New Antiretroviral Drugs

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## Newer ART Agents (partial list)

<table>
<thead>
<tr>
<th>Phase</th>
<th>NRTI</th>
<th>NNRTI</th>
<th>PI</th>
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NRTI

Needs:

• Less long-term toxicity
Drug Delivery: TDF vs. Tenofovir Alafenamide (TAF)
Phase 3 Studies: TDF vs. TAF + (/FTC/EVG/c)

Randomized, double-blind; 2-pill, once-daily regimen
Study population: Rx-naïve, VL >1000, eGFR >50 cc/min (N=1733)

VL<50 at week 48

• E/C/F/TAF non-inferior to E/C/F/TDF at week 48
  - No difference by BL VL (above/below 100K or CD4 above/below 200)

Sax Lancet 2015;385:2606-15
TAF Phase 3: Renal and Bone
Studies 104 and 111: Week 48 Combined Analysis

Mean (SD) Change from Baseline eGFR*

Time (Weeks)

* Cockroft-Gault (mL/min).

Sax Lancet 2015;385:2606-15
Phase 3: TAF/FTC vs. TDF/FTC + 3\textsuperscript{rd} Drug

- Phase 3, randomized, placebo-controlled study
- Study pop: Suppressed on stable TDF/FTC-containing regimen X >6 months (N=663)
- Study treatment: continue TDF/FTC or change to TAF/FTC (2 doses, depending on 3\textsuperscript{rd} drug)
- Results: VL <50 at week 48:
  - TDF (93%) vs. TAF (94%), $\Delta=1.3\%$ (95% CI -2.5, +5.1%)
  - safety, toxicity-related discontinuations “similar”
  - TAF significantly less median eGFR decrease (P<0.001)
  - TAF significantly less BMD loss (p<0.001)

Gilead Press Release 9/2/15
Phase 2: TDF vs TAF + (/FTC/DRV/r)

- Randomized, placebo-controlled; 2-pill, once-daily regimen
- Study population: Rx-naïve, VL >5000, CD4>50, eGFR >70 cc/min (N=150)

Virologic Outcomes
(HIV-1 RNA <50 c/mL at W 24,48, FDA Snapshot, ITT)

TAF associated with less changes in renal markers, bone mineral density

Tenofovir alafenamide (TAF)

- Based on drug-drug interactions studies, 2 doses:
  - TAF 10 mg (with boosted PIs); 25 mg (with NNRTIs/IIIs)
    Lawson ICAAC 2014 #H-1012

- Switch to TAF improved renal markers and BMD
  - 1386 pts on TDF with CrCL >50 Mills IAS 2015 #TUAB0102
  - 242 pts on TDF (65%) or not (35%) with eGFR 30-69
    Gupta IAS 2015 #TUAB0103

- Co-formulations
  - TAF/FTC/EVG/c: FDA approved 11/5/15!; under EMA rvw
  - TAF/FTC: FDA target action date: 4/7/16; under EMA rvw
  - TAF/FTC/RPV: submitted to FDA: 7/1/15; under EMA rvw
  - TAF/FTC/DRV/c: in phase 3 clinical trials
NNRTI needs:
- Less toxicity and better tolerability
- Active against resistant viral strains
- Fewer drug interactions
doravirine (DOR)

- Investigational NNRTI
- Pre-clinical
  - Potent at low miligram dose
  - Not a CYP450 inhibitor or inducer
  - Metabolized by CYP3A4
  - Active \textit{in vitro} against viral strains with K103N, Y181C, G190A, E101K, E138K or K103N/Y181C

- Clinical
  - Multiple doses in 40 HIV- men X 10d:
    - no rash/CNS events (except HA)
    - PK supportive of once-daily dosing

\textit{Lai AAC 2014;58:1652-1663}

\textit{Anderson Antivir Ther 2015;20:397-405}
doravirine (DOR): Phase Ib
Double-blind, randomized, placebo-controlled
Study population: HIV+, treatment-naïve (N=18)
Doravirine: Phase 2b Dose Finding (Part 1)

- Randomized: TDF/FTC + 4 doses of DOR vs. EFV

Results:

VL <40

Non-CNS tox 48 wk

DOR vs. EFV

- nausea (8% vs. 2%)
- fatigue (7% vs. 5%)
- diarrhea (5% vs. 10%)
Doravirine: Phase 2b (Part 2)

