Antiretroviral Therapy: Where are we now? Where are we going?

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# Disclosures – All Research Grants

**Covid Trials**
- Ansun Pharmaceuticals
- Atea Pharmaceuticals
- Regeneron Pharmaceuticals
- Moderna
- NIH
- Lilly

**HIV Trials**
- Gilead Sciences
- ViiV Healthcare
- Janssen
- Cytodyne
- Merck
- Abbvie
- NIH
Disclaimer

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Objectives

• Discuss the clinical need for new ART options and paradigms.

• Describe the mechanism of action of new/investigational ARTs.

• Select the appropriate newly approved ART to use in certain clinical situations.
### Available ARV Classes and Medications

<table>
<thead>
<tr>
<th>NRTI</th>
<th>NNRTI</th>
<th>PI</th>
<th>Fusion Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir (ABC)</td>
<td>Delavirdine (DLV)</td>
<td>Atazanavir (ATV)</td>
<td>Enfuvirtide (ENF, T-20)</td>
</tr>
<tr>
<td>Didanosine ( ddl)</td>
<td>Doravirine ( DOR )</td>
<td>Darunavir (DRV)</td>
<td>CCR5 Antagonist</td>
</tr>
<tr>
<td>Emtricitabine (FTC)</td>
<td>Efavirenz (EFV)</td>
<td>Fosamprenavir (FPV)</td>
<td>Maraviroc (MVC)</td>
</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td>Etravirine (ETR)</td>
<td>Indinavir (IDV)</td>
<td>Entry Inhibitor</td>
</tr>
<tr>
<td>Stavudine (d4T)</td>
<td>Nevirapine ( NVP )</td>
<td>Lopinavir (LPV)</td>
<td>Fostemsavir (FOS)</td>
</tr>
<tr>
<td>Tenofovir DF ( TDF)</td>
<td>Rilpivirine (RPV)</td>
<td>Nelfinavir (NFV)</td>
<td>Ibalizumab (IBA)</td>
</tr>
<tr>
<td>Tenofovir alafenamide (TAF)</td>
<td><strong>Integrase Inhibitor (INSTI)</strong></td>
<td>Saquinavir (SQV)</td>
<td>Pharmacokinetic (PK)</td>
</tr>
<tr>
<td>Zidovudine (AZT, ZDV)</td>
<td></td>
<td>Tipranavir (TPV)</td>
<td>Booster (RTV, /r)</td>
</tr>
<tr>
<td><strong>Long-acting injectables</strong></td>
<td></td>
<td></td>
<td>Cobicistat (COBI, /c)</td>
</tr>
<tr>
<td>Cabotegravir (CAB)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rilpivirine (RPV)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

71 FDA approved compounds and formulations (32 unique compounds)
In 2022 Where Are We At With Antiretroviral Therapy for Newly Diagnosed Individuals?

• Test & Treat is the current paradigm for initiating therapy.
  – Rapid start (Same day and/or w/in 2 weeks of Dx)

• Utilizing single-pill combination therapy is a best practice to encourage adherence.
  – There are 12 STRs that are FDA approved

• So, are there any controversies?
Single Pill Regimens

**efavirenz + tenofovir disoproxil fumarate + emtricitabine**
One tablet once a day. Each tablet contains 600 mg efavirenz + 300 mg tenofovir disoproxil fumarate + 200 mg emtricitabine. Take on an empty stomach. Dose should be taken at bedtime to minimize dizziness, drowsiness and impaired concentration.

**bictegravir + tenofovir alafenamide + emtricitabine**
One tablet once a day. Each tablet contains 50 mg bictegravir + 25 mg tenofovir alafenamide + 200 mg emtricitabine. Take with or without food.

**rilpivirine + tenofovir disoproxil fumarate + emtricitabine**
One tablet once a day. Each tablet contains 25 mg rilpivirine + 300 mg tenofovir disoproxil fumarate + 200 mg emtricitabine. Take with a meal.

**doravirine + tenofovir disoproxil fumarate + lamivudine**
One tablet once a day. Each tablet contains 100 mg doravirine + 300 mg tenofovir disoproxil fumarate + 300 mg lamivudine. Take with or without food.

**dolutegravir + lamivudine**
One tablet once a day. Each tablet contains 50 mg dolutegravir + 300 mg lamivudine. Take with or without food.

**dolutegravir + bictegravir + tenofovir disoproxil fumarate + emtricitabine**
One tablet once a day. Each tablet contains 150 mg dolutegravir + 25 mg bictegravir + 10 mg tenofovir alafenamide + 200 mg emtricitabine. Take with food.

