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Short Communication: Higher Tenofovir Concentrations in Hair Are Associated with Decreases in Viral Load and Not Self-Reported Adherence in HIV-Infected Adolescents with Second-Line Virological Treatment Failure

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Abstract

Objective methods of measuring antiretroviral adherence are limited. We assessed the relationship between tenofovir disoproxil fumarate (TDF) hair concentrations, self-reported adherence, and virological outcomes in HIV-infected adolescents in Harare, Zimbabwe. HIV-infected adolescents on atazanavir/ritonavir-based second-line treatment for >6 months with viral load (VL) ≥1,000 copies/mL were randomized to either modified directly administered antiretroviral therapy (mDAART) or standard of care. Hair and VL samples were collected at baseline and after 90 days. Treatment outcome was defined as TDF concentrations in hair. Virological suppression was defined as VL <1,000 copies/mL. Thirty-four adolescents had TDF concentrations measured at baseline and follow-up. Mean (median); range age was 16 (16); 13–18 years and 53% were females. Nineteen (56%) were randomized to mDAART. Mean (SD); range TDF concentrations were 0.03 (0.04); 0–0.17 ng/mg hair and 0.06 (0.06); 0–0.3 ng/mg hair at baseline and follow-up, respectively. Higher TDF concentrations were associated with decreased VL [regression coefficient (RC) 0.8; 95% confidence interval (CI) 0.7–1.0; $p = .008$] and mDAART (RC 0.5; 95% CI 0.3–1.0; $p = .04$), but were not associated with self-reported adherence and virological suppression (VL <1,000 copies/mL). Higher TDF hair concentrations were observed with virological decrease and an adherence intervention. Hair antiretroviral concentrations could be useful in triggering adherence interventions among adolescents with second-line virological failure.

Keywords: adolescents, virological treatment failure, tenofovir hair concentrations

The benefits of antiretroviral therapy (ART) on morbidity and mortality are highly dependent on adherence to treatment. Measuring antiretroviral adherence accurately is challenging. Self-reported adherence and pill charts/diaries often overestimate adherence.[1,2] Pill counts, directly observed treatment, and composite adherence scores are intrusive and labor intensive. Pharmacy refill data assume collection of drugs equals dose ingestion, whereas electronic drug monitoring assumes that bottle opening represents drug consumption.[1,2] Viral load (VL) assays are affected by factors other than adherence, such as drug resistance and inadequate drug exposure, and are rationed in resource-limited settings.[2,3]

These limitations of various adherence metrics have led to an interest in objective monitoring, where drug levels are measured in a biomatrix such as plasma, urine, dried blood spots (intracellular), or hair. However, drug levels in plasma and urine represent adherence over the short term only, which can be impacted by white coat effects.[1,2]

Antiretroviral concentrations in hair strongly predict treatment failure in multiple studies involving adults, but data

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are scarce for adolescents, a group that is crucial to study to curb the propagation of HIV and drug resistance.[3–6] No studies before this examined tenofovir disoproxil fumarate (TDF) concentrations in hair among adolescents, although this is the preferred nucleotide reverse transcriptase inhibitor for both HIV treatment and pre-exposure prophylaxis due to its high efficacy, favorable toxicity profile, low pill burden, availability in fixed dose combinations (FDC), and once daily dosing.[5] This study assessed the relationship between TDF concentrations in hair, virological outcomes, and self-reported adherence among HIV-infected adolescents who were virologically failing second-line ART in Harare, Zimbabwe.

A randomized controlled trial of modified directly administered antiretroviral therapy (mDAART) (intervention) was conducted among 34 HIV-positive adolescents at Harare hospital. All 34 participants were on TDF/lamivudine FDC and atazanavir/ritonavir FDC-based second-line treatment for ≥6 months and had virological failure (HIV VL ≥1,000 copies/mL). The intervention consisted of structured home visits during the week, SMS text messages during weekends and standard-of-care adherence counseling for 90 days.[4,7] The control arm received standard-of-care adherence counseling alone. Hair and VL samples were collected at baseline and at 90 days.

Hair samples were collected according to a standard protocol.[4,8] TDF hair concentrations were measured using liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS), with an assay range of 0.002–0.4 ng/mg hair.[1] The LC/MS/MS receives prevention maintenances biannually and is calibrated every 2 months. A hair sample from a participant well adhered to TDF, whose concentration was confirmed to be stable for 3 years and was within acceptance criteria (percentage error of concentration less than ±15% of the original) was used as a positive control. Self-reported adherence was measured by visual analog scale (VAS). More details about the trial were published elsewhere.[4,7]

The study was registered with Pan African Clinical Trial Registry (PACTR201502001028169) and NIH Clinical Trials .gov (NCT02689895), and approved by the Harare Hospital Institutional Review Board, Joint Research Ethics Committee (JREC/51/14), Medical Research Council of Zimbabwe (MRCZ/A/1840), Research Council of Zimbabwe (Ref: 02810), and UCSF Committee on Human Research (CHR #11-07442).

Data were entered into Research Electronic Data Capture (REDCap) and analyzed in Stata 14. Treatment outcome was defined as TDF hair concentrations at follow-up. TDF concentrations were treated as continuous in linear regression analysis and were first checked for normality using skewness and kurtosis, and collinearity was checked for. TDF concentrations were log-transformed to meet normality assumptions. Stepwise regression analysis was used in multivariate linear regression models. We reported regression coefficients (RCs) back-transformed using the exponentiality function. p Values ≤.05 were considered statistically significant. Self-reported adherence was assessed by a VAS.

