Investigational Approaches to Antiretroviral Therapy: New Strategies and Novel Agents
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Learning Objectives
After attending this presentation, learners will be able to:

▪ List several two-drug combinations that are being evaluated for initial or maintenance therapy
▪ Describe characteristics of the long acting injectable antiretroviral therapy in late-stage development
▪ Describe the mechanisms of action and potential uses of 2 entry inhibitors in development for patients with resistant virus

Outline of the Talk
▪ New Two-drug Strategies for Initial ART and treatment switch (long-acting therapy)
▪ Novel Agents for Resistant Virus
▪ New Agents in Early Development
ARS Question 1

- Your “go to” initial ART is
  1. Bictegravir/FTC/TAF
  2. Dolutegravir/abacavir/lamivudine
  3. Dolutegravir plus TAF (or TDF)/FTC
  4. Elvitegravir/cobi/TAF (or TDF)/FTC
  5. Darunavir/r (or cobi) plus TAF(or TDF)/FTC
  6. Rilpivirine/TAF (or TDF)/FTC
  7. Something else

What is needed for initial therapy?

- We have convenient, safe, effective unboosted integrase inhibitor therapy – do we need something else?
- Alternatives to INSTI – based therapy?
  - NNRTI – based therapy
    - with better tolerability,
    - less resistance and fewer dosing restrictions?
  - PI - based therapy
    - more convenient
    - Fewer drug-drug interactions
- Exposure to fewer agents?
  - Two drug combinations
- Alternative dosing strategies

Two Drug Regimens for Initial Therapy

- Rationale
  - “nuc-sparing” – a need that seems less critical now
  - advanced renal disease or TFV or ABC intolerance
  - Minimize ARV exposure for therapy that will last for decades
  - Cost
- Strategies
  - Boosted PI plus INSTI (NEAT 001)
  - Boosted PI plus 3TC (GARDEL and ANDES studies)
  - Dolutegravir plus 3TC (PADDLE, A5353, GEMINI)
Based on Cochran-Mantel-Haenszel stratified analysis adjusting for the following baseline stratification factors: plasma HIV-1 RNA (≤100,000 vs >100,000 c/mL) and CD4+ cell count (≤200 vs >200 cells/mm³).

Calculated from a repeated measures model adjusting for study, treatment, visit (repeated factor), baseline plasma HIV-1 RNA, baseline CD4+ cell count, treatment and visit interaction, and baseline CD4+ cell count and visit interaction.

**ARS Question 2**

- Based on the GEMINI 48 week data, in what setting will you use dolutegravir/3TC?
  1. As initial therapy with any baseline viral load
  2. As initial therapy in specific patients with lower viral loads
  3. As maintenance therapy in patients who are suppressed on 3-drug treatment
  4. I will wait until we have longer term (96 week data) with DTG/3TC to decide
  5. Only when insurance companies tell me to use it
  6. Something else
LATTE: Study of Long Acting Cabotegravir and Rilpivirine – 96 week data

Inclusion criteria
• ≥18 years old
• Naive to antiretroviral therapy
• CD4+ ≥200 cells/mm³

Exclusion criteria
• Positive for hepatitis B
• ALT ≥5 × ULN
• Creatinine clearance <50 mL/min

Qualification for maintenance
• HIV-1 RNA <50 c/mL between Week -4 and Day 1

Comparable Response Across Arms
Week 96 HIV-1 RNA <50 c/mL by Snapshot (ITT-ME)

Latte 2 Outcomes at 160 Weeks
256 completed MP with 252 entering EP

Table 1. Snapshot Outcomes at Week 160

<table>
<thead>
<tr>
<th>Outcome at Week 160</th>
<th>QSW IM n (%)</th>
<th>QSW IM n (%)</th>
<th>Optimized QSW IM n (%)</th>
<th>Optimized QSW IM n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1 RNA &lt;50 c/mL</td>
<td>N:115</td>
<td>N:115</td>
<td>N:10</td>
<td>N:10</td>
</tr>
<tr>
<td>Data in window not &lt;50 c/mL</td>
<td>1(1)*</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>DC for lack of efficacy</td>
<td>1(1)*</td>
<td>1(1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>DC for other reason not &lt;50 c/mL</td>
<td>3(3)*</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No virologic data in window</td>
<td>0 (3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>W/D due to AE or death</td>
<td>1(1)</td>
<td>12 (10)*</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>W/D due to other reasons</td>
<td>5 (1)</td>
<td>5 (1)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Data presented for the randomized QSW IM arms are inclusive of MP and EP. Data presented for thesnapshot QSW IM arms are inclusive of randomization-exposed subjects only. Thus, the ratio of live person-time is not the same as the ratio of person-time in the randomized trial. For the snapshot arms, person-time was calculated from Day 1 to the last HIV-1 RNA measurement at a snapshot visit, or the termination date (at any time point during the trial). For the randomized arms, person-time was calculated from randomization to the last HIV-1 RNA measurement at a snapshot visit, or the termination date (at any time point during the trial).
LA CAB and LA RPV Phase III studies

- **ATLAS** – randomized, open-label, non-inferiority study in participants stably suppressed on 3-drug ART comparing CAB LA 400 mg + RPV LA 600 mg q 4 weeks with maintenance of current ART regimen (2 NRTIs plus an INI, NNRTI, or a PI). 618 participants were randomized (1:1) to continue current ART or switch to oral therapy with CAB 30 mg + RPV 25 mg daily for 4 Weeks followed by Q4 weekly CAB LA + RPV LA injections.

