University of California
San Francisco

Hair Analytical Laboratory (HAL)
University of California, San Francisco (UCSF)

Panel Discussion

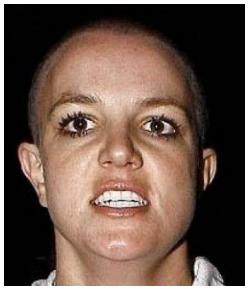
Innovative Measures of Adherence: New Thinking, New Approaches

Monica Gandhi MD, MPH
Professor of Medicine
Division of HIV, Infectious Diseases, and Global Medicine

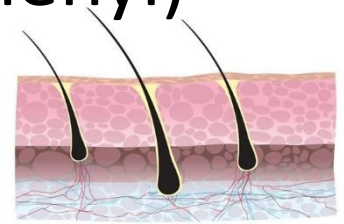
Outline of talk

- Why hair?
- Hair levels of ARVs
  - Treatment
  - PrEP
  - Monitor toxicity
- Pros and cons

Hair it is! The precedent

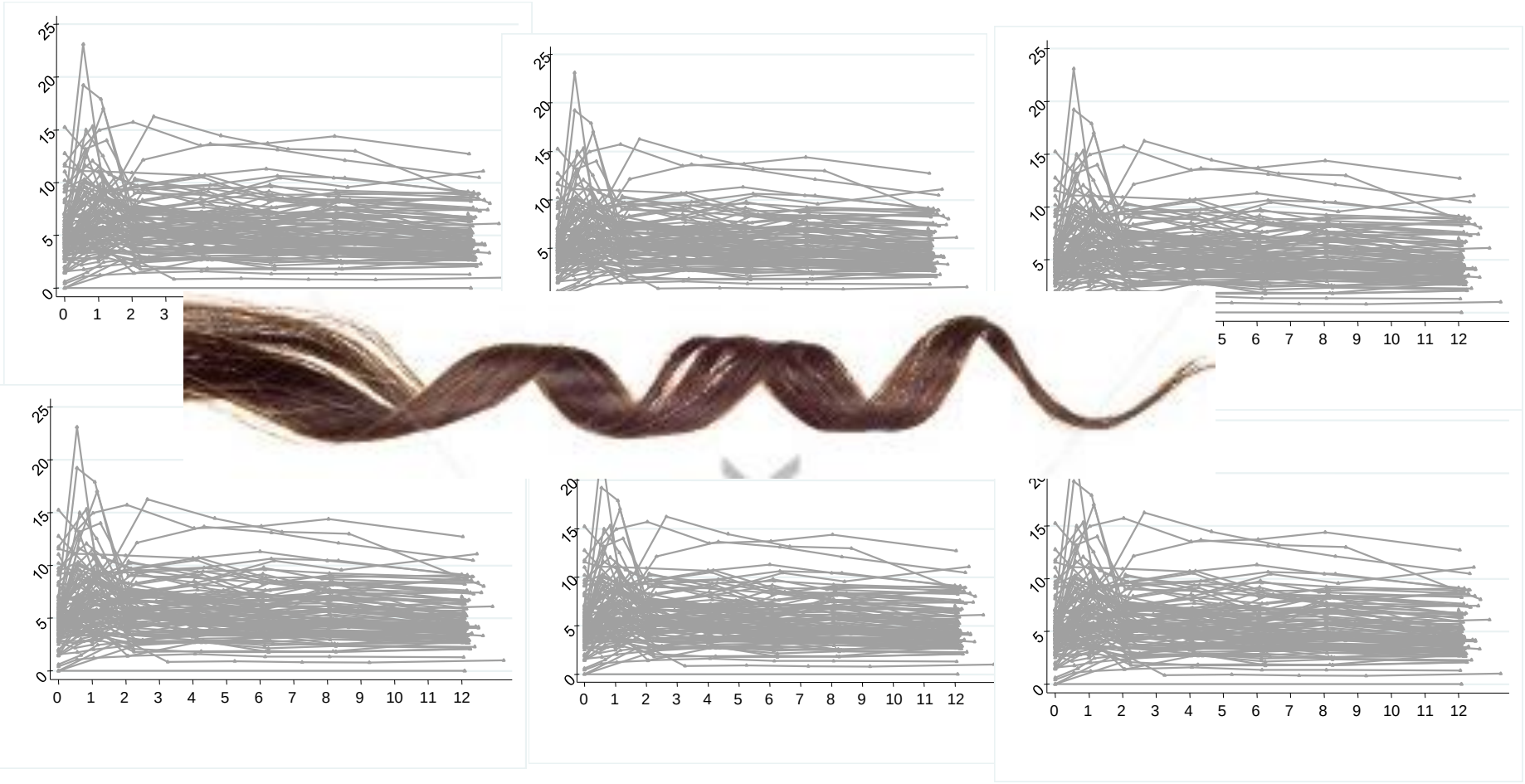


- Substance use
- Forensic analysis
  - Lead poisoning (Beethoven)
  - Arsenic (Napoleon)
  - Thallium, mercury, antimony (Newton)
- Epilepsy and antipsychotic medications
- Organochlorine pollutants (DDT and biphenyl)