**elvitegravir + cobicistat + tenofovir disoproxil fumarate + emtricitabine**
One tablet once a day. Each tablet contains 100 mg elvitegravir + 150 mg cobicistat + 300 mg tenofovir disoproxil fumarate + 200 mg emtricitabine. Take with food.

**elavire + tenofovir disoproxil fumarate + lamivudine**
One tablet of either Symfi or Symfi Lo once a day. Each tablet of Symfi contains 600 mg efavirenz + 300 mg tenofovir disoproxil fumarate + 300 mg lamivudine. Each tablet of Symfi Lo (above) contains 400 mg efavirenz + 300 mg tenofovir disoproxil fumarate + 300 mg lamivudine. Take on an empty stomach. Dose should be taken at bedtime to minimize dizziness, drowsiness and impaired concentration.

**dolutegravir + abacavir + lamivudine**
One tablet once a day. Each tablet contains 50 mg dolutegravir + 600 mg abacavir + 300 mg lamivudine. Take with or without food. Should be used only by individuals who are HLA-B*5701 negative.
**Guidelines have complicated provisos:**
- CD4 counts
- HIV viral load limits
- HLA testing
- Start before HIV genotype

**Other Considerations:**
- Food intake and PK
- Hepatitis B
- Kidney Function
- Pregnancy

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<table>
<thead>
<tr>
<th>Patient or Regimen Characteristics</th>
<th>Clinical Scenario</th>
<th>Consideration(s)</th>
<th>Rationale/Comments</th>
</tr>
</thead>
</table>
| **Pre-ART Characteristics**        | CD4 count <200 cells/mm³ | **Do Not Use the Following Regimens:**
  • RPV-based regimens
  • DRV/r plus RAL | A higher rate of virologic failure has been observed in those with low pretreatment CD4 counts. |
| HIV RNA >100,000 copies/mL (also see next row if HIV RNA >500,000 copies/mL) | **Do Not Use the Following Regimens:**
  • RPV-based regimens
  • ABC/3TC with EFV or ATV/r
  • DRV/r plus RAL | Higher rates of virologic failure have been observed in those with high pretreatment HIV RNA levels |
| HIV RNA >500,000 copies/mL | **Do Not Use the Following Regimens:**
  • RPV-based regimens
  • ABC/3TC with EFV or ATV/r
  • DRV/r plus RAL
  • DTG/3TC | For DTG/3TC, limited data are available in patients above this viral load threshold. |
| HLA-B*5701 positive or result unknown | Do not use ABC-containing regimens. | ABC hypersensitivity, a potentially fatal reaction, is highly associated with the presence of the HLA-B*5701 allele. |
| ARV should be started before HIV drug resistance results are available (e.g., in a person with acute HIV) or when ART is being initiated rapidly. | **Avoid NNRTI-based regimens and DTG/3TC.**
**Avoid ABC.**
**Recommended ART Regimens:**
  • BIC/TAF/FTC
  • DTG plus (TAF or TDF)³ plus (3TC or FTC)
  • (DRV/r or DRV/c) plus (TAF or TDF)³ plus (3TC or FTC) | Transmitted mutations conferring NNRTI and NRTI resistance are more likely than mutations associated with PI or INSTI resistance.
HLA-B*5701 results may not be available rapidly.
Transmitted resistance to DRV, BIC, and DTG is rare, and these drugs have high barriers to resistance. |

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Recommended ART Regimens

- BIC/TAF/FTC (Single Pill)

- DTG plus (TAF or TDF) plus (3TC or FTC)
  - Two pill option

- (DRV/r or DRV/c) plus (TAF or TDF) plus (3TC or FTC)
  - Single Pill (DRV/c/TAF/FTC)
  - Two pill option

DHHS Recommended Single Pill Regimens

**Complete Regimen**

- **efavirenz + tenofovir disoproxil fumarate + emtricitabine**
  One tablet once a day. Each tablet contains 600 mg efavirenz + 300 mg tenofovir disoproxil fumarate + 200 mg emtricitabine. Take on an empty stomach. Dose should be taken at bedtime to minimize dizziness, drowsiness and impaired concentration.

- **bicaprivir + tenofovir alafenamide + emtricitabine**
  One tablet once a day. Each tablet contains 50 mg bicaprivir + 25 mg tenofovir alafenamide + 200 mg emtricitabine. Take with or without food.

