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Measuring adherence to antiretroviral therapy via hair concentrations in India

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Abstract

Background: Objective adherence measures are of increasing interest in antiretroviral treatment (ART) monitoring. Hair ART levels predict virologic suppression and hair is easy to collect and store. No prior study has examined hair levels in an India-based cohort or laboratory.

Methods: Small hair samples were collected from HIV-positive participants on either efavirenz-based or nevirapine-based ART in a South India-based study. Hair samples were split and analyzed for efavirenz or nevirapine in the UCSF-based Hair Analytical Laboratory (HAL) and the Division of Nutrition-analytic lab based at St. John's Research Institute (SJRI), Bangalore, India using liquid chromatography/tandem-mass-spectrometry. Agreement (using Bland-Altman methods) and rank correlation between the two laboratories' hair levels were calculated. Rank correlation between self-reported adherence (SRA) over the prior month using a visual analog scale and hair ART levels was calculated.

Results: Among 75 participants (38 on nevirapine; 37 on efavirenz), the correlation between nevirapine levels generated by the two laboratories was 0.66 ($p < 0.0001$) and between efavirenz levels was 0.87 ($p < 0.0001$). Measurements from SJRI were usually within 20% of those from the

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UCSF HAL. SRA was essentially uncorrelated with hair ARV levels for either drug (all correlations<0.04). Hair levels showed variability in adherence although SRA was >85% in all participants.

Conclusions: Hair ART levels measured by both an India-based laboratory and the standard U.S.-based laboratory showed generally high agreement and correlation, demonstrating local capacity. As in many other cohorts, hair ART levels and SRA were not well-correlated, likely indicating limitations in self-report and the need for objective adherence monitoring in resource-limited settings.

Keywords

Hair levels; India; HIV; adherence; antiretroviral treatment; self-report; local capacity

INTRODUCTION:

Adequate adherence to antiretroviral therapy (ART) is essential to achieving optimal outcomes. In pre-exposure prophylaxis (PrEP) trials, pharmacologic measures of adherence - where drug levels were measured in a biomatrix such as plasma or cells- were critical to study interpretation,[1] far exceeding self-reported adherence in predicting outcomes.[2,3] Despite the increasing use of drug level monitoring in PrEP demonstration projects or roll-out programs, the use of pharmacologic measures to assess adherence in the context of HIV treatment is rare. Virologic failure is the most common way to objectively diagnose low adherence to ART. However, by the time virologic failure has developed on ART, opportunities for adherence intervention have been lost. There is therefore burgeoning interest in pharmacologic adherence monitoring for ART, if it can be performed readily and economically, to avert virologic resistance and the need for second or third-line regimens.[4]

As ART is rolled-out in resource-limited settings (RLS), tools to monitor adherence or other treatment parameters that are practical, low-cost and performed locally should be developed and deployed. The use of hair concentrations of antiretrovirals (ARVs) as objective metrics of adherence has some advantages in RLS, including that hair is collected noninvasively and can be stored and shipped without a cold chain or biohazardous precautions.[5] Our group has shown that hair ART concentrations are associated with virologic outcomes in multiple cohorts[6–14] and in a clinical trial[15] demonstrating the pharmacodynamic relevance of hair ARV monitoring. However, adherence monitoring via hair concentrations has never been examined in India, despite a massive scale-up in ART access across the country.[16] Moreover, U.S.-based analytic laboratories have typically performed the hair ARV assays for studies based in Africa and other RLS. This study examines adherence to ART via hair concentrations in an India-based cohort of people living with HIV for the first time. Moreover, to help expand the use of this tool in the Indian context, we examine the level of agreement and correlation between hair ARV levels performed in an India-based analytical laboratory to those performed in a certified U.S.-based laboratory.

METHODS:

Study Population:

The Tel-Me-Box (TMB) study is designed to validate a new low-cost wireless adherence monitoring device as an innovative monitoring tool to assess ART adherence and predict treatment outcomes among Indian people living with HIV (PLWH). This study recruits participants from two urban government ART clinics in Karnataka, India. All participants enrolled in TMB are at least 18 years of age, HIV-positive, and on ART. Self-reported adherence is measured using a visual analog scale[17,18] to assess percent of pills taken in the past month. To ensure sufficient variability in adherence among enrollees, one-third of TMB participants are required to be adherence-challenged at their eligibility screening visit i.e. self-report of at least 10% missed ART doses or a >2 day treatment interruption in the past 3 months. The baseline visit in TMB occurs one month after the screening visit.

