Point-of-Care Technologies for Supporting HIV Treatment Adherence

Optimizing ART Adherence Panel

Monica Gandhi MD, MPH, Professor of Medicine, UCSF

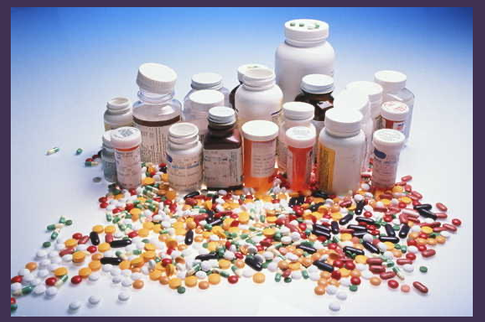
Adherence 2023 · June 11-13 · Puerto Rico

Adherence – we are not the only ones

The World Health Organization has decla
that more people wo
would benefit from *e*
improve medication adherence than from development of new treatments

"Drugs don't work in patients who don't take them"

C. Everett Koop



0% of patients
statins within
treatment

ociety $290 billion
cancer treatment)

World Health Organization. Adherence to Long-Term Therapy. Evidence to Action. 2003; National Council on Patient Information and Education. Enhancing Prescription Medication Adherence: A National Action Plan 2007. Chobanian AV. JAMA 2003; Cohen JD. J Clinical Lipid 2012; Osterberg & Blaschke. NEJM 2005; Blaschke. Ann Rev Pharm Tox '12

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)

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)

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

McComsey, G. A., et al. Real-World Adherence to Antiretroviral Therapy Among HIV-1 Patients Across the United States. *Advances in therapy*, *2021*

Min Han W et al. Global estimates of viral suppression in children and adolescents and adults on antiretroviral therapy adjusted for missing viral load measurements: a multiregional, retrospective cohort study in 31 countries. Lancet HIV 2021.

Shubber, Z., et al. Patient-Reported Barriers to Adherence to Antiretroviral Therapy: A Systematic Review and Meta-Analysis*. PLoS medicine, 2016.* 13(11), e1002183.

Altice, F., et al. . Adherence to HIV treatment regimens: systematic literature review and meta-analysis. *Patient preference and adherence*, 2019

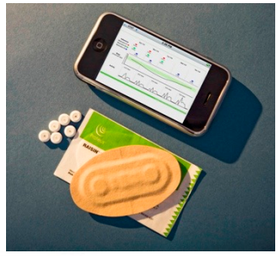
UNAIDS Global AIDS Update **2022**

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



Automatic compilation of dosing history data

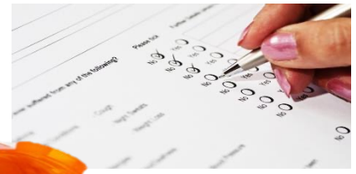
Electronic monitoring

Sensor devices (ingested)

Pharmacologic measures

Pharmacy refill data

Retrospective questionnaire



Pill Counts

Patient diaries

Self-report

More Subjective Measures

Modified from Vrijens & Urquhart, 2005 Journal of Antimicrobial Chemotherapy.