- **rilpivirine + tenofovir disoproxil fumarate + emtricitabine**
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- **doravirine + tenofovir disoproxil fumarate + lamivudine**
  One tablet once a day. Each tablet contains 100 mg doravirine + 300 mg tenofovir disoproxil fumarate + 300 mg lamivudine. Take with or without food.

- **dolutegravir + lamivudine**
  One tablet once a day. Each tablet contains 50 mg dolutegravir + 300 mg lamivudine. Take with or without food.

- **elvitegravir + cobicistat + tenofovir alafenamide + emtricitabine**
  One tablet once a day. Each tablet contains 150 mg elvitegravir + 150 mg cobicistat + 300 mg tenofovir alafenamide + 200 mg emtricitabine. Take with food.

- **elvitegravir + cobicistat + tenofovir disoproxil fumarate + emtricitabine**
  One tablet once a day. Each tablet contains 150 mg elvitegravir + 150 mg cobicistat + 300 mg tenofovir disoproxil fumarate + 200 mg emtricitabine. Take with food.

- **efavirenz + tenofovir disoproxil fumarate + lamivudine**
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- **dolutegravir + alcavir + lamivudine**
  One tablet once a day. Each tablet contains 50 mg dolutegravir + 600 mg alcavir + 300 mg lamivudine. Take with or without food. Should be used only by individuals who are HLA-B*5701 negative.
So, is it really so simple?

• You have 2 Single Pill Choices for Test & Treat Paradigm.
• So, is there data to support both options in the Test & Treat paradigm?
• Are there any comparative trials of these two or other agents?
Rapid Start RCTs is Better than SOC

AIDS 2018, 32:17–23
## Table 3. Major studies evaluating “test-and-treat” ART approaches

<table>
<thead>
<tr>
<th>Study</th>
<th>Region</th>
<th>ART initiation (Rapid arm)</th>
<th>Results (at 12 months)</th>
<th>Rapid arm</th>
<th>Standard arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>RapIT(^{18})</td>
<td>South Africa</td>
<td>&lt;90 days</td>
<td>n</td>
<td>187</td>
<td>190</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>VL suppression (%)</td>
<td>64</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>In care (%)</td>
<td>81</td>
<td>64</td>
</tr>
<tr>
<td>START ART(^{19})</td>
<td>Uganda</td>
<td>&lt;4 days</td>
<td>n</td>
<td>347</td>
<td>356</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>VL (%)</td>
<td>53</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>In care (%)</td>
<td>80</td>
<td>72</td>
</tr>
<tr>
<td>Koenig, et al.(^{20})</td>
<td>Haiti</td>
<td>Same day</td>
<td>n</td>
<td>206</td>
<td>208</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>VL suppression (%)</td>
<td>66</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>In care (%)</td>
<td>84</td>
<td>84</td>
</tr>
<tr>
<td>Labhardt, et al.(^{21})</td>
<td>Lesotho</td>
<td>Same day</td>
<td>n</td>
<td>137</td>
<td>137</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>VL suppression (%)</td>
<td>50</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>In care (%)</td>
<td>67</td>
<td>43</td>
</tr>
</tbody>
</table>

ART: Antiretroviral therapy
DIAMOND Study

Key Characteristics:
- Men – 87%
- Black/Afr-American – 32%
- HIV ≥100K cpm – 25%
- CD4 <200 – 21%

Intervention:
- HIV Dx w/in 2 weeks
- Same Day Initiation
- DRV/Cobi/TAF/FTC

AIDS Rev. 2019;21:55-64
STAT Study

Intervention:
HIV Dx w/in 2 weeks
Same Day Initiation
DOL/3TC

Key Characteristics:
N=131
Men – 89%
Black/Afr-American – 47%
HIV ≥100K cpm – 40%
CD4 <200 – 28%.

Table 3. Participants who switched from dolutegravir/lamivudine before the Week 24 HIV-1 RNA assessment.

