Investigational Approaches to Antiretroviral Therapy

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Financial Relationships With Commercial Entities

Dr Gandhi has served as a consultant or advisor to Merck & Co, Inc. (Updated 11/11/19)

Learning Objectives

After attending this presentation, learners will be able to:
• Describe investigational approaches for treating people with HIV infection
• Discuss the pipeline for novel antiretroviral agents
Investigational Approaches to Antiretroviral Therapy

- Have we moved into the era of 2-drug therapy? New, emerging and investigational 2-drug regimens.
- What are the ART options in someone who has difficulty taking daily drugs? Long-acting ART.
- What about new medicines for treating someone with multi-drug resistant HIV?
- What’s on the horizon?

What to Start in Most People with HIV: Integrase Inhibitor + 2 NRTI

<table>
<thead>
<tr>
<th>DHHS (10/2018) Recommended for Most People with HIV</th>
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<tbody>
<tr>
<td>- Bictegravir/TAF/FTC</td>
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<tr>
<td>- Dolutegravir/abacavir/3TC</td>
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<td>- Dolutegravir + TAF/FTC or TDF/FTC</td>
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<td>- Raltegravir + TAF/FTC or TDF/FTC</td>
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<tr>
<th>IAS-USA (7/2018) Recommended Initial Regimens</th>
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- If substantial cost difference, TDF (with FTC or 3TC) is effective and generally well-tolerated, esp. if patient not at high risk for bone, renal disease
- Differences between TAF and TDF accentuated when TDF is used with ritonavir or cobicistat

GEMINI-1 and -2: DTG + 3TC vs DTG + TDF/FTC in Treatment Naïve People with HIV

- International, double-blind phase III noninferiority studies
- ART-naive adults
- No major RT or PI resistance
- HIV RNA level: Mean: 4.4 log₁₀ c/mL; >100K: 20%
- CD4 count: Mean: 562; ≤200 8%
- Male: 85%
- Age: 32-33 years.
- Black: 12%
- No HBV infection

Who was in GEMINI?
- Patients, 20%
- Age ≥ 32-33 years.
- Black: 12%
- HIV RNA level: Mean: 4.4 log₁₀ c/mL; >100K: 20%
- CD4 count: Mean: 562; ≤200 8%

Other 2-drug options for treatment of HIV

- **Initial therapy**
  - **DRV/r + RAL**: but not as good as 3-drug therapy when CD4 <200, VL >100K
  - **Maintenance therapy (once VL suppressed on 3-drug therapy)**
    - **DTG/RPV (SWORD)**
    - **LPV/r + 3TC/FTC (OLE)**
    - **ATV/r + 3TC (SALT, ATLAS-M)**
    - **DRV/r + 3TC (DUAL)**

Emerging and investigational 2-drug options for treatment of HIV

- **Initial therapy**
  - **DRV/r + 3TC (ANDES)**: promising in small randomized trial
  - **Istratavir + Doravirine**: investigational
- **Second-line therapy**
  - **DRV/r + DOR** (vs. 2 NRTI + DRV/r or DTG) [D2EFT], N=1010. Ongoing.
  - **Maintenance therapy (once VL suppressed on 3-drug therapy)**
    - **DRV/r + RPV** (n=46)
    - **DRV/r + DOR** (DUALS): similar 48 wk results as 3-drug therapy (n=265)
    - **LA Cabotegravir/Rilpivirine**: (ATLAS, FLAIR, ATLAS-2M)

ART Options in Someone Who Has Difficulty Taking Daily Drugs

- 55 yo M with HIV, achalasia, dysphagia
- Long-standing difficulty swallowing pills
- Virologically suppressed on dolutegravir and rilpivirine
- He asks whether there are long-acting HIV medicines that he can take instead of a daily oral regimen

How do you respond?
A. Yes
B. No
C. Not yet
D. I don’t know

Long-acting Cabotegravir and Rilpivirine

- Cabotegravir (CAB), an INSTI, and rilpivirine (RPV), an NNRTI, available in long-acting nanosuspension formulations; half-lives of months