- Randomized: TDF/FTC + DOR 100 mg vs. EFV (N=132)

- Results (combining parts 1 and 2; N=216):
  - CNS Toxicity (48 wks)
    - overall (DOR 22% vs. EFV 44%; p<0.001)
      - dizziness (DOR 9% vs. EFV 28%)
      - insomnia (DOR 6% vs. EFV 3%)
      - abnormal dreams (DOR 6% vs. EFV 17%)
      - nightmares (DOR 6% vs. EFV 8%)

- Significant interaction with rifampin (↓DOR >57%)

Gatell Glasgow 2014 #O434
Judge CROI 2015 #521
DOR Phase 2: Study 007

Study population: Treatment-naïve, VL $\geq 1000$, CD4 $\geq 100$ (N=216)

Study regimen: TDF/FTC + **DOR** or **EFV**

Results: VL <40 at 24 weeks: **74% (DOR)** vs. **73% (EFV)**

Patients with $\geq 1$ CNS event: **27% (DOR)** vs. **46% (EFV)**

*Excludes: Patients who discontinued due to non-treatment related reasons but with last RNA <40 c/mL, or due to AE, or who lack data in week 24 window.

Gatell IAS 2015 #TUAB0104
INSTI needs:

• less frequent dosing
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
- $T\frac{1}{2}$ 21-50 days!
- Supports monthly or quarterly dosing
- Safety: ISR (all mild) and nodules with SC dosing
- treatment + prevention Spreen JAIDS 2014;67:481
**LATTE 1: CAB and RPV Oral Maintenance**

**Study Design**

- HIV ART-naïve
- VL ≥1000 c/mL
- CD4 ≥ 200 cells/mm³
- 1:1:1:1 Randomization
- Stratified by VL and NRTI
- Blinded to CAB dose
- N=243

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<th>oral_induction_phase</th>
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<tr>
<td>CAB 10 mg + 2 NRTIs*</td>
<td>CAB 10 mg + RPV 25 mg</td>
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<tr>
<td>CAB 30 mg + 2 NRTIs</td>
<td>CAB 30 mg + RPV 25 mg</td>
</tr>
<tr>
<td>CAB 60 mg + 2 NRTIs</td>
<td>CAB 60 mg + RPV 25 mg</td>
</tr>
<tr>
<td>EFV 600 mg + 2 NRTIs</td>
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*ABC/3TC or TDF/FTC

Margolis Lancet ID 2015 (epub 7/17/15)
LATTE 1: CAB and RPV Oral Maintenance

Virologic Success: HIV-1 RNA <50 c/mL by FDA Snapshot (ITT-E)

Proportion, % (95% CI)

Margolis Lancet ID 2015 (epub 7/17/15)
LATTE 2: CAB LAP + RPV-LA as Maintenance Therapy

Phase 2b open-label 96-wk study in rx-naïve (N=309)

Start with CAB oral + 2 NRTIs; 93% suppressed and randomized 2:2:1 to: CAB LAP + RPV-LA q4 weeks, q8 weeks or continue oral CAB + 2 NRTIs

Results: At 32 weeks of maintenance (primary endpoint):
HIV RNA <50: 94% (4 wks), 95% (8 wks), 91% (oral)
AEs withdrawal: 5% (4 wks), 2% (8 wks), 2% (oral)
93% of injection participants reported ISR

Janssen and ViiV Press Releases 11/3/15
CD4 Attachment Inhibitor

needs:

• novel mechanism of action
HIV Entry Inhibitors

Adapted from Moore JP, PNAS 2003;100:10598-10602.
**BMS-663068: Oral HIV Attachment Inhibitor**

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

- **Prodrug of BMS-626529**
- 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$_{50}$
- **M426L** substitution correlated with resistance (↑IC50 and poor VR); no selection of M426L day 1 to 8

**Nettles JID 2012;206:1002**

**Zhou JAC 2014;69:573**
BMS-663068: Phase 2b -- 24 weeks

- Randomized, partially blinded (to 068 dose)
- Rx-experienced pts (≥1 wk on ≥1 ART) with IC50<100nM for '529 (N=251)
- Randomized to TDF + RAL +
  - 1 of 4 doses of 068 [400 or 800 bid or 600 or 1200 qd] or ATV/r
- Results:
  - 8d monotherapy: up to 1.5 log ↓ with 1200 mg qd
  - Wk 24 VL <50
    - 068 69-80% vs. ATV/r 75%; no difference by BL VL/CD4
  - 068: no SAE or rx d/c