<table>
<thead>
<tr>
<th>Reason for switch</th>
<th>Visit window</th>
<th>Modified ART</th>
<th>Plasma HIV-1 RNA at Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline HBV</td>
<td>Week 1</td>
<td>DTG/3TC + TAF</td>
<td>&lt;40 copies/ml</td>
</tr>
<tr>
<td>Baseline HBV</td>
<td>Week 1</td>
<td>BIC/FTC/TAF</td>
<td>NA^a</td>
</tr>
<tr>
<td>Baseline HBV</td>
<td>Week 4</td>
<td>DTG + TDF/FTC</td>
<td>&lt;40 copies/ml</td>
</tr>
<tr>
<td>Baseline HBV</td>
<td>Week 4</td>
<td>BIC/FTC/TAF, or DTG + TDF/FTC</td>
<td>49 copies/ml</td>
</tr>
<tr>
<td>Decision by participant or proxy</td>
<td>Week 4</td>
<td>BIC/FTC/TAF</td>
<td>NA^c</td>
</tr>
<tr>
<td>Baseline HBV</td>
<td>Week 8</td>
<td>DTG/3TC + TAF</td>
<td>&lt;40 copies/ml</td>
</tr>
<tr>
<td>Baseline M184V</td>
<td>Week 8</td>
<td>DTG/RPV</td>
<td>NA^d</td>
</tr>
<tr>
<td>Adverse event (rash)</td>
<td>Week 12; Week 12</td>
<td>DRV/COBI/FTC/TAF; BIC/FTC/TAF</td>
<td>&lt;40 copies/ml</td>
</tr>
</tbody>
</table>

Table 4. Adverse events reported under treatment with dolutegravir/lamivudine.

<table>
<thead>
<tr>
<th>n (%)</th>
<th>DTG/3TC, N = 131*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>85 (65)</td>
</tr>
<tr>
<td>AEs occurring in &gt;5% of participants</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>10 (8)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Most common AEs by SOC occurring in &gt;15% of participants</td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>39 (30)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>29 (22)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>22 (17)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>21 (16)</td>
</tr>
<tr>
<td>Drug-related AEs</td>
<td>9 (7)</td>
</tr>
<tr>
<td>Grade 2–5 AEs</td>
<td>2 (2)</td>
</tr>
<tr>
<td>AEs leading to discontinuation of DTG/3TC</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Any SAE</td>
<td>2 (2)</td>
</tr>
<tr>
<td>AEs of special interest</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>19 (15)</td>
</tr>
</tbody>
</table>

AIDS 2021, 35:1957–1965
Bictegravir Rapid Start Studies

B-HASTE
- Prospective Pilot Study of the Efficacy, Safety and Tolerability of Bictegravir-Based HIV ART Same-Day Treatment Evaluations (B-HASTE)
  - Rapid start vs. Standard of Care
  - Planned N=100
  - Enrollment started December 2020.

Barcelona study of B/F/TAF
- Single arm trial of rapid start
  - Planned N=100
  - Enrollment started October 5, 2020

Clinicaltrials.gov - NCT04249037 and NCT04416906
Summary of Rapid Start

• Standard approach is to try to get people started on ART within 2 weeks of diagnosis.
• DHHS guidelines recommend 3 options.
• There are prospective trials to support the use of 2 regimens and plenty of RCTs to support other options.
• Can always tell patient, “Let’s start you on this treatment and when labs come in, we might need to adjust”
Dilemmas for Treatment Naïve Studies

- Do we need more ART studies in newly diagnosed persons?
  - Are there enough choices now?
  - What about long-acting agents?
  - What about novel targets?
  - What about safer compounds?

- Should we revise FDA pathway for novel antiretrovirals?
  - Placebo-control for 7-14 days initially
  - Most trials require lab tests to meet INC/EXC criteria prior to randomization/drug initiation.
  - HIV resistance testing is commonplace prior to treatment start.

- What about RAPID start ART; is it ethical to wait for 2-4 weeks?
Proposal: Future Treatment Naïve Studies

- Consent and randomize same day.
- Initiate therapy same day (Step 1).
- Obtain screening labs.
- Bring back participants 2 weeks later for confirmation of participation visit (Step 2).
  - Continue study if meet all INC/EXC criteria
  - “Screen fail” don’t go on to Step 2.
  - Can always fail sooner if safety concerns arise (e.g., Hepatitis B infection, Low GFR)
HIV pipeline 2021: targets in the HIV lifecycle

Stages in the HIV lifecycle
1. HIV attaches to a CD4 cell.
2. HIV enters a CD4 cell and the capsid is released into the cell.
3. The capsid enters the cell nucleus where HIV proteins and enzymes are released.*
4. Reverse transcriptase (RT) makes double strand HIV.
5. Integrase enables HIV DNA to join the cell DNA.
6. New viral material is made.
7. Protease cuts and reassembles new HIV.
8. Each cell produces hundreds of new virions.

* Updated in 2021.