- **FLAIR** – randomized, open-label, non-inferiority study in ART-naïve adult participants comparing CAB LA 400 mg + RPV LA 600 mg q 4 weeks to remaining on ABC/DTG/3TC over 48 weeks. 631 participants started ABC/DTG/3TC for 20 weeks and those with HIV RNA <50 c/mL after 16 weeks were randomized at 20 weeks to continue ABC/DTG/3TC or switch to oral therapy with CAB 30 mg + RPV 25 mg daily for 4 weeks, followed by monthly CAB LA + RPV LA injections.

- Both studies met their primary endpoints at 48 week (ViiV Press Releases)

- **ATLAS-2M** study compares q 8 wk CAB LA + RPV LA to q 4 wk CAB LA + RPV LA over a 48-week treatment period in approximately 2020 adult HIV-1 infected subjects.

Recently approved or in Phase III

**NEW THERAPY FOR RESISTANT VIRUS**
HIV Entry Inhibitors

- gp41
- gp120
- V3 loop
- CD4
- Binding
- Coreceptor Binding
- Virus-Cell Fusion

Ibalizumab

- Humanized monoclonal Ab: binds CD4 on host cells; blocks HIV entry (post attachment inhibitor)\(^1\)
- Active against CCR5 and CXCR4 tropic HIV
- No cross resistance with other ARVs\(^2\)
- IV infusion: 2,000 mg loading dose then 800 mg every 2 wks
- Duration of infusion: 15–30 min

Ibalizumab in Persons with Multi-Drug Resistant HIV

- Phase 3 trial: 40 heavily treatment experienced pts with 3-class ARV resistance, ≥1 active drug
- Primary endpt: VL drop >0.5 \(\log_{10}\) C/mL
  - 3% during control period
  - 83% after loading dose
- Regimen optimized at day 14
  - Wk 24: VL <200 in 50%
  - Expanded access: viral suppression to wk 48

\(^1\)Emu B et al, Abstract 1686, IDWeek 2017; Weinheimer S et al, CROI 2018
\(^2\)Ibalizumab in Persons with Multi-Drug Resistant HIV

Approved March 6, 2018
Fostemsavir (FTR): Oral HIV Attachment Inhibitor

- Prodrug of tamsavir: binds to gp120, inhibits HIV attachment to CD4
- Phase 3 trial in heavily treatment experienced patients with VF (BRIGHTe)

Kozal M et al, 16th EACS, 2017

Fostemsavir (FTR): Phase 3 Trial (BRIGHTe)

Mean VL Change at day 8

Randomized Cohort (n = 272)

Nonrandomized Cohort (n = 99)

Virologic response through wk 24 (observed analysis)

BRIGHTE: Efficacy at Wk 48 (FDA Snapshot)

<table>
<thead>
<tr>
<th>Outcome at Wk 48 [%]</th>
<th>Randomized Cohort (n = 272)</th>
<th>Nonrandomized Cohort (n = 99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1 RNA &lt; 40 c/mL (virologic success)</td>
<td>146 (54)</td>
<td>38 (38)</td>
</tr>
<tr>
<td>HIV-1 RNA = 40-400 c/mL (virologic failure)</td>
<td>104 (38)</td>
<td>32 (33)</td>
</tr>
<tr>
<td>Data in window below below threshold</td>
<td>72 (26)</td>
<td>33 (33)</td>
</tr>
<tr>
<td>D/C for lack of efficacy</td>
<td>6 (2)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>D/C due to other reasons while below threshold</td>
<td>9 (3)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Change in OBT</td>
<td>17 (6)</td>
<td>14 (14)</td>
</tr>
<tr>
<td>No virologic data</td>
<td>22 (8)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>D/C due to AE or death</td>
<td>15 (5)</td>
<td>8 (8)</td>
</tr>
<tr>
<td>D/C due to other reasons</td>
<td>5 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Missing data during window but on study</td>
<td>2 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Median CD4+ cell count change vs BL, cells/mm³ (IQR)</td>
<td>127 (14 to 264)</td>
<td>35 (1 to 121)</td>
</tr>
</tbody>
</table>
NOVEL AGENTS IN EARLY DEVELOPMENT

MK-8591 is More Potent Against WT and M184I Viruses Than Approved NRTIs

<table>
<thead>
<tr>
<th>Compound</th>
<th>Virus</th>
<th>IC50 (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MK-8591</td>
<td>W/T</td>
<td>0.2 ± 0.3 (n=8)</td>
</tr>
<tr>
<td>TAF</td>
<td>W/T</td>
<td>1.6 ± 0.6 (n=4)</td>
</tr>
<tr>
<td>TDF</td>
<td>W/T</td>
<td>2.8 ± 0.9 (n=8)</td>
</tr>
<tr>
<td>AZT</td>
<td>W/T</td>
<td>2.0 ± 0.5 (n=8)</td>
</tr>
<tr>
<td>STC</td>
<td>W/T</td>
<td>12.3 ± 10.3 (n=4)</td>
</tr>
</tbody>
</table>