Pharmacologic measures –important x >12 years

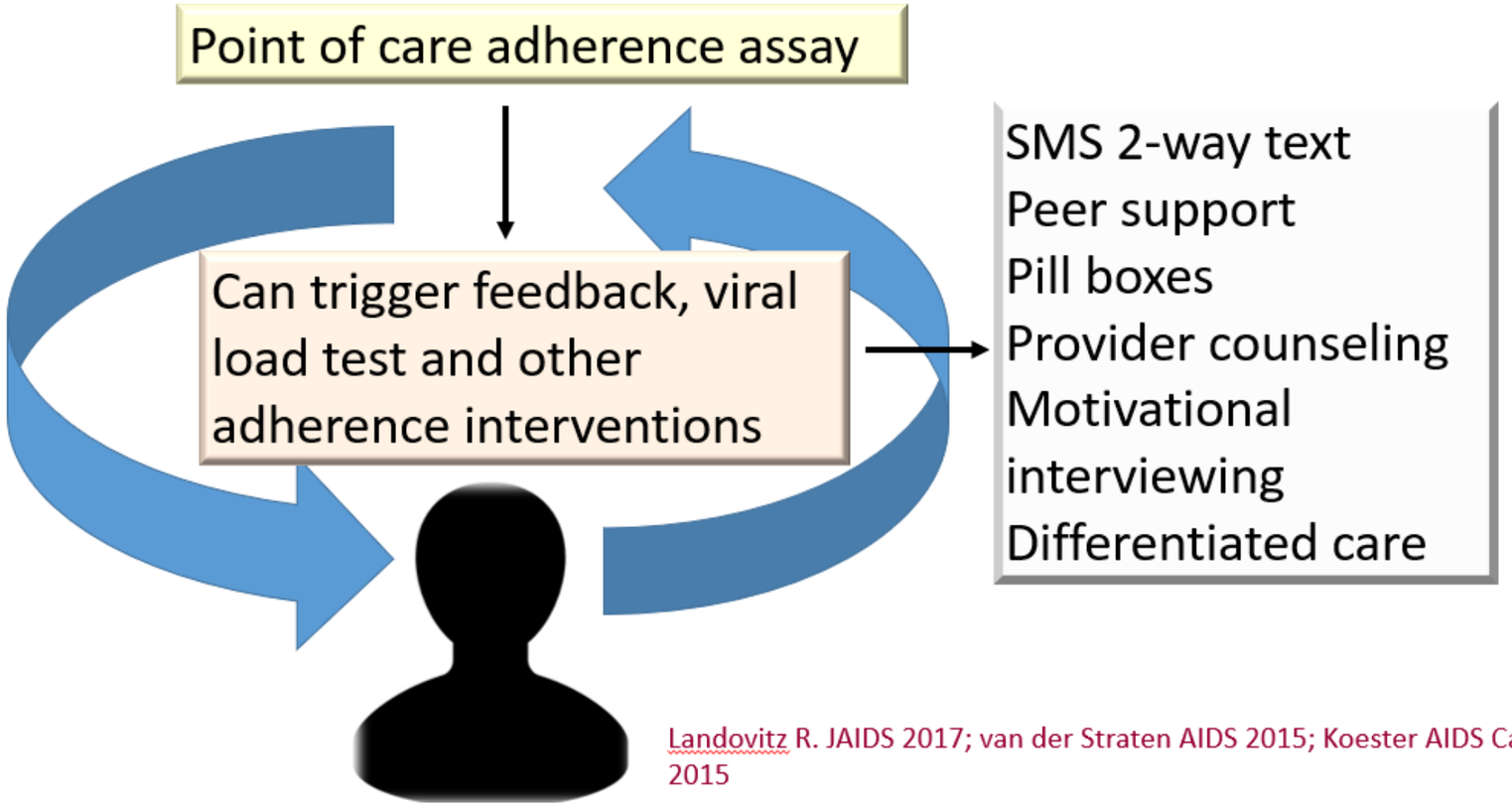
- Pharmacologic adherence measures *critical* to interpretation of placebo-controlled PrEP trials
- Efficacy of TDF/FTC in iPrEx rose from 44% to an estimated 92% (CI 40, 99%) among those with detectable drug levels (plasma or PBMC)
- Two trials (FEM-PrEP & VOICE) showed no efficacy but was determined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

Adherence Measure	VOICE	FEM-PrEP
Self-report	91%	95%
Returned pill counts	92%	88%
Plasma TFV detection	29%	24%

