Antiretroviral Therapy for Treatment and Prevention: Beyond Daily Oral Therapy - A New Frontier

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• Grant support
  • Merck
  • TaiMed
  • GlaxoSmithKline

• Consultant
  • Thera
  • TaiMed
  • Merck

• Speakers Bureau
  • Gilead Sciences
Outline

• Review the current recommendations for cART as treatment and prevention
  • Why do we need alternatives to daily oral therapy?
• Long acting injectable ARVs for treatment and prevention
  • LA cabotegravir and Rilpivirine for the treatment of HIV-1 infection
  • CAB LA as PrEP
• Broadly neutralizing antibodies (bNAbs) for the treatment and prevention of HIV infection
• Islatravir (MK-8591, EFdA) for the prevention of HIV infection.
Virologic Outcome at Weeks 48, 96 and 144

FDA Snapshot Analysis*

- Studies 1489 & 1490: B/F/TAF vs DTG/ABC/3TC and DTG+FTC/TDF in ART-Naïve Adults

**B/F/TAF was non-inferior to triple therapy DTG regimens in ART-naïve population through W144**

* Difference (95%CI)


* Difference (95%CI)
PrEP Works if You Take It — Effectiveness and Adherence in Trials of Oral and Topical Tenofovir-Based Prevention

![Graph showing the relationship between percentage of participants' samples with detectable drug levels and effectiveness.](image)

- CAPRISA 004 (tenofovir gel, BAT-24 dosing)
- FEM-PrEP
- IPERGAY (TDF/FTC)
- iPrEx
- Partners PrEP (TDF)
- Partners PrEP (TDF/FTC)
- PROUD (TDF/FTC)
- TDF2
- VOICE (TDF)
- VOICE (TDF/FTC)
- VOICE (tenofovir gel, daily dosing)
PrEP persistence

• Most PrEP adopters stop use in 6 to 12 months
  • SF Dept. of Public Health Primary care clinics report that the mean time of use is 8.2 months.
    • Black
    • Trans-females
    • People who inject drugs

• Factors
  • Individual
    • Perception of reduced risk
    • Side effects
    • Difficulty with adherence to daily pill taking
  • Contextual
    • Ability to afford the medication and health care associated with PrEP use (insurance)
    • Health care system relationship including clinic, provider, and pharmacy issues
    • Stigma

Laborde et al. AIDS and Behavior 2020
Beyond daily oral therapy: IM LA-CAB/RPV

• Based on Phase 2b and Phase 3 RCTs, 2-drug maintenance therapy is likely to be the first novel delivery modality approved to treat HIV infection\textsuperscript{1, 2, 3}.

• Benefit of monthly to every 2 month injections\textsuperscript{4}
  • Reduced dosing frequency
  • Adherence to visits becomes more critical than daily pill taking.

• Quality of life questionnaires in Phase II and III studies\textsuperscript{1, 5}
  • Very high levels of satisfaction despite injection site reactions- 98 to 99%
  • Participants appreciated convenience, reduced risk of inadvertent disclosure, and the daily reminder of HIV infection status when dosing daily
  • Felt stigma of HIV infection was reduced.
  • However, wanted longer intervals between treatments.

\textsuperscript{1.} Margolis et al Lancet 2017, \textsuperscript{2.} Orkin et al CROI 2019 #140, \textsuperscript{3.} Swindells et al CROI 2019 #139, \textsuperscript{4.} Fernandez et al. HIV AIDS Research and Palliative Care 2019, \textsuperscript{5.} Kerrigan et al Plos One, 2018.
LATTE 2: Study design

Margolis et al Lancet, 2017
LATTE 2: LA CAB/RPV as maintenance therapy

Margolis et al Lancet, 2017
### Flair: week 48 results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Long-Acting Therapy (N=283)</th>
<th>Oral Therapy (N=283)</th>
<th>Difference (95% CI)*</th>
<th>Adjusted Difference (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intention-to-treat exposed population</td>
<td></td>
<td></td>
<td>percentage points</td>
<td></td>
</tr>
<tr>
<td>HIV-1 RNA level — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 copies/ml</td>
<td>265 (93.6)</td>
<td>264 (93.3)</td>
<td>0.4 (-3.7 to 4.4)</td>
<td>0.4 (-3.7 to 4.5)</td>
</tr>
<tr>
<td>≥50 copies/ml†</td>
<td>6 (2.1)</td>
<td>7 (2.5)</td>
<td>-0.4 (-2.8 to 2.1)</td>
<td>-0.4 (-2.8 to 2.1)</td>
</tr>
<tr>
<td>Level not below threshold</td>
<td>2 (0.7)</td>
<td>2 (0.7)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Discontinued treatment for lack of efficacy</td>
<td>4 (1.4)</td>
<td>3 (1.1)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Discontinued treatment for other reasons</td>
<td>0</td>
<td>2 (0.7)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>No virologic data</td>
<td>12 (4.2)</td>
<td>12 (4.2)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Withdrew from trial owing to adverse event or death</td>
<td>8 (2.8)</td>
<td>2 (0.7)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Withdrew from trial for other reasons</td>
<td>4 (1.4)</td>
<td>10 (3.5)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

