Optimizing Adherence: Leveraging HIV Treatment Innovations to Achieve U=U

Monica Gandhi MD, MPH
Professor of Medicine, Division of HIV, Infectious Diseases, and Global Medicine
Medical Director, Ward 86 HIV Clinic and Director, Center for AIDS Research
University of California, San Francisco (UCSF)
September 26, 2023

Objectives of talk

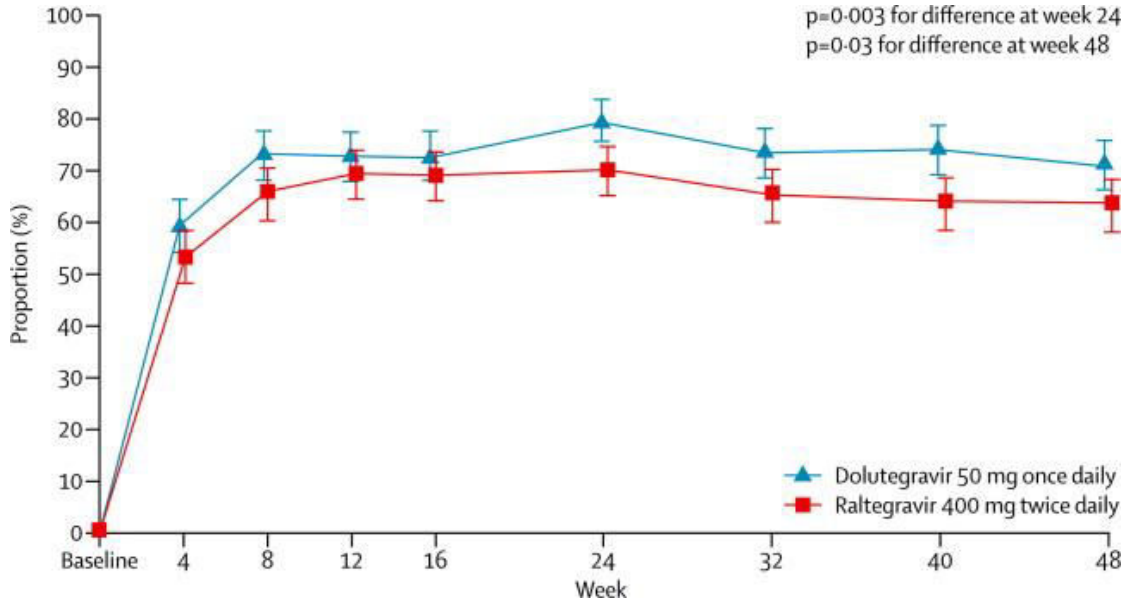
- First and second line therapy worldwide and why
- Third line therapy
- Adherence and VS rates worldwide
- Two ways to increase VS rates
  - Scalable adherence interventions
  - Long-acting ART
- How do we get there?

INSTIs FIRST-LINE AT THIS POINT FROM NAÏVE/SWITCH TRIALS WITHOUT RESISTANCE

Study	Population	Comparator	Outcome	Resistance
BICTEGRAVIR				
1489	Naïve	DTG/ABC/3TC	Non-inferior	0
1490	Naïve	DTG+FTC/TAF	Non-inferior	0
1844	Suppressed	DTG/ABC/3TC	Non-inferior	0
1878	Suppressed	Boosted PI + 2 NRTIs	Non-inferior	0 to INSTI but 1 L74V in PI arm
1961 (women)	Suppressed	E/C/F/(TAF or TDF) ATV+RTV + FTC/TDF	Non-inferior	0 to INSTI but 1 M184V in ELV/cobi
DOLUTEGRAVIR				
SINGLE	Naïve	EFV/TDF/FTC	Superior	0 in DTG arm; 7 in EFV
FLAMINGO	Naïve	DRV/r with 2 NRTI backbone	Superior	0 in either
SPRING-2	Naïve	RAL with 2 NRTI backbone	Non-inferior	0 in DTG; 1 INSTI/NRTI in RAL

ACCUMULATING DATA FOR INSTIS AS 2ND LINE IN FACE OF RESISTANCE

- SAILING STUDY –PI, NNRTI AND /OR NNRTI RESISTANCE
- Dolutegravir 50mg po daily vs Raltegravir 400mg po BID in patients with resistance to ≥ 2 classes of antiretrovirals with 1-2 remaining active agents for background therapy
- Investigator chosen background
- DTG was SUPERIOR to RTG in virologic suppression at week 48 and no development of resistance



71%

64%

Cahn P. Lancet 2013. 382(9893):700-8

VIKING STUDY: DTG in setting of NRTI, NNRTI, PI, and INSTI resistance

- Dolutegravir 50mg po **BID** vs placebo in patients with resistance to ≥ 2 classes including INSTIs (resistance to raltegravir or elvitegravir) – should have 1 other active drug
- Investigator chosen background
- DTG resulted in 53% virologic suppression (<400)
- Participants with Q148 with 2 other INSTI mutations don't have activity

Remember to double the dose of dolutegravir to 50mg po BID

Table 2. Comparison of DTG 50 mg twice daily versus PCB for change in BL HIV-1 at day 8 and antiviral efficacy of open-label DTG 50 mg twice daily with OBR at weeks 24 and 48 by BL characteristics[a]

	DTG 50 mg twice daily change from BL[b] at day 8[a] (*n*=14)		PCB 50 mg twice daily change from BL[b] at day 8[a] (*n*=16)		Combined arms, HIV-1 RNA <50 copies/ml[a] (%) (*n*=30)	
Subgroup	*n*	Mean (SD)	*n*	Mean (SD)	Week 24	Week 48
Overall[c]	14[d]	-1.06 (0.17)	16	0.10 (0.18)	14/30 (47)	12/30 (40)
DTG FC						
0–2.5	4	-1.33 (0.82)	7	0.00 (0.34)	6/11 (55)	5/11 (45)
>2.5–4	2	-1.22 (0.65)	3	-0.13 (0.28)	3/5 (60)	3/5 (60)
>4–8	5	-0.89 (0.65)	4	-0.02 (0.22)	2/9 (22)	1/9 (11)
>10–20	1	-0.86	1	-0.06	1/2 (50)	1/2 (50)
>20	1	-0.16	1	0.09	1/2 (50)	1/2 (50)
Missing	1	-1.82	0		1/1 (100)	1/1 (100)
Derived IN mutation group						
No Q148[e]	5	-1.43 (0.745)	9	-0.03 (0.325)	9/14 (64)	8/14 (57)
Q148 +1[f]	6	-0.87 (0.587)	6	-0.05 (0.182)	4/12 (33)	3/12 (25)
Q148 +≥2[f]	3	-0.90 (0.758)	1	0.09	1/4 (25)	1/4 (25)
OSS[g] of background ART						
0	–	–	–	–	2/3 (67)	2/3 (67)
1	–	–	–	–	6/15 (40)	5/15 (33)
2	–	–	–	–	3/8 (38)	3/8 (38)
>2	–	–	–	–	3/4 (75)	2/4 (50)

Bisher A. Antivir Ther. 2015;20(3):343-8

Recent studies of DTG with NRTI resistance- 1st and 2nd line worldwide

Name of study	Type of study, n	Comparison	Outcome	Emergent resistance
DAWNING	Open-label noninferiority study in PWH failing 1st line NNRTI + 2 NRTIs, n=624	DTG + 2NRTIs vs LPV/RTV + 2 NRTIs	DTG superior to LPV/RTV in subgroups	2 patients failed with INSTI resistance; none with PI resistance
NADIA	Switch study in PWH failing NNRTI/TDF/3TC (86% M184V; 50% K65R), n=464	DTG or DRV/r with either TDF/3TC or AZT/3TC	DTG + 2 NRTIs noninferior to DRV/r + 2 NRTIs (TDF/FTC works well even if resistance predicted)	9 patients in DTG arm failed with resistance; none in DRV/r arm
VISEND	Open-label study randomized PWH failing NNRTI-based therapy, n=1201	DTG or boosted PI regimens	>80% virologic suppression (<50) on DTG regimens	None reported (abstract CROI 2022)
2SD	Randomized study 2nd line therapy, Kenya, n=795	PI/r + 2 NRTIs randomized switch to DTG + 2 NRTI or continue	>90% virologic suppression each arm	No emergent resistance either arm

DAWNING: Aboud M, et al. *Lancet Infect Dis*. 2019**; NADIA:** Patton N. Lancet HIV 2022; **VISEND**: Mulenga LB, et al. CROI 2022. Abstract 135; **2SD Study**: Ombajo L N Engl J Med 2023 Jun 22;388

WHO Guidance on U=U

- Along with tenofovir-lamivudine-dolutegravir (TLD) being first-line therapy, World Health Organization issued new recommendations on undetectable= untransmittable (VL <1000) July 2023

U = U = Zero Risk

THE ROLE OF HIV VIRAL SUPPRESSION IN IMPROVING INDIVIDUAL HEALTH AND REDUCING TRANSMISSION

POLICY BRIEF

The risk of sexual transmission of HIV in individuals with low-level HIV viraemia: a systematic review

Laura N Broyles, Robert Luo, Debi Boeras, Lara Vojnov

.ancet 2023; 402: 464-71

Summary

Background The risk of sexual transmission of HIV from individuals with low-level HIV viraemia receiving

1. apps.who.int/iris/bitstream/handle/10665/360860/9789240055179-eng.pdf.
2. Broyles LN. Lancet. 2023;S0140-6736(23)00877-2.