Phase 3 Clinical Trials: ATLAS/FLAIR Week 48

- ATLAS: virologically suppressed; switch to monthly IM LA CAB/RPV vs. continue oral ART
- FLAIR: Treatment naïve; suppress with oral ART; switch to monthly IM LA CAB/RPV vs. continue oral ART
ATLAS/FLAIR Week 48 Pooled Results

Virologic outcomes

Adjusted treatment difference (95% CI)

Primary Endpoint: LA noninferior to CAR (HIV-1 RNA ≥50 c/mL) at Week 48

Key Secondary Endpoint: LA noninferior to CAR (HIV-1 RNA <50 c/mL) at Week 48

Treatment Emergent Resistance (CAB/RPV Groups)

Site/HIV subtype | Baseline Resistance (HIV DNA) | Resistance at Virologic failure | Resistance at Week 48
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<tr>
<td>ATLAS</td>
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<tr>
<td>Russia/A1</td>
<td>E138A/T</td>
<td>L74I</td>
<td>E138A/L74I</td>
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<tr>
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<td>None</td>
<td>174I</td>
<td>E138I/E1155I/L74I</td>
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<tr>
<td>FLAIR</td>
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<tr>
<td>Russia/A1</td>
<td>None</td>
<td>174I</td>
<td>E138I/V108I/L74I</td>
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L74I more common in people with HIV subtype A but did not affect treatment response. CAB, RPV conc at time of failure below population means but within range for majority who maintained suppression.

LA CAB/RPV: Questions

- Is the 4-week oral lead-in needed? What about direct to inject?
- What about the long tail in people who stop the drugs? CAB detectable up to 48 wks after single injection, longer in women
- Will the drugs be useful in people who have difficulty adhering to oral ART?
- Can LA CAB/RPV be used in someone who is viremic?
  - Case: person with bowel resection; not able to absorb oral ART; suppressed on IM CAB/RPV
- What will the cost of the drugs be? Will the cost of the administration be reimbursed?
Ongoing CAB/RPV Studies

- 2 monthly IM: ATLAS 2M (n=1049)
  - Phase 3 open-label 48 wk results in persons suppressed on oral ART or on every 4 wk CAB/RPV LA
  - Randomized 1:1 to CAB/RPV LA every 4 weeks or every 8 weeks
  - Every 8 wk therapy was non-inferior
- Poor Adherers ACTG 5359 (n=350)
  - VL >200 at entry
  - No RPV or INSTI mutations
  - Phase 1: 24 weeks of standard of care oral ART (conditional financial incentives)
  - Then open label switch CAB/RPV 48 weeks

Practical Aspects of Using CAB/RPV

- Loading dose: CAB LA 600 mg (one 3-mL injection) and RPV LA 900 mg (one 3-mL injection)
- Monthly maintenance: CAB LA 400 mg (one 2-mL injection) and RPV LA 600 mg (one 2-mL injection)
- RPV LA requires cold chain
- Injection into glutus medius (upper outer quadrant of buttock)
- Need a private place for injections
- What about people with buttock implants?

Practical Aspects of Using CAB/RPV: Continued

- Staffing and physical space to deliver injections
  - In 3000 patient clinic, if 10% want injections: 15 visits/day, 30 injections/day (if monthly)
- Are there alternative places to deliver injections? Pharmacies? Home healthcare?
- How will people remember to come in for visits? How will we remind people to come in for visits? Might pharmacies play a role?
- If people are late in coming in, will need oral ARV bridging
My take on LA Cabotegravir/Rilpivirine

- For most people, oral daily ART will remain effective and convenient option
- LA CAB/RPV may be a good option for people who struggle with taking daily oral regimen (e.g., swallowing difficulties; stigma – external or internal)
- In people who struggle with adherence with oral ART, LA CAB/RPV may be helpful as long as the person comes back for appointments
- Combining visits with other appointments may be helpful, e.g., when picking up methadone refills, psychiatrist/psychologist/support group visits
- Every 8 wk dosing (if safe and effective) will make LA CAB/RPV more attractive but adherence, long pharmacokinetic tail, oral bridging for missed injections, reminders, administration logistics, and cost will still be important considerations

New Drugs for Multi-drug Resistant HIV

Case Scenario

- 60 yo F diagnosed with HIV in 1990.
- Multiple previous regimens
- HIV RNA 20,000; CD4 cell count 150
- HIV phenotype: resistance to NRTI, NNRTI, PIs. Sensitive to INSTI
**ARS Question**

Which of the following classes are in or have completed phase 3 trials for treatment?