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

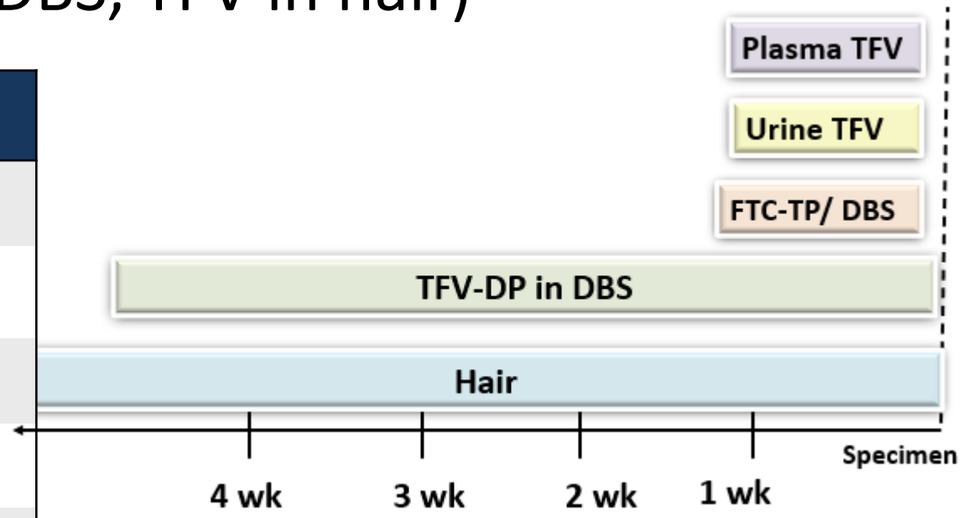


Landovitz R. JAIDS 2017; van der Straten AIDS 2015; Koester AIDS Care 2015

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)

Matrix	ART analyte measured	Analysis platform
Plasma	TFV/FTC	LC-MS/MS[1-3]
PBMC	TFV-DP/ FTC-TP	LC-MS/MS[1,4]
DBS	TFV-DP/ FTC-TP	LC-MS/MS[5-7]
Hair	TFV/ FTC	LC-MS/MS[8], IR-MALDESI[9]
Urine	TFV	LC-MS/MS[3, 10-13]



[1]Hendrix ARHR 2016; [2]Hendrix PLOS One 2013; [3]Calcagno. Pharmacogenomics 2016; [4]Anderson Sci Trans Med 2012; [5]Castillo-Mancilla. ARHR 2013; [6]Castillo-Mancilla. ARHR 2015; [7]Zheng. J Pharm Biomed Anal 2014; [8]Liu PLOS One 2014; Rosen. Anal Chem 2016;[10]Koenig HIV Med 2017; [11]Simile. J Pharm Biomed Anal. 2015; [12]Haaland AIDS 2017; [13]Lalley-Chareczko. Antiviral Ther 2017

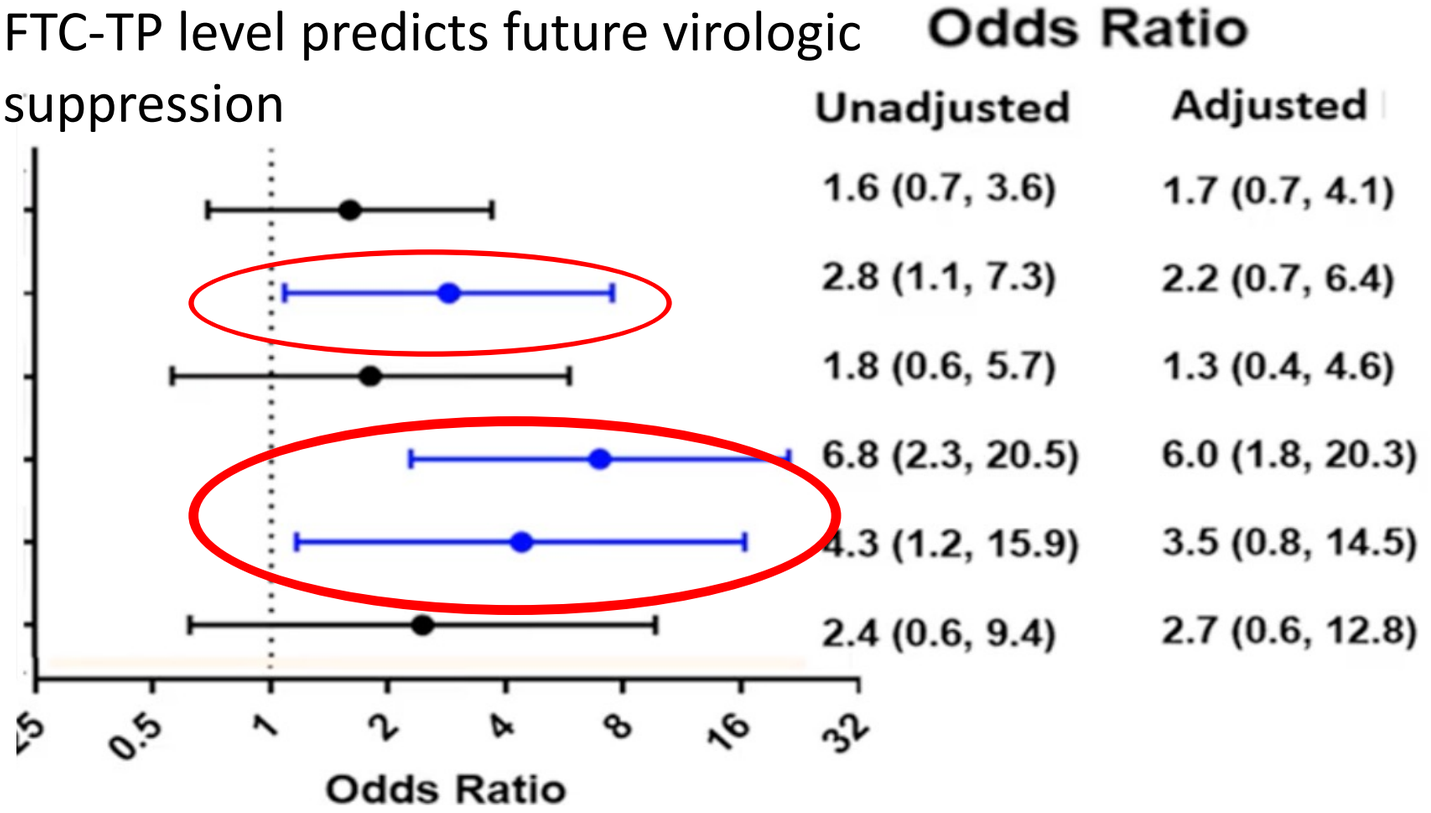
Short and Long-Term Adherence Highly Correlated & Predictive of Virologic Suppression