Mean (median); range age was 16 (16); 13–18 years, 53% were females, 56% were enrolled into mDAART and 50% were virologically suppressed (VL <1,000 copies/mL) after follow-up. Mean (SD); range TDF concentrations were 0.03 (0.04); 0–0.17 ng/mg hair and 0.06 (0.06); 0–0.3 ng/mg hair at baseline and follow-up, respectively.

In bivariate analysis, higher TDF concentrations in hair were associated with virological suppression [RC 0.5; standard error (SE) 0.2; 95% confidence interval (CI) 0.3–1.0; $p = .04$], VL change (a net decrease) after follow-up (RC 0.8; SE 0.08; 95% CI 0.6–1; $p = .02$), time on first-line ART (RC 1.0; SE 0.01; 95% CI 0.96–0.99; $p = .01$) and total time on ART (RC 1.0; SE 0.01; 95% CI 0.96–0.99; $p = .002$).

In multivariate analysis (Table 1), higher TDF concentrations in hair were positively associated with decreased VL (RC 0.8; SE 0.06; 95% CI 0.7–1.0; $p = .008$), being in the mDAART arm (RC 0.5; SE 0.2; 95% CI 0.3–1.0; $p = .04$) and older age (15–18 years) (RC 1.2; SE 0.1; 95% CI 1–1.4; $p = .05$). TDF concentrations in hair were, however, not associated with self-reported adherence and virological suppression.

Our study showed for the first time that TDF concentrations in hair were positively and strongly associated with decreased VL, a short adherence intervention, and older age among adolescents failing second-line ART. Our findings concur with previous studies that showed that antiretroviral concentrations in hair strongly predict decreases in VL, including atazanavir concentrations in hair in our adolescent cohort and TDF concentrations in breastfeeding women in Africa.[3,4] The difference between the correlation of atazanavir and tenofovir hair concentrations with VL suppression could be due to the smaller sample size of 34 participants for tenofovir versus 50 for atazanavir analysis. To the best of our knowledge, this is the first study to measure TDF concentrations in hair in adolescents and in a setting where a home-based adherence intervention is administered.

Self-reported adherence was not associated with TDF concentrations in hair and is consistent with previous studies showing that self-reported adherence is often overestimated and unreliable.[1,2] Antiretroviral concentrations in hair reflect adherence for the past few weeks to months, and also reflect drug exposure, which is important in this group, which may have stunted growth and metabolic challenges from chronic HIV disease, delayed HIV testing, and long-term ART.[6,7,9–11] Uptake of antiretroviral drugs in hair is not affected by antiretroviral drug resistance (as HIV RNA would be), so this metric can be helpful in distinguishing resistance-related treatment failure from adherence-related treatment failure. Drug resistance testing is expensive and largely unavailable in resource-limited countries, yet it is required when switching to third-line treatment.[9] An adequate hair level with a high VL could trigger the need for resistance testing. Measuring TDF concentrations

Table 1. Multivariate Linear Regression to Determine Factors Associated with Tenofovir Disoproxil Fumarate Concentrations in Hair

Variable	*Regression coefficient (SE); 95% CI* (n = *34*)	p
Age in years: 15–18	1.2 (0.1); 1 to 1.4	.05
Treatment arm: mDAART	0.5 (0.2); 0.3 to 1.0	.04
Time on first-line ART	1.2 (0.3); −0.7 to 2.0	.5
Time on second-line ART	1.2 (0.3); −0.7 to 0.2	.6
Total time on ART	0.8 (0.2); −0.5 to 1.4	.5
Log_{10} viral load change from baseline	0.8 (0.1); −0.7 to 1.0	.008

ART, antiretroviral therapy; CI, confidence interval; mDAART, modified directly antiretroviral therapy; SE, standard error.

in hair could prove more useful in the recent rollout of TDF/lamivudine/dolutegravir FDC. TDF concentrations in hair could indirectly assess exposure to dolutegravir.

Enrolment into the mDAART intervention was associated with higher TDF concentrations in hair. Perinatally infected adolescents have been on treatment for a long time, with treatment fatigue setting in. Moreover, adolescents living with HIV are often multidrug experienced and are often going to school. Many are orphaned with complex psychosocial circumstances, and adolescence may coincide with disclosure of HIV status and transition from supervised caregiver-management to nonsupervised self-management in perinatally infected adolescents. An intermittent home-based adherence intervention could be useful in re-enforcing adherence at times when adherence is low until maturity sets in. Nearly half of new HIV-infections occur in adolescents and nearly half of HIV-infected of adolescents are failing second-line ART.[9;12] It is, therefore, crucial to develop strategies to accurately measure and maintain adequate adherence to achieve virological suppression in this vulnerable group.

Our study comes with some limitations. Our adherence intervention was relatively short, and our cohort was small. In addition, home visits were more frequent at the beginning of the study and reduced gradually to reduce intrusiveness and maintain acceptability. Studies with longer follow-up, higher sample size, and uniform observation of dose ingestion may provide more clarity.

In conclusion, higher TDF concentrations were associated with VL decrease and a short-term adherence intervention in our cohort of adolescents. Measuring antiretroviral concentrations in hair in resource-limited settings could be useful in triggering adherence interventions. An intermittent home-based adherence intervention may improve adherence in high-risk adolescents with virological failure to second-line ART.

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Authors' Contributions

T.C., D.K., C.N., K.N., and M.G. developed the concept and design of the study. T.C. collected the data. T.C., C.N., K.N., B.N., H.O., A.L., K.K., D.K., J.M., and M.G. analyzed and interpreted the data, drafted, critically revised, and approved the final article.

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Author Disclosure Statement

No competing financial interests exist.

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