Hair samples are collected at the baseline visit and every 6 months over a total of 24 months using previously published methods.[19] At the baseline visit, the first 75 participants enrolled in TMB had larger hair samples collected (~100 strands instead of the usual 50 strands) in order to perform ARV testing both in a U.S.-based and India-based laboratory. The baseline visits for these 75 participants took place between November 2017 and April 2018 and the current study examines hair ARV concentrations among these 75 enrollees at these visits. We planned this substudy to include those with baseline visits in the period noted above, with an expectation that this would be at least 50 participants. The actual number was 75, and these happened to be almost evenly split between those taking nevirapine and efavirenz (one person on neither drug, but on atazanavir, was excluded). Because this is a descriptive, rather than hypothesis-testing study, calculation of power was not applicable.

This study was approved by the Institutional Review Boards of the University of California, San Francisco (UCSF), St. John's Medical College, Bangalore, India and cleared by the Health Ministry Screening Committee (HMSC) of the government of India.

Laboratory procedures:

The most commonly used ARVs in the Indian setting are efavirenz (EFV)[20] and nevirapine (NVP), usually in a fixed dose combination with two nucleoside reverse transcriptase inhibitors (NRTIs). Hair samples collected in TMB were split into two parts for NVP or EFV measurement in both the Hair Analytical Laboratory (HAL) at UCSF and in the analytical laboratory of the Division of Nutrition at SJRI, Bangalore, India. The UCSF-based HAL has developed and reported on methods to analyze EFV[21] and NVP[14] in small hair samples. NVP is extracted from hair using methanol : trifluoroacetic acid (9:1) and EFV is extracted using 100% methanol with subsequent quantification of drug levels using liquid chromatography/tandem mass spectrometry (LC-MS/MS). The HAL methods have been validated from 0.05 to 20 nanograms/milligrams (ng/mg) hair for EFV and 0.25 to 100 ng/mg hair for NVP with good linearity (R^2>0.99) and reproducibility (percent coefficients of variation (%CV)<15%). HAL assays have been peer validated by the National Institutes of Health-based Division of AIDS' Clinical Pharmacology and Quality Assurance (CPQA) program.[22]

The analytical laboratory at the Division of Nutrition in SJRI, Bangalore, India, developed and validated methods to analyze NVP and EFV in small hair samples for the TMB study. Methods were similar to those developed in the HAL except that modified extraction and LC-MS/MS (Agilent 6460) procedures were used to quantify both drugs simultaneously in a single protocol. Both NVP and EFV were extracted using 100% methanol. Hair samples were incubated at 37 °C in a shaking water bath overnight (>14 hrs) and dried at 40°C for 3 hrs in a vacuum concentrator (Labconco, MO) after which 1 mL of 50 mM ammonium acetate (pH 8.5) and 20 μL of internal standard (IS) mixture (Efavirenz-d4 and Nevirapine-d3) were added and vortex mixed for 1 min.[21] MTBE: ethyl acetate (1:1) solution was then added to each sample and again vortex mixed for 1 min, followed by centrifugation at 3000 rpm for 10 min. The upper organic layer was transferred to another tube and dried in a vacuum concentrator. The dried residues were reconstituted with 300 μL of 100% methanol and analyzed by LC-MS/MS. Both NVP and EFV drugs were quantified simultaneously in a single run using electrospray ionization (ESI) in positive mode. The drugs were separated on a C18 column (Pursuit XRs 5 C18 column, 50 × 4.6 mm,5 μm particle size, Agilent Technologies), maintained at 40°C with mobile phase A composed of methanol/water (10/90) (*v*/*v*) and B composed of 5 mM ammonium formate buffer in 100% methanol (adjusted to pH 5.5 by acetic acid). The flow rate was set at 0.8 mL/min. The total run time for EFV and NVP was 10 min. The gas temperature (300°C), gas flow (12 L/min), capillary voltage (4000V) and nebulizer pressure (40 psi) were similar to that of the method developed by Theron et al.[23] Agilent Technologies MassHunter Workstation Software (Version B.07.00, 2014) was used for data collection and quantitative analysis. Standard curves were linear in the range of 0.05– 500 ng for both NVP and EFV drugs with good linearity and reproducibility. Intra and inter assay %CVs were 3.99 and 6.90% for EFV and 1.09 and 1.37% for NVP.

