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# Hair Concentrations of Antiretrovirals Predict Viral Suppression in HIV-Infected Pregnant and Breastfeeding Ugandan Women

**Catherine A. KOSS**[a,b], **Paul NATUREEBA**[b], **Julia MWESIGWA**[b,c], **Deborah COHAN**[b,d], **Bridget NZARUBARA**[b], **Peter BACCHETTI**[e], **Howard HORNG**[f], **Tamara D. CLARK**[a,b], **Albert PLENTY**[b,g], **Theodore D. RUEL**[b,h], **Jane ACHAN**[b,c], **Edwin D. CHARLEBOIS**[b,g], **Moses R. KAMYA**[b,i], **Diane V. HAVLIR**[a,b], and **Monica GANDHI**[a,b]

[a]HIV/AIDS Division, San Francisco General Hospital, University of California, San Francisco, San Francisco, CA, USA [b]Makerere University-University of California, San Francisco Research Collaboration, Kampala, Uganda [c]Medical Research Council Unit, The Gambia [d]Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco, San Francisco, CA, USA [e]Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA, USA [f]Drug Studies Unit, University of California, San Francisco, San Francisco, CA, USA [g]Center for AIDS Prevention Studies, University of California, San Francisco, San Francisco, CA, USA [h]Department of Pediatrics, University of California, San Francisco, San Francisco, CA, USA [i]Department of Medicine, Makerere University College of Health Sciences, Kampala, Uganda

## Abstract

**Objective—**Hair concentrations are a non-invasive measure of cumulative antiretroviral (ARV) exposure and the strongest predictor of viral suppression in large cohorts of non-pregnant patients. We examined hair concentrations of ARVs in relation to virologic outcomes in pregnant and breastfeeding women for the first time.

**Design/Methods—**The PROMOTE trial (NCT00993031) enrolled HIV-infected pregnant Ugandan women at 12–28 weeks gestation who were randomized to lopinavir or efavirenz-based antiretroviral therapy (ART). Small hair samples were collected at 30–34 weeks gestation and 10–25 weeks postpartum. Efavirenz and lopinavir hair concentrations were measured via liquid chromatography/tandem mass spectrometry. Multivariate logistic regression models examined predictors of viral suppression (HIV-1 RNA ≤400 copies/ml) at delivery and 24 weeks postpartum.

Corresponding Author: Monica Gandhi, M.D., M.P.H., HIV/AIDS Division, San Francisco General Hospital, University of California, San Francisco, Box 0874, San Francisco, CA 94143-0874, monica.gandhi@ucsf.edu, Tel +1 415 502 6285, Fax +1 415 476 6953.
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**Conflicts of Interest:** Potential conflict of interest: Gilead donates medications for participants in a separate NIH-funded study led by Dr. Havlir but provides no financial support. All other authors declare no conflicts of interest.

**Results—**Among 325 women, median CD4 cell count was 366 cells/mm$^3$ (IQR 270–488) at ART initiation. Mean self-reported 3-day adherence was >97% in each arm. Viral suppression was achieved by 98.0% (efavirenz) and 87.4% (lopinavir) at delivery. At 24 weeks postpartum, 92.5% (efavirenz) and 90.6% (lopinavir) achieved viral suppression; 88% of women were breastfeeding. In multivariate models including self-reported adherence and pretreatment HIV-1 RNA, ARV hair concentrations were the strongest predictors of viral suppression at delivery (efavirenz: aOR 1.86 per doubling in concentration, 95% CI 1.14–3.1, *P*=0.013; lopinavir: aOR 1.90, 95% CI 1.33–2.7, *P*=0.0004) and 24 weeks postpartum (efavirenz: aOR 1.81, 95% CI 1.22–2.7, *P*=0.003; lopinavir: aOR 1.53, 95% CI: 1.05–2.2, *P*=0.026).

**Conclusions—**ARV hair concentrations represent an innovative tool that strongly predicts viral suppression among HIV-infected childbearing women during the critical periods of delivery and breastfeeding.