- Stress – cortisol levels



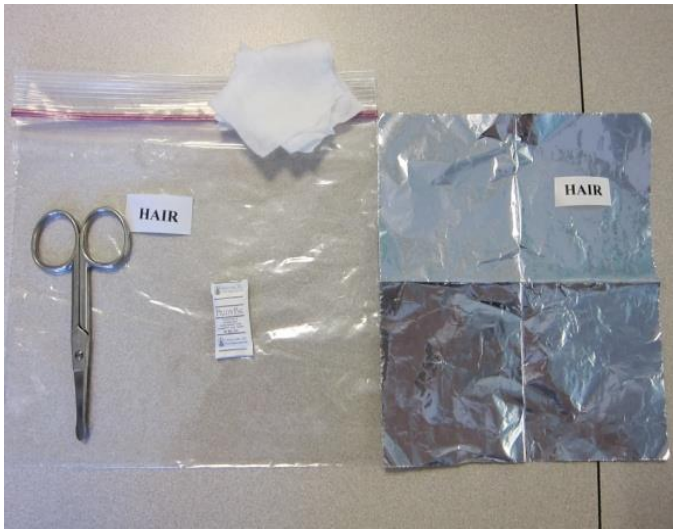
Beumer JH. Int J Clin Practice 2001;Williams J Therap. Drug Monitoring 2001;Covaci A. Chemospheres 2002; Flanagan RJ. Toxicol Rev 2005; Lugli A. Adv Anat Pathol. 2011; Thieme D. Forensic Sci Int. Mar 2007; Schoeman K.TDM 2010; Moller M. TDM 2010; Pelander A. TDM 2008; Karlen J. BMC Clin Pathol. 2011; Eisenhut M. Tuberc Res Treat. 2012; Gandhi M. Ann Intern Med 2002; Baciu T. Analytica Chimica Acta 2015

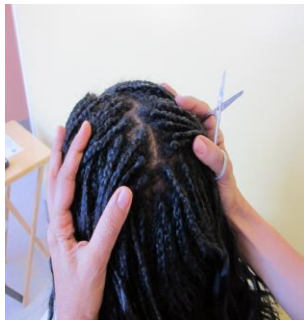
Hair measures cumulative exposure: AUC of AUCs



Easy six step process to collect

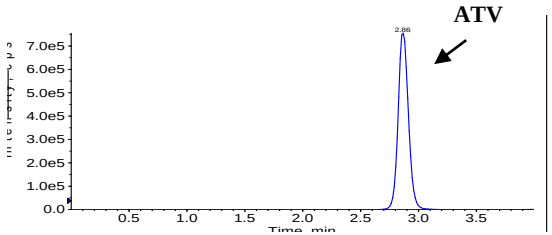
- Takes about 2 minutes of time
- Tiny snip of hair cut from back of the head, cheap materials
- Painless – no need for blood draw (children)