NRTIs/NRTTIs (nukes)
- islatravir (EFdA)

NNRTIs (non-nukes)
- eltsulfavirine MK-8507

INIs (INSTIs)
- cabotegravir LA

Monoclonal antibodies (mAb)
- UB-421 (CD4 receptor)
- VRC01/LS and VRC07/LS
- 3BNC117/LS and 10-1074/LS
- PGDM1400, 10E8.4/iMab
- PGT121 and elipivomab (GS-9722)
- N6LS (gp120)
- leneronlimab PRO-140 (CCR5)

Capsid inhibitors
- lenacapavir (GS-6207)
- GSK (pre-clinical)

Maturation inhibitors
- GSK’254 (oral)
- GSK ’937 (LA)

New HIV
Classes in clinical development for treatment and prevention

Entry inhibitors  bNAb  NRTI  NNRTI  Integrase inhibitor  Protease inhibitor  Capsid inhibitor  Maturation inhibitor  Topical IVR / MPT

1. Attachment
2. Fusion
3. Reverse transcription
4. Integration
5. Transcription
6. Translation
7. Assembly/cleavage
8. Maturation
Compounds by modality and indication

**Treatment**

- Islatravir
- Lenacapavir
- MI 254
- Albuvirtide
- bNabs
- MI 934
- Lenacapavir
- Elsulfavirine

**Prevention**

- Dapivirine IVR
- MIV 150 PC1005
- TAF/EVG insert
- Tenofovir IVR
- EVO-100 gel
- Dapivirine + C
- MB66 film
- Dual prevention pill
- Lenacapavir
- Islatravir implant
- INSTI MAP
- TAF implant
- RPV IM

Chloe L. Orkin, CROI 2022
## Maturation Inhibitors

**Block protein processing late in life cycle**

**MI 254** oral in phase II
Single entity and with FDC + DTG
5 studies scheduled

**MI 937** in phase I:
Long-acting: injectable SC and IM

2 monthly or less frequent

Long-acting MI possible partner for CAB LA
Maturation Inhibitor GSK3640254

- Phase IIa double-blind placebo-controlled RCT.
- GSK’254 in treatment-naive adults
- Part 1 (10 mg, 200 mg or placebo) daily x 10d
- Part 2 (40, 80, or 140 mg or placebo) daily x 7d
  Followed by combination therapy on day 8.

N=34 participants
4 of 12 participants in Part 1 developed the RAM A364A/V at Day 11 (1 w/A364V).

No resistance in 7-day group.

Adverse Events
22 (65%) reported AEs (GSK’254 Arms only)
GI disturbances / Headache most common

ClinicalTrials.gov: NCT03784079
Broadly Neutralizing Antibodies
Broadly Neutralizing Antibodies (bNAbs): treatment & PrEP

Delivered as long-acting Q6 infusions

Resistance: need combination & tri-specific

Current trials:
Lenacapavir + GS-5423 + GS-2872 Q6
CAB: N6LS in phase 2

PrEP: Antibody Mediated Prevention trials:
VRC01 did not prevent overall HIV-1 acquisition

Wu X. et al. Science 2010; Mascola JR. et al. Nat Medicine 2000;
BNAB Combination Study

PGDM1400 + PGT121 + VRC07-523LS
20 mg/kg IV infusion (each)

Mean -1.76Log10 HIV RNA drop by day 7
Viral rebound, median 20 days (range 13 – 70)

PGDM1400 – V1/V2 Mab
PGT121 – V3 Mab
VRC07-523LS – CD4 binding site Mab

No resistance in VRC07-523LS
Resistance to PGDM1400, PGT121

Julg et al. CROI 2022, Abstract 12
HIV-1 bNAbs: Activity During Viremia

- **Across studies:** A subset of participants with baseline bNAb resistance
- **Reduction in plasma viremia** of $\sim 1.5 \log_{10}$ cp/ml.
- Selection of resistant viral strains with monotherapy.
- Viral suppression only achieved with low starting VLs
- **In contrast,** the **two-bNAb combination** can maintain viral suppression after ART interruption (Mendoza, Nature et al. 2018)
3BNC117 (CD4bs) & 10-1074 (V3 loop): 
*In Vitro* Neutralizing Activity

**Pseudovirus Panel (Multi-Clade)**

- **10-1074**
- **3BNC117**
- **10-1074 + 3BNC117**

Coverage of **96%** - IC$_{50}$ < 10 µg/ml
GeoMean IC$_{50}$ of **0.04 µg/ml** and IC$_{80}$ 0.15 µg/ml.