**Subgroup analysis of HIV-1 RNA level ≥50 copies/ml — no./total no. (%)**

| Sex at birth                                |                             |                      |                       |                               |
|---------------------------------------------|-----------------------------|----------------------|                       |                               |
| Male                                        | 3/270 (1.4)                 | 6/219 (2.7)          | -1.4 (-4.7 to 1.6)   | —                             |
| Female                                      | 3/63 (4.8)                  | 1/64 (1.6)           | 3.2 (-4.3 to 12.0)   | —                             |

| Baseline HIV-1 RNA level                   |                             |                      |                       |                               |
|--------------------------------------------|-----------------------------|----------------------|                       |                               |
| <100,000 copies/ml                         | 4/227 (1.8)                 | 5/227 (2.2)          | -0.4 (-3.6 to 2.5)   | —                             |
| ≥100,000 copies/ml                         | 2/56 (3.6)                  | 2/56 (3.6)           | 0.0 (-9.2 to 9.2)    | —                             |

| Per-protocol population                    |                             |                      |                       |                               |
|--------------------------------------------|-----------------------------|----------------------|                       |                               |
| HIV-1 RNA level — no./total no. (%)       |                             |                      |                       |                               |
| <50 copies/ml                               | 262/278 (91.5)             | 263/282 (93.1)       | 0.3 (-3.9 to 4.4)    | 0.3 (-3.8 to 4.4)             |
| ≥50 copies/ml                               | 5/278 (1.8)                 | 7/282 (2.5)          | -0.3 (-2.8 to 2.2)   | -0.3 (-2.8 to 2.2)            |

Orkin et al NEJM 2020
Atlas: week 48 result

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Long-Acting Therapy (N=308)</th>
<th>Oral Therapy (N=308)</th>
<th>Difference (95% CI)</th>
<th>Adjusted Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intention-to-treat exposed population</strong></td>
<td>percentage points</td>
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</tr>
<tr>
<td>HIV-1 RNA level — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 copies/ml</td>
<td>283 (92.5)</td>
<td>284 (93.9)</td>
<td>-2.9 (-6.7 to 0.8)</td>
<td>-2.9 (-6.7 to 0.7)</td>
</tr>
<tr>
<td>&gt;50 copies/ml</td>
<td>5 (1.6)</td>
<td>3 (1.0)</td>
<td>0.6 (-1.1 to 2.4)</td>
<td>0.6 (-1.1 to 2.4)</td>
</tr>
<tr>
<td>Level not below threshold — no. (%)</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Discontinued treatment for lack of efficacy — no. (%)</td>
<td>3 (1.0)</td>
<td>2 (0.6)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Discontinued treatment for other reason — no. (%)</td>
<td>1 (0.3)</td>
<td>0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>No virologic data — no. (%)</td>
<td>18 (5.8)</td>
<td>11 (3.6)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Withdrawn from trial because of adverse event or death</td>
<td>11 (3.6)</td>
<td>5 (1.6)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Withdrawn from trial for other reasons</td>
<td>7 (2.3)</td>
<td>6 (1.9)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>HIV-1 RNA level ≥200 copies/ml — no. (%)</td>
<td>286 (92.9)</td>
<td>295 (95.8)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

**Subgroup analysis of HIV-1 RNA level ≥50 copies/ml — no. (%)**

<table>
<thead>
<tr>
<th>Sex at birth</th>
<th>Percentage (95% CI)</th>
<th>Percentage (95% CI)</th>
<th>Difference (95% CI)</th>
<th>Adjusted Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>2/99 (2.0)</td>
<td>0/104</td>
<td>2.0 (-1.7 to 7.1)</td>
<td>—</td>
</tr>
<tr>
<td>Male</td>
<td>3/209 (1.4)</td>
<td>3/204 (1.5)</td>
<td>0.0 (-3.0 to 2.9)</td>
<td>—</td>
</tr>
</tbody>
</table>

