Measuring Intermittent and Daily PrEP Adherence by Hair Levels, Self-Report and MEMS Caps Openings

Sanjiv M. Baxi[1], Albert Liu[2], Peter Bacchetti[3], Gaudensia Mutua[4], Eduard Joachim Sanders[5], Freddie M. Kibengo[6], Jessica E. Haberer[7], James Rooney[8], Frances Priddy[9], Monica Gandhi[1]

[1]HIV/AIDS and Infectious Diseases Divisions, University of California San Francisco (UCSF), San Francisco, CA, U.S., [2]San Francisco Department of Public Health, San Francisco, CA, U.S.,[3]Epidemiology & Biostatistics, UCSF,U.S,[4]Kenya AIDS Vaccine Initiative, Nairobi, Kenya,[5]Centre for Geographic Medicine Research Coast, Kilifi, Kenya,[6]Medical Research Council (MRC)/Uganda Virus Research Institute (UVRI), Entebbe, Uganda,[7]Infectious Diseases, Center for Global Health, Boston, MA, U.S.,[8]Gilead Sciences, Foster City, CA, U.S.,[9]International AIDS Vaccine Initiative, New York, NY, U.S.

For additional information:
Sanjiv M. Baxi, MS, MD
513 Parnassus, Med Sci, S380
San Francisco, CA 94143, USA
Tel: +1-(415)-476-9363
Fax: +1-(415)-476-9364
Email: sanjiv.baxi@ucsf.edu

#953

BACKGROUND

- **Pre-exposure prophylaxis** (**PrEP**) with tenofovir/emtricitabine (TFV/FTC) is effective with once daily dosing (iPrEx, Partners PrEP, TDF2, Bangkok TFV Study)
- **Adherence to PrEP is paramount**, but traditional measures of medication administration (e.g. self-report) can be biased ("social desirability", recall)
- Plasma and intracellular drug levels have been critical to trial interpretation (iPrEx, FEMPrEP, VOICE) but also have limitations (plasma→ short-term measure; intracellular→ difficult to process, assay; both require expertise to collect)
- **Hair ARV concentrations** measure long-term exposure to ARVs; hair easy to collect and assay; strong relationship between TFV dose and hair level (Liu, PLoS ONE 2014)
- Intermittent PrEP demonstrates safety and tolerability
- Important to understand correlation among **pharmacologic measures of adherence/exposure** (plasma, intracellular and hair levels) and between **traditional measures** (e.g. self-report, medication electronic monitoring system (MEMS) caps opening) when incorporating into PrEP trials, demonstration projects and real use

METHODS

Population. Two randomized controlled phase II PrEP trials with TFV/FTC as daily or intermittent (Mondays, Fridays, within 2 hours post-coital other days; all pills were counted) PrEP (vs placebo) in Uganda (HIV discordant couples, Kibengo, PLoS ONE 2013) and Kenya (MSM, Mutua, PLoS ONE 2012); participants in active arms (n=88) were included in this analysis

Outcomes. Collected at 8 weeks and 16 weeks after enrollment
- Pharmacologic measures: Levels of TFV and FTC in hair (**Figure 1**), plasma and peripheral blood mononuclear cells (PBMCs)- latter available in only ½ participants
- Traditional measures: Number of pills taken over month by self-report; number of pills recorded via MEMS caps openings (all pills counted, irrespective of timing)

Retained Predictors (**Table 1** - retained only if significant on univariate analysis):
Continuous: Age (years), height (cm), weight (kg), serum alanine aminotransferase (ALT, IU/L) and aspartate aminotransferase (AST, IU/L), serum creatinine (mg/dL), calculated creatinine clearance (CrCl, mL/min), hemoglobin (g/dL)
Categorical: Sex at birth, dosing frequency, khat or marijuana use over past 28 days

Statistical Analysis. Univariate random intercept linear regression models of each outcome by each predictor; multivariate regression modeling in a forward stepwise manner with predictor variables being retained in final model only if p-value <0·05 (**Table 2**); Pearson correlation coefficients calculated between markers of adherence and scatterplots constructed (**Figure 2**)

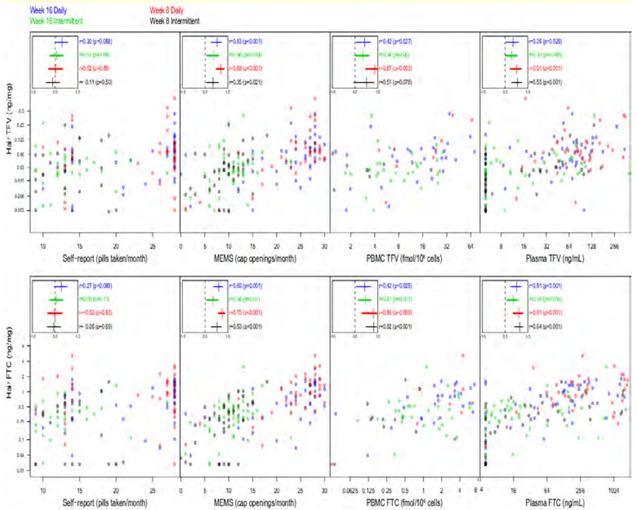
Figure 1a. Example of hair sampling procedure in a participant



