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

Adherence 2018
June 8-10, 2018 • Miami
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

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

Antiretrovirals we can measure in hair

- **Efavirenz**
- **Atazanavir**
- **Nevirapine**
- **Lopinavir**
- **Ritonavir**
- **Darunavir**
- **Raltegravir**
- **Dolutegravir**

*In development: cabotegravir, dapivirine*

- **Tenofovir** (in both TDF, TAF) and **Emtricitabine**

**20-30 strands**

**50-100 strands**
Hair ARV levels in treatment

Figure 1: OR (95% CI) of virologic response

<table>
<thead>
<tr>
<th>ATV level in hair (quintile)</th>
<th>1.0 (2.5-7.4)</th>
<th>13.8 (7.7-24.8)</th>
<th>27.8 (14.6-52.0)</th>
<th>63.3 (30.8-130.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% viral load undetectable</td>
<td>25%</td>
<td>53%</td>
<td>73%</td>
<td>79%</td>
</tr>
</tbody>
</table>

Hair strongest independent predictor of virologic response, in MV models in multiple cohorts, and a clinical trial = pharmacodynamic relevance

Hair levels also increase following adherence interventions

*p-value for each OR <0.0001

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

- Hair TFV/FTC levels to analyze PREP adherence in many studies\textsuperscript{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\textsuperscript{13}

\textsuperscript{1}Liu PLOS One 2014; \textsuperscript{2}Baxi JAIDS 2014; \textsuperscript{3}Gandhi JID 2015; \textsuperscript{4}Gandhi Lancet HIV 2016; \textsuperscript{5}Koss ARHR 2017; \textsuperscript{6}Koss CID 2018; \textsuperscript{7}Gandhi AIDS 2017; \textsuperscript{8}Abaasa AIDS Behav 2017; \textsuperscript{9}Seifert JAIDS 2017; \textsuperscript{10}Baxi PLOS One 2018; \textsuperscript{11}Markowitz JAIDS 2017; \textsuperscript{12}Colby CID 2018; \textsuperscript{13}Thaden AIDS 2018; \textsuperscript{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

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

"HIV exposures?"

50% adherence holiday 50% adherence QOD

Courtesy Pete Anderson, CROI 2016

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

Paul K. Drain\textsuperscript{a, b, c, d} and Christine Rousseau\textsuperscript{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