New HIV Drugs and Regimens

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Disclosures

The speaker is a consultant and/or has received speaking honoraria and/or grant support from the following companies relevant to this talk:

- Gilead
- GlaxoSmithKline
- Janssen (J&J)
- Merck
- Teva
- ViiV
# FDA-Approved Antiretroviral Agents and Fixed-dose Combinations

<table>
<thead>
<tr>
<th><strong>NRTI</strong></th>
<th><strong>Protease Inhibitors</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine</td>
<td>Saquinavir</td>
</tr>
<tr>
<td>Didanosine</td>
<td>Ritonavir</td>
</tr>
<tr>
<td>Stavudine</td>
<td>Indinavir</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>Nelfinavir</td>
</tr>
<tr>
<td>Abacavir</td>
<td>Fosamprenavir</td>
</tr>
<tr>
<td>Tenofovir*</td>
<td>Lopinavir/ritonavir</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>Atazanavir</td>
</tr>
<tr>
<td>ZDV/3TC</td>
<td>Atazanavir/cobicistat</td>
</tr>
<tr>
<td>ABC/3TC</td>
<td>Tipranavir**</td>
</tr>
<tr>
<td>TDF/FTC</td>
<td>Darunavir</td>
</tr>
<tr>
<td>FTC/TAF</td>
<td>Darunavir/cobicistat</td>
</tr>
<tr>
<td>ZDV/3TC/ABC</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>NNRTI</strong></th>
<th><strong>Fusion Inhibitors</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nevirapine</td>
<td>Enfuvirtide (T-20)**</td>
</tr>
<tr>
<td>Efavirenz</td>
<td></td>
</tr>
<tr>
<td>Etravirine**</td>
<td></td>
</tr>
<tr>
<td>Rilpivirine</td>
<td></td>
</tr>
<tr>
<td>TDF/FTC/EFV</td>
<td></td>
</tr>
<tr>
<td>TDF/FTC/RPV</td>
<td></td>
</tr>
<tr>
<td>RPV/FTC/TAF</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Integrase inhibitors</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Raltegravir</td>
</tr>
<tr>
<td>Elvitegravir/cobicistat/FTC/TDF</td>
</tr>
<tr>
<td>E/C/F/TAF</td>
</tr>
<tr>
<td>Dolutegravir</td>
</tr>
<tr>
<td>Dolutegravir/ABC/3TC</td>
</tr>
</tbody>
</table>

*Nucleotide RT inhibitor

**Approved only for treatment-experienced patients
Why do we need new drugs?

- Side-effects of current therapies
- Potential long-term toxicities of current ART
- Resistance
- Need for less frequent dosing
Tenofovir alefenamide (TAF)
Tenofovir Alafenamide Fumarate (TAF)

Tenofovir Disoproxil Fumarate

Gut

Plasma

Lymphoid Cells

TFV

TDF

TAF

TFV

TDF/TFV

TAF

TFV

TFV-MP

TFV-DP

Plasma and intracellular levels of tenofovir diphosphate

**PBMC TFV-DP AUC\(_{0-24h}\) at Week 4 or 8**

- **Geometric Mean**
- **6.5 X**

- **D/C/F/TAF**
  - PBMC TFV-DP exposure was 6.5-fold higher
  - Plasma TFV exposure (AUC\(_{tau}\)) was 91% lower

<table>
<thead>
<tr>
<th>Plasma TFV PK Mean (Coefficient of Variance)</th>
<th>D/C/F/TAF (n=21)</th>
<th>DRV + COBI + TVD (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(C_{tau}) (ng/ml)</td>
<td>11.7 (39.3)</td>
<td>75.4 (30.9)</td>
</tr>
<tr>
<td>(C_{max}) (ng/mL)</td>
<td>18.8 (37.6)</td>
<td>413.2 (28.3)</td>
</tr>
<tr>
<td>(AUC_{tau}) (ng.hr/ml)</td>
<td>339.0 (37.1)</td>
<td>3737.0 (26.8)</td>
</tr>
</tbody>
</table>

Mills A et al ICAAC 2014
Relative efficacy of TDF- and TAF-containing ART

Sax et al Lancet 2015
Effect of TDF and TAF on renal tubular function and bone density

