ART Progress: New Drugs

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Chief, Division of Infectious Diseases
Weill Cornell Medicine
Antiretroviral Drug Approval:
1987 - 2017
# Newer ART Agents (partial list)

<table>
<thead>
<tr>
<th>Phase</th>
<th>NRTI</th>
<th>NNRTI</th>
<th>PI</th>
<th>Entry Inh</th>
<th>II</th>
<th>MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 3</td>
<td></td>
<td>doravirine</td>
<td></td>
<td></td>
<td>bictegravir</td>
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<td>albuvirtide</td>
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<td>fosinavir</td>
<td>ritonavir</td>
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<td>fostemsavir</td>
<td>elbalizumab</td>
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<td>PRO140</td>
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<tr>
<td>Phase 2</td>
<td>apricitabine</td>
<td>dexelvucitabine</td>
<td>festinavir</td>
<td>elsulfavirine</td>
<td>cenicriviroc</td>
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<td>BILR 355</td>
<td>TMC 310911</td>
<td></td>
<td>HGS004</td>
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<tr>
<td>Phases 1/2</td>
<td>elvucitabine</td>
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<td>UB-421</td>
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<tr>
<td>Phase 1</td>
<td>MK-8591 (EFdA)</td>
<td>CMX157</td>
<td>RDEA 806</td>
<td>CTP-298</td>
<td>BMS-986197</td>
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<td></td>
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<td>CTP-518</td>
<td>SCH532706</td>
<td>ME-224436</td>
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<td></td>
<td>PPL-100</td>
<td>VIR-576</td>
<td>INH-1001</td>
</tr>
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<td></td>
<td>SPI-256</td>
<td></td>
<td>GSK-2838232</td>
</tr>
</tbody>
</table>
NRTI

Needs:
• More convenient
MK-8591 (EFdA)

• 4’-ethynyl-2-fluoro-2’-deoxyadenosine; EFdA
• Nonobligate chain terminator
• Inhibits RT by preventing translocation (NRTTI)
• Potent antiviral activity (PBMC EC$_{50}$ = 0.2 nM) with broad coverage (HIV-1, HIV-2, MDR strains)
• Accumulates in LN, vagina, rectum (animals)
• Low-dose formulations

A single 10 mg oral dose in HIV-infected patients results in 1.6 log decrease in viral load at day 7-10
• Intracellular MK-8591-TP t$_{1/2}$ = 103 hr
• No evidence of resistance out to Day 10
MK-8591 (EFdA)

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
NNRTI

Needs:
• Less toxicity and better tolerability
• Active against NNRTI-resistant viruses
• Fewer drug interactions
Doravirine (DOR; MK-1439)

- Investigational NNRTI
- Preclinical
  - Potent at low-milligram dose
  - Metabolized by CYP3A4; not a CYP450 inhibitor or inducer
  - Active in vitro against viral strains with:
    - K103N
    - Y181C
    - G190A
    - E101K
    - E138K
    - K103N/Y181C

Lai AAC 2014;58:1652-1663
Doravirine (DOR): Phase Ib

Double-blind, randomized, placebo-controlled
Study population: HIV+, treatment-naïve (N = 18)

Schurmann AIDS 2016;30:57-63
Doravirine (DOR) – Phase 2
Randomized, double-blind, 2-part study
Study population: Rx-naïve participants, VL >1000, CD4 >100 (N = 216)

Drug-related AEs:
31% (DOR) vs. 56% (EFV)
Doravirine (DOR) – Phase 3

Phase 3, multicenter, double-blind, placebo-controlled randomized study
Study population: Rx-naïve, VL >1000, no GT resistance to study drugs (N = 769)
Study treatment: 2 NRTIs + [DOR 100 mg vs. DRV 800 mg/RTV 100 mg]