**Baseline third-agent class**

<table>
<thead>
<tr>
<th>Class</th>
<th>Percentage (95% CI)</th>
<th>Percentage (95% CI)</th>
<th>Difference (95% CI)</th>
<th>Adjusted Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI</td>
<td>1/15 (2.0)</td>
<td>0/54</td>
<td>2.0 (-5.0 to 10.0)</td>
<td>—</td>
</tr>
<tr>
<td>INSTI</td>
<td>0/102</td>
<td>2/99 (2.0)</td>
<td>-2.0 (-7.1 to 1.8)</td>
<td>—</td>
</tr>
<tr>
<td>NNRTI</td>
<td>4/155 (2.6)</td>
<td>4/155 (0.5)</td>
<td>1.9 (-1.3 to 5.9)</td>
<td>—</td>
</tr>
</tbody>
</table>

**Median change from baseline in CD4+ lymphocyte count (range) — per mm³**

<table>
<thead>
<tr>
<th>HIV-1 RNA level ≥50 copies/ml — no. (%)</th>
<th>Percentage (95% CI)</th>
<th>Percentage (95% CI)</th>
<th>Difference (95% CI)</th>
<th>Adjusted Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.0 (-536 to 801)</td>
<td>13.3 (-1043 to 521)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Swindells et al NEJM 2020
Caveats

• Adverse events common
  • Pain at the injection site was the most common adverse event
    • Flair: 86% lasting 3 days on average
    • Atlas: 83% lasting 3 days on average
    • Nearly all mild-moderate
  • ISRs results in treatment discontinuation in a total of 8 subjects in the 2 studies

• Two-class resistance is demonstrated in a small number of subjects with virologic failure
  • Degree of resistance is low-level to both RPV and CAB
  • Clinical significance is not known

• Loss to follow up likely to result in emergence of resistance
  • Long tail of drugs following injection

CAB-LA protects RM against repeated low dose rectal challenge of SHIV162P3: a PrEP model

Treated animals had a 28.2-fold lower risk of infection
With a 95% C.I. of 5.8-136.8

Andrews et al Science 2014
CAB-LA is 100% effective at >3xPAIC$_{90}$
ÉCLAIR- Phase 2a: 800 mg CAB-LA every 12 weeks

- Long acting Cabotegravir was safe
- Injection site reactions were common
- Mild to moderate pain lasting 5 days

Markowitz et al, Lancet HIV 2017
HPTN077 Phase 2a: 600 mg CAB-LA every 8 weeks

Landovitz et al, PLOS Med. 2018
Phase 3 studies of CAB-LA as PrEP

- HPTN 083- PI: Landovitz (UCLA)
  - Double blind double dummy comparison to FTC/TDF in MSM/TGW
  - Enrolled 4,569 out of planned 5,000
    - Powered for non-inferiority
  - 43 sites in the US, Peru, Brazil, Argentina, South Africa, Thailand, and Vietnam
  - Enrollment is frozen due to SARS-CoV-2 pandemic

- HPTN 084- PI: Delany-Moretiwe (S.A.)
  - Double-blinded double dummy study comparison to FTC/TDF in cisgender women in sub-Saharan Africa
  - Enrolled 3032 out of planned 3200
    - Powered for superiority
  - 20 sites in 7 countries including SA, eSwatini, Botswana, Zimbabwe, Kenya, Malawi and Uganda
  - Enrollment is frozen due to SARS-CoV-2 pandemic however reduced frequency of follow-up visits continue
Press release: May 18, 2020

• Interim analysis from HPTN 083 study shows investigational, long-acting injectable cabotegravir (CAB LA) administered every two months is 69% more effective than daily pills in preventing HIV acquisition.

• The study achieved its primary objective of non-inferiority with the difference approaching superiority in favor of cabotegravir, pending final analysis.

• 50 people in the trial acquired HIV
  • 12-long-acting cabotegravir arm
  • 38- daily, oral FTC/TDF arm.
  • HIV incidence rate of 0.38% (95% confidence interval [CI] 0.20%- 0.66%) in the cabotegravir group and 1.21% (95% CI 0.86%-1.66%) in the FTC/TDF group.

• Adherence to oral FTC/TDF was high, based on a random subset sampling that detected tenofovir (> 0.31 ng/ml) in 87% of all samples tested.
Broadly neutralizing monoclonal antibodies to HIV

• Cloned from B cells of HIV-1 infected individuals\(^1\)
  • Generally infected for long periods of time
  • Highly mutated from germ line sequences
  • Have emerged from advances in science- “single antibody cloning methods”\(^2,3\)
  • Have entered clinical trials in both HIV infected and uninfected individuals.