### Keywords

Antiretroviral therapy; hair concentrations; adherence; perinatal transmission; pharmacokinetics; pregnancy; breastfeeding

## INTRODUCTION

The World Health Organization (WHO) now recommends combination antiretroviral therapy (ART) for pregnant and breastfeeding HIV-infected women at all CD4 cell counts.[1] This policy promises to preserve maternal health and reduce HIV transmission to infants[2] if adequate antiretroviral (ARV) exposure and viral suppression can be achieved throughout pregnancy, breastfeeding, and beyond. During pregnancy, barriers to drug adherence and physiologic changes that alter ARV pharmacokinetics may result in reduced drug exposure, thereby placing women at risk for virologic failure and infants at risk for HIV acquisition.[3–6]

Hair concentrations are a non-invasive, quantitative measure of cumulative ARV exposure that integrate the effects of adherence and pharmacokinetics. In cohorts in North America and South Africa, ARV hair concentrations were strong predictors of viral suppression and predicted subsequent virologic failure among patients with inadequate drug exposure.[7–9] However, studies of the utility of measuring ARV hair concentrations during pregnancy and breastfeeding, when ARV pharmacokinetics can be dynamic due to changes in drug absorption, distribution, metabolism, and elimination, have not previously been conducted. Drug concentrations in hair offer several advantages over other measures of ARV adherence and exposure. Whereas single plasma drug levels record exposure over the prior 24–48 hours and may vary significantly from day-to-day, ARV hair concentrations reflect uptake from the systemic circulation over weeks to months.[10–14] Hair samples can be collected without specialized training or equipment and stored and shipped at room temperature. Furthermore, hair concentrations and other pharmacologic measures do not rely on patient self-report (which is subject to recall and social desirability biases) and are less susceptible to transient improvements in adherence prior to clinic/study visits than plasma measures.[15–18]

Given the potential consequences of inadequate ARV exposure during pregnancy and breastfeeding for both mother and infant, there is a pressing need for an objective, quantifiable measure of ARV adherence and exposure during these periods, particularly in resource-limited settings. We present the first analysis of hair concentrations of ARVs among pregnant and breastfeeding women in relation to virologic outcomes. We examined this association in a cohort of women randomized to efavirenz or lopinavir/ritonavir-based ART, which are now considered first- and second-line regimens, respectively, by the WHO for HIV-infected adults globally, including pregnant women.

## METHODS

### Study Design and Population

We conducted a secondary analysis of the PROMOTE-Pregnant Women and Infants study (ClinitalTrials.gov, NCT00993031), an open-label randomized trial designed to test the hypothesis that lopinavir would reduce placental malaria rates. The trial was conducted in Tororo, in rural Uganda, from December 2009 to March 2013. We have previously reported on the results of the primary malaria endpoint, pregnancy outcomes, ART efficacy and safety, and the use of ARV hair concentrations to assess mother-to-infant transfer of ARVs.[19–22]

HIV-infected, ART-naïve pregnant women at 12–28 weeks gestation were enrolled in PROMOTE regardless of CD4 cell count. Participants were randomized to initiate lopinavir/ritonavir or efavirenz-based combination ART and continue through 1 year postpartum. Participants received lamivudine/zidovudine 150 mg/300 mg twice daily and either efavirenz 600 mg once daily or lopinavir/ritonavir 200 mg/50 mg two tablets twice daily, increased to three tablets twice daily from 30 weeks gestation until delivery. One participant randomized to lopinavir switched to efavirenz due to the need for concomitant tuberculosis treatment; all other participants remained on their assigned study drug, regardless of subsequent viral loads. AbbVie Pharmaceuticals (North Chicago, Illinois, USA) provided lopinavir/ritonavir (Aluvia), but had no other role in the study. The study protocol was approved by the Makerere University School of Medicine Research and Ethics Committee, the Uganda National Council of Science and Technology, and the University of California, San Francisco Committee on Human Research; all participants provided written informed consent in their preferred language.