A. Entry/attachment inhibitors  
B. Maturation inhibitors  
C. Capsid inhibitors  
D. Broadly neutralizing antibodies

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**HIV Entry Inhibitors**

- **Fostemsavir**  
  * FDA approved

**Ibalizumab**  
- Humanized monoclonal Ab: binds CD4 on host cells; blocks HIV entry (post attachment inhibitor)  
- Active against CCR5 and CXCR4 tropic HIV  
- In phase 3 clinical trial (n=40), 50% of those who received ibalizumab + optimized background regimen achieved VL <200  
- IV infusion: 2,000 mg loading dose then 800 mg every 2 weeks  
- Duration of infusion: 15-30 min

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*Images courtesy of Trip Gulick, MD; Adapted from Moore JP, *PNAS* 2003;100:10598-10602.*

*Images courtesy of Emu B et al, NEJM, 2018.*

Fostemsavir (FTR): Oral HIV Attachment Inhibitor

- Prodrug of temsavir: binds to gp120, inhibits HIV attachment to CD4
- Phase 3 trial in heavily treatment experienced patients with virologic failure (BRIGHTE)
- Randomized: 272 pts with ≥1 fully active drug in 1 or 2 classes. 8 days blinded therapy (FTR or placebo), then FTR + OBT
- Non-Randomized: 99 pts with no fully active approved drug. FTR + OBT

BRIGHTE: Most Common ARVs in Initial Optimized Background Therapy (OBT)

BRIGHTE: ITT-E Virologic Response Through Wk 96
On the Horizon

- Islatravir
- Capsid inhibitor
- CD4 antibody
- CCR5 antibody
- Broadly neutralizing Ab
- Other novel agents
- Novel delivery systems

Islatravir (MK-8591)

- Nucleoside RT translocation inhibitor (NRTTI)
- Potent at low doses: single oral dose as low as 0.5 mg suppressed HIV RNA for >7 days
- High barrier to resistance
- Long half-life (about 120 h)
  - Potential for once daily, once weekly or less frequent dosing

Phase 2b study for treatment: DRIVE2Simplify: ISL + DOR vs. DOR/3TC/TDF

Participants initially received ISL+DOR+3TC; then switched to ISL+DOR during week 24-48 after achieving virologic suppression. Week 48 virologic outcomes (FDA Snapshot)

- All participants with protocol-defined virologic failure had confirmatory VS <80
- No participants met criteria for resistance testing
ISL + DOR

- Phase 3 treatment program being launched:
  - Trial for treatment-experienced participants.
  - Two trials for participants switching therapy.
  - Trial for treatment naïve participants.

Future possibilities:
- Based on pharmacokinetics (PK), ISL has potential for once weekly dosing for treatment.
- Also being considered for PrEP (promising PK results with ISL implant).

HIV Capsid Inhibitor: Sustained levels for >24 weeks after single subcutaneous injection

HIV Capsid Inhibitor: Antiviral activity after single subcutaneous dose in people with HIV

Recently announced¹:
- Phase 2/3 study in treatment experienced/multi-drug resistant HIV
- Phase 2 trial in treatment naïve
- Capsid inhibitor: two-week oral lead-in followed by subcutaneous injection every 6 mo.