Statistical analysis:

To compare the ARV levels in hair from the U.S. and India based laboratories, we calculated the Spearman rank correlation between NVP and EFV levels generated by the two laboratories. Agreement between hair NVP and EFV concentrations in each laboratory was calculated using Bland-Altman methods.[24] We estimated levels of adherence to the ART regimens in TMB participants based on concentration of NVP and EFV associated with virologic success in the Women's Interagency HIV Study (WIHS).[14,25] Finally, Spearman rank correlations assessed the relationship between self-reported adherence over the past month and ARV concentrations in hair.

RESULTS:

Study Population:

Table 1 shows the demographics of the first 75 participants in the TMB study. Over 50% of the participants were women; the median age was 41 years; 61.3% were married; and 72% were employed. Approximately half of participants (38) were on NVP-based ART and the remainder were on EFV-based ART. The acceptability rate for hair collection at the baseline visit for these 75 participants was 100%. Most participants reported perfect adherence over

the past month (76% of NVP users and 62% of EFV users), with the remainder reporting taking at least 85% of their doses.

Comparison of hair NVP and EFV levels in the two laboratories:

Figure 1 shows the correlation between NVP and EFV hair levels generated by the two laboratories. The correlation between NVP levels generated by the two assays was 0.66 ($p < 0.0001$). The correlation between the EFV levels generated by the two assays was 0.87 ($p < 0.0001$). The analysis of the differences between log-transformed values in the NVP hair samples using Bland-Altman methods[24] suggested that 95% of the India lab values would fall within 61% below and 141% above the UCSF HAL-generated value.[24] The analysis of the differences between log-transformed values in the EFV hair samples suggested that 95% of the India lab values would fall within 66% below and 89% above the UCSF HAL-generated value.[24]

Correlations of hair levels with self-reported adherence:

Self-reported adherence was essentially uncorrelated with drug levels in hair for either drug measured by either lab (all rank correlations < 0.04). Of note, approximately 25% of individuals on NVP and EFV had levels predicted to be associated with virologic nonsuppression in the WIHS (58 ng/mg hair and 6 ng/mg hair, respectively),[14,25] suggesting inadequate adherence.

DISCUSSION:

This paper examines hair levels as objective markers of antiretroviral adherence among people living with HIV on ART in India for the first time, further exploring the transfer of the hair testing methodology to an India-based laboratory. We found moderate (higher for efavirenz) levels of agreement and correlation between the hair ARV concentrations measured in the India-based laboratory to those measured in the U.S.-based laboratory (the UCSF HAL[26]), whose assays are reviewed by the Clinical Pharmacology and Quality Assurance program.[22] Moreover, as in previous studies, we found that self-reported adherence was not well-correlated with an objective metric of adherence using hair levels.[19,27–31]

To truly deploy objective adherence monitoring to HIV treatment and prevention in RLS, local capacity to assay ARV drug levels in different biomatrices must be demonstrated and scaled-up in these settings. An objective adherence assay may help avert virologic failure and drug resistance by providing monitoring between less frequent viral load measurements in RLS.[32] Moreover, in many settings, the return of viral load results from public health laboratories requires a substantial turnaround time, thus making a locally-performed objective adherence metric particularly useful. Hair assays for multiple studies around the world have generally been performed in U.S.-based laboratories, which prolongs time for results. This study shows for the first time the development and validation of methods to measure commonly-used ARVs in RLS among people living with HIV in an India-based laboratory. The correlation and agreement between hair NVP and EFV levels measured in each laboratory were moderate (higher for efavirenz) and ongoing work will determine

whether the hair levels measured by the India-based laboratory are predictive of virologic suppression

Of particular note, despite the TMB study attempting to enroll participants with wide variability in adherence at the screening visit, and despite hair levels reflecting such variability, self-reported adherence was still high among participants at their baseline visit (one month after screening), with all participants reporting ≥ 85% adherence over the past month. This discrepancy between self-reported adherence and objective adherence metrics has been observed in multiple HIV prevention and treatment settings,[1–3,33–37] likely reflecting social desirability bias when reporting adherence to providers. Social desirability bias may be more prominent in RLS,[19] providing further evidence for the value of using objective adherence monitoring in RLS.

The limitations of this study are its small sample size and data gathered from two large government ART clinics in one state in India, limiting generalizability. The combined method employed by the India-based laboratory for both nevirapine and efavirenz is more efficient and feasible, but may limit accuracy for nevirapine. The higher level of agreement and correlation between hair efavirenz levels measured in the two laboratories portends well for the India-lab based efavirenz assay. Further work to analyze the relationship between hair levels analyzed by both labs as a predictor of future virologic suppression will be conducted as the study progresses to ensure that the new method yields predictive utility for virologic suppression similar to that seen in previous studies using hair levels.[6–15] Of note, with increasing roll out of integrase inhibitors worldwide, such as dolutegravir (DTG), and the availability of a DTG hair assay in the HAL,[38] translating the DTG assay to RLS will be similarly important..