Sax et al. Lancet 2015
Two-drug ART
## Dual Therapy: Potential Boosted PI Regimens for Initial/Maintenance Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Setting</th>
<th>N</th>
<th>Regimen</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEAT001</td>
<td>Initial</td>
<td>805</td>
<td>DRV/RTV + RAL</td>
<td>Similar efficacy as DRV/RTV + FTC/TDF; poor efficacy in pts with high HIV-1 RNA, low CD4+ cell counts</td>
</tr>
<tr>
<td>GARDEL</td>
<td>Initial</td>
<td>426</td>
<td>LPV/RTV + 3TC</td>
<td>Similar efficacy as LPV/RTV + 2 NRTIs</td>
</tr>
<tr>
<td>MODERN</td>
<td>Initial</td>
<td>813</td>
<td>DRV/RTV + MVC</td>
<td>Inferior efficacy vs DRV/RTV + FTC/TDF</td>
</tr>
<tr>
<td>SPARTAN</td>
<td>Initial</td>
<td>94</td>
<td>ATV + RAL</td>
<td>Similar virologic suppression, higher VF and hyperbilirubinemia rates vs ATV/RTV + FTC/TDF</td>
</tr>
<tr>
<td>OLE</td>
<td>Switch</td>
<td>250</td>
<td>LPV/RTV + 3TC</td>
<td>Similar efficacy as continued standard ART</td>
</tr>
<tr>
<td>KITE</td>
<td>Switch</td>
<td>60</td>
<td>LPV/RTV + RAL</td>
<td>Small study; encouraging efficacy</td>
</tr>
<tr>
<td>SALT</td>
<td>Switch</td>
<td>286</td>
<td>ATV/RTV + 3TC</td>
<td>Similar efficacy as ATV/RTV + 2 NRTIs</td>
</tr>
<tr>
<td>ATLAS-M</td>
<td>Switch</td>
<td>266</td>
<td>ATV/RTV + 3TC</td>
<td>Improved efficacy vs ATV/RTV + 2 NRTIs</td>
</tr>
<tr>
<td>DUAL-GESIDA</td>
<td>Switch</td>
<td>257</td>
<td>DRV/RTV + 3TC</td>
<td>Similar efficacy as DRV/RTV + 2 NRTIs</td>
</tr>
</tbody>
</table>
PADDLE: Dolutegravir + Lamivudine for Treatment-Naive Pts

Open-label, single-arm phase IV exploratory trial

Treatment-naive pts with HIV-1 RNA > 5000-100,000 c/mL, CD4+ cell count ≥ 200 cells/mm³, HBsAg negative (N = 20)

18/20 pts achieved HIV-1 RNA < 50 c/mL at Wk 48

- 1 pt committed suicide (deemed unrelated to study drugs)
- 1 pt experienced protocol-defined virologic failure at Wk 36 (baseline HIV-1 RNA > 100,000 c/mL); resuppressed HIV-1 RNA without ART change by discontinuation visit (Wk 52)
- 3 pts with BL HIV-1 RNA > 100,000 c/mL suppressed at Wk 48

DTG 50 mg QD + 3TC 300 mg QD (N = 20*)


Slide credit: clinicaloptions.com
LAMIDOL study

- Single-arm pilot study
- Patients on suppressive 3-drug ART switched to DTG+2 NRTIs (Phase 1) then DTG+3TC (Phase 2)

Joly V et al CROI 2017 Abstr 458
Other DTG/3TC studies

- ACTG A5353
- Gemini I and II
- ASPIRE (planned)
NEW HIV DRUGS, FORMULATIONS, COMBINATIONS, AND RESISTANCE

PHASE III SWORD 1&2: SWITCH TO DTG+RPV MAINTAINS VIROLOGIC SUPPRESSION THROUGH 48 WKS

Josep M Llibre
Univ Hosp Germans Trias, Badalona, Barcelona, Spain
SWORD-1 and SWORD-2 Phase III Study Design

Identically designed, randomized, multicenter, open-label, parallel-group, non-inferiority studies

**Screening**
- VL <50 c/mL on INI, NNRTI, or PI + 2 NRTIs

**1:1**
- DTG + RPV (N=513)
- CAR (N=511)

**Early switch phase**
- DTG + RPV

**Late switch phase**
- DTG + RPV

**Continuation phase**
- DTG + RPV

**Inclusion criteria**
- On stable CAR >6 months before screening
- 1st or 2nd ART with no change in prior regimen due to VF
- Confirmed HIV-1 RNA <50 c/mL during the 12 months before screening
- HBV negative

**Primary endpoint at 48 weeks:** subjects with VL <50 c/mL (ITT-E snapshot)

**Countries**
- Argentina
- Australia
- Belgium
- Brazil
- Canada
- France
- Germany
- Italy
- Netherlands
- Russia
- Spain
- Taiwan
- United States
- United Kingdom