Broadly neutralizing antibodies to sites on HIV-1 gp120/gp41

McCoy and Burton, Imm Rev. 2017
Alterations to bNAbS to improve pharmacokinetics

- IgG binds to the neonatal Fc receptor on endothelial cells
- Endocytosis brings IgG into the endothelial cell where it becomes unbound and degraded.
- IgG that remains bound is recirculated to the serum
- Increased affinity of the bNab for the neonatal Fc receptor results in more favorable PK profiles; referred to as LS variants

<table>
<thead>
<tr>
<th>MONOCLONAL ANTIBODY</th>
<th>SERUM HALF LIFE IN VIVO (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VRC01</td>
<td>15 ± 3.9</td>
</tr>
<tr>
<td>VRC01-LS</td>
<td>71 ± 18</td>
</tr>
<tr>
<td>VRC07</td>
<td>ND</td>
</tr>
<tr>
<td>VRC07-523LS</td>
<td>33+ 10</td>
</tr>
</tbody>
</table>

Caskey Nat Med 2019
bNAbs for HIV treatment: 3BNC117 and 10-1074

Bar-On et al. Nature Medicine 2018
bNAbs for HIV treatment: 3BNC117 and 10-1074

Bar-On et al. Nature Medicine 2018
bNAbs for HIV treatment: 3BNC117 and 10-1074

Bar-On et al. Nature Medicine 2018
Caveats: bNAbs for treatment and prevention

• Safety
  • To date bNAbs appear to be safe with minimal adverse events related to administration.
  • Clinically significant anti-drug antibodies are rare
• Combination therapy will be required for treatment
  • Cost
  • Can the antibodies be dosed subcutaneously?
  • Challenge to the health care delivery system
• Unclear whether a single broad and potent bNAb is adequate for prevention
• Resistance issues
  • Requires identification of broadest and most potent to avoid resistance as treatment
  • To avoid rapid emergence of resistance, maintenance may be preferable to de novo therapy

Caskey et al, Nat Med 2019
Trispecific bNAb: VRC01 + 10E8.4+ PGDM1400

Xu et al. Science 2017
Trispecific bNAb: activity in vitro and in vivo: protects against rectal challenge with SHIV in RM

Xu et al. Science 2017
Islatravir (MK-8591, EFdA): the first nucleoside reverse transcriptase translocation inhibitor

Markowitz and Grobler Curr Opin HIV AIDS 2020
ISL is a long-acting antiretroviral agent in vivo

Matthews et al, IAS 2017
Grobler et al, CROI 2016
The Continuum of HIV Prevention

**Preexposure Prophylaxis**
- Proven effective when adhered to in high-risk MSM, discordant couples, and high-risk women
- FTC/TDF current standard of care though FTC/TAF shown non-inferior to FTC/TDF in MSM

**Postexposure Prophylaxis (PEP)**
- Current standard of care is daily combination antiretroviral therapy for 30 days initiated <72 hours following exposure

**On Demand**
- Studied in MSM only
- Requirement for both pre- and post-exposure administration of FTC/TDF

Markowitz  CROI 2020
ISL as PrEP

41.5-fold lower risk of infection (95% C.I. 7.3, 237.9)
P<0.0001 log rank test

Markowitz et al JID 2019
ISL as PrEP

10% Tween 5mL/kg with MK-8591 1.3 mg/kg/week (6 time points)
10% Tween 5mL/kg with MK-8591 0.43mg/kg/week (6 time points)

Repeated Low Dose IR Challenge- 50TCID50 SHIV (4 challenges x 2)

Blood draws

Washout/ Follow-up Phase

Percent uninfected

Placebo
MK-8591

0.0 0.1 0.2 0.3 0.4
MK8591-TP (pmol/10^6 PBMC)

1 2 3 4
challenges

41.5-fold lower risk of infection (95% C.I. 7.3, 237.9)
P<0.0001 log rank test

Markowitz et al JID 2019
Markowitz et al JID 2019
Levels of ISL-TP affording statistically significant protection in the RM/SHIV model