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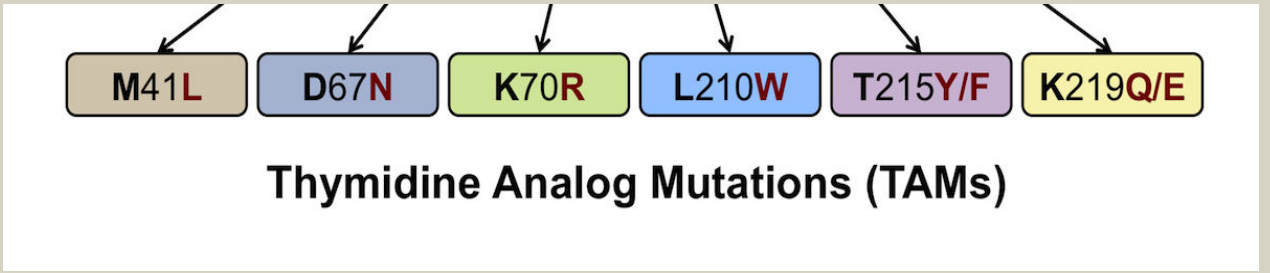
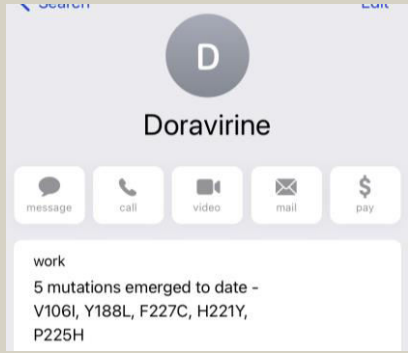
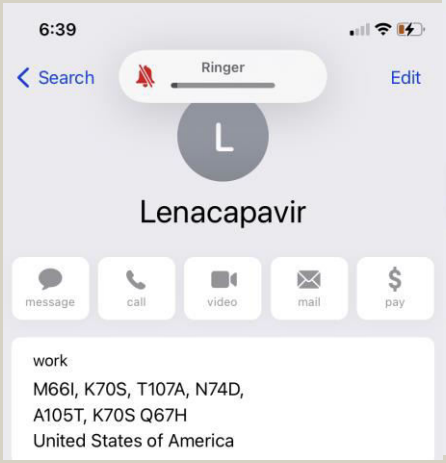
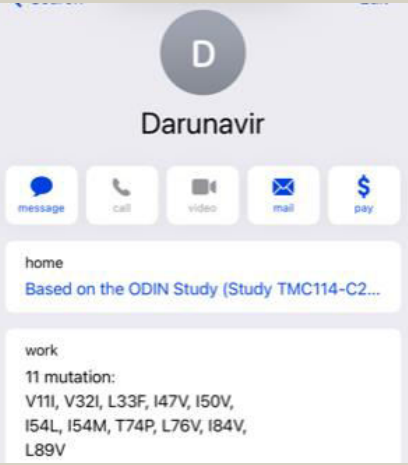
The 12 mutations every HIV provider should know

- **NRTI**
  - **M184V (3TC), K65R (TDF), L74V (ABC)**
  - 6 Thymidine-associated mutations (TAMs) - **M41L, D67N, K70R, L210W, T215Y/F, K219Q**
- **NNRTI**
  - **K103N** (EFV, NVP)
  - **Y181C** (ETR)
  - **E138K** (RPV)
  - I will send you doravirine contact
- **PI, INSTI**
  - None (can look up and will send darunavir contact)
- **Capsid inhibitor**
  - None (can look up and will send lenacapavir contact)



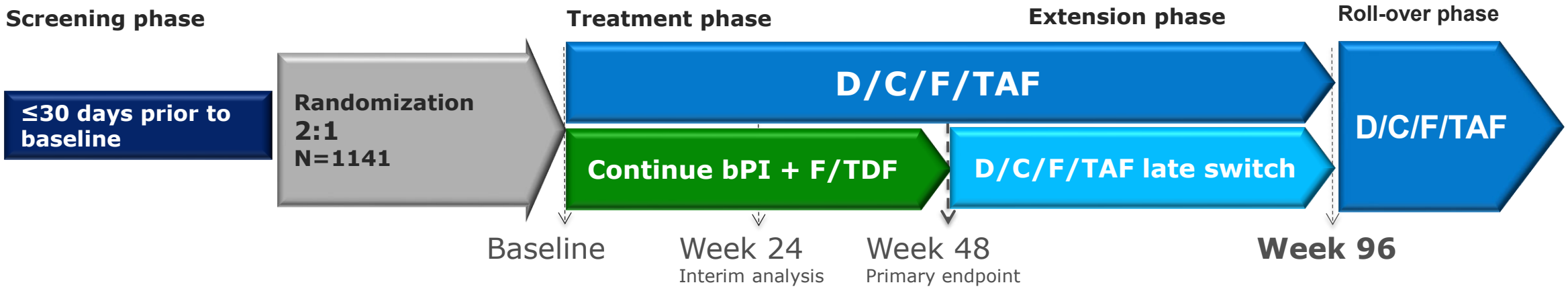






DHHS Guidelines available at http://aidsinfo.nih.gov/guidelines

3rd line: Boosted PIs with darunavir/ritonavir being best



EMERALD study helped us know about DRV/r with NRTI mutations:

- Was actually to evaluate switching to single pill combination of DRV/cobi/TAF/FTC but importantly was in resistant population
- Previous ART VF allowed (no history of VF on DRV-based regimens), and if historical genotypes were available, absence of DRV RAMs[1]; **no restriction on FTC or tenofovir RAMs**
- 38% with emtricitabine RAMs, mainly M184V
- 4% with tenofovir RAMs
- 21% ≥ 3 thymidine analog-associated mutations (24% not fully susceptible to tenofovir) detected at screening
- 91% VS rate at 96 weeks, no DRV associated RAMs developed

[1]Eron. AntiViral Research 2019

DTG + DRV/r - D2EFT study

Wednesday

Oral Abstract Session-12 ANTIVIRAL
STRATEGIES FOR TREATMENT AND PREVENTIONS
Ballroom 1 (Level 5) 10:00 AM - 12:00 PM

198
11:24
LB

D2EFT: DOLUTEGRAVIR AND DARUNAVIR EVALUATION IN ADULTS FAILING FIRST-LINE HIV THERAPY

Gail Matthews, Margaret Borok, Nnekelu Eriobou, Richard Kaplan, N Kumarasamy, Anchalee Avihingsanon, Marcelo H. Losso, Iskander Shah Azwa, Muhammad Karyana, Sounkalo Dao, Mohamed Cisse, Emmanuelle Papot, Simone Jacoby, Jolie Hutchison, Matthew G. Law, Leo Perelis, Fafa Addo Boateng, Dannae Brown

Name of study	Type of study, n	Comparison	Outcome	Emergent resistance
D2EFT	international randomized open-label trial in patients failing NNRTI therapy, n=831	DTG + DRV/r vs DTG + 2NRTIs vs DRV/r + 2 NRTIs	DTG + DRV/r **superior** to either regimen	None but doesn't mean DTG/DRV/r needed, would stick with DRV as 2nd line with 2 NRTIs

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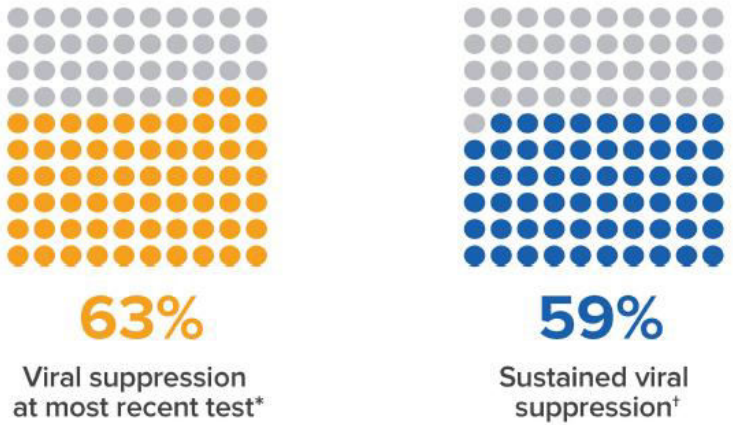
Adherence Challenges with ARTs

Figure 4. Percentage of adults with diagnosed HIV who were virally suppressed during the 12 months befo… interview—Medical Monitoring Project, United States, 2020



Overall rates of VS in US 59% sustained (CDC HIV Special Surveillance Report 8/23)

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

- Among all people living with HIV, 86% [73– >98%] knew their status, 76% [65–89%] were accessing treatment and 71% [60–83%] were virally suppressed in 2022.

