Future Horizons:
Innovations Shaping the ART Landscape

Moti Ramgopal, MD, FACP, FIDSA
Medical Director | Midway Immunology and Research Center
Founder and Chairman | Midway Specialty Care Center
Clinical Professor | Florida State University College of Medicine

Continuum 2024 • June 9-11, 2024 • Puerto Rico
Disclosures

• Speaker’s Bureau: Gilead and ViiV
• Consultant: Gilead, Merck, ViiV, Abbott, AbbVie
Objectives


2. Identify investigational HIV drugs in development.

3. Discuss emerging future strategies in HIV management.
# Evolution of ART: Past to Present

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<tbody>
<tr>
<td></td>
<td>1997 Tenofovir (NRTI)</td>
<td>2002 Stavudine XR* (NRTI)</td>
<td>2003 Atazanavir (PI)</td>
<td>2007 Maraviroc (CA)</td>
<td>2013 Dolutegravir (INSTI)</td>
<td>2017 Julastra (FDC)</td>
<td>2022 Triumeq PD (FDC)</td>
</tr>
</tbody>
</table>

**Drug Class Abbreviations:**
- AI: Attachment Inhibitor
- CA: CCR5 Antagonist
- CI: Capsid Inhibitors
- FDC: Fixed-Dose Combination
- FI: Fusion Inhibitor
- INSTI: Integrase Inhibitor
- NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor
- NRTI: Nucleoside Reverse Transcriptase Inhibitor
- PE: Pharmacokinetic Enhancer
- PI: Protease Inhibitor
- PAI: Post-Attachment Inhibitor
- PrEP: Pre-exposure prophylaxis

*Note: Approvals are for HIV treatment, unless otherwise indicated. Drugs in gray are no longer available and/or no longer recommended for use in the United States by the HHS HIV/AIDS medical practice guidelines. These drugs may still be used in fixed-dose combination formulations. Fixed-dose combination brand products in gray may be available as generics.*
## Future Interventions

### INSTIs
- CAB-ULA Q4M
- GS-1720 Oral QWk
- VH-184 LA Inj
- GS-6212 Q3M
- GS-1219 Q6M
- GS-3242 Q6M
- ULA BIC Q6M
- ULA pro-CAB ≥Q6M
- DTG Implant Q6M

### NNRTIs
- MK-8507 Oral QWk
- GS-5894 Oral QWk

### PIs
- GS-9770 Oral QWk, unboosted
- VH-289
- VH-499
- GS-4182 pro-LEN

### Capsid Inhibitors
- VH-937 QWk

### Maturation Inhibitor
- VH-937 QWk

### bNAbs
- ABBV-181
- ABBV-382
- TMB-380
- N6LS (+CAB)
- ZAB, TAB (+LEN)
- SAR441236
- VRCO7-523LS (+CAB)
- PGDM1400 + PGT121 + VRC07-523LS
- TMB-365 + VRC07-523LS

### NRTTIs
- Islatravir
- MK-8527 Oral QWk (ART) or QM (PrEP)
- GS-1614 ISL prodrug;

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Adapted from: Thompson, M. The Future of HIV Care (and Prevention), ACTHIV 2024.
Emerging Technologies

• Long-Acting and Ultra Long-Acting (ULA)
• Gene-Based Therapies
• Immunotherapy
  – Monoclonal Therapy
• Functional Cure
Long-Acting ART

- MK-8527 (PrEP)
  - NRTTI
  - Single doses of MK-8527 as low as 0.5 mg achieved ≥1 log10 decreases in HIV-1 RNA at Day 7
  - Longer T ½ than ISL

- GS-1720
  - INSTI
  - Single dose of 450mg has T ½ 9.4 days
  - > 2 log decline for 150, 450, 900 mg dose levels
  - Target therapeutic range reached in all participants in 450 mg and 900 mg arms
  - No treatment emergent resistance in 150 mg and 450 mg arms; testing ongoing in 30mg and 900 mg cohorts