Kong et al, J Virol 2015

**Primary Isolates (Clades A, C, D)**

- **IC$_{50}$**
  - CD4bs
  - V3
  - V2
  - V3 + CD4bs

Coverage **84%**
GeoMean IC$_{50}$ **0.65 µg/ml**

Lorenzi et al, J Virol 2020

Caskey et al. CROI 2022, Abstract 140
LS Variants: Study Design and Endpoints

- **Design:** This was a phase 1 open-label, single arm study to evaluate the safety, PK and antiviral activity of the combination of 3BNC117-LS and 10-1074-LS in **viremic PWH not on ART.**
  - Single infusions of 30 mg/kg, each mAb at 30 mg/kg
  - Follow up of 24 weeks.

![Study Design Diagram](image)

**Study Population:**
- Age > 18 yrs
- Off ART for 4 weeks, with HIV-1 RNA 500 – 125,000 cp/ml
- Current CD4 count > 300 cells/ml
- Without hx of AIDS-defining illness within last 3 yrs
- Without chronic HBV or HCV infection

**Study Endpoints:**
- Safety – treatment related solicited or unsolicited grade 3 AEs and SAEs
- PK parameters
- Decline in plasma viremia through week 4 after bNAb infusions

Note: participants encouraged to initiate ART at study week 8.
**Study Flow**

**Screens:** 14 participants
- 8 ineligible
- Low CD4 count: 4
- VL outside the study range: 2
- Active IVDU

**Dosing:** 6 Participants received 3BNCl17-LS + 10-1074-LS

**Endpoint:** 6 participants reached virologic endpoint

**Follow up:** 4 participants completed 24 weeks of follow up

**Male participants / 1 ART-naïve**
- Median age = 34 yrs (range 26 - 56)
- Median HIV-1 RNA cp/ml = 48,700 (range 1,050 - 275,000)
- Median CD4 count = 523 (range 360 - 891)
- Median time since HIV diagnosis = 8 yrs

**Study Sites:** Rockefeller, Weil Cornell, UPenn
Serum Antibody Levels

- 10-1074-LS showed slower decay than 3BNC117-LS
- Faster decay of both bNAbs in viremic participants
Effects on Plasma Viremia: 3BNC117-LS and 10-1074-LS

- 3R02: -1.1 log_{10}
- 3R03: -1.7 log_{10}
- 3R01*: -2.0 log_{10} *Rebound at wk 36
- 3R04: -1.4 log_{10}
- 3P05: -2.5 log_{10}
- 3R06: -2.1 log_{10}

➤ Reduction in plasma viremia of ~ 1.9 log_{10} cp/ml.
PhenoSense Monoclonal Antibody (mAb) Assay

Pseudovirus

HIV genomic luciferase vector

Expression vector

Transfection

Target Cells

No neutralization

Infection in the absence and presence of different concentrations of mAb

mAb neutralization

Jackie Reeves, Monogram

Caskey et al. CROI 2022, Abstract 140
Viral Responses and Baseline Antibody Sensitivity of Plasma Viruses

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Summary of BNABs

• Measure neutralization prior to use
• Combination therapy is better than monotherapy
• Average of 1.5 – 2.5 log decline
• Viral rebound typically occurs in most persons within 3-4 weeks, but some have prolonged viremic control
• Multiple infusions required likely
Perfect = choices for all

- Long-acting injection
- Microneedle drug patch
- Subdermal implant
- Vaginal ring
- Wearable infusion pump
- Long-acting Orals

What about Treatment Experienced Individuals Failing Therapy?

• Fostemavir
BRIGHTE STUDY – 96 weeks

Main Entry Criteria
HIV VL > 400 cpm
Currently taking ART (failing)
≤ 2 ART Class Options remaining

Randomized Cohort
8 days of Fostemavir vs. Placebo
Optimized background, day 8

Non-randomized Cohort
No active treatment options
Fostemavir+optimized background

ITT-Snapshot Randomized Group

ITT-Snapshot Non-randomized Group

Observed-Snapshot Randomized Group

Lancet HIV 2020; 7: e740–51
Case presentation

- 44 y/o man with HIV since 2004.
- Placed on TDF/FTC/EFV on 2/7/2005 but did not get to VL<200.
- Genotype in 8/12/2005 shows extensive resistance.
- Was off antiretroviral therapy from 2006-2013. (No Insurance)
- Placed on ZDV/3TC+Lopinavir/ritonavir 2013-2015.
- Off treatment for 6 months due to lack of insurance
- On ABC/3TC/Dolutegravir since 3/15/16
- Had CVA on 8/27/2019
- Saw HIV provider 3/5/20 to review ART

Courtesy of Dr. Kelli Williams
8/12/2005
Regimen – TDF/FTC/EFV
HIV VL = 2,900 cpm

5/24/2015
Regimen – No ARVs
HIV VL = 283,218 cpm

2/24/2018
Regimen – ABC/3TC/DOL
HIV VL = 24 cpm

Key Historical Mutations: K65R, K101E, V106M, V108I, Y181C
What would you do?