Development of hair assays

- UCSF Hair Analytical Laboratory (HAL)
- Shaved heads of patients on different ARVs, suppressed, adherent
- Large quantities –assay optimization
  - Finely chop (pulverization)
  - Organic solvent and then extraction
  - Injection into liquid chromatography/tandem mass-spectrometry
  - 10-20 strands required for most (50-100 for TFV); only 1 strand for nevirapine
  - Good linearity (R^2>0.99), reproducibility (CV <15%); working with DAIDS-supported CPQA



Give Your Hair for Science

Huang Y. Rapid Comm. Mass Spec 2008; Huang Y. Ana & Bioan Chem 2011; Phung Rapid Comm Mass Spec 2018

Antiretrovirals we can measure in hair

Efavirenz

Atazanavir

Nevirapine

Lopinavir

In development: cabotegravir, dapivirine

20-30 strands

Ritonavir

Darunavir

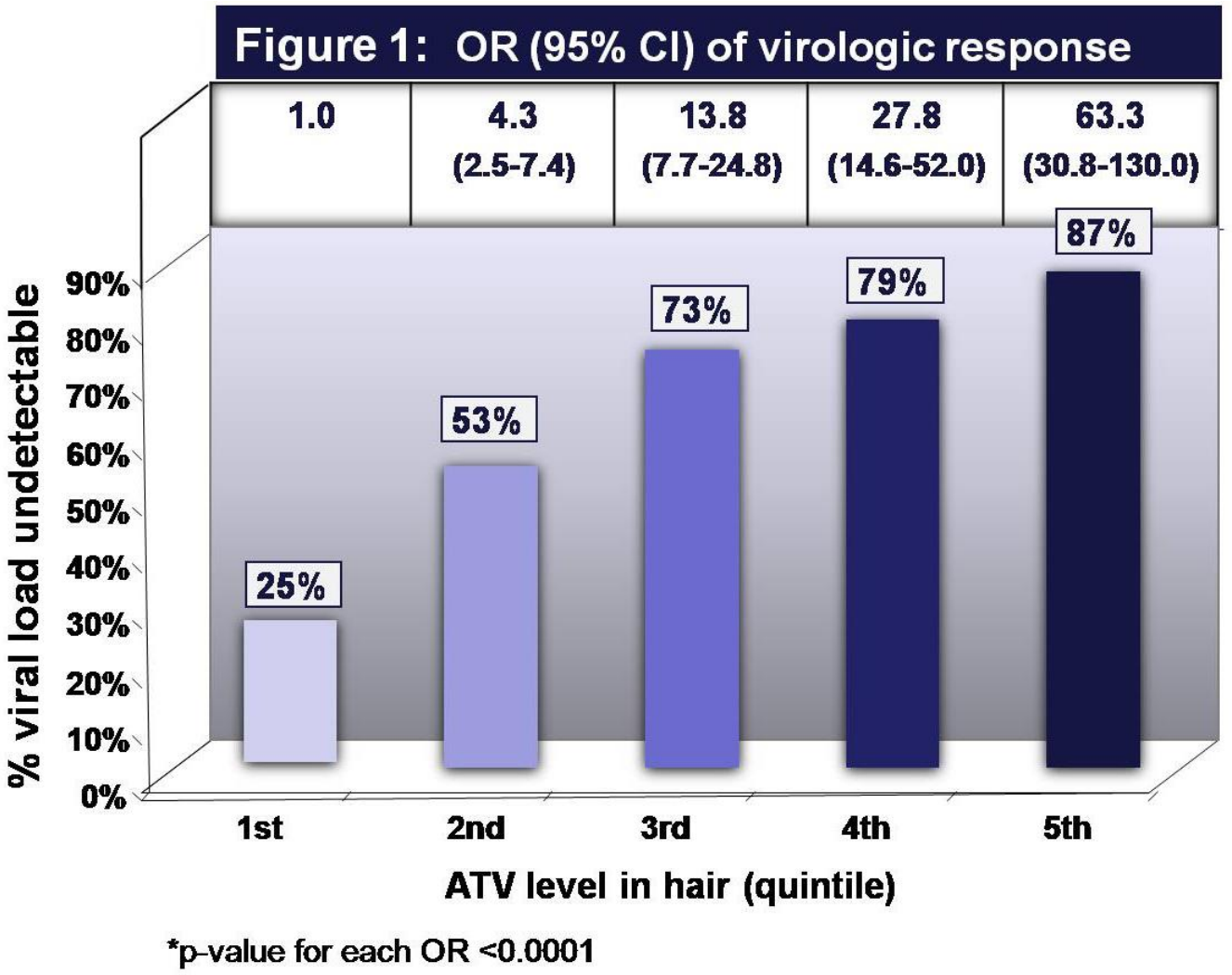
Raltegravir

Dolutegravir

50-100 strands

Tenofovir (in both TDF, TAF) and Emtricitabine

Hair ARV levels in treatment

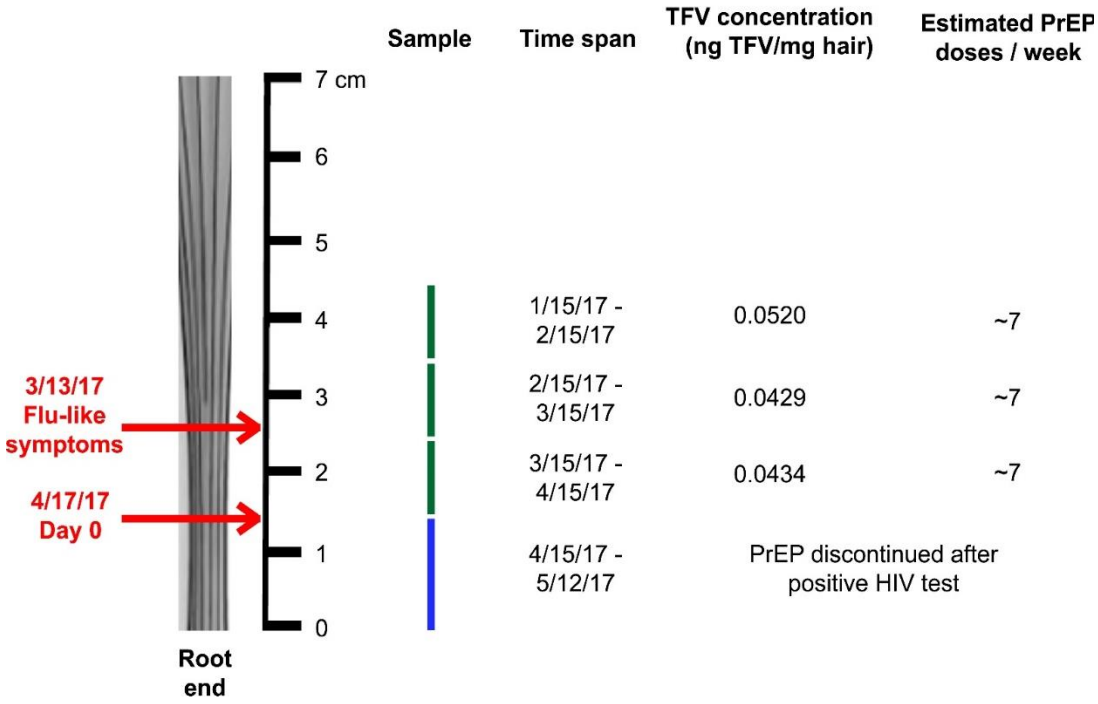


- **Hair strongest independent predictor of virologic response, in MV models in multiple cohorts[1-9], and a clinical trial[10]= pharmacodynamic relevance**
- Hair levels also increase following adherence interventions[11, 12]

