Point-of-Care Technologies for Supporting HIV Treatment Adherence

Optimizing ART Adherence Panel
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Adherence 2023 · June 11-13 · Puerto Rico
The World Health Organization has declared that more people worldwide would benefit from efforts to improve medication adherence than from the development of new medical treatments.

“Drugs don’t work in patients who don’t take them”

C. Everett Koop

Adherence – we are not the only ones

Adherence Challenges with ARTs

Overall adherence to ART in US

• Among 206,474 adults with HIV treated with ART, majority had suboptimal adherence:
  • 60% had adherence < 90% and 40% had adherence < 80% (McComsey. Adv in Ther. 2021)

Barriers to ART adherence:

• Systematic review of 125 studies identified main barriers to ART adherence
  • Forgetting
  • Being away from home
  • Change to daily routine
  • Depression
  • Alcohol/substance misuse
  • Secrecy/stigma
  • Feeling sick
  • Far distance to clinic
  • Stock outs

Rates of virologic suppression worldwide:

• In adults on ART, 79% suppression at 1 year, 65% by 3 years
• In children/adolescents on ART, 36% suppression at 1 year, 24% at 3 years (Han. Lancet HIV 2021)

Altice, F., et al. Adherence to HIV treatment regimens: systematic literature review and meta-analysis. Patient preference and adherence, 2019
UNAIDS: Major setbacks to HIV response during COVID (TB, malaria, etc.)

| 38.4 million people with HIV (highest), 1.5 million new infections last year, 650K deaths last year, 40.3 million deaths total, only 75% of adults (52%) children have ART access |
How do we measure adherence (point of care)

More Objective Measures

- Pharmacologic measures
  - Pharmacy refill data
- Automatic compilation of dosing history data
- Electronic monitoring
  - Sensor devices (ingested)

More Subjective Measures

- Retrospective questionnaire
- Pill Counts
- Patient diaries
- Self-report

Modified from Vrijens & Urquhart, 2005 Journal of Antimicrobial Chemotherapy.
Pharmacologic measures – important x >12 years

- Pharmacologic adherence measures critical to interpretation of placebo-controlled PrEP trials
- Efficacy of TDF/FTC in iPrEx rose from 44% to an estimated 92% (CI 40, 99%) among those with detectable drug levels (plasma or PBMC)
- Two trials (FEM-PrEP & VOICE) showed no efficacy but was determined only due to measuring tenofovir in plasma

<table>
<thead>
<tr>
<th>Adherence Measure</th>
<th>VOICE</th>
<th>FEM-PrEP</th>
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<tbody>
<tr>
<td>Self-report</td>
<td>91%</td>
<td>95%</td>
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<tr>
<td>Returned pill counts</td>
<td>92%</td>
<td>88%</td>
</tr>
<tr>
<td>Plasma TFV detection</td>
<td>29%</td>
<td>24%</td>
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Grant et al. NEJM 2010; Marrazzo et al. NEJM 2015; Van Damme et al. NEJM 2012; Baeten et al. NEJM 2012; Donnell et al. JAIDS 2014
Need point-of-care metric for ART for real-time feedback (TFV is right drug)

- Backbone of most ART regimens worldwide: formulation of tenofovir (TDF or TAF - 95% of patients worldwide on this, including 19 million in PEPFAR)
- Oral PrEP is tenofovir-based

Point of care adherence assay

Can trigger feedback, viral load test and other adherence interventions

SMS 2-way text
Peer support
Pill boxes
Provider counseling
Motivational interviewing
Differentiated care

References:
Landovitz R. JAIDS 2017; van der Straten AIDS 2015; Koester AIDS Care 2015
LC-MS/MS based pharmacologic metrics for tenofovir & other ART, but not yet point-of-care

- Pharmacologic measures (ART levels in plasma, dried blood spots (DBS), hair)
- Current methods to measure ART drugs in biomatrices involve mainly LC-MS/MS → trained personnel, machines, working on real-time measures
- Tenofovir-emtricitabine intracellularly metabolized so metrics range from short (plasma, urine, FTC-TP) to long (TFV-DP in DBS, TFV in hair)

<table>
<thead>
<tr>
<th>Matrix</th>
<th>ART analyte measured</th>
<th>Analysis platform</th>
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<tbody>
<tr>
<td>Plasma</td>
<td>TFV/FTC</td>
<td>LC-MS/MS(^1-3)</td>
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<tr>
<td>PBMC</td>
<td>TFV-DP/ FTC-TP</td>
<td>LC-MS/MS(^1,4)</td>
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<tr>
<td>DBS</td>
<td>TFV-DP/ FTC-TP</td>
<td>LC-MS/MS(^5-7)</td>
</tr>
<tr>
<td>Hair</td>
<td>TFV/ FTC</td>
<td>LC-MS/MS(^8), IR-MALDESI(^9)</td>
</tr>
<tr>
<td>Urine</td>
<td>TFV</td>
<td>LC-MS/MS(^3, 10-13)</td>
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![Diagram showing TFV-DP in DBS and Hair over time]
Short and Long-Term Adherence Highly Correlated & Predictive of Virologic Suppression