Carstens, et al. CROI 2024, Abstract 115,
ARTISTRY-1: Phase 2 Study of Switch to Daily BIC + LEN in Individuals on a Complex HIV Treatment Regimen

- Mounzer, et al. CROI 2024, Abstract 642,
ARTISTRY-1: Virologic Outcomes at Week 24

Data: Mounzer, et al. CROI 2024, Abstract 642,
Weekly ISL + LEN in PWH: A Phase 2 Study

Inclusion criteria
- Aged ≥18 years
- Viral load <50 c/mL on B/F/TAF
- No history of virologic failure
- CD4 count ≥350 cells/μL
- Lymphocytes ≥900 cells/μL
- No HBV infection

A Phase 2, open-label, active-controlled study in virologically suppressed PWH

N=106
1:1

ISL 2 mg + LEN 300 mg oral QW

B/F/TAF QD

ISL 2 mg + LEN 300 mg oral QW

Extension phase

Visits every 12 weeks

Colson et al. CROI 2024, Abstract 208
Weekly ISL + LEN in PWH: Virologic Efficacy at Week 24

Colson et al. CROI 2024, Abstract 208
CAB-ULA PHARMACOKINETICS

Part C: CAB-ULA

<table>
<thead>
<tr>
<th>Parameter, geometric mean (%CVb)</th>
<th>SC</th>
<th>IM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax, µg/mL</td>
<td>0.7 (35.5)</td>
<td>0.8 (39.0)</td>
</tr>
<tr>
<td>tmax, hours</td>
<td>570 (158)</td>
<td>349 (147)</td>
</tr>
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CAB-ULA has slower absorption and longer $t_{1/2}$ than CAB200 IM
- PK profiles were flatter than CAB200 IM
- CAB-ULA Cmax was lower with SC than IM; both were lower than CAB200 IM
- tmax was longer than CAB200 IM
- CAB-ULA $t_{1/2}$ for SC and IM was predicted to be >6x and >2x the $t_{1/2}$ of CAB200 IM, respectively\(^1,\text{a}\)

\(\text{BQL} = \text{below quantification limit of 0.025 µg/mL} \)

Han, et al. CROI 2024, Abstract 130

1200mg CAB-ULA IM

800mg CAB-ULA IM
**Gene-based Therapies**
- CRISPR/Cas9
  - Excision EBT-101
    - Safe and well tolerated but did not prevent viral rebound in three participants who stopped antiretroviral treatment
Immunotherapy

- N6LS
  - VH3810109 (N6LS) in Adults With HIV-1 Who Are ART-Naive: Phase IIa BANNER Efficacy Data
  - Robust antiviral effect when given at 40 mg/kg IV in PLWH

Losos, et al. CROI 2024; Oral Abstract 117
# BANNER Part 2: SC Antiviral Activity

- Lower exposures were observed with SC vs IV administration using the same N6LS dose
- Lower SC exposure due to first-pass lymphatic elimination
- The SC response was as expected when considering N6LS exposures achieved

<table>
<thead>
<tr>
<th>Viral dynamic measures, median (range)</th>
<th>Part 1</th>
<th>Part 2</th>
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<tbody>
<tr>
<td><em>N6LS</em> 40 mg/kg IV (N=8)</td>
<td>N6LS 280 mg IV (~4 mg/kg)</td>
<td>N6LS 700 mg IV (~10 mg/kg)</td>
</tr>
<tr>
<td>Viral nadir from baseline, log_{10} c/mL</td>
<td>-1.72 (-2.60, -0.60)</td>
<td>-1.18 (-2.18, -0.30)</td>
</tr>
<tr>
<td>Time to viral nadir, days</td>
<td>16 (5-21)</td>
<td>9 (7-16)</td>
</tr>
<tr>
<td>Time to viral rebound among responders, days</td>
<td>35 (12-78) [n=8]</td>
<td>18 (14-29) [n=5]</td>
</tr>
<tr>
<td>Time to viral rebound among responders, days</td>
<td>17 (11-63) [n=8]</td>
<td></td>
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IV, intravenous; N6LS, VH3810109; SC, subcutaneous; VL, viral load.