Pts with protocol-defined VF: DOR 19 (5%) vs DRV/r 24 (6%) → NO drug resistance
Discontinued due to AE: DOR 2% vs DRV/r 3%
most common: diarrhea DOR 14% vs DRV/r 22%; nausea DOR 11% vs DRV/r 12%
lipids decreased with DOR (chol -1, triglyc -3 mg/dL), increased with DRV/r (chol +18, triglyc +22)

Molina/Squires CROI 2017 #45LB
INSTI

Needs:

• Active against INSTI-resistant virus
• More convenient
Bictegravir (GS-9883): In vitro

- In vitro EC\textsubscript{50} 0.75 nM against wt clinical isolates of HIV-1 and -2
- T\textsubscript{1/2} 18 hours (once-daily); no PK boosting required
- No inhibition or induction of CYP3A4 or UGT -- low potential for drug interactions

Tsiang Antimicrob Agents Chemo 2016;60:7086-7097

Zhang/Custodio CROI 2017 #40
Bictegravir (GS-9883): Phase 1

• Study population: HIV+, naïve/off ART X ≥12 wks, no prior INSTI, VL 10K-400K, CD4 >200 (N = 20)

Gallant, ASM Microbe 2016, abstract #415
Bictegravir (GS-9883): Phase 2

- Study population: Rx-naïve, VL ≥1000, CD4 ≥200, HBV/HCV-neg (N=98)
- Study rx: TAF/FTC + [BIC or DTG] (2:1 randomization)

Results: Virologic Outcomes at Weeks 24 and 48 by FDA Snapshot
HIV-1 RNA <50 copies/mL

Adverse events and lab abnormalities similar; no drug resistance detected

Phase 3 studies in progress: TAF/FTC/BIC
Cabotegravir (CAB)

- Integrase inhibitor similar to DTG; similar resistance
- Potent in HIV+ individuals (5, 10, 30, 60 mg oral)  
  Margolis EACS 2013; Spreen HIV Clin Trials 2013;14:192
- Nanotechnology formulation; SC + IM injections
- $T_{1/2}$ 21-50 days!
- Supports monthly or quarterly dosing
- Safety: ISR (all mild) nodules with SC dosing

![Figure 4. Mean Plasma S/GSK1265744 Concentration-Time Profiles Following Single Dose LAP Formulation Administration](image)

Spreen JAIDS 2014;67:481
LATTE-2: CAB + RPV IM Maintenance

Phase 2b multicenter, parallel group, open-label study
Study population: Rx-naïve individuals (N = 309)
LATTE-2: Virologic Suppression

LATTE-2 Week 48 Results: HIV-1 RNA <50 c/mL by Snapshot (ITT-ME)

Induction period

Maintenance period

Proportion of patients with virological suppression, %

Study visit

BL W-16 W-12 W-8 W-4 D1 W4 W8 W12 W16 W20 W24 W28 W32 W36 W40 W44 W48

Snapshot success

<table>
<thead>
<tr>
<th></th>
<th>D1</th>
<th>W32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q4W</td>
<td>99%</td>
<td>95%</td>
</tr>
<tr>
<td>Q8W</td>
<td>95%</td>
<td>94%</td>
</tr>
<tr>
<td>Oral</td>
<td>98%</td>
<td>91%</td>
</tr>
</tbody>
</table>

Margolis IAS 2016 #THAB02LB
LATTE-2: Efficacy

HIV-1 RNA <50 c/mL at Week 48
ITT-ME (Snapshot)

Virologic outcomes

<table>
<thead>
<tr>
<th></th>
<th>Oral Q8W IM</th>
<th>IM Q4W IM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virologic success</td>
<td>92 (n=115)</td>
<td>89 (n=115)</td>
</tr>
<tr>
<td>Virologic non-response</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>No virologic data</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>CAB 744 (n=56)</td>
<td>8</td>
<td>9</td>
</tr>
</tbody>
</table>