In conclusion, we show for the first time the potential utility of hair levels monitoring for ART adherence in an India-based treatment setting and demonstrate local capacity building for the use of this adherence-monitoring tool. Building local capacity for measuring adherence objectively, rather than relying on shipment of samples to U.S.-based laboratories, will expedite the roll-out of the tool. Hair collection may have particular advantages in RLS due to the ease of collection and storage.[5] Further work to develop lower-cost hair assays and low-cost, point-of-care urine-based assays[39,40] to measure adherence in commonly-used ARVs in RLS[41] is underway. Further dissemination of hair assay methods, and objective adherence monitoring on ART in international settings, is warranted.

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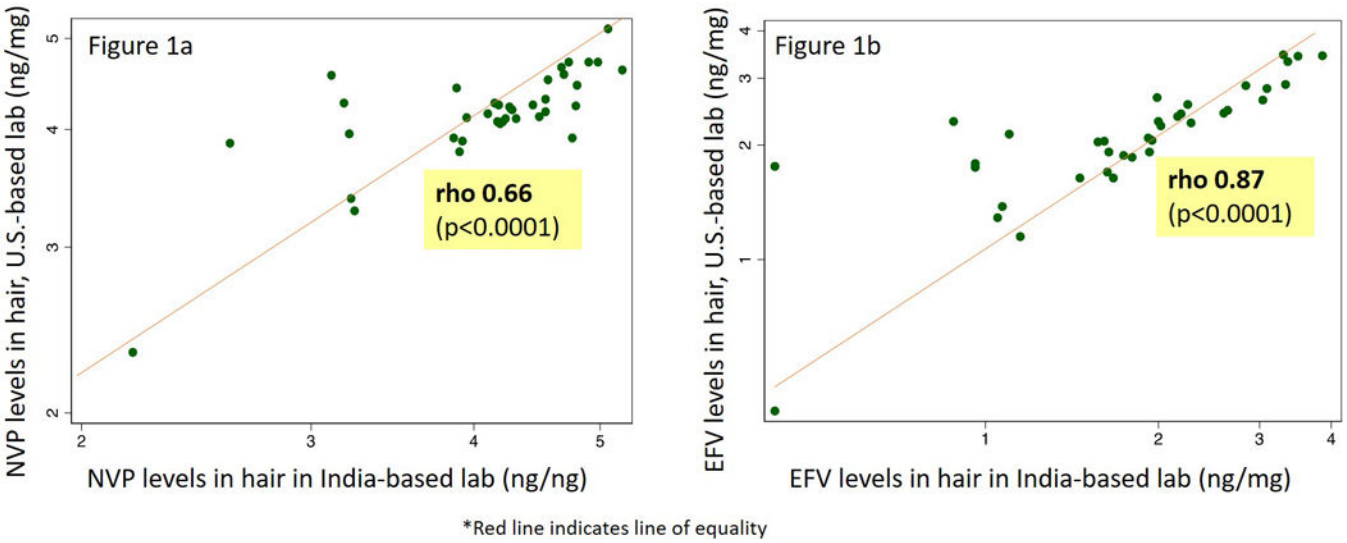

Figure 1:

Rank correlation between NVP hair levels (Figure 1a) and EFV hair levels (Figure 1b) measured by India-based SJRI laboratory compared to UCSF HAL.

TABLE 1:

Demographics of participants in TMB hair validation substudy (n=75)

Characteristic	n	%
Age, mean (SD), years	40.9	(8.3)
Female sex	38	50.7
Marital status		
Married Widowed Divorced/separated Single	46 20 4 5	61.3 26.7 5.3 6.7
Employed	54	72.0
Education		
<4 years	12	16.0
4–9 years	20	26.7
10 years	26	34.7
>10 years	17	22.7
Hindu religion	70	93.3
On NVP-based regimen	38	50.7
NVP hair level, HAL, median (range)	67.0 ng/mg	(10.2–168.0)
NVP level, Kurpad, median (range)	69.9 ng/mg	(8.9–181.6)
On EFV-based regimen	37	49.3
EFV hair level, HAL, median (range)	8.5 ng/mg	(1.5–31.8)
EFV level, Kurpad, median (range)	6.9 ng/mg	(1.5–47.5)
Percent reporting perfect adherence (100%) to ART over past month	29 23	76% NVP 62% EFV