THE PATH THAT ENDS AIDS

2023 UNAIDS GLOBAL AIDS UPDATE

- UNAIDS cannot include countries where viral loads are not done frequently in these metrics so could be lower, closer to the 59-65% seen in the U.S and Lancet HIV study across 31 countries
- Rates lower for children and adolescents (and only 57% of children ages 0-14 years had access to treatment compared to 77% of adults)

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  - **Scalable adherence interventions**
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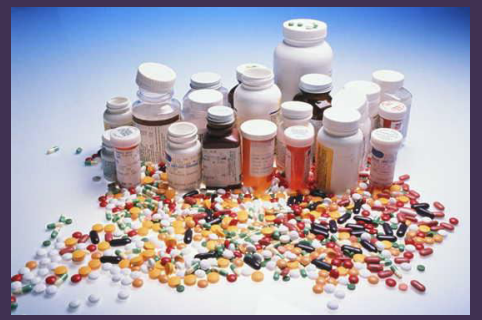
Adherence – we are not the only ones

The World Health Organization has decla
that more people wo
would benefit from *ef*
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 interventions need to be scalable and low-cost to be globally adapted (most below are either not cost effective in LMICs or no CE analysis done)

Nurse-delivered home visits

2-way SMS text messaging

Motivational interviewing / cognitive behavioral therapy

Interactive computer-based adherence promotion

Peer mentoring or peer delivered

Adherence clubs

Contingency management

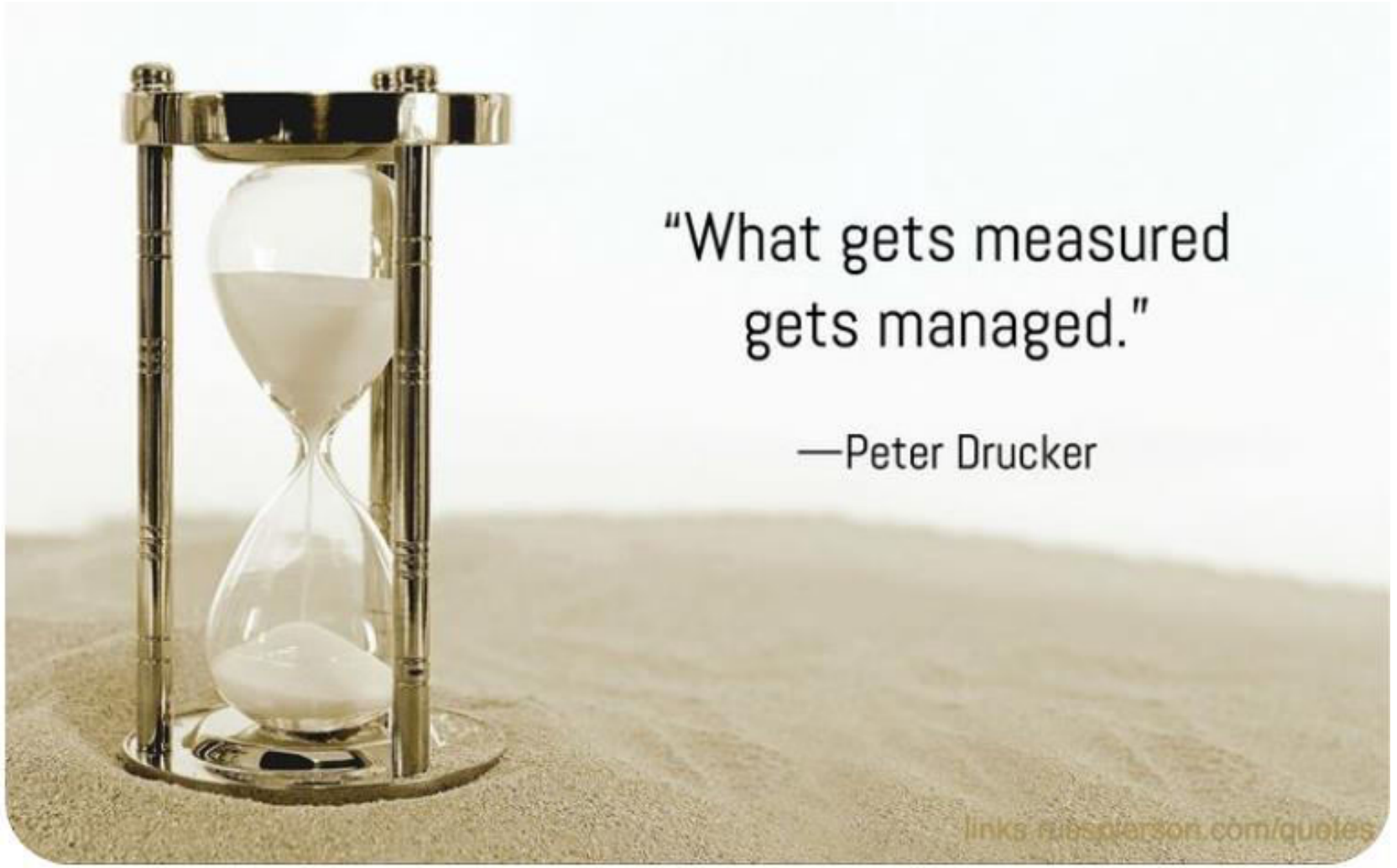
Electronic monitoring (e.g. pill bottle opening) feedback

Drug level feedback of antiretroviral levels

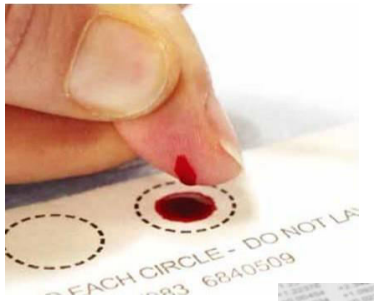
Modified directly observed therapy (DOT)

Mbuagbaw L. AIDS Patient Care and STDs 2015; Freedberg KA. JAIDS 2006; Ownby RL. BMC Med Inform Decis Mak 2013; Wijnen BFM CID 2019

Scalable adherence interventions need objective measures which are cheap



What are current ways to measure adherence?



More Objective Measures

Pharmacologic measures

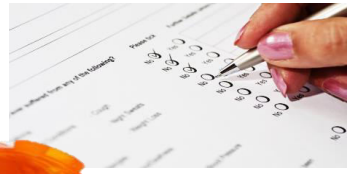
Pharmacy refill data

Automatic compilation of dosing history data

Electronic monitoring

Sensor devices (ingested)

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

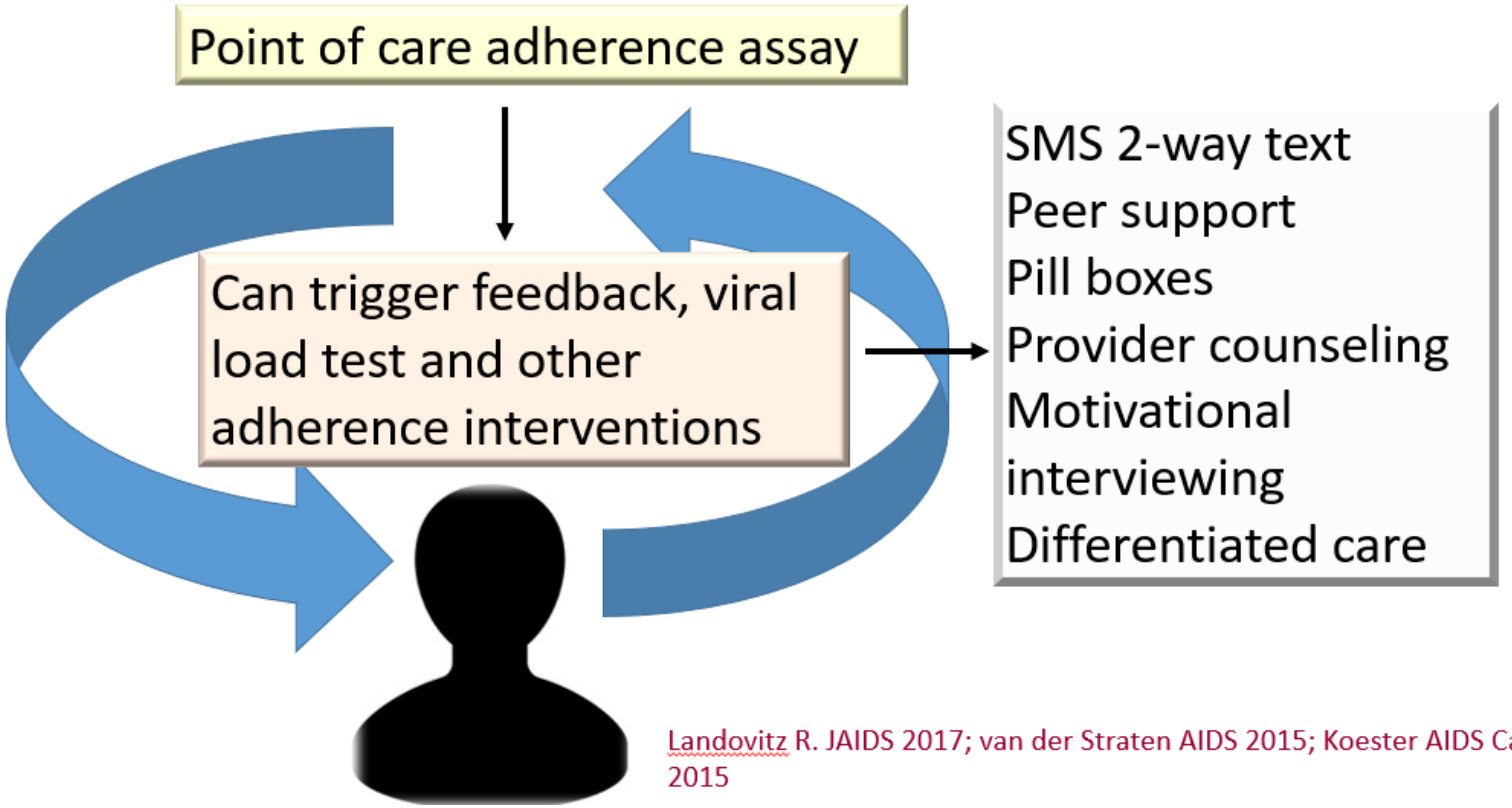
- Pharmacologic adherence measures *critical* to interpretation of placebo-controlled PrEP trials
- Efficacy of TDF/FTC in iPrEx rose from 44% to an estimated 92% (CI 40, 99%) among those with detectable drug levels (plasma or PBMC)
- Two trials (FEM-PrEP & VOICE) showed no efficacy but was determined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



