The ARV Pipeline 2017 Update

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Treatment Action Group

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2017 ARV Pipeline Update

- Pipeline is robust!
  - Several drugs, coformulations, and biologics in late-stage development and Phase I trials

- Trends are clear
  - Maximizing safety and efficacy of three-drug regimens
  - Validating two-drug regimens as durable maintenance therapy and, potentially, for PLWHIV starting treatment for the first time
  - Advancing long-acting and extended release products
  - Development new drugs and biologics for multi-drug/class-resistant HIV
  - Cost considerations in high- and middle-income countries
## Coming Soon!

<table>
<thead>
<tr>
<th>Compound</th>
<th>Class/Type</th>
<th>Company</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DRUGS</strong></td>
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<td></td>
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<tr>
<td>Isentress HD</td>
<td>INSTI</td>
<td>Merck</td>
<td>FDA Approved 5/30/17</td>
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<tr>
<td>Bictegravir plus TAF/FTC</td>
<td>INSTI plus NtRTI &amp; NRTI</td>
<td>Gilead</td>
<td>Phase III; mid-2018 approval</td>
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<tr>
<td>Doravirine (plus TDF/3TC)</td>
<td>NNRTI (plus NtRTI &amp; NRTI)</td>
<td>Merck</td>
<td>Phase III; mid-2018 approval</td>
</tr>
<tr>
<td>Darunavir plus cobicistat, TAF &amp; FTC</td>
<td>PI plus PK booster, NtRTI &amp; NRTI</td>
<td>Janssen</td>
<td>Phase III; mid-2018 approval</td>
</tr>
<tr>
<td>Dolutegravir plus rilpivirine</td>
<td>INSTI plus NNRTI</td>
<td>ViiV/Janssen</td>
<td>Phase III; early 2018 approval</td>
</tr>
<tr>
<td>Dolutegravir plus lamivudine</td>
<td>INSTI plus NRTI</td>
<td>ViiV</td>
<td>Phase III; late 2018 approval</td>
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<tr>
<td><strong>BIOLOGICS</strong></td>
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<tr>
<td>Ibalizumab</td>
<td>Entry Inhibitor</td>
<td>TaiMed Biologics</td>
<td>Phase III; late 2017 or early 2018</td>
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## Other ARVs to Watch For

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<td>LA Cabotegravir + LA Rilpivirine</td>
<td>INSTI + NNRTI</td>
<td>ViiV/ Janssen</td>
<td>Phase III</td>
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<tr>
<td>Albuvirtide</td>
<td>Fusion Inhibitor</td>
<td>Frontier Biologics</td>
<td>Phase III; China is primary launch target</td>
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<tr>
<td>Fostemsavir</td>
<td>CD4 attachment inhibitor</td>
<td>ViiV</td>
<td>Phase III</td>
</tr>
<tr>
<td>Elsulfavirine</td>
<td>NNRTI</td>
<td>Viriom</td>
<td>Phase II; Russia, Ukraine, Belarus, and Kazakhstan primary launch targets</td>
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<tr>
<td>GS-CA1</td>
<td>Capsid inhibitor</td>
<td>Gilead</td>
<td>Phase I</td>
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<tr>
<td>GS-9131</td>
<td>NtRTI</td>
<td>Gilead</td>
<td>Preclinical</td>
</tr>
<tr>
<td>GS-PI1</td>
<td>PI</td>
<td>Gilead</td>
<td>Preclinical</td>
</tr>
<tr>
<td>GSK1264</td>
<td>INSTI</td>
<td>ViiV</td>
<td>Preclinical</td>
</tr>
<tr>
<td>GSK3640254</td>
<td>Maturation inhibitor</td>
<td>ViiV</td>
<td>Preclinical</td>
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<td><strong>BIOLOGICS</strong></td>
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<tr>
<td>PRO 140</td>
<td>CCR5 antagonist</td>
<td>CytoDyn</td>
<td>Phase II/III</td>
</tr>
<tr>
<td>UB-421</td>
<td>CD4 attachment inhibitor</td>
<td>BioPharma</td>
<td>Phase II</td>
</tr>
<tr>
<td>Combinectin (GSK3732394)</td>
<td>Adnectins and fusion inhibitor peptide</td>
<td>ViiV</td>
<td>Preclinical</td>
</tr>
</tbody>
</table>
Bictegravir

- Bictegravir (BIC; GS-9883): once-daily, unboosted INSTI
- Potent *in vitro* activity against wild-type and most INSTI-resistant variants
- Substrate of CYP3A4 and UGT1A1; inhibition or induction of both necessary for PK changes, therefore significant drug interactions expected to be limited
- Being developed in coformulation with TAF and FTC
  - No plans for stand-alone formulation
- Phase II trial results reported; Phase III trials still ongoing
- New Drug Application (NDA) filed June 12th
- Phase II, 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

BIC vs. DTG: Results

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

Week 24
- 97% (63/65) BIC + FTC/TAF
- 94% (31/33) DTG + FTC/TAF

Week 48
- 97% (63/65) BIC + FTC/TAF
- 91% (30/33) DTG + FTC/TAF

Treatment Difference
- Wk 24: 8.5% (95% CI: -8.5 to 24.5)
- Wk 48: 6.4% (95% CI: -6 to 18.8)

Favors BIC + FTC/TAF

Most common treatment-related adverse event was diarrhea (12% in both groups), followed by nausea, arthralgia, fatigue, and headache.

