Update on Current and Near Future Antiretroviral Therapy

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HIV+ Patients are living longer

In the United States, a 20-year-old HIV-positive patient can now expect to live into his/her early 70s.

ART, antiretroviral therapy; PY, person years.

COMORBIDITIES ARE MORE PREVALENT IN HIV-POSITIVE PATIENTS

Subjects ≥45 Years With Age-Associated Noncommunicable Comorbidities, by HIV Serostatus
(AGE_{hi}IV Study, 2010-2012)²

- Similarities between aging and the courses of HIV and AIDS suggest that HIV infection may compress certain aging processes, thereby accelerating comorbidities and frailty¹
- Duration of ART use (OR 1.24 per 5 additional years of ART use) and lower nadir CD4 cell count (OR 1.12 per 100 fewer cells) were associated with an increased risk of a higher number of comorbidities

CLD, chronic liver disease; HTN, hypertension; MI, myocardial infarction; OR, odds ratio; PAD, peripheral artery disease.
# Current Antiretroviral Medications

<table>
<thead>
<tr>
<th>NRTI</th>
<th>PI</th>
<th>Fusion Inhibitor</th>
<th>CCR5 Antagonist</th>
<th>Integrase Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>•Abacavir</td>
<td>•Atazanavir</td>
<td>•Ritonavir</td>
<td>•Maraviroc</td>
<td>•Raltegravir</td>
</tr>
<tr>
<td>•Emtricitabine</td>
<td>•Darunavir</td>
<td>•Lopinavir</td>
<td></td>
<td>•Elvitegravir</td>
</tr>
<tr>
<td>•Lamivudine</td>
<td></td>
<td></td>
<td></td>
<td>•Dolutegravir</td>
</tr>
<tr>
<td>•Tenofovir</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>•Zidovudine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NNRTI

•Efavirenz
•Rilpivirine
•Etravirine
Combined Drugs

NRTI
• Lamivudine
• Zidovudine

NNRTI

PI
Fusion Inhibitor

PI

COMBIVIR

CCR5 Antagonist

Integrase Inhibitor
Combined Drugs

NRTI
- Abacavir
- Lamivudine

NNRTI
- EPZICOM

PI
- Fusion Inhibitor

CCR5 Antagonist
- CCR5 Antagonist

Integrase Inhibitor
Combined Drugs

NRTI
• Abacavir
• Lamivudine
• Zidovudine

NNRTI

PI

Fusion Inhibitor

CCR5 Antagonist

Integrase Inhibitor

TRIZIVIR
# Combined Drugs

<table>
<thead>
<tr>
<th>NRTI</th>
<th>PI</th>
<th>Fusion Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emtricitabine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir (TDF)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NNRTI</th>
<th>TRUVADA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- NRTI: Emtricitabine, Tenofovir (TDF)
- PI: TRUVADA (CCR5 Antagonist, Integrase Inhibitor)
Combined Drugs

NRTI

• Emtricitabine

• Tenofovir (TAF)

PI

Fusion Inhibitor

CCR5 Antagonist

NNRTI

Integrase Inhibitor

DESCOVY
Combined Drugs

**NRTI**

**PI**
- Atazanavir

**Fusion Inhibitor**

**CCR5 Antagonist**

**Integrase Inhibitor**

**EVOTAZ**

**NNRTI**

+Cobicistat
## Combined Drugs

<table>
<thead>
<tr>
<th>NRTI</th>
<th>PI</th>
<th>Fusion Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Darunavir</td>
<td>CCR5 Antagonist</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PREZCOBIX</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Integrase Inhibitor</td>
</tr>
</tbody>
</table>

| NNRTI | + Cobicistat |
Combined Drugs (STR)

NRTI
- Emtricitabine
- Tenofovir (TDF)

NNRTI
- Efavirenz

PI

Fusion Inhibitor

CCR5 Antagonist

Integrase Inhibitor

ATRIPLA
Combined Drugs (STR)