Both Q8W and Q4W comparable to Oral CAB at Week 48

Margolis IAS 2016 #THAB02LB
### LATTE-2: Injection Site Reactions

<table>
<thead>
<tr>
<th></th>
<th>Q8W IM (n=115)</th>
<th>Q4W IM (n=115)</th>
<th>IM subtotal (N=230)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of injections</td>
<td>1623</td>
<td>2663</td>
<td>4286</td>
</tr>
<tr>
<td>Number of ISRs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(events/injection)</td>
<td>1054 (0.65)</td>
<td>1228 (0.46)</td>
<td>2282 (0.53)</td>
</tr>
<tr>
<td>Grades</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>839 (80%)</td>
<td>1021 (83%)</td>
<td>1860 (82%)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>202 (19%)</td>
<td>197 (16%)</td>
<td>399 (17%)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>12 (1%)</td>
<td>10 (&lt;1%)</td>
<td>22 (&lt;1%)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Duration, days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤7</td>
<td>943 (89%)</td>
<td>1121 (91%)</td>
<td>2064 (90%)</td>
</tr>
<tr>
<td>Median</td>
<td>3.0</td>
<td>3.0</td>
<td>3.0</td>
</tr>
</tbody>
</table>

- Most common ISR events overall were pain (67%), swelling (7%), and nodules (6%).
- Number of subjects reporting ISRs decreased over time, from 86% (Day 1) to 33% (Week 32)
- 2/230 subjects (1%) withdrew as a result of injection reactions (Q8W)
HPTN 083: PrEP with TDF/FTC oral vs CAB IM

- Study population: Adult MSM and TGW, at high-risk for HIV acquisition (N = 4500)
  - High risk
    - Any non-condom receptive anal intercourse (RAI)
    - >5 partners
    - Stimulant drug use
    - Rectal or urethral STI in past 6 months

- Study regimen: TDF/FTC daily oral vs CAB q2-month injections
  - Double-blind, double-dummy design

- Design: noninferiority, efficacy study

- NY area: Weill Cornell Chelsea, Rutgers, Harlem, NY Blood Center, Bronx -- First participant enrolled 12/16!
Entry Inhibitors

Needs:

- Novel mechanism of action
- More convenient dosing
HIV Entry Inhibitors

Adapted from Moore JP, PNAS 2003;100:10598-10602.

* = FDA approved
Fostemsavir: Oral HIV Attachment Inhibitor

Study pop: CD4 ≥200, VL ≥5000 off ART X ≥8 wks or ART-naive (N = 50)

- Prodrug of *temsavir*
- Inhibits CD4 binding by binding to gp120
- PK suggest QD or BID dosing without boosting
- ↓ baseline susceptibility in 12% of pts due to envelope polymorphisms; screened by baseline IC\textsubscript{50}

Nettles JID 2012;206:1002
Fostemsavir: Phase 2b

Phase 2b, randomized, controlled, partially blinded (to ‘068 dose)
Study pop: Rx-experienced (≥1 wk on ≥1 ART); IC$_{50}$ <100 nM for ‘529 (N = 254)

Lalezari Lancet HIV 2015;2:e427-37
Thompson Antivir Ther (epub 12/16)
Fostemsavir: Phase 2b Efficacy

- Week 48 VL <50:
  - MITT: 61-82% (fostemsavir) vs 71% (ATV/r)
  - Observed: 77-95% (fostemsavir) vs 88% (ATV/r)

Table 2: Proportion of subjects achieving HIV-1 RNA <50 c/mL (Week 96 Snapshot): mITT analysis

<table>
<thead>
<tr>
<th>Parameter, n (%)</th>
<th>BMS-663068 + TDF + RAL 1200 mg QD* N=200</th>
<th>ATV/r + TDF + RAL 300 mg/100 mg QD N=51</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1 RNA &lt;50 c/mL</td>
<td>122 (61%)</td>
<td>27 (53%)</td>
</tr>
<tr>
<td>HIV-1 RNA ≥ 50 c/mL</td>
<td>14 (7%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Reasons for not achieving HIV-1 RNA &lt;50 c/mL</td>
<td>64 (32%)</td>
<td>21 (41%)</td>
</tr>
<tr>
<td>Discontinued due to lack of efficacy</td>
<td>21 (10.5%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Discontinued due to other reasons</td>
<td>24 (12%)</td>
<td>6 (12%)</td>
</tr>
<tr>
<td>No virologic data at Week 96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinued due to AEs</td>
<td>6 (3%)</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>Discontinued for other reasons</td>
<td>13 (6.5%)</td>
<td>7 (14%)</td>
</tr>
</tbody>
</table>