Overall incidence of grade 2–4 laboratory abnormalities was similar in both groups (44% in the BIC group, versus 47% in the DTG group):
- Rate of hyperglycemia was slightly higher in the DTG group (13% versus 8%).
- Rates of grade 2–4 AST (9% versus 3%) and ALT increases (6% versus 0%) were slightly higher in the BIC group.

No discontinuations due to renal adverse events and no tubulopathy in either arm

Doravirine

- Doravirine (DOR): once daily with or without food
- Low potential for drug-drug interactions
- Unique resistance profile with in vitro activity against wild-type HIV-1 and the most prevalent NNRTI resistance mutations (K103N, Y181C, G190A, K103N/Y181C, and E138K)
- Being developed as single entity and as single-tablet regimen with tenofovir disoproxil fumarate (TDF) and lamivudine (3TC)
  - Inclusion of nonproprietary ARVs has potential for significantly low(er) launch price
  - Potential good news for U.S.; likely good news in global marketplace

Doravirine vs. Darunavir/r

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

Key Entry Criteria:
- HIV-1 RNA ≥10000 c/ml, within 45 days before Day 1
- Antiretroviral naïve
- 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 vs. DRVr**

**Virologic Outcome at Week 48, FDA Snapshot Approach**

### 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>
</tbody>
</table>

Most Common AEs (≥10% in either group):

- Diarrhea: 54 (14%), 86 (22%)
- Nausea: 41 (11%), 46 (12%)
- Nasopharyngitis: 30 (8%), 39 (10%)
- Headache: 53 (14%), 41 (11%)

AEs of Clinical Interest:

- Rash*: 28 (7%), 32 (8%)
- Neuropsychiatric*: 44 (11%), 50 (13%)

*Only 1 DOR participant 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.

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Dolutegravir + Rilpivirine

- Coformulation of INSTI and NNRTI
- On course to be first two-drug regimen approved as HIV maintenance therapy
  - FDA and EMA approval applications filed; launches expected in first half of 2018
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
- Canada
- France
- Germany
- Italy
- Netherlands
- Russia
- Spain
- Taiwan
- United Kingdom
- United States

DTG + RPV

Phase III SWORD-1 and SWORD-2: Identically designed, randomized, multicenter, open-label, parallel-group, non-inferiority studies (N=513)

Day 1
Early switch phase
• VL <50 c/mL on INI, NNRTI, or PI + 2 NRTIs
• DTG + RPV (N=513)
• CAR (N=511)

Week 52
Late switch phase
• DTG + RPV

Week 148
Continuation phase
• DTG + RPV

**DTG + RPV**

### Virologic outcomes

<table>
<thead>
<tr>
<th></th>
<th>SWORD-1</th>
<th>SWORD-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1 RNA &lt;50 c/mL, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Virologic success</td>
<td>95</td>
<td>95</td>
</tr>
<tr>
<td>Virologic non-response</td>
<td>96</td>
<td>96</td>
</tr>
<tr>
<td>No virologic data</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

**Adjusted treatment differences (95% CI)**[^a]

- **SWORD-1**
  - CAR: -4.3
  - DTG + RPV: 3.0

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

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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[^a]: Indicates statistical analysis conducted using appropriate statistical methods.

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DTG + RPV

- Adverse event rates were comparable in both groups
  - 77% among those receiving DTG/RPV, compared with 71% of those in the studies’ control groups
- Adverse events leading to withdrawal were higher in the DTG + RPV group (4% versus <1%)
- Caveat: Discontinuations as a result of adverse events are not uncommon in switch studies!
- Question: What is the advantage of this two-drug regimen over standard three-drug regimen?
  - Safety/adverse event advantages not yet known
  - Could cost of two- versus three-drug regimen prove advantageous in U.S. and global markets?
Long-acting ARVs

- Long-acting formulations of ARVs:
  - Potential for improved clinical outcomes for those with adherence challenges or who prefer injectables to daily pills
  - May have better tolerability (e.g., GI adverse events)
  - May be cheaper to produce
    - Less active pharmaceutical ingredient (API) and packaging
    - Fewer distribution costs

- Potential challenges:
  - Once injected cannot be removed
    - What if drug toxicity occurs?
  - Sub-therapeutic “tail”

