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

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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?
<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Comparator</th>
<th>Outcome</th>
<th>Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1489</td>
<td>Naïve</td>
<td>DTG/ABC/3TC</td>
<td>Non-inferior</td>
<td>0</td>
</tr>
<tr>
<td>1490</td>
<td>Naïve</td>
<td>DTG+FTC/TAF</td>
<td>Non-inferior</td>
<td>0</td>
</tr>
<tr>
<td>1844</td>
<td>Suppressed</td>
<td>DTG/ABC/3TC</td>
<td>Non-inferior</td>
<td>0</td>
</tr>
<tr>
<td>1878</td>
<td>Suppressed</td>
<td>Boosted PI + 2 NRTIs</td>
<td>Non-inferior</td>
<td>0 to INSTI but 1 L74V in PI arm</td>
</tr>
<tr>
<td>1961</td>
<td>Suppressed</td>
<td>E/C/F/(TAF or TDF) ATV+RTV + FTC/TDF</td>
<td>Non-inferior</td>
<td>0 to INSTI but 1 M184V in ELV/cobi</td>
</tr>
</tbody>
</table>

**BICTEGRAVIR**

**DOLUTEGRAVIR**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Comparator</th>
<th>Outcome</th>
<th>Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>SINGLE</td>
<td>Naïve</td>
<td>EFV/TDF/FTC</td>
<td>Superior</td>
<td>0 in DTG arm; 7 in EFV</td>
</tr>
<tr>
<td>FLAMINGO</td>
<td>Naïve</td>
<td>DRV/r with 2 NRTI backbone</td>
<td>Superior</td>
<td>0 in either</td>
</tr>
<tr>
<td>SPRING-2</td>
<td>Naïve</td>
<td>RAL with 2 NRTI backbone</td>
<td>Non-inferior</td>
<td>0 in DTG; 1 INSTI/NRTI in RAL</td>
</tr>
</tbody>
</table>
ACCUMULATING DATA FOR INSTIS AS 2\textsuperscript{ND} 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 \geq 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

Cahn P. Lancet 2013. 382(9893):700-8
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
## Recent studies of DTG with NRTI resistance-1st and 2nd line worldwide

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

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

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

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

Summary
- Background: The risk of sexual transmission of HIV from individuals with low-level HIV viraemia receiving...
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?
The 12 mutations every HIV provider should know

- **NNRTI**
  - K103N (EFV, NVP)
  - Y181C (ETR)
  - E138K (RPV)
  - I will send you doravirine contact

- **NNRTI**
  - K103N (EFV, NVP)
  - Y181C (ETR)
  - E138K (RPV)

- **PI, INSTI**
  - None (can look up and will send darunavir contact)

- **Capsid inhibitor**
  - None (can look up and will send lenacapavir contact)

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
## D2EFT Study

**DTG + DRV/r - D2EFT study**

<table>
<thead>
<tr>
<th>Name of study</th>
<th>Type of study, n</th>
<th>Comparison</th>
<th>Outcome</th>
<th>Emergent resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>D2EFT</strong></td>
<td>international randomized open-label trial in patients failing NNRTI therapy, n=831</td>
<td>DTG + DRV/r vs DTG + 2NRTIs vs DRV/r + 2 NRTIs</td>
<td>DTG + DRV/r superior to either regimen</td>
<td>None but doesn’t mean DTG/DRV/r needed, would stick with DRV as 2&lt;sup&gt;nd&lt;/sup&gt; line with 2 NRTIs</td>
</tr>
</tbody>
</table>
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**Adherence Challenges with ARTs**

**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)

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

**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

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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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Adherence – we are not the only ones

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


About 25-50% of patients discontinue statins within one year of treatment.

Cost to society $290 billion (rivaling cancer treatment)

Nonadherence has been labeled America’s "other drug problem"
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 gets measured gets managed.”

—Peter Drucker
What are current ways to measure adherence?

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

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>
</tr>
</thead>
<tbody>
<tr>
<td>Self-report</td>
<td>91%</td>
<td>95%</td>
</tr>
<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>
</tr>
</tbody>
</table>

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

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>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>TFV/FTC</td>
<td>LC-MS/MS(^1)-(^3)</td>
</tr>
<tr>
<td>PBMC</td>
<td>TFV-DP/ FTC-TP</td>
<td>LC-MS/MS(^1),(^4)</td>
</tr>
<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>
</tr>
</tbody>
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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. 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

- **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 adherent¹
- 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

¹Gandhi Eclinical Medicine 2018; Gandhi JAIDS 2019; Spinelli JAIDS 2020; Gandhi AIDS 2020
STUDIES DEMONSTRATING UTILITY OF TEST
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
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

Jennings AIDS Res Hum Retro 2022; McCluskey S CID 2023; Hermann L CID 2023
Intermittent adherence (drug detectability of DTG) sets up conditions for resistance.

Comparison with previous surveys in South Africa 2019-2022

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

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

- **Months 0, 1, 2, 3, 4, 5**
  - Urine TFV assay-informed counseling delivered.
  - Acceptability surveys, qualitative interviews

- **Month 6**
  - EAC alone delivered.
  - Urine collected but assayed at end of study.

- **Months 9, 12, 18, 24**
  - All participants
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### 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 518
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
RESULTS

- 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)

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

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

*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

Gandhi Annals of Internal Medicine 2023
RESULTS (continued)

- 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 \rightarrow 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 \rightarrow 4,371 copies/mL); Developed R263K, E138K mutations.

*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.
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)
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.
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

Lenacapavir (LEN) EC₅₀: 50–100 pM

Capsid assembly

Virus assembly and release

Gag/Gag-Pol (capsid precursors)

Nuclear transport

Reverse transcription begins

Nuclear pore complex

Reverse transcription completes

Capsid disassembly

Viral DNA

Integration

Host chromosome

Cytoplasm

Nucleus

Early-stage events

Late-stage events
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

- 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

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

- 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)
Case continued

- Despite adherence counseling, viral load now >1.5 million, CD4 142 cells/mm³
- 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
Thank you to IAPAC and Fast Track Cities conference, Division of HIV, ID and Global Medicine, the HIV movement, and Ward 86!