[1]Gandhi AIDS 2009; [2]Gandhi CID 2011; [3]Baxi PLOS One 2015; [4]Van Zyl G. JAIDS 2011; Prasitsuebsai W. ARHR 2015; Pintye J. JAIDS 2017; [6]Chawana JAIDS 2017; [8]Tabb AIDS 2018; [9]Koss AIDS 2015; [10]Gandhi CROI 2018; [11]Gwadz AIDS Behav

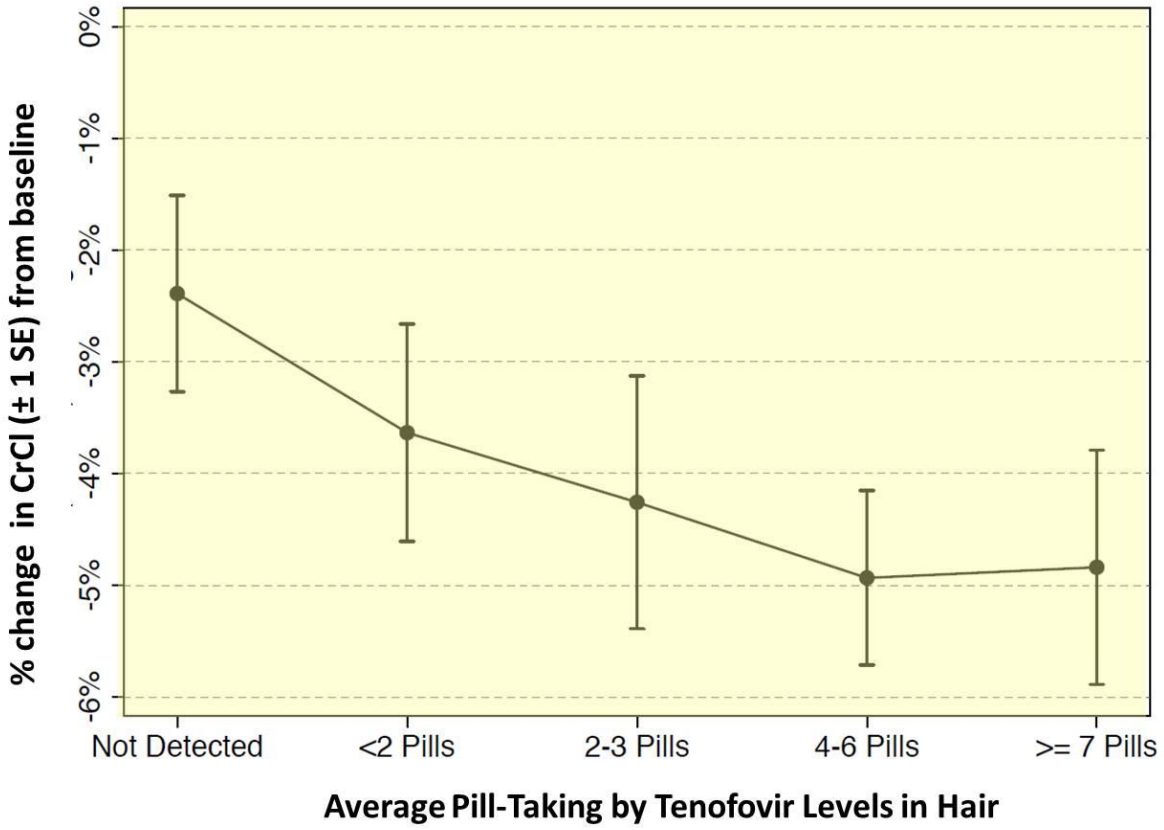
Hair levels in PrEP…and a novel application - Segmental hair analysis