*For a 70-kg individual.

Losos, et al. CROI 2024; Oral Abstract 117
Krishnan, et al. CROI 2024; Oral 106

Study M19-939 (NCT04223804) is a Phase 1b randomized double-blind study investigating low-dose budigalimab in PLWH undergoing ATI

Key study details
- Budigalimab is an investigational humanized, recombinant IgG1 L234A L235A mAb
- Study objective: identify potential efficacious dose and regimen of budigalimab with favorable safety in PLWH
- Study outcomes: safety, PK, PD-1 receptor saturation, biomarkers, and viral kinetics

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>Stage I: Q4W×2</th>
<th>Stage II: Q2W×4</th>
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<tr>
<td></td>
<td>Placebo N=5</td>
<td>2 mg IV N=10</td>
</tr>
<tr>
<td>Male</td>
<td>5 (100)</td>
<td>10 (100)</td>
</tr>
<tr>
<td>Age, y</td>
<td>44 (14)</td>
<td>42 (13)</td>
</tr>
<tr>
<td>HIV-1 disease, y</td>
<td>11 (13)</td>
<td>9 (8)</td>
</tr>
<tr>
<td>CD4+ cell count, cells/µl</td>
<td>652 (143)</td>
<td>887 (263)</td>
</tr>
<tr>
<td>Viral suppression on ART, y</td>
<td>10 (12)</td>
<td>7 (5)</td>
</tr>
<tr>
<td>%CD8+ PD-1+ cells</td>
<td>45 (14)</td>
<td>39 (16)</td>
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Data are expressed as number (%) or mean [SD]
Krishnan: Biomarker signatures in Phase 1b study with PD-1 inhibitor, budigalimab, in PLWH undergoing ATI (2 of 2) (oral)

Biweekly administration of budigalimab 10 mg IV for 4 doses led to delayed viral rebound and/or ART-free viral control in 6 of 9 participants who completed dosing, with 2 participants remaining off ART until the end of the study.

Key findings:

- Budigalimab administered for short duration at low doses was well tolerated in PLWH. Target engagement was observed at all doses with near-complete PD-1 receptor saturation for ~10 weeks post-ATI with four 10-mg biweekly IV doses.
- Trends in budigalimab-dependent increase in T follicular helper-like cells, CD8+CXCR5+ cells, and CD4+CCR6+ cells were observed in participants with low viral load.
- Viremia during ATI was associated with increased CD8+ T-cell activation, proliferation, differential transcriptomic trajectories, and TCR clonality/diversity.
Ng: ABBV-382, an anti-α4β7 Ab that enhances HIV-1 antigen presentation for immune-mediated viral control (poster)

ABBV-382 inhibits HIV-1 replication/cell-to-cell spread via direct antagonism of the interaction of α4β7 with its cognate ligand MadCAM-1 or HIV-1 gp120. Additionally, ABBV-382 can bind to α4β7 incorporated in the HIV-1 virions to form immune-complexes that can bind to FcγRs expressed on antigen-presenting cells and enhance viral antigen presentation to T cells, potentially inducing immune responses to control viral replication.

**Key study details:**

- ABBV-382 is a novel anti-human α4β7 mAb with preserved Fc functionality
- ABBV-382 was evaluated in vitro in biochemical, virological, immunosafety, and immunopeptidomics studies to characterize its properties and determine its mechanisms of action for immune-mediated HIV-1 control
- ABBV-382, in combination with budigalimab, an anti–PD-1 mAb, is being studied in a Phase 2 study examining ART-free viral control
Functional Cure?
Summary

• Moving Away from Daily Drugs
• New Direction → Weekly Oral Dosing
• bNAbs Expanding
• Innovative Delivery Systems
THANK YOU!