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*a*-8% non-inferiority margin for pooled data. -10% non-inferiority margin for individual studies
Snapshot Outcomes at Week 48 (SWORD-1&2)

**Virologic outcomes**

<table>
<thead>
<tr>
<th></th>
<th>SWORD-1</th>
<th>SWORD-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTG + RPV (n=252)</td>
<td>95%</td>
<td>96%</td>
</tr>
<tr>
<td>CAR (n=256)</td>
<td>94%</td>
<td>94%</td>
</tr>
</tbody>
</table>

**Adjusted treatment differences (95% CI)**

- **SWORD-1**
  - CAR: -0.6%
  - DTG + RPV: 3.0%

- **SWORD-2**
  - CAR: -3.9%
  - DTG + RPV: 4.2%

**Percentage-point difference**

DTG + RPV is non-inferior to CAR with respect to snapshot in the ITT-E population (<50 c/mL) at Week 48 in both studies.

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*Adjusted for age and baseline 3rd agent.

Liiboe et al. CROI 2017; Seattle, WA. Abstract 2421.
New Molecules
Doravirine

- Novel, next-generation NNRTI
- Unique resistance profile
  - Active against HIV with common NNRTI resistance mutations (K103N, Y181C, G190A, K103N/Y181C, E138K)
- Low potential for drug-drug interactions
- Once-daily dosing without regard to food
- Doravirine 100mg compared favorably to EFV with respect to efficacy in phase 2b; superior neurological side effect profile
Study Design

Phase 3, multicenter, double-blind, randomized study in treatment-naïve adults with HIV-1 infection

Key Entry Criteria:
- HIV-1 RNA ≥1000 c/mL within 45 days before Day 1
- Antiretroviral naive
- No genotypic resistance to any study drugs
- Stratification factors: HIV-1 RNA > 100,000 and NRTI choice

Group 1: DOR 100 mg + DRV-PBO + r-PBO + 2 NRTIs

Group 2: DOR-PBO + DRV 800 mg + r 100 mg + 2 NRTIs

Primary Analysis Time Point

DOR = doravirine; DRV = darunavir; PBO = placebo; r = ritonavir
NRTIs = open-label TDF/FTC or ABC/3TC, as chosen by the investigator before randomization
All study therapy components were taken once daily
Efficacy: Proportion with HIV-1 RNA <50 c/mL

DOR is non-inferior to DRV+r at Week 48

% of Participants (95% CI)

- DOR:
  - Week 0: 22%
  - Week 4: 38%
  - Week 8: 42%
  - Week 16: 71%
  - Week 24: 76%
  - Week 32: 83%
  - Week 48: 86%

- DRV+r:
  - Week 0: 15%
  - Week 4: 15%
  - Week 8: 15%
  - Week 16: 15%
  - Week 24: 15%
  - Week 32: 15%
  - Week 48: 84%

Difference (95% CI): 3.9% (-1.6%, 9.4%)

† FDA Snapshot Approach

Treatment Week

CROI 2017, Abstract 45LB. Copyright © 2017 Merck & Co., Inc. All Rights Reserved
### Summary of Clinical Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>DOR (N=383)</th>
<th>DRV+r (N=383)</th>
</tr>
</thead>
<tbody>
<tr>
<td>One or more AE</td>
<td>307 (80%)</td>
<td>300 (78%)</td>
</tr>
<tr>
<td>Drug-related AE</td>
<td>117 (31%)</td>
<td>123 (32%)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>19 (5%)</td>
<td>23 (6%)</td>
</tr>
<tr>
<td>Discontinued due to AE</td>
<td>6 (2%)</td>
<td>12 (3%)</td>
</tr>
<tr>
<td>Most Common AE’s (≥ 10% in either group)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>54 (14%)</td>
<td>86 (22%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>41 (11%)</td>
<td>46 (12%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>30 (8%)</td>
<td>39 (10%)</td>
</tr>
<tr>
<td>Headache</td>
<td>53 (14%)</td>
<td>41 (11%)</td>
</tr>
<tr>
<td>AEs of Clinical Interest</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash†</td>
<td>28 (7%)</td>
<td>32 (8%)</td>
</tr>
<tr>
<td>Neuropsychiatric†</td>
<td>44 (11%)</td>
<td>50 (13%)</td>
</tr>
</tbody>
</table>