- Adherence behaviors tend to be stable over time (stably low or high)
- FTC-TP (short-term) correlates with TFV-DP (long-term) & predicts future virologic suppression
- Urine TFV correlates with FTC-TP, TFV-DP

Urine TFV predicts DBS TFV-DP levels

FTC-TP level predicts future virologic suppression

Mustanski B et al. CROI 2023; Morrow M. AIDS 2021
URINE POINT-OF-CARE TENOFOVIR TEST
One test is collaboration between UCSF & Abbott

- UCSF Hair Analytical Laboratory (HAL) formed collaboration with Alere™ Rapid Diagnostics in 2015 (now Abbott)- with funding provided by NIH
- First scrutinized molecular structure of TFV (tenofovir- main drug in ART/PrEP) to identify unique derivatives with structural distinction from endogenous nucleotides & developed selective antibody
- UrSure® has another test (purchased by OraSure®)
LC-MS/MS levels closely correlated with ELISA-measured values

- 100% specific (98-100%)
- 96% sensitive (88-99%)
- Precise (%CV<15%)
- ELISA TFV levels highly correlated with those from LC-MS/MS (r=0.95)

Joint patent filed 2020
Lateral flow assay developed

• Directly observed therapy study using 637 samples helped establish test cut-off: Cut-off of 1500ng/ml for TDF correctly classified 98% of those who took dose 24 hrs. ago as adherent\(^1\)
• Urine test now in lateral flow assay as a rapid strip test
• LFA TFV assay 97% accurate vs. LC-MS/MS (n=637), 98% accurate vs ELISA (n=684); tested among transgender men and women, cisgender men and women

\(^1\)Gandhi Eclinical Medicine 2018; Gandhi JAIDS 2019; Spinelli JAIDS 2020; Gandhi AIDS 2020
STUDIES DEMONSTRATING UTILITY OF TEST
CDC study: Adherence Intervention Using Urine Assay Improves VS

- Urine TFV test put into 38 HIV clinics for patients on TLD in Namibia
- Used for participants who did not suppress despite enhanced adherence counseling (EAC) ≥ 3 months
- N=195 enrolled with viral load >1000 copies/mL
- Data available to date:
  - 92% (180/200) virologically suppressed by month 6; p<0.001 (88% by month 3)
  - 86% of participants and 91% of providers agreed/strongly agreed that the urine test should be in care
  - Remarkable as group did not originally suppress after counseling

Viral Suppression by Region in Namibia
6 times higher rate of virologic failure after low urine TFV in San Francisco at Ward 86

- Among PLWH with housing instability in San Francisco (at Ward HIV clinic), 22% with VF
- Urine collected 1-3 months prior to viral load
- Adjusted odds ratio (aOR) 6.00 for future VF with low urine TFV (<1500) (95% CI 1.73-20.75; p=0.005)
- Can use same cut-off for TAF and TDF
- POC test can predict future virologic suppression for people with HIV

Johnson K, CID 2023
In S. Africa and Uganda, our POC test accurately predicts drug-resistance on low barrier regimens

- Among participants with elevated vital load and low genetic barrier regimens (tenofovir-lamivudine-efavirenz)
- Low urine TFV with 100% sensitivity for 2-class resistance
- Positive predictive value 96% for resistance
- Among those on efavirenz; combination of elevated viral load and low tenofovir 100% sensitive for major resistance

Jennings AIDS Res Hum Retro 2022; McCluskey S CID 2023; Hermann L CID 2023
Urine TFV Predicts Adherence Challenges on High Genetic Barrier ART (TLD)

- WHO recommends viral load only every year, virologic failure often missed
- Participants in South Africa
- High specificity (94%; 95% CI: 81%-99%) for virologic suppression
- Urine POC testing predicts virologic suppression on the increasing standard of care (tenofovir lamivudine dolutegravir) in which resistance is uncommon

Van Zyl JAIDS 2022; McCluskey S CID 2023
Urine tenofovir test predicts seroconversion in large PrEP trials (Partners PrEP, iPrEx OLE): negative test in past predicts further HIV infection
PEPFAR Treatment Programs

19 million people on HIV ART

~3.99 million are not suppressed

Monthly urine testing in Namibia took suppression from 0% to 92%

For 14.4 million suppressed, 1 or 2 tests per year

PrEP programs

UNAIDS estimates 10 million to start in next 5 years

(Tests will be less than $2 per test and should be commercially available in 2025; initial costing analysis shows $1,071 per unsuppressed patient)
Presenter: Phelix Okello
Conclusion

- Taggants, sensors & electronic monitors point-of-care too but more expensive
- Pharmacologic measures range from short-term and long-term - DBS, hair, and plasma levels have all been used
- Urine metrics are point-of-care- increase adherence in a pre-and-post trial in Namibia
- Urine easy-to-collect, non-invasive; test is cheap and gives results in 2 minutes; doesn’t need trained personnel (staff often used to urine pregnancy tests)
- Randomized study comparing urine assay-informed counseling vs standard of care in those failing ART in S. Africa being planned