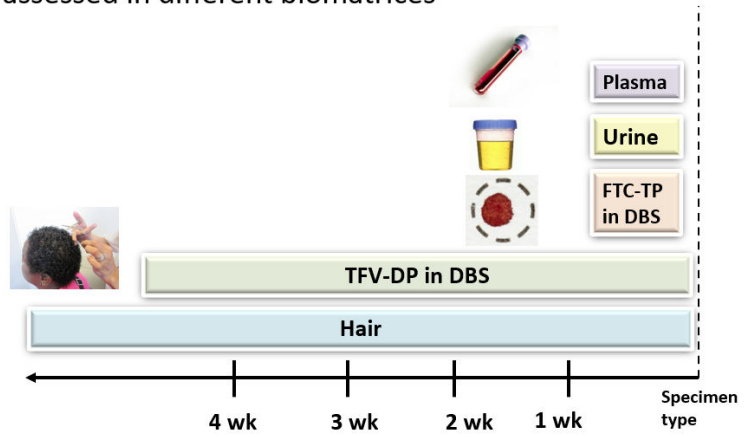
Landovitz R. JAIDS 2017; van der Straten AIDS 2015; Koester AIDS Care 2015

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]

Duration of time over which adherence to tenofovir is assessed in different biomatrices



FTC-TP: Emtricitabine-triphosphate; TFV-DP: Tenofovir diphosphate; DBS: Dried blood spot

[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

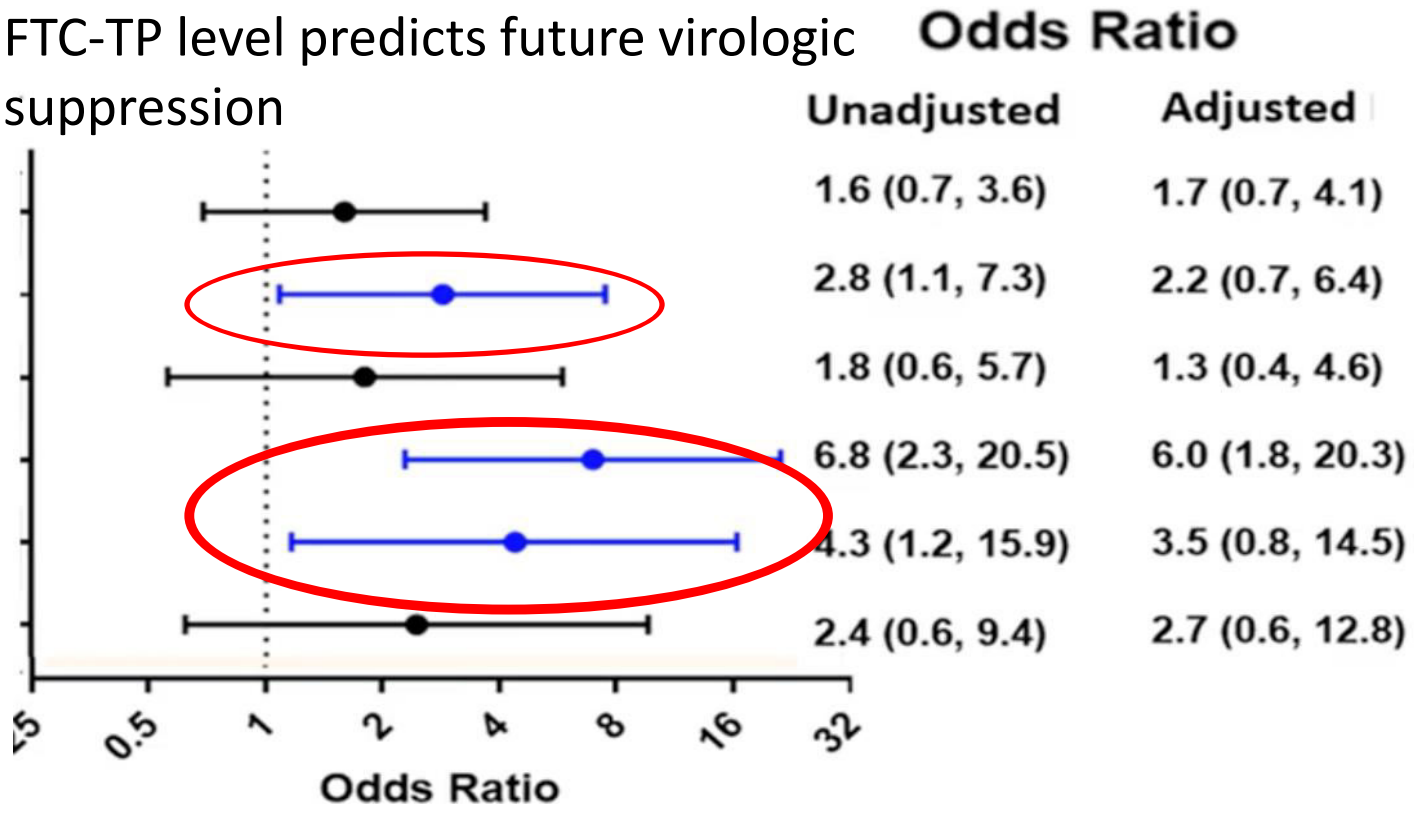
Short and Long-Term Adherence Highly Correlated & Predictive of Virologic Suppression

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



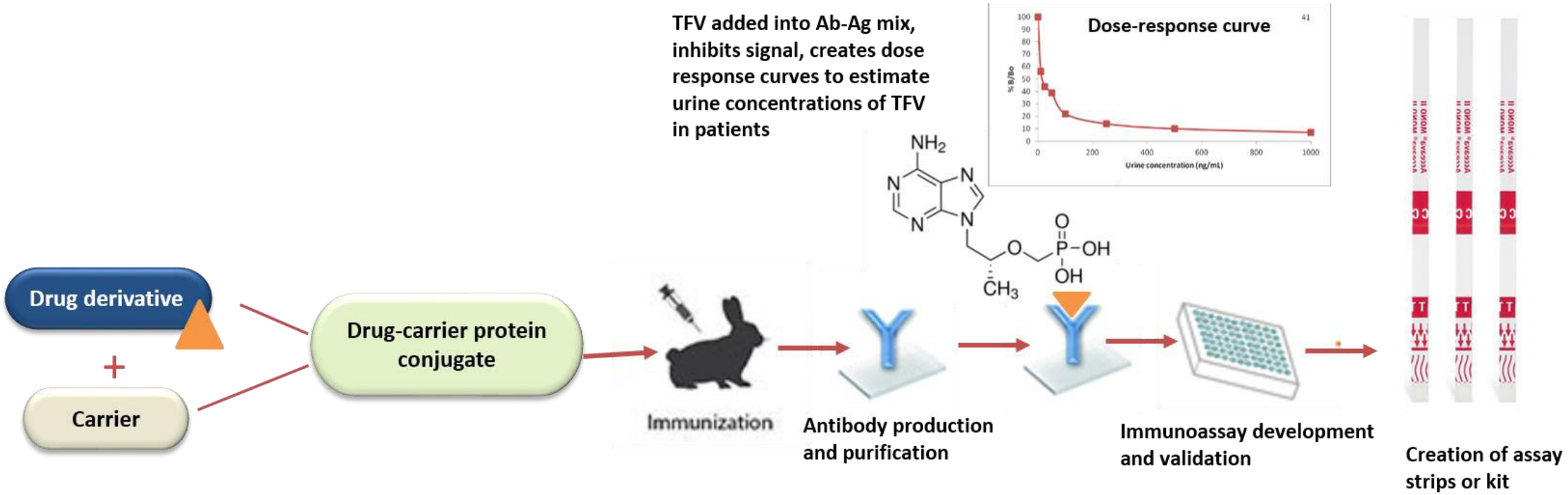
- Adherence behaviors tend to be stable over time (stably low or high)
- FTC-TP (short-term) correlates with TFV-DP (long-term) & predicts future virologic suppression
- Urine TFV correlates with FTC-TP, TFV-DP