DeJesus CROI 2016 #472
Thompson Antivir Ther (epub 12/16)
# Fostemsavir: Phase 2b Safety

<table>
<thead>
<tr>
<th>Parameter, number of subjects (%)</th>
<th>BMS-663068 + TDF + RAL 1200 mg QD* N=200</th>
<th>ATV/r + TDF + RAL 300 mg/100 mg QD N=51</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAEs*</td>
<td>24 (12%)</td>
<td>7 (14%)</td>
</tr>
<tr>
<td>AEs leading to discontinuation*</td>
<td>5 (2.5%)</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>Grade 2-4-related clinical AEs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total subjects with an event</td>
<td>17 (8.5%)</td>
<td>19 (37%)</td>
</tr>
<tr>
<td>Present in ≥2 subjects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>0</td>
<td>6 (12%)</td>
</tr>
<tr>
<td>Blood bilirubin increased</td>
<td>0</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1 (0.5%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Jaundice</td>
<td>0</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (0.5%)</td>
<td>2 (4%)</td>
</tr>
</tbody>
</table>

## Table 5: Select Grade 3–4 laboratory abnormalities (≥2 subjects)

<table>
<thead>
<tr>
<th>Parameter, number of subjects (%)</th>
<th>BMS-663068 + TDF + RAL 1200 mg QD* N=200</th>
<th>ATV/r + TDF + RAL 300 mg/100 mg QD N=51</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>6 (3%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
<td>2 (1%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Aspartate aminotransferase</td>
<td>4 (2%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>0</td>
<td>31 (62%)</td>
</tr>
<tr>
<td>Creatinine kinase</td>
<td>6 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Glucose fasting serum</td>
<td>2 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Uric acid</td>
<td>3 (2%)</td>
<td>0</td>
</tr>
</tbody>
</table>

FDA “Breakthrough Status” 7/15
Phase 3 in treatment-experienced enrolled
Ibalizumab: HIV Entry Inhibitor

- Monoclonal antibody; IV, SC
- Binds to CD4 receptor
- Dosing every 1-4 weeks
- Phase 1a Kuritzkes JID 2004;189:286
- Phase 1b Jacobson AAC 2009;53:450
- Phase 2a Norris IAS 2006 #TuPE0058
- Phase 2b Khanlou IDSA 2011 #LB9

Rx-experienced; 3-class resistance (N = 113)
Ibalizumab: HIV Entry Inhibitor

• Phase 3
  – Study population: VL>1000, on ART >6 months, 3-class resistance, ≥1 sensitive drug (N = 40)
  – Study treatment: continue ART, +ibalizumab 800 mg day 7, +OBR day 14, +ibalizumab day 21 and q 2 wks → 24 wks

Primary Endpoint: VL Reduction at Day 14
Following 2000 mg loading dose of Ibalizumab (Day 7)

Efficacy at Week 24
- Mean viral load decrease of 1.6 log₁₀ from Baseline
- 55% and 48% of patients with a ≥1 and ≥2 log₁₀ reduction, respectively
- Undetectable viral load in 43% of patients; 50% with <200 copies

FDA: orphan drug; breakthrough designation
Acknowledgments

- Cornell HIV Clinical Trials Unit (CCTU)
- Division of Infectious Diseases
- Weill Cornell Medicine
- AIDS Clinical Trials Group (ACTG)
- HIV Prevention Trials Network (HPTN)
- Division of AIDS, NIAID, NIH

- The patient volunteers!