### Measurements

HIV-1 RNA was measured at screening, delivery, and 24 weeks postpartum, using standardized assays, as previously described.[19] The primary outcome for this analysis was viral suppression (plasma HIV-1 RNA ≤400 copies/ml, based on the lower limit of detection of the assays) at delivery and 24 weeks postpartum, with a 2-week measurement window for the latter. Adherence was assessed by self-reported recall over the 3 days prior to each study visit and analyzed as a continuous predictor.

Small hair samples were collected using previously described methods[7] at 30–34 weeks gestation and 10–25 weeks postpartum. Women were on antiretrovirals for at least 4 weeks

prior to hair collection. Efavirenz and lopinavir hair concentrations were measured via liquid chromatography/tandem mass spectrometry (LC/MS/MS) after extraction and assessed as continuous variables. Methods to analyze lopinavir and efavirenz levels in hair have been described previously.[9, 13, 23] These methods have been validated for lopinavir and efavirenz from 0.05 to 20 ng drug/mg hair, with good linearity ($R^2$ >0.99) and reproducibility (coefficients of variation <15%).[24]

### Statistical Analysis

Multivariate logistic regression models examined predictors of viral suppression at delivery (among women on ART ≥6 weeks) and 24 weeks postpartum. Models were chosen by forward stepwise selection of predictors, with hair level and self-reported adherence included in all models. The high rates of self-reported adherence resulted in wide confidence intervals for its effect on viral suppression and, for the efavirenz group, precluded meaningful estimates at delivery. An exact logistic regression model was run for the efavirenz arm at delivery (which produced similar results to those reported below) because of the small number of participants without viral suppression at this time point. For women with more than one hair specimen available postpartum, we used the level measured on the specimen closest to the 24-week time point. The hair concentration used in the models at delivery was interpolated or extrapolated from a mixed-effects repeated measures model[25] that accounted for weeks of gestation or weeks since delivery, duration on the higher third-trimester dose for women on lopinavir/ritonavir, and a random person effect. Because of few virologic failures, we decided *a priori* to use ARV hair concentration as a continuous predictor; addition of quadratic terms revealed no strong evidence for departures from linearity (all p>0.60). Statistical analyses were performed using SAS software versions 9.2 and 9.4 (SAS Institute, Cary, North Carolina, USA).

## RESULTS

### Characteristics of Study Participants

Of 389 women in this study, 325 provided hair samples (162 in the efavirenz arm and 163 in the lopinavir/ritonavir arm). The acceptability of hair collection was 84%. Among women who provided hair samples, clinical characteristics at enrollment were similar between the two study arms, including median CD4 cell count (efavirenz: 373 cells/$mm^3$ [range 14–1080]; lopinavir: 358 cells/$mm^3$ [range 81–1030]), and median $log_{10}$ HIV-1 RNA (efavirenz: 4.3 copies/ml [range 2.6–4.9]; lopinavir: 4.1 copies/ml [range 2.6–5.9]) prior to ART initiation (Table 1). At 24 weeks postpartum, 87.5% of women were breastfeeding their infants. One infant acquired HIV. The median (and interquartile range) hair concentrations of efavirenz and lopinavir are shown in Table 1. Mean self-reported adherence was >97% for women in both arms at delivery and 24 weeks postpartum.

### Virologic Outcomes

At delivery, 98.0% of women in the efavirenz arm and 87.4% of women in the lopinavir arm achieved viral suppression ($P$<0.001). Median time from ART initiation to delivery was 16.9 weeks (range 4.6–27.9) in the efavirenz arm and 17.7 weeks (range 3.9–27.1) in the lopinavir arm. At 24 weeks postpartum, 92.5% of women on efavirenz and 90.6% of women

on lopinavir were virologically suppressed (*P*=0.57). Of the 20 participants on lopinavir with detectable viral loads at delivery, 17 had viral loads measured at 24 weeks postpartum; 3 participants had detectable viral loads at both time points. The 3 women on efavirenz who had detectable viral loads at delivery did not have viral load measurements at 24 weeks postpartum, although 2 had undetectable viral loads at other postpartum time points that were not included in this analysis.