- Long-Acting/Extended Release ARV Resource Program: longactinghiv.org
Induction period

Day 1
Randomization
2:2:1

Primary analysis
Dosing regimen selection

Maintenance period

CAB 400 mg IM + RPV 600 mg IM
Q4W (n=115)

CAB 600 mg IM + RPV 900 mg IM
Q8W (n=115)

CAB 30 mg + ABC/3TC PO QD (n=56)

Add RPV
4 weeks

LA CAB + RPV

Virologic outcomes

- Oral: 92, 91, 89%
- Q8W IM: 7, <1, 2, <1, 8, 9%
- Q4W IM: 12.4, 2.9, 6.6

Treatment differences (95% CI)

(ITT-ME, FDA Snapshot Analysis)

- Q8W (n=115)
- Q4W (n=115)
- CAB 744 (n=56)

LA CAB + RPV

- Generally well tolerated
- Higher rates of fever (3-4%) and flu-like illness (2%) were observed in the injection groups.
- Patient satisfaction: 85–88% of patients in the IM groups said they would be “very satisfied” to continue their present form of treatment, as compared with 55% of those in the oral CAB group
- Q4W dosing has been advanced for registration safety and efficacy evaluation in two Phase III trials, now under way
Ibalizumab

- To be the first biologic (anti-CD4 IgG4 monoclonal antibody) approved for HIV
- Developed by TaiMed; to be commercialized by Theratechnologies, Inc.
- To be first orphan drug approval for HIV
  - Meets important need: option for heavily treatment-experienced PLWHIV
- FDA action date: January 3, 2018 (probably earlier)
- Currently requires IV infusions every two weeks
- IM administration currently being evaluated
  - 800 mg biweekly Phase I data presented at CROI 2017

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- HIV-RNA >1,000 copies/mL
- Documented resistance to at least 1 ARV from three classes
- Have sensitivity to at least 1 ARV (for OBR)
- Receiving stable ARV therapy for ≥8 weeks before screening

Primary endpoint: 83% and 60% had VL reductions of at least $0.5 \log_{10}$ and $1 \log_{10}$ copies/mL

Week 24: Mean viral load decrease of $1.6 \log_{10}$ copies/mL from baseline

Week 24: Undetectable viral load in 43% of patients (<50 copies/mL)

Most adverse events Grade 1 or 2

One case of IRIS; 8/9 discontinuations in patients with low CD4s

Four deaths: liver failure, KS, “end-stage AIDS,” lymphoma

## U.S. Generic Products

<table>
<thead>
<tr>
<th>Generics 505(j) ANDA</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
<th>2019</th>
<th>2020–21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir + Lamivudine (ABC/3TC)</td>
<td>Atazanavir (ATZ)</td>
<td>Efavirenz (EFV) Tenofovir disoproxil fumarate (TDF)</td>
<td>Darunavir</td>
<td>Emtricitabine (FTC) TDF/FTC EFV/TDF/ FTC</td>
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<table>
<thead>
<tr>
<th>Quasi-generics 505(b)(2)</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
<th>2019</th>
<th>2020–21</th>
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<tbody>
<tr>
<td></td>
<td>TDF/3TC EFV/TDF/3TC EFV400/TDF/3TC</td>
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<table>
<thead>
<tr>
<th>Innovator drugs 505(b)(1)</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
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<tbody>
<tr>
<td></td>
<td>DOR/TDF/3TC DTG/3TC</td>
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</table>
Summary

- A number of compounds with potentially significant clinical value to people living with HIV continue to make their way through the development pipeline.

- As ARV treatment and virologic suppression targets have been expanded domestically and globally in the face of increasingly vulnerable domestic and international funding streams, the cost of ARV therapy remains a factor with which we must all contend.

- Several ARV products in development potentially illustrate awareness of economics as an important research and development consideration.
Recommendations

- Manufacturers should commit to the drug prices—and remain committed to rebates and discounts—required to achieve cost-contained HIV care and service delivery in high-income countries.

- National and regional treatment guidelines, particularly those in the U.S., should start considering ARV prices and net costs across payer systems when refining first-line therapy recommendations.

- Manufacturers developing new oral drugs are strongly encouraged to follow the emerging trend of evaluating coformulations with historically potent and safe generic ARVs, notably TDF and 3TC.
Recommendations

- Long-acting drug formulations and technologies carry unique structural and behavioral opportunities and challenges
- The development of new drugs for the treatment of multi-drug-resistant HIV should remain a priority. It is very encouraging to see progress in this area
- Manufacturers, working in collaboration with government, academic, civil society, and community stakeholders, should commit to the health systems research and implementation science required to ensure effective linkage, engagement, and virologic suppression in all populations of people living with HIV
www.pipelinereport.org
www.treatmentactiongroup.org