- Hair TFV/FTC levels to analyze PREP adherence in many studies[1-14]
- Patterns of adherence over time may be determined via segmental analysis (measuring TFV/FTC levels in each segment from the scalp) - may be particularly helpful in PrEP failures[13]



[1]Liu PLOS One 2014; [2]Baxi JAIDS 2014; [3]Gandhi JID 2015; [4]Gandhi Lancet HIV 2016; [5]Koss ARHR 2017; [6]Koss CID 2018; [7]Gandhi AIDS 2017; [6]Abaasa AIDS Behav 2017; [9]Seifert JAIDS 2017; [10]Baxi PLOS One 2018; [11]Markowitz JAIDS 2017; [12]Colby CID 2018; [13]Thaden AIDS 2018; [14]Koss AIDS 2018

TFV levels in hair (age, starting CrCl) associated with renal toxicities in PrEP



- Renal function decreased moderately over time on TDF/FTC
- Hair collected q12 weeks on subset
- Higher hair levels of TFV or FTC associated with greater declines in CrCl (daily dosing)
- Age >40 and baseline CrCl <90ml/min also associated with greater declines in CrCl

Gandhi. Lancet HIV 2016; Gandhi AIDS 2017

Pros (long and short of it) of hair levels as adherence/exposure measure

- Hair grows steadily in occiput at rate of ~1cm/month
- Long-term metric of exposure
- Hair shaft therefore becomes a marker of time
- Hair easy and cheap to collect
- No special skills (no phlebotomy)
- Stored at room temperature
- Shipped without biohazard
- Feasible for resource-limited settings
- Not subject to white-coat adherence

Beumer JH. Int J Clin Prac 2001; Gandhi M. Ann Int Med 2002

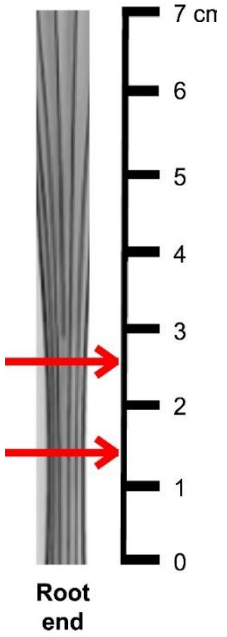
Cons: Acceptability of hair collection variable

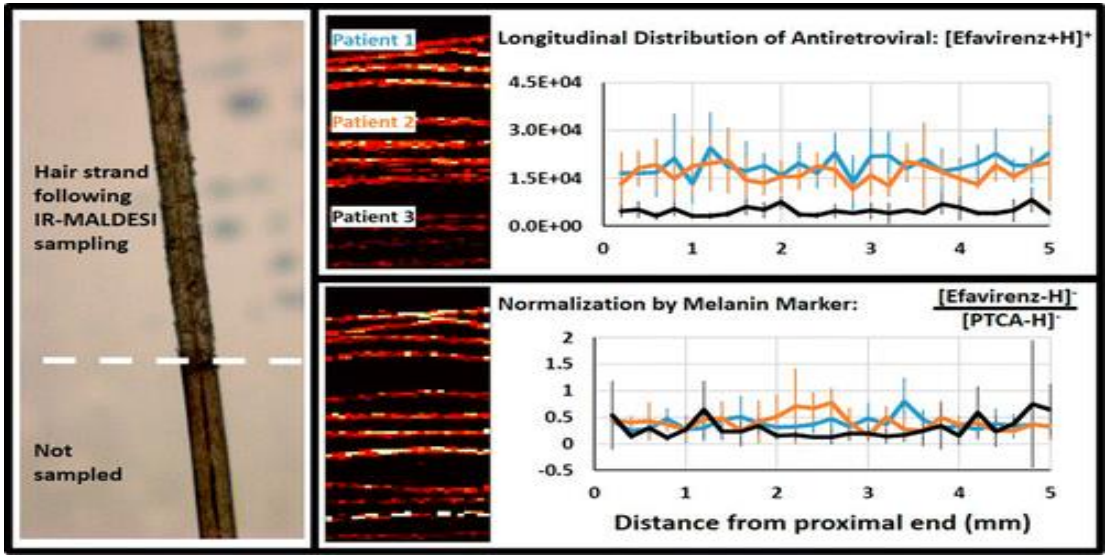
- **Variable**
  - Rural Kenya, Asia, Uganda -Acceptability 95% as marker of adherence[1-3]
  - South Africa qualitative study - high acceptability of hair collection pregnant women, different ethnicities[4]
  - ATN 110, 113: >95% in young diverse MSM in U.S.[5]
  - Lower rates in white MSM -ACTG (~55%)[6]; U.S. PrEP Demo project, (58%)[7,] children in Uganda[8]