### Predictors of Viral Suppression

Hair concentrations of efavirenz and lopinavir at 30–34 weeks gestation were significantly associated with viral suppression at delivery (Table 2; efavirenz: odds ratio [OR] 1.86 per doubling in hair concentration, 95% CI 1.14–3.1, *P*=0.013; lopinavir: OR 1.62 per doubling, 95% CI 1.19–2.2, *P*=0.002). Among women taking lopinavir, other predictors of viral suppression at delivery in univariate models included pretreatment HIV-1 RNA (OR 0.31 per 10-fold increase, 95% CI 0.16–0.62, *P*=0.001) and self-reported adherence (OR 3.69 per 10% of prescribed dose, 95% CI 1.10–12.4, *P*=0.035). At 24 weeks postpartum, ARV hair concentrations (which represent preceding long-term exposure) obtained at 10–25 weeks postpartum were similarly associated with viral suppression (efavirenz: OR 1.58 per doubling, 95% CI 1.18–2.1, *P*=0.002; lopinavir: OR 1.51 per doubling, 95% CI 1.05–2.2, *P*=0.027) in both arms.

In multivariate models including self-reported adherence and pretreatment HIV-1 RNA, ARV hair concentrations were the strongest predictor of viral suppression at delivery (efavirenz: adjusted OR [aOR] 1.86 per doubling, 95% CI 1.14–3.1, *P*=0.013; lopinavir: aOR 1.90 per doubling, 95% CI: 1.33–2.7, *P*=0.0004) and 24 weeks postpartum (efavirenz: aOR 1.81 per doubling, 95% CI: 1.22–2.7, *P*=0.003; lopinavir: aOR 1.53 per doubling, 95% CI: 1.05–2.2, *P*=0.026). Self-reported adherence was not statistically significantly associated with virologic outcomes for either drug in multivariate models.

## DISCUSSION

In this cohort of HIV-infected pregnant and breastfeeding women in rural Uganda, hair concentrations of efavirenz and lopinavir were the strongest predictors of viral suppression at delivery and 24 weeks postpartum in multivariate models, surpassing self-reported adherence and pretreatment HIV-1 RNA levels. Moreover, the acceptability and feasibility of hair collection were high. To our knowledge, this is the first study to report on ARV concentrations in hair samples in relation to virologic outcomes during pregnancy and breastfeeding among HIV-infected women. We have previously demonstrated strong associations between ARV hair concentrations and viral suppression in non-pregnant populations,[7, 8, 26] but the current study has implications for monitoring treatment outcomes relevant to both maternal and infant health during high-risk periods for perinatal transmission and during periods of pharmacokinetic flux.

The higher rate of viral suppression observed at delivery among women in this sub-study who were randomized to the efavirenz-containing regimen is consistent with published results from the parent study.[19] Self-reported perfect adherence was high in both arms (>97%), but was not statistically significantly associated with virologic outcomes, consistent

with known limitations of this measure.[17, 27] Pre-treatment HIV RNA level is a common predictor of subsequent outcomes,[28] and was associated with lower rates of viral suppression in our study as well.

Several studies have reported that hair collection is acceptable among HIV-infected patients in resource-limited settings and that ARV hair concentrations could be useful for treatment management or in research studies. In a cohort of HIV-infected adults in rural Kenya, hair collection was feasible and highly acceptable (>95%) and cost less than an HIV viral load test in the region.[16] A recent report from two phase II pre-exposure prophylaxis (PrEP) trials in Kenya and Uganda also demonstrated high acceptability (>95%) for hair collection.[29] A study in South Africa found that low lopinavir levels in hair were associated with virologic failure among patients on second-line ART.[9] Given the well-known limitations of current methods to monitor adherence, hair levels, which integrate adherence and variations in pharmacokinetics, may become useful tools in the peripartum setting. Of note, in this study, adaptively searching for threshold hair levels for predicting virologic failure would have been likely to produce overfitting of this limited dataset. Further studies by our group in a larger cohort of pregnant and breastfeeding women will allow us to define such thresholds. Finally, the hair assays used for this study have been standardized and validated using LC/MS/MS, but widespread applicability, especially in clinical settings, will rely on the availability of modified hair assays, currently under development, [30] harnessing lower-cost technology.