Urine TFV predicts DBS TFV-DP levels

	DBS TFV-DP (average dosing over prior month)		DBS FTC-TP (recent dosing in past 2-3 days)	
	Positive predictive value	Negative predictive value	Positive predictive value	Negative predictive value
Urine TFV	91%	87%	97%	95%

- In multivariable logistic regression analyses, urine TFV assay was a significant predictor of DBS TFV-DP (OR = 30.2, $p < 0.0001$); self-report did not add significantly to prediction.

FTC-TP level predicts future virologic suppression



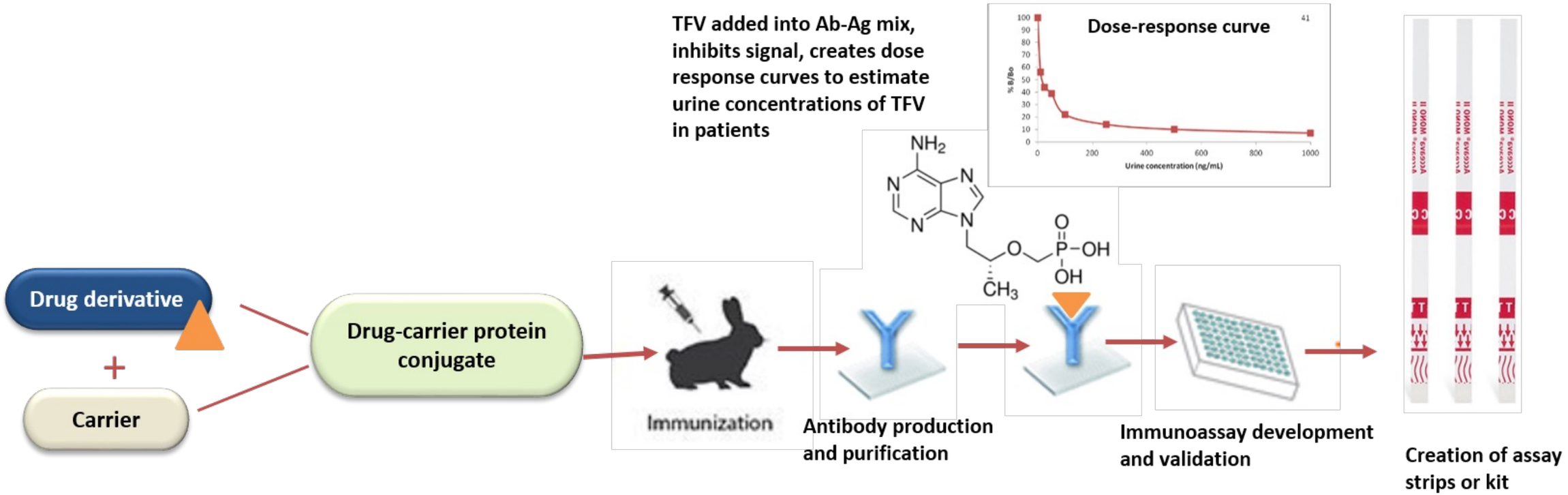
- Adherence behaviors tend to be stable over time (stably low or high)
- FTC-TP (short-term) correlates with TFV-DP (long-term) & predicts future virologic suppression
- Urine TFV correlates with FTC-TP, TFV-DP