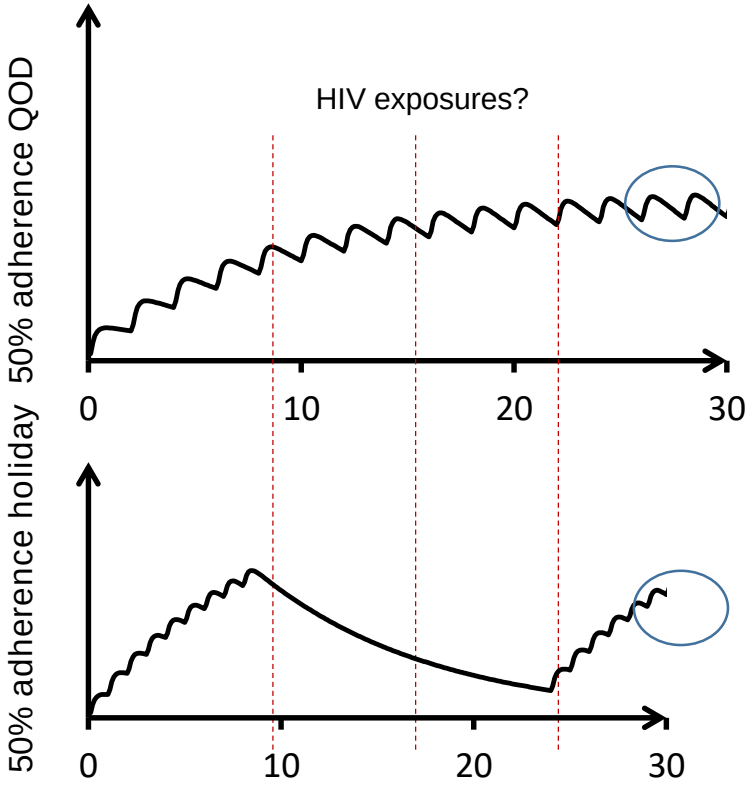
[1]Hickey M. JAIDS 2014; [2]Pintye J. JAIDS 2017; [3]Koss AIDS 2015; [4]Coetzee B. Future Virology 2012; [5]Koss CID 2017; [6]Gandhi CROI 2018; [7]Gandhi AIDS 2017; [8]Olds. AIDS Care. 2015

Cons: Long-term measures and not POC

- Represents average, cannot determine dosing patterns
- Segmental analysis[1] or IR-MALDESI[2] for patterns
- Spectrometry not as fast for POC







Courtesy Pete Anderson, CROI 2016

Thaden AIDS 2018; Rosen..Kashuba. Anal. Chem 2016

CURRENT OPINION

Point-of-care diagnostics: extending the laboratory network to reach the last mile

Paul K. Drain[a,b,c,d] *and Christine Rousseau*[a,e]

Purpose of review

More point-of-care (POC) diagnostic tests are becoming available for HIV diagnosis and treatment in resource-limited settings. These novel technologies have the potential to foster decentralized HIV care and treatment for the benefit of clinical laboratories, HIV clinics, and HIV-infected patients. There continue to be many business, technological, and operational challenges that limit product development and regulatory