Close monitoring of ARV exposure during pregnancy and breastfeeding may help to ensure the critical outcome of virologic suppression in mothers. Measuring drug exposure during this time, when pharmacokinetic parameters can vary, may be important for predicting and influencing outcomes. In this cohort of childbearing HIV-infected women, hair concentrations of ARVs were the strongest predictor of viral suppression. Hair concentrations of ARVs could serve as an innovative tool for optimizing maternal health and minimizing the risk of perinatal HIV transmission.

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## Table 1

Characteristics and HIV outcomes of participants at enrollment, delivery and 24 weeks postpartum, by ART regimen

| Characteristic | N | Efavirenz | N | Lopinavir |
|---|---|---|---|---|
| **Enrollment** | | | | |
| **Maternal age,** years, mean (SD) | 162 | 30.3 (5.5) | 161 | 29.3 (5.3) |
| **Gestational age,** weeks, median (min-max) | 162 | 21.8 (13.6–28) | 163 | 20.7 (13–29.3) |
| **Body mass index,** kg/m$^2$, mean (SD) | 160 | 21.6 (2.7) | 162 | 22.2 (2.9) |
| **CD4 cell count,** cells/mm$^3$, median (min-max) | 160 | 373 (14–1080) | 160 | 358 (81–1030) |
| **HIV-1 RNA** | 159 | | 162 | |
| <100,000 copies/ml, n (%) | | 125 (78.6%) | | 138 (85.2%) |
| ≥100,000 copies/ml, n (%) | | 34 (21.4%) | | 24 (14.8%) |
| $\log_{10}$ copies/ml, median (min-max) | | 4.3 (2.6–5.9) | | 4.1 (2.6–5.9) |
| **Delivery** | | | | |
| **Weeks since ART initiation**, median (min-max)[a] | 162 | 16.9 (4.6–27.9) | 163 | 17.7 (3.9–27.1) |
| **Self-reported adherence** | 162 | | 163 | |
| %, mean (SD) | | 97.7 (8.4) | | 99.1 (3.1) |
| %, median (min-max) | | 100 (33.3–100) | | 100 (77.8–100) |
| **ARV hair concentration,** ng/mg, median (IQR)[b] | 162 | 3.7 (2.4, 7.3) | 163 | 5.7 (3.1, 8.8) |
| **HIV-1 RNA ≤400 copies/ml,** %[c] | 152 | 98.0% | 159 | 87.4% |
| **24 weeks postpartum** | | | | |
| **Weeks since ART initiation,** median (min-max) | 149 | 40.6 (28.6–52) | 151 | 41.9 (27.9–50.9) |
| **Self-reported adherence** | 143 | | 147 | |
| %, mean (SD) | | 99.2 (2.7) | | 99.3 (2.8) |
| %, median (min-max) | | 100 (80–100) | | 100 (80.6–100) |
| **ARV hair concentration,** ng/mg, median (IQR)[d] | 137 | 4.2 (2.5, 7.7) | 139 | 5.2 (3.5, 7.4) |
| **HIV-1 RNA ≤400 copies/ml,** % | 134 | 92.5% | 139 | 90.6% |

ART, antiretroviral therapy; IQR, inter-quartile range; ARV, antiretroviral.

[a] Weeks since ART initiation is reported for all study participants. Participants on ART for fewer than 6 weeks at the time of delivery were excluded from models of viral suppression at delivery.

[b] Measured at 30–34 weeks gestation. Among participants with detectable compared to undetectable viral loads at delivery, median ARV hair concentrations were 3.7 ng/mg (IQR 1.3–6.2) vs. 5.9 ng/mg (IQR 3.6–8.9) (lopinavir) and 0.5 ng/mg (IQR 0.1–4.9) vs. 3.8 (IQR 2.4–7.3) (efavirenz).

[c] $p < 0.001$.