Mustanski B et al. CROI 2023; Morrow M. AIDS 2021

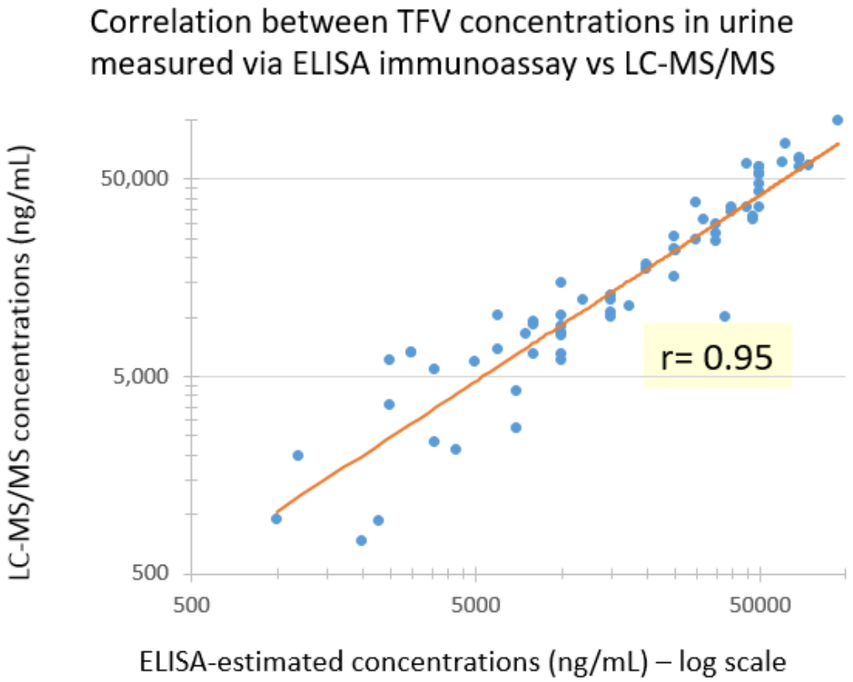
URINE POINT-OF-CARE TENOFOVIR TEST

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



Joint patent filed 2020

PTO/AIA/01 (06-12)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	ANTIBODIES DIRECTED AGAINST TENOFOVIR AND DERIVATIVES THEREOF

As the below named inventor, I hereby declare that:

This declaration is directed to:

