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Strong Correlation between Concentrations of Antiretrovirals in Home-Collected and Study-Collected Hair Samples: Implications for Adherence Monitoring

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BACKGROUND

Sub-optimal adherence to either HIV therapy or pre-exposure prophylaxis (PrEP) increases the risk of virologic failure, drug resistance, and HIV transmission or acquisition^{1–3}. Hair concentrations of antiretrovirals (ARVs), which reflect cumulative exposure over weeks to months, are more strongly predictive of virologic response than self-reported adherence in HIV treatment^{4–6} and predict toxicities⁷ and dosing patterns⁸ among individuals on PrEP.

Measuring hair concentrations of ARVs to estimate adherence and exposure has several advantages, including lower susceptibility to “white coat adherence” patterns⁹ and the ability

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(3) These data have not been presented at any meetings.

CONFLICT OF INTEREST

All authors report no conflicts.

to estimate long-term adherence¹⁰. Hair samples are collected non-invasively, do not require sterile equipment, and can be stored and shipped at room temperature and without biohazardous precautions.

In studies examining hair concentrations of ARVs to date, trained staff have collected hair samples from the back of participants' heads. However, just as self-collection of genital swabs can facilitate testing for sexually transmitted infections¹¹, home-collection of hair samples may increase recruitment and retention in research due to reduced travel time and expense. Additionally, because hair is more readily self-sampled from the side of the head, confirming that ARV concentrations are similar across the scalp would bolster the case for home-collection.

We conducted a pilot study to: (1) evaluate the feasibility and acceptability of home-collection of hair samples; and (2) examine the correlation and agreement between ARV levels in hair collected at a study site by staff and hair collected at home by participants, as well as the correlation and agreement between ARV levels in hair collected from the back versus the side of the head.

METHODS

Participants and Sample Collection

We recruited participants 18 years of age on tenofovir (TFV) disoproxil fumarate (TDF)/emtricitabine (FTC)-containing ARV regimens for at least three months. TDF/FTC is a backbone for ARV regimens and the combination used for PrEP and has the most comprehensive data on dose-hair concentration relationships⁸. Participants with renal insufficiency were excluded.

Individuals who met study criteria were emailed a video link (<http://rxpix.ucsf.edu/study-archives>) describing the overall study objectives and demonstrating home-collection of hair. Consenting participants attended study visits at University of California, San Francisco (UCSF) at baseline, six, and 12 weeks. Trained staff collected hair samples from the back and side of participants' heads at these three time points. At six and 12 weeks, we mailed the participants hair collection kits that included detailed instructions for home-collection of hair (<http://rxpix.ucsf.edu/study-archives>), supplies for hair sample collection, and a pre-stamped addressed envelope to mail the hair samples back to study staff. Participants were instructed to collect hair samples from the back and side of their heads and ask for assistance from a friend or family member if desired. The study protocol was approved by the UCSF Institutional Review Board.

Laboratory Methods

The UCSF Hair Analytical Laboratory (HAL) has developed, validated, and reported on methods to analyze TFV, FTC, and other ARVs in small hair samples using liquid chromatography/tandem mass spectrometry^{5,10,12,13}. The laboratory's hair assays for TFV and FTC have been peer-reviewed and approved by the Division of AIDS Clinical Pharmacology and Quality Assurance program¹⁴. Detailed methods for hair analyses have been previously described⁸.

Data Analysis

Feasibility of home-collection of hair samples was defined as the proportion of participants who mailed back adequate hair samples to the study site. Acceptability of home-collection was evaluated via qualitative exit interviews focused on participants' opinions on home-collection of hair samples.

Qualitative data—The first and third authors identified themes from exit interview and entered them into a matrix using Microsoft Excel where columns and rows represented themes and participants, respectively, to facilitate data analysis¹⁵. The third author categorized each interview using this matrix and coding was reviewed for accuracy by the first author.

Quantitative data—Univariate analyses were conducted to examine demographics, feasibility, and acceptability variables. In study-collected and home-collected hair samples from the back and side of the head, we examined: (1) Pearson correlation coefficients to determine relative correlation between log10-transformed TFV and FTC levels, (2) concordance correlation coefficients to evaluate the agreement (i.e., reproducibility) between hair levels, and (3) the Bland-Altman limits of agreement to estimate measurement bias. We used Stata 14 (StataCorp, College Station, TX) for analyses.

RESULTS

We collected baseline data on eight individuals who met entry criteria. One participant withdrew after the baseline visit due to life circumstances unrelated to the study and another participant withdrew at 12 weeks due to a family emergency. Participants had a mean age of 50.8 years, were 88% male, and 38% African American.

Feasibility

Of the 26 home-collected hair samples that were expected from enrolled participants, we received 24 samples. One participant did not mail the 6-week home-collected samples, citing "chaos in life." Of the 42 study-collected hair samples that were expected from enrolled participants, we collected 40 samples. One participant did not attend the 12-week study visit due to an infection but mailed back the home-collected hair samples and completed the exit interview by telephone.

Study staff received the home-collected samples a mean of nine days from the date that hair kits were mailed and all samples were in good condition for hair analysis. The HAL was unable to report TFV levels in two hair samples - both collected by study staff - due to a matrix effect (i.e., unknown variables interfering with the assay).