Long-acting NRTI: MK-8591 (EFdA)

- Nucleoside RT translocation inhibitor (NRTI)
- Half life of active anabolite: ≈ 80-130 hr
- Humans: single oral dose as low as 0.5 mg suppressed HIV RNA for >7 days

Change From Baseline HIV-1 RNA

<table>
<thead>
<tr>
<th>Time (days)</th>
<th>Phase 1b, single-dose, monotherapy study</th>
</tr>
</thead>
<tbody>
<tr>
<td>MK-8591 0.5 mg</td>
<td>-3.0 ± 2.0</td>
</tr>
<tr>
<td>MK-8591 1 mg</td>
<td>-3.5 ± 2.5</td>
</tr>
<tr>
<td>MK-8591 30 mg</td>
<td>-3.0 ± 2.0</td>
</tr>
</tbody>
</table>

Grobler et al CROI 2017 #435
Matthews et al IAS 2017 #TUPDB0202LB

Study population: ART naïve (N=30)
Long-acting NRTI: MK-8591 (EFdA)

- Study in healthy volunteers: daily doses as low as 0.25 mg expected to lead to HIV suppression
- Phase 2b trial in people with HIV, in combination with doravirine (NNRTI) and 3TC, has started (DRIVE2Simplify)
  - Daily dosing
- Potential for once weekly or even once monthly dosing
  - "Partners wanted"

MK-8591 Parenteral Formulations Release Effective Drug Levels for >180 days

- Low dose amenable to extended-duration parenteral formulation
- >180-day extended release from solid state formulations after a single injection in rat
- Data suggest the potential to provide coverage for durations up to 1 year

GS-6207

HIV Capsid Acts at Multiple Stages in the Viral Life Cycle

Gilead’s capsid inhibitors inhibit HIV capsid function, resulting in aberrant core assembly/disassembly via multiple steps in HIV replication cycle
Potency

**ATV, atazanavir. DTG, dolutegravir. EFV, efavirenz. paEC, protein-adjusted effective concentration. RPV, rilpivirine.**

<table>
<thead>
<tr>
<th>Drug</th>
<th>EC50 (nM)</th>
<th>paEC95 (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFV</td>
<td>0.79 ± 0.06</td>
<td>44 ± 3</td>
</tr>
<tr>
<td>RPV</td>
<td>0.007 ± 0.005</td>
<td>46 ± 2</td>
</tr>
<tr>
<td>DTG</td>
<td>1.28 ± 0.14</td>
<td>106 ± 16</td>
</tr>
<tr>
<td>ATV</td>
<td>7.23 ± 0.50</td>
<td>150 ± 11</td>
</tr>
</tbody>
</table>

**GS-6207** is a potent inhibitor of all major HIV-1 subtypes

**GS-6207** is more potent than currently marketed ARVs

**GS-6207: Novel HIV Capsid Inhibitor with Long-Acting Potential**


**EC50** and Hill slope values (mean ± SD) obtained from at least 3 independent experiments performed in quadruplicate.

**EC95 = EC50 x (95/51/hillslope)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>EC50 (nM)</th>
<th>EC95 (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GS-6207 (0.10 ± 0.01)</td>
<td>4.0 ± 0.4</td>
<td></td>
</tr>
</tbody>
</table>

**GS-6207** is a potent inhibitor of all major HIV-1 subtypes

**GS-6207** is more potent than currently marketed ARVs

**Plasma PK in Rats and Dogs Following a Single SC Dose**

- Single subcutaneous injection maintains plasma concentrations well above paEC95 for >24 weeks in dogs
- PK supports long-acting administration, potentially Q3M or longer, in humans

**paEC95, plasma binding-adjusted effective concentration required to inhibit replication by 95%**

**Plasma PK in Rats and Dogs Following a Single SC Dose**

- **Rat 50 mg/kg (0.125 mL/kg)**
- **Dog 12 mg/kg (0.03 mL/kg)**

**Broadly Neutralizing Antibodies against HIV**

- Phase 2 studies in HIV infected patients
- Clear antiretroviral activity
- Combinations likely necessary
- Can be modified for longer half-life
- Every 3 to 6 month infusions possible

**MFGE12**

**V1/V2**

**V3 loop antigen**

**CD4-binding site**

**MIPER**

**Phase 1**

**Phase 2**

**Phase 3**

**Phase 4**

**New drug development**

**National Harbor, Maryland, December 9-11, 2018**
Combination bNAb, long-acting bNAb being studied for treatment, prevention.

Antiretroviral Therapy: The Future

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Question-and-Answer
Investigational Approaches to Antiretroviral Therapy: New Strategies and Novel Agents
Joseph J. Eron, Jr, MD

SUGGESTED READINGS