**NRTI**
- Emtricitabine
- Tenofovir (TDF)

**NNRTI**
- Rilpivirine

**PI**
- Fusion Inhibitor
- CCR5 Antagonist
- Integrase Inhibitor

**COMPLERA**
Combined Drugs (STR)

**NRTI**
- Abacavir
- Lamivudine

**NNRTI**

**PI**
- Fusion Inhibitor
- CCR5 Antagonist
- Integrase Inhibitor
  - Dolutegravir

**TRIUMEQ**
Combined Drugs (STR)

NRTI
- Emtricitabine
- Tenofovir (TDF)

PI

NNRTI

Fusion Inhibitor
- CCR5 Antagonist

Integrase Inhibitor
- Elvitegravir

STRIBILD
- Cobicistat
Combined Drugs (STR)

NRTI
• Emtricitabine
• Tenofovir (TAF)

NNRTI
• Rilpivirine

PI

Fusion Inhibitor

CCR5 Antagonist

Integrase Inhibitor

ODEFSEY
Combined Drugs (STR)

NRTI
- Emtricitabine
- Tenofovir (TAF)

NNRTI

PI

Fusion Inhibitor

CCR5 Antagonist

Integrase Inhibitor

Elvitegravir

GENVOYA

Cobicistat
Studies 104/111: TAF vs TDF in Treatment-Naive Pts

- Parallel, randomized, double-blind, active-controlled phase III studies
  - Primary endpoint: HIV-1 RNA < 50 c/mL at Wk 48 (FDA Snapshot)

Stratified by HIV-1 RNA, CD4+ cell count, geographic region

**Wk 48:**
- Primary Endpoint
- EVG/COBI/FTC/TAF* single-tablet regimen (n = 866)
- EVG/COBI/FTC/TDF† single-tablet regimen (n = 867)

*150/150/200/10 mg once daily.
†150/150/200/300 mg once daily

Treatment-naive HIV-infected pts with HIV-1 RNA ≥ 1000 copies/mL, eGFR ≥ 50 mL/min (N = 1733)

Initial ART With E/C/F/TAF Superior to E/C/F/TDF at Wk 144

- Efficacy similar across pt subgroups, trending toward or significantly better with TAF in each group
  - By baseline HIV-1 RNA, baseline CD4+ cell count, adherence, age, sex, race, region
- Virologic failure with resistance by Wk 144: 1.4% in each arm

Rate of discontinuation for AEs higher with TDF vs TAF regimen
- 3.3% vs 1.3% ($P = .01$)

Spine and hip BMD loss greater with TDF vs TAF regimen
- 6 discontinuations for bone AEs in TDF arm vs 0 in TAF arm

TC, LDL, and HDL increases greater with TAF vs TDF regimen, but no difference in TC:HDL ratio
- Rates of lipid-modifying therapy initiation similar: 5.5% vs 5.8%

### Renal Events Leading to Discontinuation, n

<table>
<thead>
<tr>
<th>Event</th>
<th>E/C/F/TAF (n = 866)</th>
<th>E/C/F/TDF (n = 867)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal renal tubulopathy</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Cr elevation or eGFR decrease</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Renal failure</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Bladder spasm</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>0</td>
<td>12</td>
</tr>
</tbody>
</table>

Future Combined Drugs (STR)

NRTI
• Lamivudine

PI

NNRTI

Fusion Inhibitor

CCR5 Antagonist
• Dolutegravir

Integrase Inhibitor
• Dolutegravir
Switch to DTG + 3TC From Virologically Suppressive Triple ART

- Noncomparative, open-label, single-arm multicenter trial
  - Primary endpoint: therapeutic success at Wk 56 (ie, after 48 wks of dual therapy)
  - Therapeutic failure: HIV-1 RNA > 50 copies/mL, interruption, lost to f/u, death

HIV-infected pts with HIV-1 RNA ≤ 50 copies/mL for ≥ 2 yrs on first-line ART; ≤ 2 ART modifications allowed, except within 6 mos of study start; CD4+ cell count > 200 cells/mm³ (N = 110)

*Pts with HIV-1 RNA ≤ 50 copies/mL proceeded to phase II.
†In phase I, third agent in regimen replaced with DTG; baseline NRTI backbone maintained.