¹ clinicaltrials.gov: NCT04150068; NCT04143594
**HIV Entry Inhibitors: Novel Antibodies**

**UB-421: Antibody against CD4**
- 29 people with virologic suppression on oral ART
- Received up to 8 infusions of UB-421
  - Weekly: cohort 1
  - Every 2 wks: cohort 2
- Oral ART stopped after first infusion
- All participants remained virologically suppressed during infusions
- Rash: 52% mild and transitory; 1 person stopped Ab because of more severe rash
- Approval in China for a phase 3 ART substitution trial

**Leronlimab (PRO 140)**
- Monoclonal antibody against CCR5
- Weekly subcutaneous injection
- Being studied as a single agent for maintenance of suppression and for people with drug resistant HIV
- Single agent for maintenance of suppression
  - Participants with virologic suppression and R5 tropic HIV (Trofile DNA)
  - Virologic failure rate: 14-66%
  - Participants who had virologic failure re-suppressed on baseline ART
  - No tropism shifts
Leronlimab (PRO 140) in people with drug-resistant HIV

- Treatment-experienced people with multi-drug resistant R5-tropic HIV
- Randomized to receive PRO140 + baseline ART vs. placebo + baseline ART
- All participants then start open label PRO140 + optimized background regimen
- Results:
  - >0.5 log reduction in VL after single injection: 64% in PRO 140 treated group vs. 23% in placebo group
  - Week 25: 81% of participants with VL <50

Broadly Neutralizing Antibodies against HIV

Combination of 2 Antibodies Maintained HIV suppression in Absence of ART in Some People

- 15 participants received a combination of 2 bNAb and then stopped ART after first dose
- Combination of 2 bNAb maintained viral suppression for median of 15 wk after last dose
- 2 participants maintained HIV suppression > 24 weeks

Will need to combine antibodies with multiple specificities
### Antibodies with improved potency and breadth:

**Reduction in VL after VRC01LS or VRC07-523LS Infusion**

<table>
<thead>
<tr>
<th>Subject</th>
<th>VRC01LS</th>
<th>VRC07-523LS</th>
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<tbody>
<tr>
<td>Day 7</td>
<td>2/7 decrease of at least 0.9 log10 7/9 decrease of at least 1.6 log10 (all subjects)</td>
<td>Day 7 2/7 decrease of at least 1.2 log10 7/9 decrease of at least 2 log10 (all subjects)</td>
</tr>
<tr>
<td>Day 14</td>
<td>6/9 decrease of at least 1.6 log10 7/9 decrease of at least 0.6 log10 (all subjects) until after Day 14</td>
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### Selected other investigational drugs in the pipeline

- **Long Acting Injectables:**
  - Elsulfavirine (NNRTI); raltegravir; atazanavir/ritonavir; combinectin (entry inhibitor)
  - Considerations: managing toxicities if they develop; what to do if recipients become pregnant; what happens if doses missed

- **Implants:**
  - Istlatravir: NRTI
  - TAF: NRTI
  - Biodegradable, removable, polymer-based implants with multiple drugs

- **Patches**

- **Oral once-weekly delivery system**

- **Novel antibody delivery systems:** viral vectors; synthetic DNA

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**New Delivery Systems (in development)**

- Long acting injectables:
  - Elsulfavirine (NNRTI); raltegravir; atazanavir/ritonavir; combinectin (entry inhibitor)
  - Considerations: managing toxicities if they develop; what to do if recipients become pregnant; what happens if doses missed

- **Implants:**
  - Istlatravir: NRTI
  - TAF: NRTI
  - Biodegradable, removable, polymer-based implants with multiple drugs

- **Patches**

- **Oral once-weekly delivery system**

- **Novel antibody delivery systems:** viral vectors; synthetic DNA

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**Study of LA cabotegravir + VRC07-523 LS being launched (ACTG)**
Investigational Approaches to Antiretroviral Therapy

- Have we moved into era of 2-drug therapy? Dolutegravir/3TC is an approved option; new & investigational regimens under evaluation.
- What are the ART options in someone who has difficulty taking daily drugs? Long-acting IM cabotegravir/rilpivirine may be approved soon.
- What do you give to someone with highly drug resistant HIV? Ibalizumab approved; fostemsavir (attachment inhibitor): promising results in phase 3 trial.
- What’s on the horizon? Islatravir, capsid inhibitor, antibodies against CCR5 or CD4, broadly neutralizing antibodies, new delivery systems, and more!

Question-and-Answer Period