Acceptability

During recruitment, only one person did not participate due to not wanting to cut their hair. Six individuals were unable to participate due to baldness (N=3) or having a finely shaved head (N=3). All eight individuals who participated stated that they had a positive study

experience, found home-collection of hair easy, and reported that they would participate in a similar future study.

“I just reached down and grabbed me a good little piece and felt it, looked in the mirror, clipped it, held it, put it on there, then taped it, folded it up, and sent it to you all.” (56 year-old African American transgender woman)

“It depends on an individual, how attached they are to a little piece of hair or not. But it’s going to grow back, my god, it’s not like chemo where it all fell out or something. They just have to let go of a little hair, that’s all.” (57 year-old multiracial man)

“At home is a lot easier than actually having to come out here every month. Because the same thing you did here every month, I do it at home.” (50 year-old White man)

Correlation and Agreement

As shown in the Table, hair levels of TFV and FTC, regardless of the region of the head or whether collected by staff and at home, had high correlation and agreement with each other (all Pearson correlation coefficients 0.85 and concordance correlation coefficients 0.83). FTC concentrations revealed a slightly higher correlation among the samples collected (correlation coefficients 0.95) than TFV concentrations in various samples (correlation coefficients 0.85). There was no evidence of measurement bias (mean differences 0.08).

DISCUSSION

We demonstrated that home-collection of hair is feasible and acceptable and yields ARV concentrations that were essentially equivalent to concentrations from study-collected samples. Participants reported that the home-collection of hair samples was easy and unimposing. There was a high degree of correlation and agreement between ARV levels in hair collected by trained staff and at home by participants - and between hair collected from the back and side of the head - without any evidence of measurement bias.

This is the first study to examine the potential for home-collection of hair for adherence monitoring. Our findings suggest this pharmacologic measure of adherence can be collected without the need for study visits, thereby broadening the reach of this biomarker (i.e., hair levels) to diverse geographies and participant groups. This is also the first study to show that ARV levels from hair collected from the side of the head (an area easier to reach for home-collection) is comparable to hair concentrations collected from the back of the head (the region from which research samples are typically collected). Finally, the correlation between FTC hair levels in samples collected at home versus those collected in the clinic was higher than the correlation for TFV in each set of samples. Therefore, if patients are switched from TDF/FTC to tenofovir alafenamide (TAF)/FTC, hair concentrations of FTC can continue to serve as a reliable adherence biomarker.

Study limitations include a small sample size from a single geographic area and a focus on two ARVs (TDF/FTC). A larger six-month study to examine the feasibility and acceptability

of home-collection of hair samples among participants taking other ARVs from various geographic regions across the U.S. is in progress.

Adherence monitoring for PrEP during this implementation period and for achieving the UNAIDS “90:90:90” targets worldwide is essential. Hair ARV concentrations are predictive of future virologic failure⁴ and, if measured economically, may reduce the need for frequent viral load monitoring. Home-collection of samples and remote monitoring can reduce missing data, decrease visit burden for research participants and clinic patients, enhance research participation of traditionally “hard-to-reach” populations, and increase generalizability of results. Home collection of hair samples may be an important step to expanding objective adherence monitoring in the context of HIV treatment and prevention worldwide.

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Table

Correlation and agreement of tenofovir and emtricitabine from home- and study-collected samples over a 12-week interval collected from the back and side of head (column numbers in from top to bottom represent the Pearson correlation coefficient (p-value), concordance correlation coefficient (95% confidence interval), Bland-Altman mean difference (95% limits of agreement), and the number of hair samples).

		Emtricitabine			
		Clinic Back	Clinic Side	Home Back	Home Side
Tenofovir	Clinic Back	-	0.97 (<0.0001) 0.97 (0.93, 0.99) -0.02 (-0.30, 0.26) 20	0.96 (<0.0001) 0.96 (0.87, 0.99) 0.02 (-0.31, 0.36) 11	0.96 (<0.0001) 0.96 (0.85, 0.99) 0.04 (-0.31, 0.39) 11
	Clinic Side	0.89 (<0.0001) 0.87 (0.70, 0.95) -0.05 (-0.28, 0.19) 18	-	0.95 (<0.0001) 0.95 (0.82, 0.99) 0.06 (-0.33, 0.44) 11	0.99 (<0.0001) 0.98 (0.94, 0.99) 0.08 (-0.11, 0.26) 11
	Home Back	0.92 (0.0001) 0.92 (0.73, 0.98) -0.02 (-0.32, 0.28) 11	0.86 (0.002) 0.84 (0.51, 0.95) 0.03 (-0.29, 0.34) 10	-	0.97 (<0.0001) 0.97 (0.91, 0.99) 0.02 (-0.28, 0.32) 12
	Home Side	0.85 (0.001) 0.83 (0.51, 0.95) -0.05 (-0.44, 0.34) 11	0.91 (0.0003) 0.90 (0.66, 0.97) 0.03 (-0.21, 0.26) 10	0.96 (<0.0001) 0.94 (0.84, 0.98) -0.02 (-0.24, 0.20) 12	-