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

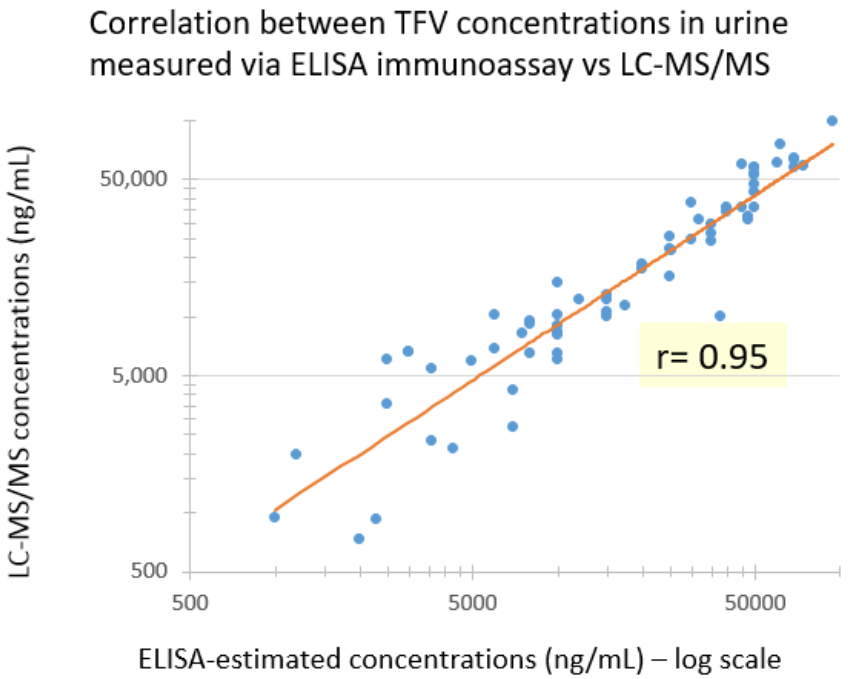
URINE POINT-OF-CARE TENOFOVIR TEST

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:

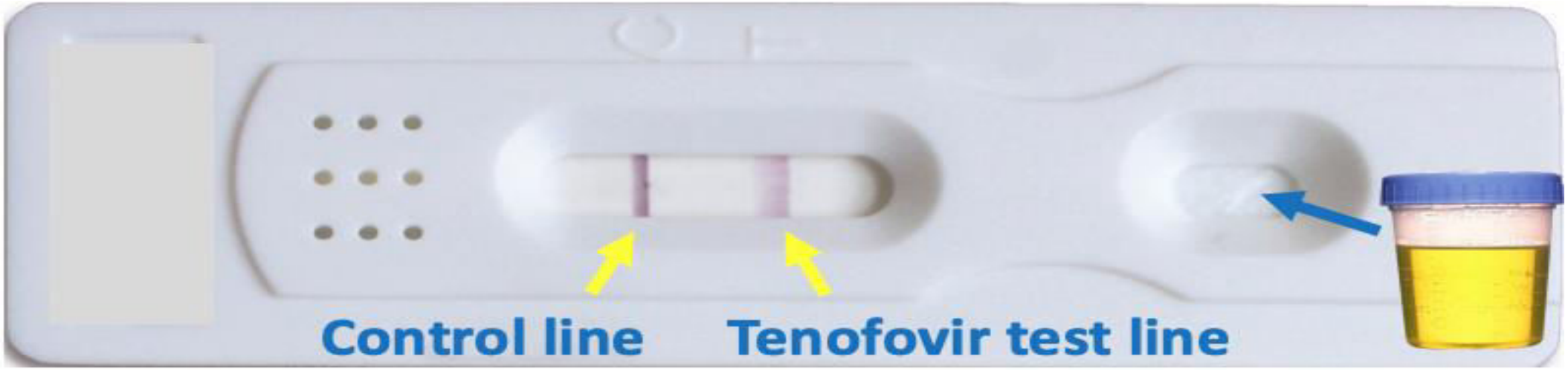
☐ The attached application, or

☒ 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



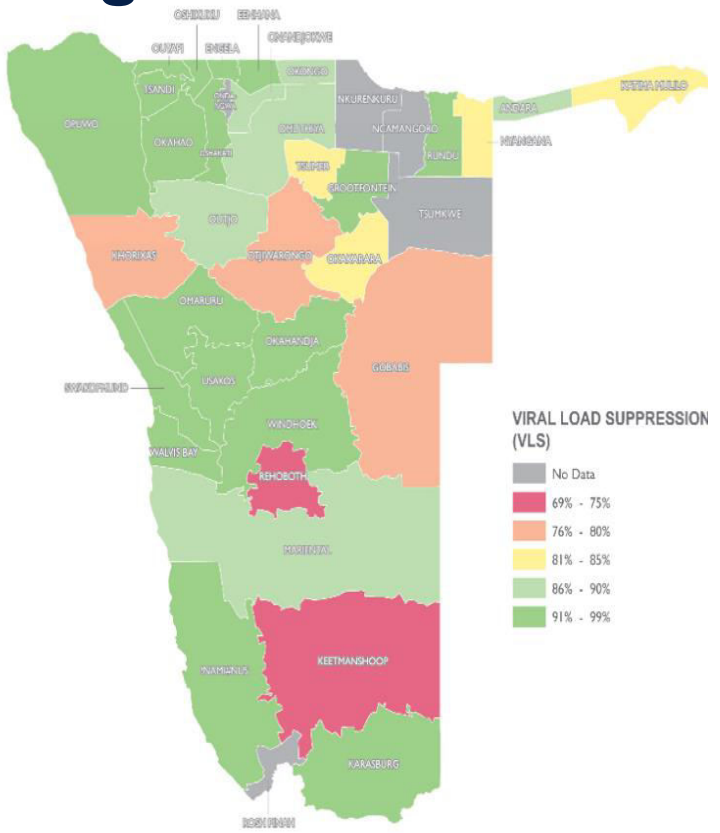
[1]Gandhi Eclinical Medicine 2018; Gandhi JAIDS 2019; Spinelli JAIDS 2020; Gandhi AIDS 2020

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

In S. Africa and Uganda, POC TFV 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

Intermittent adherence (drug detectability of DTG) sets up conditions for resistance

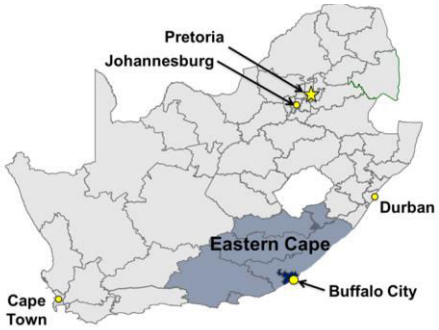
Comparison with previous surveys in South Africa 2019-2022

	2019	2021	2022
Total number of samples tested	779	621	709
Succesful DLT	779	621	708
Any ARV detected	55.7%	52.0%	58.6%
EFV detected	42.5%	35.8%	22.7%
FTC detected	30.1%	23.5%	8.3%
3TC detected	12.6%	9.6%	8.3%
LPV detected	3.9%	6.9%	5.8%
DTG detected	NA	7.2%	15.0%
Succesful HIVDR	753	538	595
Any resistance	72.1%	67.6%	57.9%
NNRTI resistance	70.5%	66.4%	56.0%
NRTI resistance	49.0%	41.4%	28.5%
PI resistance	2.2%	4.1%	3.1%
INSTI resistance	NA	0.2%	1.6%

DTG resistance in patients with laboratory confirmed DTG exposure increased from **2.7%** in 2021 to **11.9%** in 2022

Van Zyl JAIDS 2022; McCluskey S CID 2023; Kim XXX International Workshop on HIV Drug Resistance and Treatment Strategies. Cape Town. September 18-20, 2023

RCT being planned to compare WHO recommended enhanced adherence counseling vs urine-assay informed counseling to increase VS rates



Study Schema for an RCT to compare standard of care (enhanced adherence counseling) with urine TFV assay counseling

N=500 participants with VL > 1000 copies/mL 6 months or more after initiation of TLD

Baseline visit (month 0)

All participants

N=250 **Intervention arm** (POC-EAC)

N=250 **Standard of care arm** (SoC-EAC)

Months 0, 1, 2, 3, 4, 5	Month 6	Months 9, 12, 18, 24
Urine TFV assay-informed counseling delivered.	*Acceptability surveys, qualitative interviews*	All participants
EAC alone delivered. Urine collected but assayed at end of study.		

HIV viral loads for study collected at months 3, 6, 9, 12, 18, 24 and assayed at study end; other lab testing (including VL) per clinical care

Objectives of talk

- First, second line therapy worldwide and why
- Third line therapy
- Adherence and VS rates worldwide
- Two ways to increase VS rates
  - Scalable adherence interventions
  - **Long-acting ART**
- How do we get there?