<table>
<thead>
<tr>
<th>MK-8591 Dose (mg/kg)</th>
<th>MK-8591 Dose Ratio to Index(^1)</th>
<th>Mean MK-8591-TP Levels at Challenge (fmol per 10(^6) PBMC) Mean (range)</th>
<th>Ratio of Mean MK-8591-TP Level to Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.9</td>
<td>1</td>
<td>810 (339 – 1616)</td>
<td>1</td>
</tr>
<tr>
<td>1.3</td>
<td>0.33</td>
<td>282 (161 – 399)</td>
<td>0.35</td>
</tr>
<tr>
<td>0.43</td>
<td>0.11</td>
<td>102 (68 – 159)</td>
<td>0.125</td>
</tr>
<tr>
<td>0.10</td>
<td>0.025</td>
<td>24(^2)</td>
<td>0.029</td>
</tr>
</tbody>
</table>

\(^1\) Markowitz et al JID 2019
ISL Implant Design Similar to Nexplanon®

- ISL implant based on Implanon®/Nexplanon®
  - Uses same polymer
  - Removable (not bioerodible)
- Able to use Nexplanon® applicator

- Initial trial uses prototype implant

Matthews et al IAS 2019
62 mg Implant Projected to Lead to Concentrations Above Threshold for at Least 12 Months

- 62 mg implant will continue to release through 52 weeks
- ISL-TP should be above threshold (0.05 pmol/10⁶ cells) for >12 months
  - Projected concentration at 12 months: **0.076 pmol/10⁶ cells**
  - Projected time at which concentration falls below 0.05 pmol/10⁶ cells: 68-70 weeks (~16 months) Matthews et al IAS 2019
Conclusions: ISL as PrEP

• ISL is completely protective against low dose rectal challenge with SHIV 109CP3 in the rhesus macaque model at doses as low as 0.43 mg/kg orally weekly
  • The EC$_{90}$ of ISL-TP is 24 fmol/10$^6$ PBMC- comparable to that for TDF-DP in RM
  • The half life of ISL-TP in humans is 130 to 210 hrs. compared to 50 hrs. in RM
  • The concentrations at which ISL is highly protective are clinically relevant

• ISL can be formulated in a polymeric matrix and has been shown to release clinically relevant doses of ISL for up to 52 weeks in vivo
  • Implants are removable
  • May be combined with other modalities such as contraceptives
Evaluation of PEP Efficacy With Up To Four Weekly ISL Oral Doses in Rhesus Macaques

- **Stage 1:** 4 weekly doses starting 24 hours after inoculation
- **Stage 2:** 3 weekly doses starting 24 hours after inoculation
- **Stage 3:** 2 weekly doses starting 24 hours after inoculation
- **Stage 4:** 1 weekly dose starting 24 hours after inoculation

ISL-TP is not detectable in rhesus PBMCs **3 weeks** following the last dose of 3.9-mpk ISL.

- The same animals were used in each stage
- Stages were separated by **7 weeks** after the last ISL dose

Markowitz CROI 2020
ISL Provides Complete Protection Against Infection When Administered 24 Hours After IV Challenge with SIVmac251 with Two or More Weekly Doses

Markowitz CROI 2020
ISL Administered Once 24 Hours After Challenge Is Effective in Reducing Infection

- When ISL was administered only once 24 hours after challenge, two of six animals became infected with M184M SIVmac251 (viremia detected at Day 14 and Day 49)
Single Oral Doses of ISL Given Within 24 Hours of Infection May Provide an Effective PEP Option in Humans

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Minimum ISL-TP Trough Exposure (pmol/10^6 cells) Post Last Dose</th>
<th>Response (protection)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>Day 7 0.005, Day 14 0.007</td>
<td>Full (6/6)</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Day 7 0.026, Day 14 0.007</td>
<td>Full (6/6)</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Day 7 0.079, Day 14 0.016</td>
<td>Full (6/6)</td>
</tr>
<tr>
<td>Stage 4</td>
<td>Day 7 0.050, Day 14 0.033</td>
<td>Partial (4/6)</td>
</tr>
</tbody>
</table>

Exposure response relationship in monkey PEP study

Single oral doses of ISL in humans may be effective for PEP

Markowitz et al CROI 2020
Conclusions

• Advances in daily oral therapy for HIV treatment and prevention have resulted in the availability of conveniently dosed once-pill once-daily options that are well tolerated.

• Nevertheless there remains a need for alternatives to daily oral therapy for treatment and prevention to improve treatment and prevention outcomes.

• Injectable intramuscular LA CAB/RPV therapy is non-inferior to triple combination therapy as maintenance.

• CAB LA has been found to be non-inferior to daily oral TDF/FTC

• bNAbs will surely change the treatment and prevention landscape.

• Implantable ISL is on the horizon for prevention
  • Removable in the event of adverse events
  • May be combined with other implantables such as contraceptives

• ISL may be the “morning after pill” for HIV prevention as NPEP