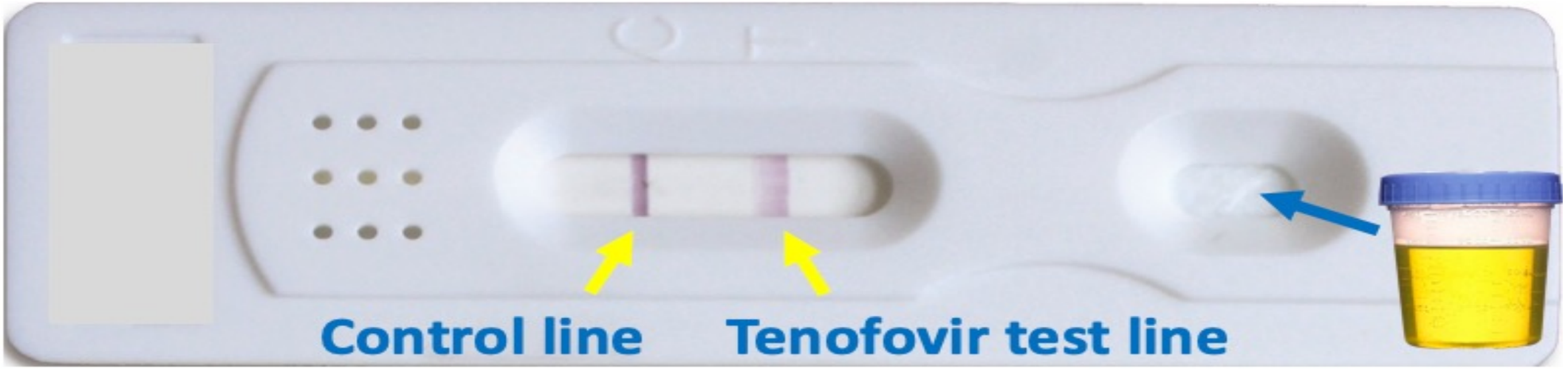
☐ The attached application, or

■ United States application or PCT international application number 17/761,928 filed on 18-Mar-2022.

- 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)

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



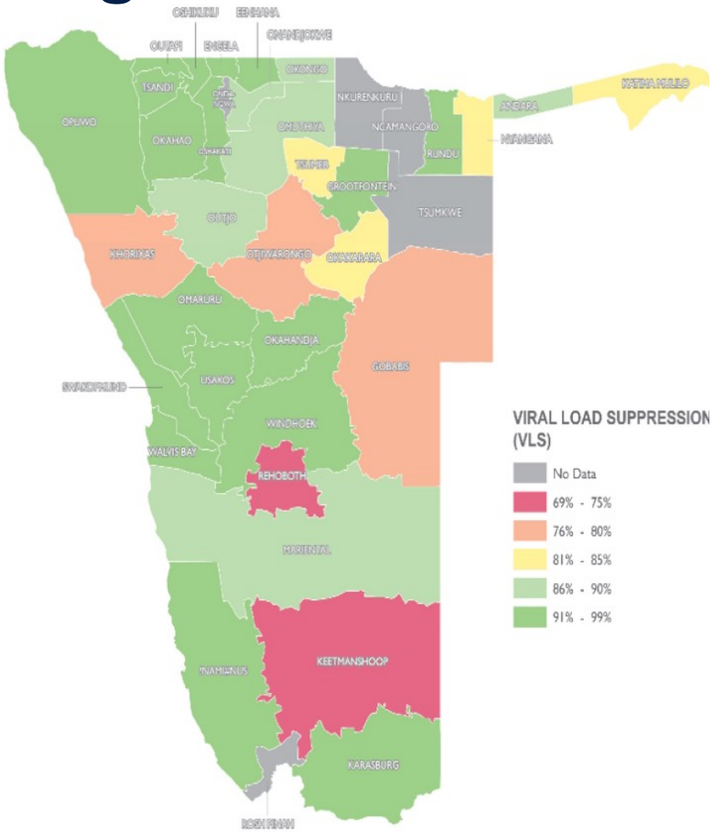
[1]Gandhi Eclinical Medicine 2018; Gandhi JAIDS 2019; Spinelli JAIDS 2020; Gandhi AIDS 2020