Original registrational trials of LA CAB/RPV- FLAIR, ATLAS and ATLAS 2M

FLAIR

- CAB/RPV LA in treatment naïve participants (K103N mutation allowed); First put on DTG/ABC/3TC for 20 weeks then LA ART with virologic suppression; 80% VS at 124 weeks

ATLAS

- CAB/RPV LA in treatment experienced participants every 4 weeks (K103N okay); on suppressive regimen for 6 months prior to switch; 97% VS rate 6 months

ATLAS 2M

- CAB/RPV LA in treatment experienced participants every 8 weeks (higher dose 600mg/900mg) after VS x ≥ 6 months; 97% VS at 152 weeks

SOLAR (not registrational; after approval)

- CAB/RPV LA in treatment experienced participants every 8 weeks switched from BIC/TAF/FTC high rates of VS; 47% reported stigma (self or other) for LA ART

Orkin C. Lancet HIV 2021; Swindells S. AIDS 2022; Overton E. CID 2023; Ramgopal M. Lancet HIV 2023

Demonstration project at Ward 86 HIV Clinic

Inclusion criteria of trials:

- Virologically suppressed x at least 16 weeks on oral regimen first
- No history of virologic failure
- Only K103N in NNRTI; no INSTI mutations
- Oral CAB/RPV x 28 days but direct-to-inject approved FDA March ‘22

Inclusion criteria of Ward 86

- Need not be virologically suppressed or take oral ART before injectables
- No RPV or INSTI mutations (strengthened criteria later)
- **Express willingness to come to clinic q4 weeks, contact information, outreach from staff**
- Rigorous protocol, Biweekly review of patients

Descriptive statistics summarized patient characteristics, median/range number of injections received, viral suppression outcomes, stratified by viral load ≥30 copies/mL at LA-ART initiation; Kaplan Meier plot for viremic

Gandhi Annals of Internal Medicine 2023

Implementation of program

- Hired pharm tech to help get injectable meds
- Biweekly meetings with Pharm D, pharm tech, clinic leadership, POP-UP program leadership to review each patient on injectables or being considered
- Protocol development with ongoing refinements based on observations in our pilot program
- 243 patients have been started on long-acting ART: rigorous protocol – will present first 133 here

THE LANCET HIV

CrossMark

Realising long-acting ART as first-line treatment

RESULTS

Table 1: Demographics and clinical characteristics of cohort in Ward 86 LA ART program (n=133)

Characteristic	Distribution, n (%)
Age (median, range)	45 (38-45) years
Gender	
Cis Man	117 (88%)
Cis Woman	11 (8%)
Transgender Woman	5 (4%)
Race/ethnicity	
Black	21 (16%)
Latino/a	50 (38%)
White	43 (32%)
Multiracial	19 (14%)
Housing	
Unstable	77 (58%)
Stable	45 (34%)
Homeless	11 (8%)
Insurance	
Medicare or Medicaid or both	130 (98%)
ADAP	3 (2%)
Current stimulant use	44 (33%)
Major mental illness	51 (38%)
Virologically non-suppressed (>30 copies/ml)	57 (43%) with log10 viral load (mean, STD) 4.21 (1.30)
CD4 count (median with interquartile range)	Virologically suppressed 616 (395–818) Virologically non-suppressed 215 (75–402)

* Note: ADAP is AIDS Drug Assistance Program; Baseline CD4 defined as the CD4 count closest to and including date of first injection. Median time from CD4 count to first injection was 70 (range 0 to 882) days

- Between June 2021-November 2022, 133 PWH started on LA-ART, 76 suppressed on oral ART, 57 (43%) with viremia
- Diverse (68% non-White; 88 (66%) unstably housed; 44 (33%) endorsed substance use)
- Median CD4 count in those with viremia lower than those w/ suppression
- 74% (66-81%) on-time injections
- In those with virologic suppression, 100% (95% CI 94%-100%) remained suppressed (median 26 weeks (2-42) for whole cohort)

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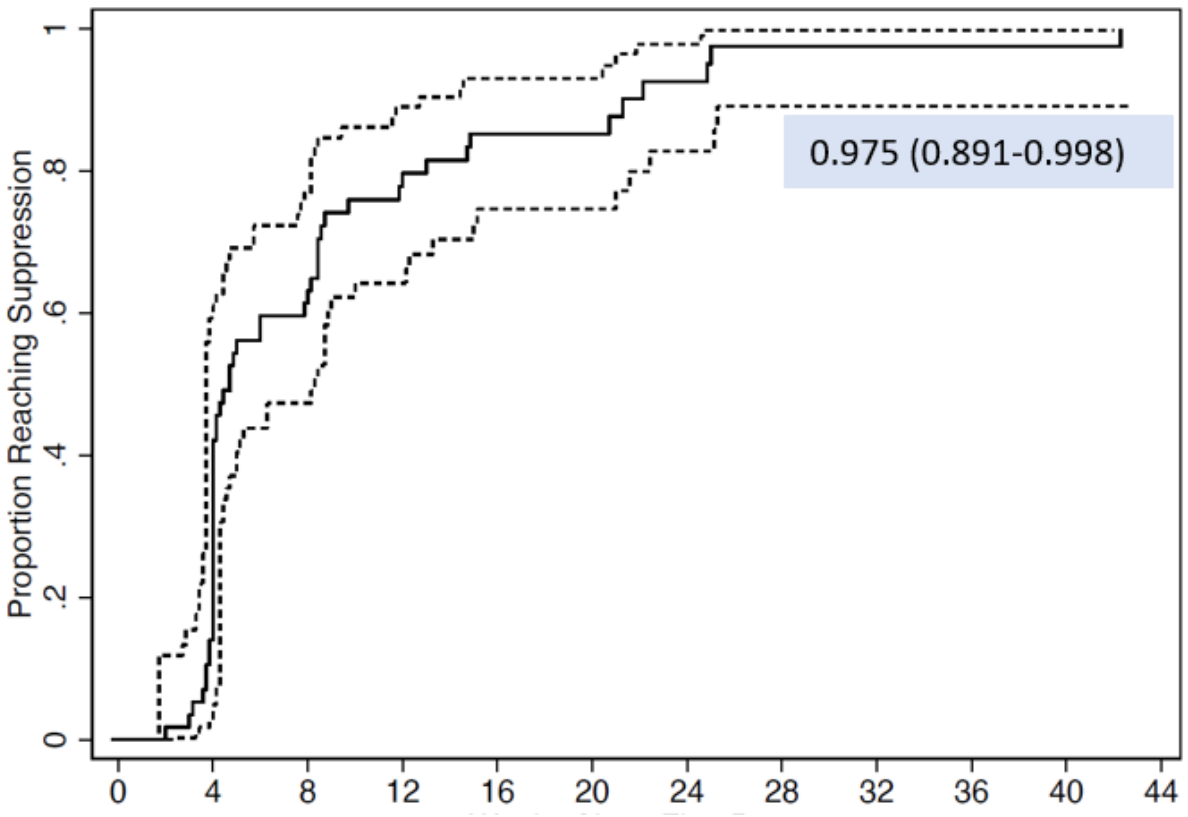
RESULTS (continued)

Figure: KM curve of probability of reaching virologic suppression (VL <30) on LA ART (n=57); dotted lines 95% CI



Neither patient who didn't have virologic suppression could take oral ART

Gandhi Annals of Internal Medicine 2023

- Among viremic PWH, at median of 33 days, 55 suppressed, 2 had early virologic failure.
- 97.5% (89.1 to 99.9%) expected to achieve virologic suppression by median 26 weeks
- Current cohort virologic failure rate 1.5% similar to that across clinical trials (1.4%) by 48 weeks (68% by 24 weeks)
- Two failures < 24 weeks, both had minor mutations so protocol tightened; 3rd didn't suppress <100 (182) so added LEN

Virologic failure #1: Started with V179I mutations, didn't show 2 $\log_{10}$ reduction by 1st visit (baseline viral load 214,540 → 39,293 copies/mL); Developed Y181C, L100I

Virologic failure #2: Started with T97A mutation, didn't show 2 $\log_{10}$ reduction by 1st (baseline viral load 137,134 → 4,371 copies/mL); Developed R263K, E138K mutations

Exploring predictors of HIV-1 virologic failure to long-acting cabotegravir and rilpivirine: a multivariable analysis

AIDS: July 15, 2021 - Volume 35 - Issue 9 - p 1333-1342

Conclusion: CVF is an infrequent multifactorial event, with a rate of approximately 1% in the long-acting CAB+RPV arms across Phase 3 studies (FLAIR, ATLAS and ATLAS-2M) through Week 48. Presence of at least two of proviral RPV RAMs, HIV-1 subtype A6/A1 and/or BMI at least 30 kg/m^2 was associated with increased CVF risk. These findings support the use of long-acting CAB+RPV in routine clinical practice.