- HIV VL = 24 copies/mL
- Recent Stroke on ABC/3TC/DOL
- Failed TDF/FTC/EFV – Resistance
- History of Treatment Failure – ZDV/3TC+LPV/r
- Mostly controlled viremia on ABC/3TC/DOL
https://hivdb.stanford.edu/
### Reverse Transcriptase

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[https://hivdb.stanford.edu/](https://hivdb.stanford.edu/)
## Drug resistance interpretation: PR

**PI Major Resistance Mutations:** None  
**PI Accessory Resistance Mutations:** None  
**Other Mutations:** L10I, M361, L63P  

### Protease Inhibitors

- **atazanavir/r (ATV/r):** Susceptible  
- **darunavir/r (DRV/r):** Susceptible  
- **lopinavir/r (LPV/r):** Susceptible  

### PR comments

- L10I/V are polymorphic PI-selected accessory mutations that increase the replication of viruses with other PI-resistance mutations.

## Mutation scoring: PR

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<tr>
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<th>DRV/r</th>
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## Drug resistance interpretation: RT

**NRTI Resistance Mutations:** K65R  
**NNRTI Resistance Mutations:** K101E, V106M, V108I, Y181C  
**Other Mutations:** None  

### Nucleoside Reverse Transcriptase Inhibitors

- **abacavir (ABC):** Intermediate Resistance  
- **zidovudine (AZT):** Susceptible  
- **emtricitabine (FTC):** Intermediate Resistance  
- **lamivudine (3TC):** Intermediate Resistance  
- **tenofovir (TDF):** High-Level Resistance  

### Non-nucleoside Reverse Transcriptase Inhibitors

- **doravirine (DOR):** High-Level Resistance  
- **efavirenz (EFV):** High-Level Resistance  
- **etravirine (ETR):** Intermediate Resistance  
- **nevirapine (NVP):** High-Level Resistance  
- **rilpivirine (RPV):** High-Level Resistance  

### RT comments

- **K65R** causes intermediate/high-level resistance to TDF, ddi, ABC and d4T and low/intermediate resistance to 3TC and FTC. K65R increases susceptibility to AZT.

- **K101E** is a non-polymorphic primarily accessory mutation that causes intermediate resistance to NVP and RPV, low-level resistance to EFV, and potentially low-level resistance to ETR. It has a weight of 1.0 in the Tibotec ETR genotypic susceptibility score. It is associated with low-level reductions in DOR susceptibility.

- **V106M** is a non-polymorphic mutation that causes high-level resistance to NVP and EFV. It is selected in vitro and in vivo by DOR and preliminary data suggests it is associated with low/intermediate reductions in DOR susceptibility.
Case plan and follow up

- Clinician decided to avoid abacavir given cardiovascular disease
- Changed therapy to dolutegravir/3TC
- History of virologic control
  - HIV-1 RNA ND 256 ND ND ND ND ND ND
Active Clinical Trials

• To learn more about active trials, call Sharon Kohrs, RN, Clinical Research Director at 513-584-6383
• DOMINO – RCT of GSK-254 at varying doses with NRTIs and then combined with DOL for treatment naïve PWH.
• ACTG A5359 – Randomized trial of injectable long-acting treatments for persons failing therapy with minimum antiretroviral resistance.
• ACTG A5391 – Randomized trial of switching to TDF/FTC/DOR in persons with excessive weight gain on TAF and Integrase containing regimens
• ACTG A5386 – IL-15 superagonist with and without BNABs to control HIV with ATI in persons doing well on ART.
Thank You!