Figure 1b: Hair sampling/analysis
(1) small thatch of hair cut close at occipital scalp
(2) distal portion labeled for directionality
(3) methods for extraction and analyses of most ARVs using LC/LC/MS have been described

RESULTS

Figure 2. Correlation of TFV (top panel) and FTC (bottom panel) hair concentrations with self-report, MEMS caps openings, PBMC and plasma drug levels at weeks 8 and 16



RESULTS (continued)

Table 1. Baseline characteristics of active arm participants in the two phase II PrEP trials (n=88 total)

Active arm group (mean ± SD unless indicated)	**Daily PrEP (n=42)**	**Intermittent PrEP (n=46)**
Age	29·4 ± 6·98	29·6 ± 7·38
Women, n (%)	12·0 (28·6)	11·0 (23·9)
Weight (kg)	64·1 ± 12·0	61·2 ± 7·81
Height (cm)	167 ± 10·1	168 ± 9·04
Khat use, n (%)	4·0 (9·5)	7·0 (15·2)
Marijuana use, n (%)	2·0 (4·8)	6·0 (13·0)
Serum ALT (IU/L)	19·2 ± 9·01	21·0 ± 9·74
Serum AST (IU/L)	24·5 ± 6·05	26·4 ± 11·9
Creatinine (µmol/L)	78·1 ± 17·7	78·5 ± 16·1
Calculated creatinine clearance (mL/min)	111 ± 28·3	107 ± 32·4
Hemoglobin (g/dL)	14·6 ± 1·63	14·7 ± 1·87

Table 2. Multivariate regression models with final factors associated with pharmacologic adherence measures (hair, plasma, intracellular) using forward stepwise selection

Biologic measure	**Predictor**	**Fold-effect (95% CI), p-value**
Hair TFV (n=172)	MEMS caps openings (per 10% increase)	1·08 (1·06-1·10), p<0·001
Hair FTC (n=172)	MEMS (per 10% increase)	1·11 (1·09-1·13), p<0·001
	Height (per 5 cm increase)	1·14 (1·06-1·23), p=0·001
	Khat (in past 28 days)	0·54 (0·36-0·82), p=0·004
	Marijuana use (in past 28 days)	0·63 (0·40-0·99), p=0·048
Plasma TFV (n=170)	MEMS (per 10% increase)	1·20 (1·15-1·25, p<0·001
	Per 10% decrease in CrCl	1·15 (1·02-1·28), p=0·020
Plasma FTC (n=170)	MEMS (per 10% increase)	1·25 (1·18-1·32), p<0·001
	Per 10% decrease in CrCl	1·19 (1·02-1·40), p=0·027
PBMC TFV (n=82)	MEMS (per 10% increase)	1·15 (1·10-1·20), p<0·001
	Site (lower in Kenya vs Uganda, controlling for MEMS)	0·52 (0·31-0·85), p=0·010
PBMC FTC (n=82)	MEMS (per 10% increase)	1·23 (1·17-1·28), p<0·001
	Weight (per 5 kg increase)	0·88 (0·76-1·01), p=0·056

DISCUSSION

- Demonstrates utility of hair TFV and FTC levels as adherence and exposure measures in PrEP trials
  - 172 hair samples from 88 active arm participants analyzed
  - **Hair collection highly acceptable** (100% at week 8, 96% at week 16) and feasible in these African PrEP studies
- **First study** to assess the relationship between multiple pharmacologic measures, self-reported consumption and MEMS caps openings in the context of PrEP
  - **Hair levels and MEMS counts were strongly associated**: for every 10% increase in MEMS caps openings, TFV and FTC hair levels increased by 8% and 10%; plasma and PBMC levels also associated with MEMS
  - Hair levels and self-report only weakly associated
- **First study** to examine hair TFV/FTC as a marker of drug exposure in daily vs intermittent dosing of PrEP
  - Hair levels for those on daily doses averaged >2x (2·6x for FTC; 2·1x for TFV) those on intermittent dosing, showing **dose-relationship**

CONCLUSIONS

- Assessing adherence to PrEP in trials and real-life **via the measurement of TFV/FTC concentrations in hair** may be a promising alternative to self-report or plasma/ PBMC drug levels (all of which have limitations)
- **Hair collection highly acceptable, feasible (98%) in these two African PrEP trials**
- Hair, plasma and PBMC TFV/FTC concentrations strongly associated with pills taken as assessed by MEMS caps openings
- **Poor correlation between self report of pills and biological markers of TFV/FTC exposure, highlighting limitations of self-report in PrEP**
- Studies evaluating association of hair TFV/FTC levels with PrEP efficacy needed

ACKNOWLEDGEMENTS

NIAID/NIH RO1 AI098472 (M·G·)

NIMH/NIH T32 MH-19105 (S·M·B·)