BMI, low rilpivirine troughs, **presence of two proviral RPV RAMS**, HIV-1 subtype A6/A1 all associated with increased risk of failure (updated CID 2023)

Clinical Infectious Diseases
MAJOR ARTICLE

Expanded Multivariable Models to Assist Patient Selection for Long-Acting Cabotegravir + Rilpivirine Treatment: Clinical Utility of a Combination of Patient, Drug Concentration, and Viral Factors Associated With Virologic Failure

Chloe Orkin,[1,©] Jonathan M. Schapiro,[2] Carlo F. Perno,[3] Daniel R. Kuritzkes,[4] Parul Patel,[5] Rebecca DeMoor,[6] David Dorey,[7] Yongwei Wang,[5] Kelong Han,[6]

TECHNICAL REPORT

HIV DRUG RESISTANCE REPORT 2021

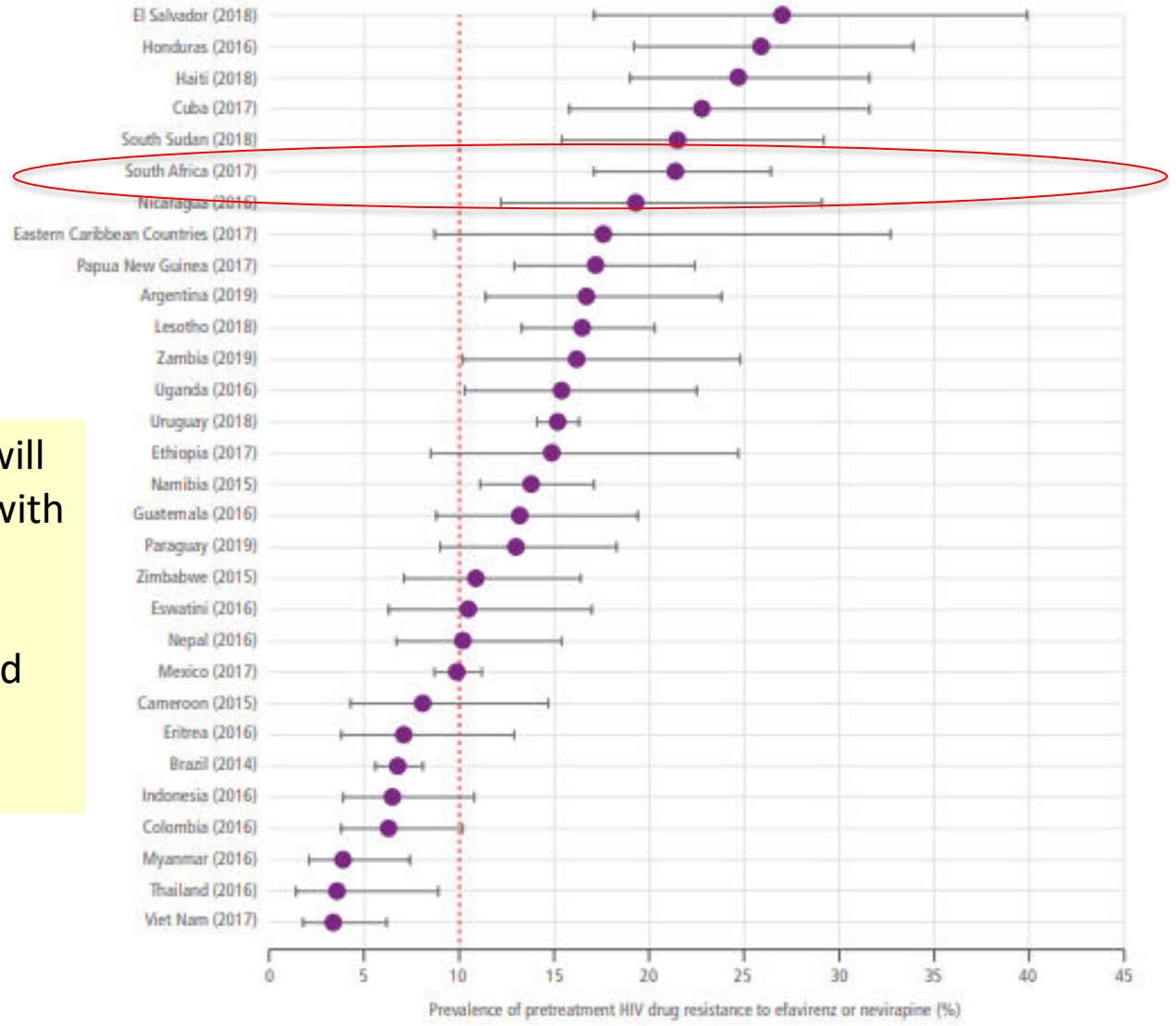
NOVEMBER 2021

HIV DRUG RESISTANCE

World Health Organization

Long-acting CAB/RPV will not work in countries with high rates of NNRTI resistance and has not been officially endorsed by the WHO for global treatment

Fig. 1.3. Prevalence of pretreatment HIV drug resistance to efavirenz or nevirapine among adults initiating antiretroviral therapy, 2014–2020



What options do we have for LA ART in LMICs?

57 yo man with HIV dx'd 1998, CD4 nadir <50, thrush in past

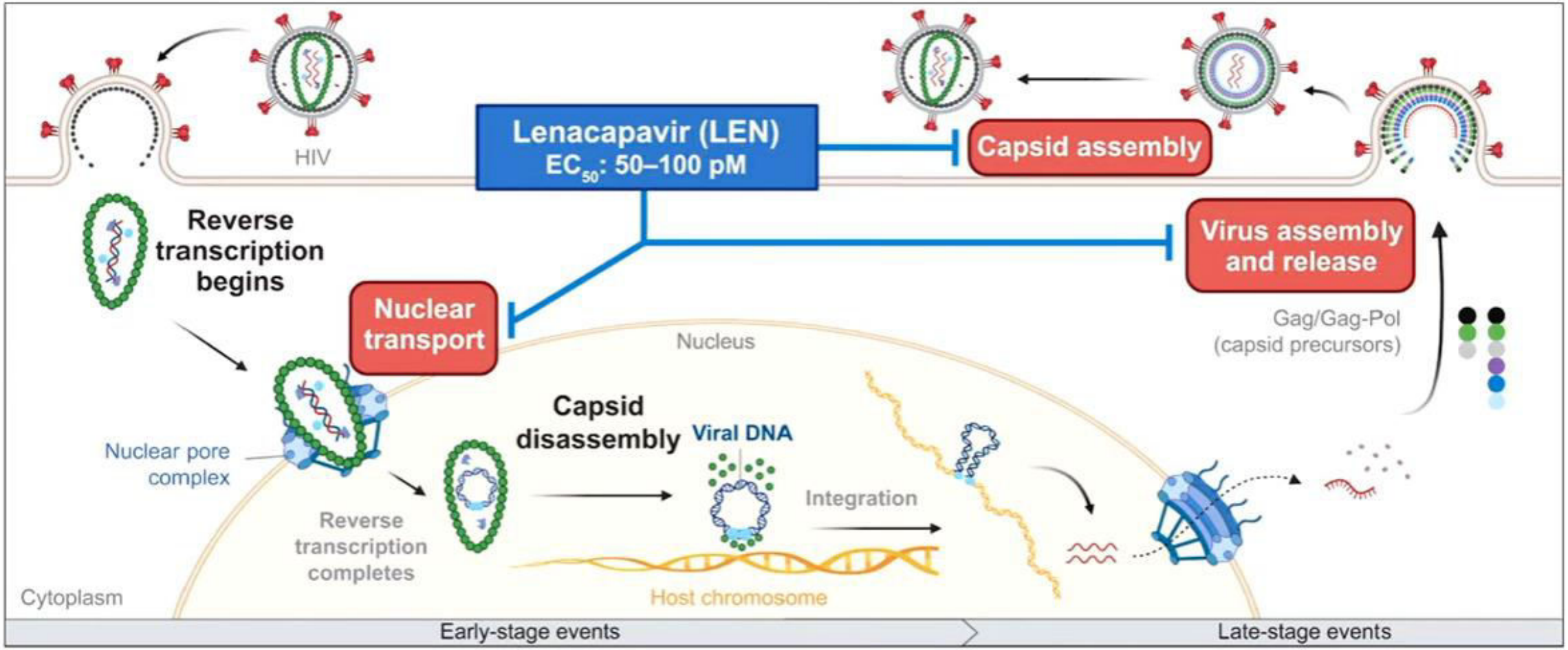
ART history

- AZT monotherapy x 6 months then dual NRTI therapy
- In mid '90's, ddI/d4T/indinavir/ritonavir as well as nelfinavir and saquinavir/RTV
- In 2001, TDF/FTC/EFV for many years with drug holidays but then viremia, NNRTI mutations
- Switched to ATV/r + RAL + TDF/FTC and eventually DRV/cobi + DTG + TAF/FTC. Suppressed but pill fatigue precludes ongoing use

Cumulative mutation history on genotypes:

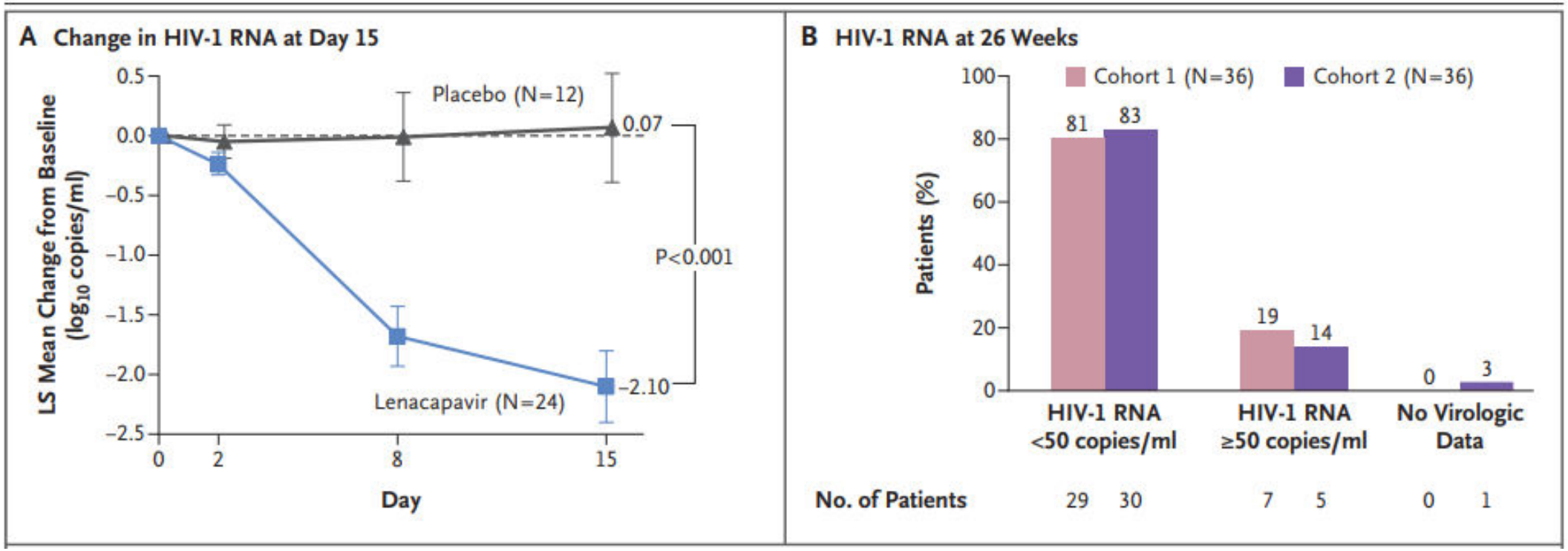
- NRTI: K67N, K219Q, T215I, M184V,
- PI: M46L
- **NNRTI: G190S, V106I, F227L, V179T**
- INSTI: none
- Not CCR5 tropic (10/2019)

LEN Targets Multiple Stages of HIV Replication Cycle



CAPELLA STUDY- Lenacapavir in MDR HIV

Approved for MDR HIV now in Europe and in the US since December 2022



Segal Maurer NEJM 2022

Bottom line on LEN resistance in MDR study

Efficacy and safety of the novel capsid inhibitor lenacapavir to treat multidrug-resistant HIV: week 52 results of a phase 2/3 trial

Published: July 11, 2023

THE LANCET HIV

Phase 2/3: LEN in HTE PLWH

Postbaseline Resistance Analysis at Week 52

Capella

Resistance category, n (%)	Randomized cohort n = 36	Nonrandomized cohort n = 36	Total N = 72
Resistance analysis population	11 (31)	11 (31)	22 (31)
With data	11 (31)	10 (28)	21 (29)
With LEN resistance	4 (11)	5 (14)	9 (13)
M66I, n	4	2	6
Q67H/K/N, n	1	3	4
K70H/N/R/S, n	1	3	4
N74D, n	3	0	3
A105S/T, n	3	1	4
T107A/C/N, n*	1	3	4

- Since Week 26, one additional participant had emergent LEN resistance at Week 52 (*Q67H*)
- All 9 participants with emergent LEN resistance were at high risk for resistance development
  - 4 had no fully active drugs in OBR
  - 5 had inadequate adherence to OBR
- All 9 remained on LEN
  - 4 participants resuppressed at a later visit (2 without OBR change and 2 with OBR change)
- The most common pattern was *M66I* ± other mutations (median LEN fold change was 234)

All nine cases of emergent LEN resistance occurred in the setting of functional monotherapy. More than half of participants who met criteria for resistance testing did not develop LEN resistance

*1 participant had emergent *T107A* mutation in capsid, with no loss in LEN susceptibility before achieving HIV -1 RNA suppression; the participant was not categorized as having emergent capsid resistance. HTE, heavily treatment-experienced; OBR, optimized background regimen

Ogbuagu O, et al. IDWeek 2022, Oral 1585

- Mutations to put into your phone contact: M66I, K70S, T107A, N74D, A105T, K70S, Q67H
- All 9 out of 72 occurred during "functional" monotherapy – not having support of OBR

Case continued

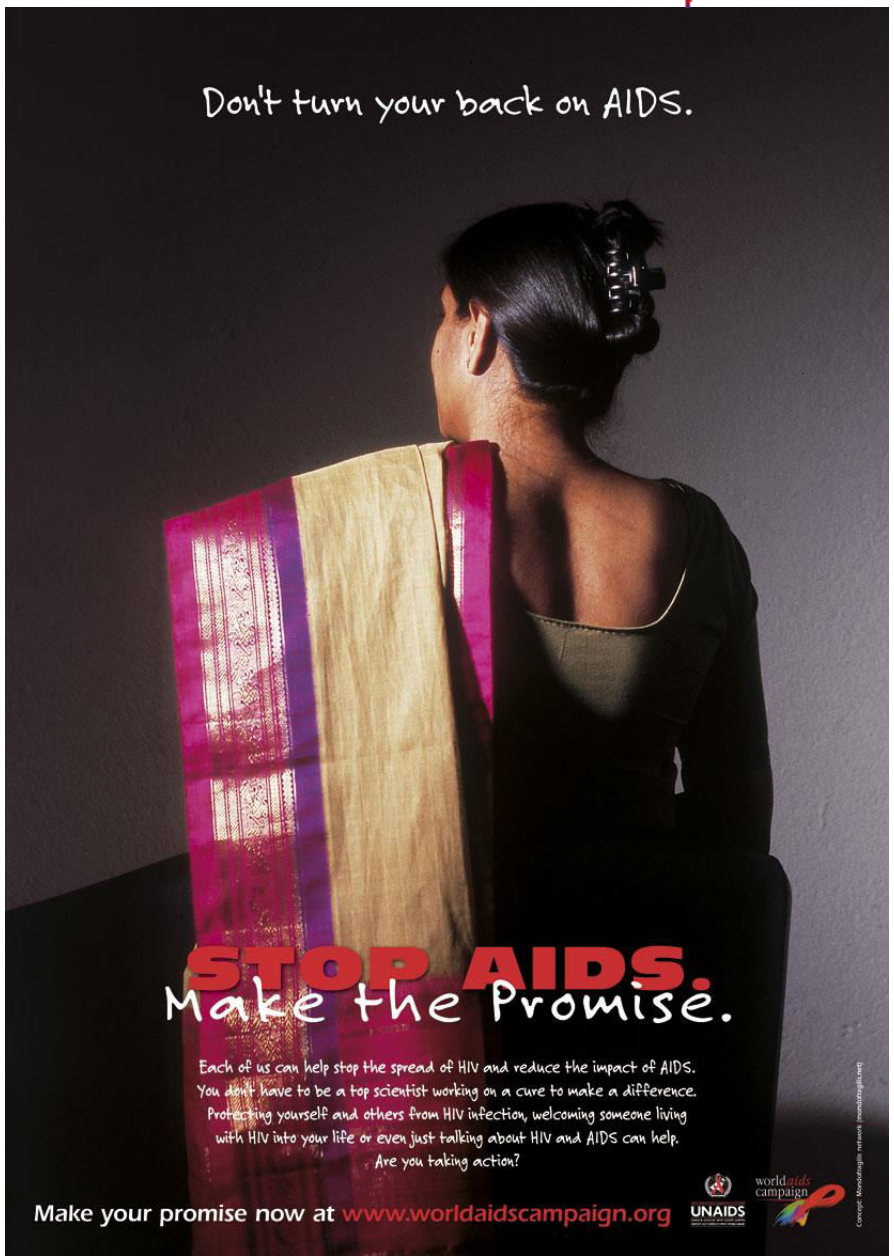
- Despite adherence counseling, viral load now >1.5 million, CD4 142 cells/mm^3
- Patient cannot take oral ART anymore
- ……
- Started patient on lenacapavir 600mg (300mg oral dose x 2) on day 0 and 1 with lenacapavir 927mg sq on day 0
- Added cabotegravir 600mg IM that day and 450mg every month
- Viral load dropped 2-log HIV RNA within 1 week and undetectable by 2 months after starting this regimen
- Case series assembled of 34 patients on LEN/CAB (submitted to CROI)- 94% VS rate

- **Bottom line**: STUDY PROPOSED IN THE ACTG OF LONG-ACTING LEN + LONG-ACTING CABOTEGRAVIR IN PARTICIPANTS WITH NNRTI RESISTANCE (~10% WORLDWIDE- WHO resistance report Nov '21)

Conclusion- how do we get there?

- First line therapy worldwide is TLD- potent, high genetic barrier to resistance but overall VS rates are still 59-71% on ART
- Increasing VS rates will help break cycle of transmission along with expanding PrEP
- Increasing VS rates will take two major intervention in my opinion
  - Scalable adherence interventions using low-cost measures
  - Providing long-acting ART in LMICs
- Given degree of NNRTI resistance worldwide, need another option for LA ART globally – LEN/CAB is closest option
- Subcutaneous formulations (long-acting) and implants in development

stop aids. make the promise



Thank you to IAPAC and Fast Track Cities conference, Division of HIV, ID and Global Medicine, the HIV movement, and Ward 86!