Lalezari Lancet HIV 2015;2:e427-37
BMS-663068: Phase 2b -- 48 weeks

• Results:
  – Wk 48 VL <50
    • 068 61-82% vs. ATV/r 71%
  – Safety

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<tr>
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<th>BMS-663068 + TDF + RAL</th>
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<th>ATV/r + TDF + RAL</th>
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<td>400 mg BID N=50</td>
<td>800 mg BID N=49</td>
<td>600 mg QD N=51</td>
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<td>Total number of subjects, n (%)</td>
<td>400 mg BID N=50</td>
<td>800 mg BID N=49</td>
<td>600 mg QD N=51</td>
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<td>SAEs</td>
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<td>Grade 2-4 related clinical AEs</td>
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<td>2 (4.0)</td>
<td>2 (3.9)</td>
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Thompson CROI 2015 #545

Clotet EACS 2015
BMS-663068: PK and Current Status

- No PK Interactions with ATV or ATV/r Zhu CROI 2013 #534
- No PK Interactions with DRV/r or DRV/r + ETR (ETR alone ↓663068) Landry CROI 2015 #523
- FDA “breakthrough” designation 7/15
- Currently in Phase 3 in heavily treatment-experienced patients
Maturation Inhibitor

needs:
• novel mechanism of action
• no baseline polymorphisms that confer resistance
HIV-1 Life Cycle
**BMS-955176: Profile of a Second-Generation MI**

- Binds tightly and reversibly to HIV-1 Gag
- Greater potency and coverage of Gag polymorphs compared with first-generation MI
- Low serum binding
- Low-dose prediction with half-life supportive of once-daily dosing
- No significant safety issues identified in early clinical studies

**Core structure of BMS-955176**

**Broad Polymorphic Coverage of BMS-955176**

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<th>Virus (HIV-1 NL&lt;sup&gt;Δ33&lt;/sup&gt;)</th>
<th>Subtype B&lt;sub&gt;S&lt;/sub&gt; % LANL database¹</th>
<th>EC&lt;sub&gt;50&lt;/sub&gt;: nM</th>
<th>Fold change in EC&lt;sub&gt;50&lt;/sub&gt; vs. WT</th>
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¹: Assay conducted in the presence of 40% human serum + 27 mg/mL human serum albumin; Surrogate genotypes for subtype C; Percentage of subtype B isolates in the Los Alamos database (2010). BVM, Bevirimat; SDM, site directed mutant; WT, wild-type.
Phase 2a, Part A

**BMS-955176: Median Change in HIV-1 RNA over Time**

- Study population: ART naïve or experienced, VL >5000, CD4 >200 (N=60)

- No serious adverse events, grade 3/4 events, no d/c due to adverse events

- Median change in HIV-1 RNA from baseline to Day 11 reached $-1.4 \log_{10} \text{c/mL}$
Study population: Subtype B, Rx-naïve, VL≥5000, CD4≥200 (N=28)

TDF/FTC 300 mg/200 mg + ATV 300 mg + RTV 100 mg*
BMS-955176 40 mg + ATV 300 mg + RTV 100 mg
BMS-955176 40 mg + ATV 400 mg
BMS-955176 80 mg + ATV 400 mg

Hwang IAS 2015 #TUAB0106LB
Study population: ART naïve or experienced, VL >5000, CD4 >200 (N=19)
BMS-955176: Safety Summary

• Part A and C (10d monotherapy, dose escalation)
  – No deaths, AE requiring discontinuation, serious AE, grade 3-4 clinical AE
  – 1 grade 3 neutropenia (transient) at 120 mg dose

• Part B (28d in combination with ATV)
  – No deaths, AE requiring discontinuation, serious AE
  – 1 neutropenia; 10 increased total bilirubin
Acknowledgments

• Cornell HIV Clinical Trials Unit (CCTU)
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• Weill Cornell Medical College
• AIDS Clinical Trials Group (ACTG)
• HIV Prevention Trials Network (HPTN)
• Division of AIDS, NIAID, NIH

• The patient volunteers!