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**

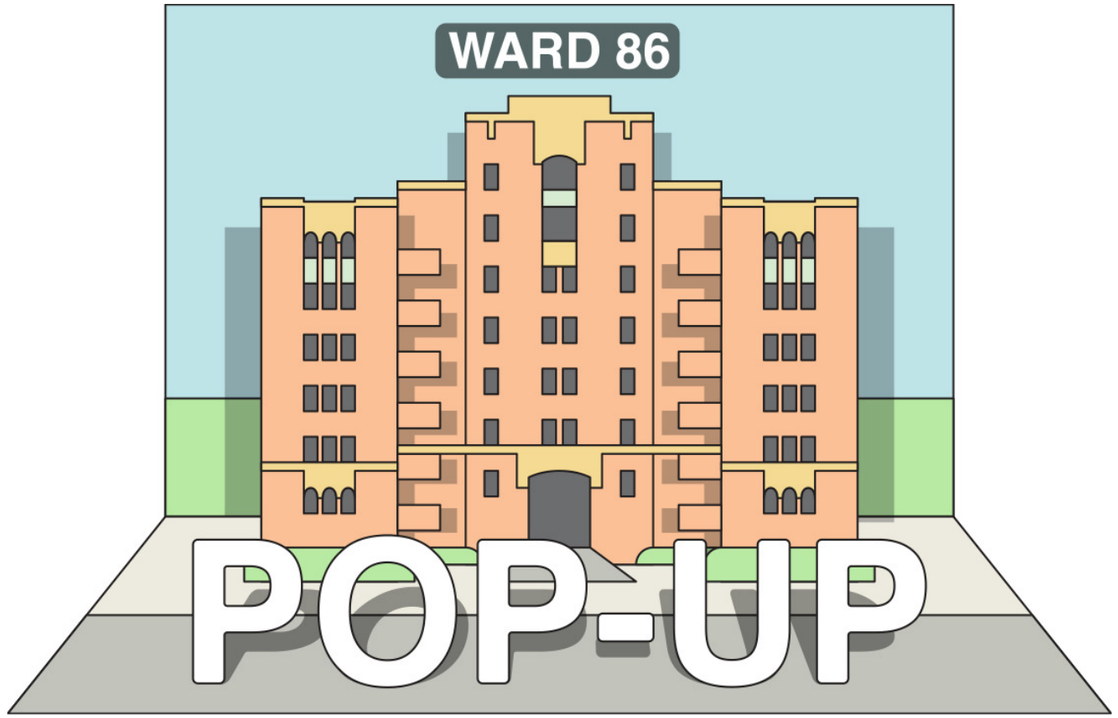
Viral Suppression by Region in Namibia



Bikinesi L. CROI 2023

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**

Clinical Infectious Diseases

Point-of-Care Tenofovir Urine Testing for the Predictic of Treatment Failure and Drug Resistance During Initia Treatment for Human Immunodeficiency Virus Type 1 (HIV-1) Infection

Lucas E. Hermans,[1,2,3,©] Chijioke N. Umunnakwe,[4] Samanta T. Lalla-Edward,[3] Shane K. Hebel,[5] Hugo A. Tempelman,[4] Monique Nijhuis,[2,6]

Jennings AIDS Res Hum Retro 2022; McCluskey S CID 2023; Hermann L CID 2023

UrSure

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

Clinical Infectious Diseases

BRIEF REPORT

Urine Tenofovir Levels Measured Using a Novel Immunoassay Predict Human Immunodeficiency Virus Protection

Randy M. Stalter,[1,2] Jared M. Baeten,[1,2,3] Deborah Donnell,[1,4] Matthew A. Spinelli,[5] David V. Glidden,[5] Warren C. Rodrigues,[6] Guohong Wang,[6] Michael Vincent,[6] Nelly Mugo,[1,7] Andrew Mujugira,[1,8] Mark Marzinke,[9] Craig Hendrix,[9] and

Low tenofovir level in urine by a novel immunoassay is associated with seroconversion in a preexposure prophylaxis demonstration project

Matthew A. Spinelli[a], David V. Glidden[b], Warren C. Rodrigues[c], Guohong Wang[c], Michael Vincent[c], Hideaki Okochi[d], Karen Kuncze[d], Megha Mehrotra[b], Patricia Defechereux[e], Susan P. Buchbinder[f], Robert M. Grant[e] and Monica Gandhi[a]

Just looking at PEPFAR program

PEPFAR
U.S. President's Emergency Plan for AIDS Relief

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)

Abstracts related to POC monitoring at this meeting

SUNDAY, JUNE 11, 2023

1093 Preferences Regarding a Real-time Urine Assay for Monitoring and Providing Feedback on Pre-Exposure Prophylaxis Adherence among Women in Kenya.
Presenter: Phelix Okello

MONDAY, JUNE 12, 2023

1183 A Lateral Flow Device to Detect Emtricitabine in Urine for PrEP and ART Adherence Monitoring
Thomas Vanderford

TUESDAY, JUNE 13, 2023

LATE BREAKER ABSTRACTS • GRAND CARIBBEAN 4

2:15pm – 3:15pm

MODERATOR: Carmen Zorrilla, University of Puerto Rico, San Juan, PR

1302 - A Point-of-Care Urine Tenofovir Adherence Feedback Intervention Improved PrEP Adherence among Kenyan Women
Matthew Spinelli presenting

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