*Only 2 DOR participants and 1 DRV+r participant discontinued due to rash

†Includes disturbance in attention, dizziness, somnolence, abnormal dreams, confusional state, depressed mood, depression, insomnia, major depression, nightmare, and psychotic disorder. No participants discontinued due to neuropsychiatric AEs
Bictegravir (GS-9883)

- Novel, once-daily, INSTI
- Potent in vitro activity against wild-type and most INSTI-resistant variants
- Low potential for drug-drug interactions
- BIC plasma half-life approximately 18 hours
Study Design

- Randomized, double-blind, active-controlled study
- Primary Endpoint: proportion with HIV-1 RNA < 50 copies/mL at Week 24
- After Week 48, all patients who completed the double-blind phase entered an extension phase and received open label BIC/FTC/TAF

Sax PE et al CROI 2017
Results: Virologic Outcomes at Weeks 24 and 48 by FDA Snapshot
HIV-1 RNA <50 copies/mL

Week 24
- Virologic Success: 97%
- Virologic Failure: 3%
- No Data: 6%

Week 48
- Virologic Success: 97%
- Virologic Failure: 2%
- No Data: 6%

% Treatment Difference (95% CI)

- Wk 24: -8.5% (Favors BIC + FTC/TAF)
- Wk 48: -6% (Favors DTG + FTC/TAF)

No resistance to study medications was detected in either arm.
Long-acting Injectables/Implantables
Cabotegravir (CAB)

- Analog of dolutegravir
- CAB and DTG have similar pre-clinical profiles
- Well-suited to use as a long-acting suspension
Cabotegravir nanosuspension

- Drug nanocrystal suspended in aqueous vehicle
- Nanomilled to increase surface area and drug dissolution rate
- Allows ~100% drug loading vs. matrix approaches for lower injection volumes

Mean Concentration-Time Profile Following Single Dose Injection

Cabotegravir 200mg/mL

<table>
<thead>
<tr>
<th>Component</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabotegravir (d50 ~200 nm)</td>
<td>Active</td>
</tr>
<tr>
<td>Mannitol</td>
<td>Tonicity agent</td>
</tr>
<tr>
<td>Surfactant System</td>
<td>Wetting/Stabilizer</td>
</tr>
<tr>
<td>Water for Injection</td>
<td>Solvent</td>
</tr>
</tbody>
</table>

Cabotegravir and Rilpivirine as Two-Drug Oral Maintenance Therapy: LATTE Week 96 results

Margolis DA et al Lancet Infect Dis 2015
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

<table>
<thead>
<tr>
<th>Study visit</th>
<th>Induction period</th>
<th>Maintenance period</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL W-16 W-12 W-8 W-4 D1 W4 W8 W12 W16 W20 W24 W28 W32 W36 W40 W44 W48</td>
<td>Oral CAB induction (ME population)</td>
<td>Oral CAB (n=56) Q4W IM (n=115) Q8W IM (n=115)</td>
</tr>
</tbody>
</table>

Snapshot success

<table>
<thead>
<tr>
<th>Treatment</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 et al. AIDS 2016; Durban, South Africa. Abstract THAB0206LB.
LA injectable INSTIs: Pros and Cons

**PRO**
- Allow monthly dosing
- Tolerated well to date
- More convenient
- Less stigma
- May promote adherence
- Potential for DOT?

**CON**
- Require i.m. injection
- Long-term tolerability?
- Very long terminal ½-life
- Cannot be self-administered
- Potential for resistance in non-adherent patients
MK-8591 (EFdA)

MK-8591 (4’-ethynyl-2-fluoro-2’-deoxyadenosine; EFdA) licensed from Yamasa

Virologic profile and mechanism of action is extensively described in the literature (Mitsuya, Sarafianos, Parniak)

- Non-obligate chain terminator
- Inhibits reverse transcriptase by preventing translocation
- Potent antiviral activity (PBMC EC₅₀ = 0.2 nM) with broad subtype and mutant coverage (HIV-1, HIV-2, MDR strains)
MK-8591: Phase 1b results

- 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

Grobler JA et al CROI 2016
MK-8591: extended release formulation

- 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
Other drugs in development

- Ibalizumab
- Fostemsavir
- PRO140
Summary

- New drugs in several classes are in various stages of clinical testing
- Novel viral and cellular targets being explored
- Greater potency, improved safety and better convenience are driving new drug development
- 2-drug ART could upend old paradigms
- Role of long-acting/injectable/implantable drugs remains to be determined