[d] Measured at 10–25 weeks postpartum. Among participants with detectable compared to undetectable viral loads at 24 weeks postpartum, median ARV hair concentrations were 5.2 ng/mg (IQR 1.1–6.1) vs. 5.1 ng/mg (IQR 3.5–7.5) (lopinavir) and 2.3 ng/mg (IQR 0.5–3.4) vs. 4.4 ng/mg (IQR 2.7–8.9) (efavirenz).

**Table 2**

Univariate and multivariate analyses of predictors of viral suppression at delivery and 24 weeks post-partum, by ART regimen

| | Delivery | | | | 24 weeks postpartum | | | |
|---|---|---|---|---|---|---|---|---|
| | Efavirenz | | Lopinavir | | Efavirenz | | Lopinavir | |
| **Variable** | **OR (95% CI)** | ***p*** | **OR (95% CI)** | ***p*** | **OR (95% CI)** | ***p*** | **OR (95% CI)** | ***p*** |
| **Maternal age,** per decade | 3.24 (0.34–31) | 0.31 | 1.90 (0.75–4.8) | 0.18 | 1.93 (0.55–6.7) | 0.30 | 1.34 (0.49–3.7) | 0.57 |
| **Gestational age at enrollment,** per week | 0.89 (0.65–1.21) | 0.44 | 0.94 (0.84–1.05) | 0.26 | 1.01 (0.87–1.18) | 0.90 | 1.04 (0.91–1.17) | 0.58 |
| **Body mass index at enrollment,** per kg/m$^2$ | 2.29 (1.01–5.2) | 0.048 | 1.02 (0.87–1.2) | 0.81 | 1.43 (1.03–1.99) | 0.034 | 1.13 (0.92–1.39) | 0.24 |
| **CD4 cell count at enrollment,** per 100 cells/mm$^3$ | 1.40 (0.66–3.0) | 0.38 | 0.81 (0.63–1.03) | 0.079 | 2.06 (1.23–3.5) | 0.006 | 1.15 (0.84–1.59) | 0.39 |
| **Pretreatment HIV-1 RNA,** per 10-fold increase | 0.54 (0.12–2.3) | 0.41 | 0.31 (0.16–0.62) | 0.001 | 0.46 (0.20–1.09) | 0.079 | 0.70 (0.36–1.35) | 0.29 |
| **Self-reported adherence,** per 10% of prescribed dose | 1.17 (0.32–4.3) | 0.81 | 3.69 (1.10–12.4) | 0.035 | * | | 3.1 (0.94–10.0) | 0.064 |
| **ART duration,** per week | 1.17 (0.89–1.53) | 0.26 | 1.02 (0.93–1.12) | 0.64 | 0.97 (0.85–1.11) | 0.66 | 0.96 (0.86–1.07) | 0.42 |
| **ARV hair concentration,** per doubling | 1.86 (1.14–3.1) | 0.013 | 1.62 (1.19–2.2) | 0.002 | 1.58 (1.18–2.1) | 0.002 | 1.51 (1.05–2.2) | 0.027 |
| | **aOR (95% CI)** | ***p*** | **aOR (95% CI)** | ***p*** | **aOR (95% CI)** | ***p*** | **aOR (95% CI)** | ***p*** |
| **Pretreatment HIV-1 RNA,** per 10-fold increase | | | 0.25 (0.11–0.54) | 0.0005 | 0.38 (0.14–1.05) | 0.062 | | |
| **Self-reported adherence,** per 10% of prescribed dose | 1.00 (0.29–3.4) | 1.00 | 2.2 (0.53–8.9) | 0.28 | * | * | 3.3 (0.88–12.4) | 0.56 |
| **ARV hair concentration,** per doubling | 1.86 (1.14–3.1) | 0.013 | 1.90 (1.33–2.7) | 0.0004 | 1.81 (1.22–2.7) | 0.003 | 1.53 (1.05–2.2) | 0.026 |

OR, odds ratio; ART, antiretroviral therapy; ARV, antiretroviral; aOR, adjusted odds ratio.

* There was too little variation in self-reported adherence to permit a meaningful estimate.