig. 1). Across all samples, the median TFV concentration was 0.04 ng/mg (IQR 0.03–0.06, range: undetected-0.25). After accounting for the estimated change in hair levels over time since delivery (2.2% decline per month, 95% CI: –5.3 to 1.0; *P* value 0.17), hair TFV levels in the post-BF period averaged 24.4% higher compared with levels during breastfeeding but with a wide confidence interval (95% CI: –5.1 to 63.1; *P* value 0.11). The rate of decline since delivery,

however, did not improve post-BF, with an estimated change in slope of 0.0% per month (95% CI: –3.8 to 3.9, *P* value 0.99). To address the possibility that women who stopped BF before or after the majority (outside the IQR of breastfeeding duration: 12–16 months) might be meaningfully different, we conducted a sensitivity analysis excluding them and found a very similar estimate for the effect of BF cessation. The results from a complete case analysis were comparable.

Hair TFV Levels and Viremia

Throughout follow-up and after 90 days on ART, 42% of women experienced viremia at least once and 25% in 2 consecutive samples. In the analysis of hair TFV levels and viremia, 54 women had 237 viral load measurements performed >90 days on ART. Hair TFV levels predicted viremia; the relative risk of viremia was 0.52 (95% CI: 0.43–0.63; *P* < 0.0001) per doubling of hair TFV.

TABLE 1. Characteristics of Postpartum Women Enrolled in the Hair Substudy of the PROMISE Trial in Zimbabwe

	N = 55
	Median (IQR) or n (%)
Baseline characteristics	
Age	26 (24–29)
Education*	
None or some primary	1 (2%)
Completed primary but not secondary	10 (25%)
Completed secondary	29 (72%)
Site	
St Mary’s CRS	15 (27%)
Seke north CRS	24 (44%)
Harare family care CRS	16 (29%)
On ART in pregnancy	29 (53%)
Parity	1 (1–2)
Gravida	3 (2–3)
Gestational age at enrollment, wk	31 (26–35)
Nadir CD4 count	502 (438–591)
WHO clinical classification	
Clinical stage I	51 (93%)
Clinical stage II	4 (7%)
Follow-up characteristics	
Breastfeeding duration, mo	13.7 (12.0–16.0)
Experienced viremia (>50 copies/mL)	
At least once	23 (42%)
In 2 consecutive samples	14 (25%)
Virologic failure (>1000 copies/mL)	
At least once	12 (22%)
In 2 consecutive samples	7 (13%)
Number of hair samples collected	
During breastfeeding	3 (2–4)
After breastfeeding	5 (3–6)
Total	8 (5–9) (max = 11)

*15 missing education.

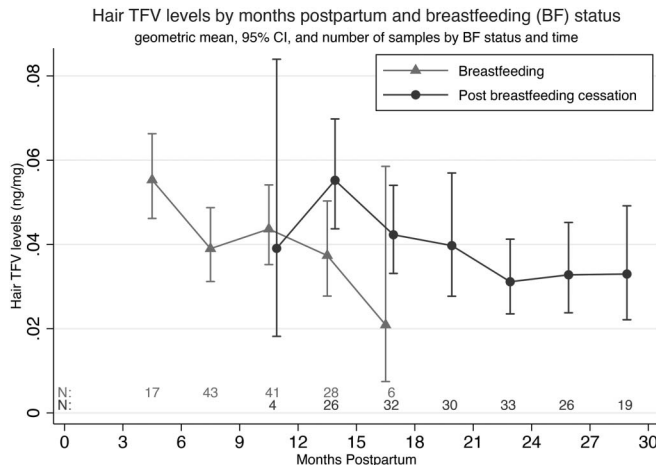


FIGURE 1. Hair TFV levels by months postpartum and breastfeeding (BF) status. [full color online](#)

DISCUSSION

In this analysis of objectively and longitudinally measured adherence to ART in postpartum women in Zimbabwe, we did not find evidence of association between breastfeeding cessation and ART adherence. Rather, we observed an estimated 24% increase and a 95% CI extending down to only a 5% decrease. Nevertheless, a decline in hair TFV levels, although not statistically significant, continued at approximately 2% per month throughout breastfeeding and the first year after cessation, and this temporal trend itself would eventually lead to lower average levels after cessation.

Consistent with previous studies, we confirmed that hair TFV levels strongly predicted viremia,^{27,40} including low-level viremia. Importantly, we observed viremia in over a third of women in the first 2.5 years after delivery which mirrors what has been reported in previous research about declining ART adherence among postpartum women who initiated on ART for life during pregnancy.^{41–43} The frequency of viremia we observed among women engaged in care and receiving intensive adherence support is concerning. Poor adherence and viremia during breastfeeding may result in HIV transmission to the child.⁴⁴ WHO recently recommended that people living with HIV with viral load >50 copies/mL should undergo enhanced adherence counseling with frequent viral load monitoring.³² This will require health worker time and additional resources to implement. In this study, women received adherence support every 3 months with viral load monitoring every 6, but many still missed doses.

In addition, an objective measure of adherence together with an elevated viral load, if availed in the public sector, could help differentiate between virologic failure because of poor adherence versus resistance and/or drug–drug interactions. Enabling health care workers to offer enhanced adherence counseling to those with challenges or to consider switching regimens or providing resistance testing earlier where appropriate. Thus, the early objective measurement could avoid development of resistant mutations which make treatment options challenging in the future.

Within our study, we were not able to assess the role of pharmacokinetic variability. To counter this, we analyzed multiple hair samples collected at various time points and demonstrated a strong association between higher hair levels and reduced risk of viremia. Women who stayed on ART for their own health were not included in this analysis because they were deemed to be naturally different from those who were eligible for randomization. In addition, the ART regimen in this study was different. It included a protease inhibitor and multitabular dosing. The currently recommended single daily tablet of tenofovir disoproxil fumarate, emtricitabine, and dolutegravir may promote better adherence and viral suppression, warranting further study of hair TFV trends postpartum and their associations with viremia. Tenofovir disoproxil fumarate remains a common component of ART regimens globally; thus, the findings remain relevant. Future research on cost-effectiveness is warranted.

In conclusion, we observed modestly declining adherence across the postpartum period, but no additional decline associated with breastfeeding cessation, which is reassuring. Nevertheless, the frequency of viremia we observed highlights the vulnerability of the postpartum period, indicating the need for added focus on long-term ART adherence to achieve the ambitious pediatric HIV elimination target by 2030.

ACKNOWLEDGMENTS

The authors would like to acknowledge the study participants for their commitment to this study, the Community Advisory Board members, the protocol team, site investigators staff at Harare Family Care CRS: Sukunena Maturure and Petronella Matibe, Seke North CRS: Betty Jowa and Lucia Mungate, St Mary's CRS: Suzen Maonera and Nelly Gurure and the PROMISE 1077BF study protocol team. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. The study products were provided free of charge by Abbott, Gilead Sciences, Boehringer Ingelheim, and GlaxoSmithKline.

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