- HAL urine immunoassay for TFV abstract #87 (Saturday 11:15am-12:15pm)

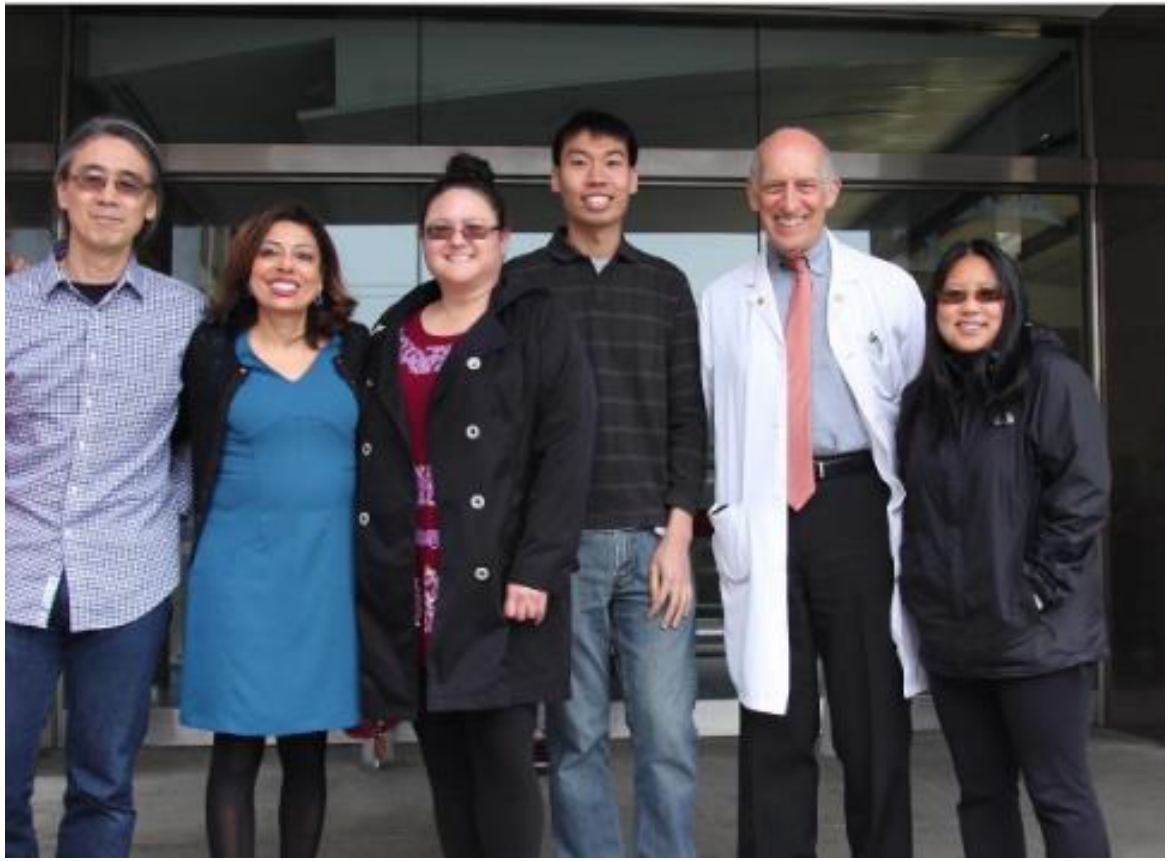
The UCSF Hair Analytical Lab (HAL)

Thanks to
IAPAC Adherence 2018 organizers for invitation

Drs. Jessica Haberer, Jose Castillo-Mancilla, Sara Browne

Diane Havlir MD

The Hair Analytical Lab at UCSF



UCSF
University of California
San Francisco
advancing health worldwide™

Hair Analytical Laboratory (HAL)
University of California, San Francisco (UCSF)