• Mary Beth Donica, MD
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• Ms. Brenda Miller
• Ms. Mary Ann Schaefer
• Pamposh Kaul, MD
• UC CME Office and College of Pharmacy
• Our sponsors
• Our speakers
• You The Audience
• Slides from Dr. Chloe L. Orkin and other CROI presenters
AETC Resources

- **Clinical Consultation Center**
  - [http://nccc.ucsf.edu/](http://nccc.ucsf.edu/)
  - HIV management
  - Perinatal HIV
  - HIV PrEP
  - HIV PEP Line
  - HCV Management
  - Substance Use Management

- **AETC National HIV Curriculum**
  - [https://aidsetc.org/nhc](https://aidsetc.org/nhc)

- **AETC National HIV-HCV Curriculum**
  - [https://aidsetc.org/hivhcv](https://aidsetc.org/hivhcv)

- **Hepatitis C Online**
  - [https://www.hepatitis.uw.edu/](https://www.hepatitis.uw.edu/)

- **AETC National Coordinating Resource Center**
  - [https://aidsetc.org/](https://aidsetc.org/)
Back up Slides Only
HIV Cure

Cases of HIV-1 Cure

Berlin Patient (2009)

Timothy Ray Brown (1966-2020)
Caucasian male
Provided proof-of-concept for cure with transplantation of CCR5Δ32/Δ32 cells

Strategy that led to cure
- Chemotherapy for relapsed AML
- Stem cell transplant x2 (chemo & TBI conditioning)
- Graft: adult donor CCR5Δ32/Δ32 bone marrow cells (10/10 HLA match)
- Graft versus host disease
- ART stopped immediately after transplant
- HIV-1 remission 20 months; >12 years (deemed cured)

London Patient (2019)

Adam Castillejo (40 years old)
Latino male

Strategy that led to cure
- Chemotherapy for Hodgkin’s lymphoma
- Stem cell transplant (chemo conditioning)
- Graft: adult donor CCR5Δ32/Δ32 homozygous peripheral blood stem cells (9/10 HLA match)
- Graft versus host disease
- ART stopped 16 months after transplant
- HIV-1 remission 18 months; 30 months


Gupta R et al, Nature 2019
CASE REPORT.

- 59 yr/old female mixed race
- DX acute HIV 2013
- High risk AML monsomy 7, 2017
- 3 partially matched CCR5 delta 32/32 cord units (Stemcyte)
HIV and AML Treatment Course

- Induction chemo
- Haplo/cord transplantation
- Post-ATI HIV rebound monitor program

HIV-1 (copies/ml)

- P1107 Enrollment
- AT1 counseling
- Fludarabine/melphalan/TBI400/ATG
- ART stopped 37 months post T
- ATI: antiretroviral treatment interruption
- LOD: limit of detection
- LOD < 20 cp/ml
Immune Reconstitution Profiles

- Induction chemo
- HIV diagnosis
- Conditioning
- UCB and Haplo Graft
- Tacrolimus
- Antiretroviral Treatment
- ATI
  - 14m
- 100%CCR5Δ32/Δ32 cord chimerism by day 100 until present

Cell count/ul

Pre-transplant | Post-transplant

- CD19
- CD8
- CD4
- CD16CD56
- Rituxan
- Rituxan x 1 (EBV)
Decrease of Immune activation of CD4 and CD8 T cells

No HIV-1 antigen (HIV-1 gag)- specific T cells were detected, while polyclonal responses (SEB) were intact. Data not shown
Cell-Associated HIV-1 DNA Levels, Latent Reservoir Size and Low-level Viremia Pre-and Post-Transplantation and Following ART Interruption

Pre-Transplant

Post-Transplant

- HIV-1 DNA (copies/10^6 PBMCs)
- 2LTR DNA (copies/10^6 PBMCs)
- Replication Competent Reservoir (IUPM)
- Plasma Viral Load (copies/mL)

HIV-1 DNA
LOD <4.09 c/10^6 cells

Single copy plasma viral load (<0.5-<0.9 c/mL)

Reservoir studies: Persaud Laboratory Johns Hopkins University
Single-copy viral load assay: Mellors Laboratory; University of Pittsburg
Loss of HIV-1-specific antibody responses (WB) by Week 55 post-transplant through 52 weeks post ATI.
IMPAACT P1107: Conclusions

- First US woman of mixed race living with HIV-1 successfully transplanted with CCR5Δ32/Δ32 cord/haplo SCT with 100% sustained engraftment of cord blood and in HIV-1 remission
- Durable remission of AML 4 years 6 months post SCT
- 14 months off ART no viral rebound (no ARV’s in plasma)
- No detectable replication-competent latent reservoir (74.5 million CD4T cells)
- Undetectable HIV-1-specific cellular immune responses and HIV antibody negative, in vitro resistance to lab & autologous virus
- Negative- (transient trace) HIV DNA by ddPCR
- Remains clinically well with NO GVHD