Switch to DTG + 3TC Maintains Viral Suppression

- 97% (101/104) pts maintained therapeutic success through 40 wks of dual therapy (study Wk 48)[1]
  - No INSTI resistance in 3 pts with virologic failure
  - 7 pts with serious AEs, only 2 related to dual therapy
- DTG + 3TC dual therapy currently under phase III evaluation as both initial ART[2,3] and as a switch strategy for virologically suppressed pts[4]

<table>
<thead>
<tr>
<th>Therapeutic Success, n/N* (%)</th>
<th>DTG + 3TC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wk 0 (entry; on BL triple therapy)</td>
<td>110/110 (100)</td>
</tr>
<tr>
<td>Wk 8 (end of phase I, start of phase II)</td>
<td>104/104 (100)</td>
</tr>
<tr>
<td>Wk 12</td>
<td>104/104 (100)</td>
</tr>
<tr>
<td>Wk 16</td>
<td>103/104 (99)</td>
</tr>
<tr>
<td>Wk 24</td>
<td>103/104 (99)</td>
</tr>
<tr>
<td>Wk 32</td>
<td>103/104 (99)</td>
</tr>
<tr>
<td>Wk 40</td>
<td>102/104 (98)</td>
</tr>
<tr>
<td>Wk 48</td>
<td>101/104 (97)</td>
</tr>
</tbody>
</table>

*Pts enrolled in phase I, N = 110; pts enrolled in phase II, N = 104.

Future Combined Drugs (STR)

NRTI | PI | Fusion Inhibitor
--- | --- | ---
NNRTI | ? | CCR5 Antagonist
• Rilpivirine | ? | Integrase Inhibitor
• Dolutegravir
SWORD 1 & 2: Switch From Suppressive ART to DTG + RPV Dual Therapy

• Randomized, open-label, multicenter phase III trials
  – Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 48 (ITT-E snapshot)

- HIV-infected pts with HIV-1 RNA < 50 c/mL for ≥ 12 mos while receiving first or second ART regimen with 2 NRTIs + INSTI, NNRTI, or PI; no previous VF; HBV negative (N = 1024)

<table>
<thead>
<tr>
<th>Wk 52</th>
<th>Wk 148</th>
</tr>
</thead>
<tbody>
<tr>
<td>Switch to DTG + RPV (n = 513)</td>
<td>Continue DTG + RPV</td>
</tr>
<tr>
<td>Continue Baseline ART (n = 511)</td>
<td>Switch to DTG + RPV</td>
</tr>
<tr>
<td>DTG + RPV</td>
<td></td>
</tr>
</tbody>
</table>

• 70% to 73% of pts receiving TDF at baseline

Llibre JM, et al. CROI 2017. Abstract 44LB.
Switch From Suppressive ART to DTG + RPV Noninferior to Cont. BL ART at Wk 48

- 1 pt with confirmed criteria for virologic withdrawal at Wk 36 in DTG + RPV arm had K101K/E
  - Documented nonadherence at VF
  - Resuppressed with continued DTG + RPV
  - No INSTI resistance

Llibre JM, et al. CROI 2017. Abstract 44LB.
Switch From Suppressive ART to DTG + RPV: Safety Outcomes

- AE rates generally similar between treatment arms through Wk 52
  - Numerically higher rate of drug-related grade 1/2 AEs with switch: 17% vs 2%
  - Numerically higher rate of withdrawal for AEs with switch: 4% vs < 1%

- No notable change in serum lipid values from baseline to Wk 48 in either treatment arm

Llibre JM, et al. CROI 2017. Abstract 44LB.
Future Combined Drugs (STR)

NRTI
- Emtricitabine
- Tenofovir (TAF)

NNRTI

PI
- Darunavir + Cobicistat

Fusion Inhibitor

CCR5 Antagonist

Integrase Inhibitor
Future New Drugs in Existing Classes

- **NNRTI**: Doravirine.
- **INSTI**: Bictegravir
Doravirine or Darunavir + RTV Both With 2 NRTIs in Treatment-Naive Pts

- Doravirine: next-gen NNRTI, unique resistance profile, low DDI potential, no food or PPI effects
- Multicenter, randomized, double-blind phase III trial
  - Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 48

Doravirine Is Noninferior to DRV + RTV at Wk 48

- Efficacy similar in both arms regardless of baseline HIV-1 RNA or CD4+ cell count
- No drug resistance detected in pts with PDVF through Wk 48 in either arm
  - n = 1 pt with noncompliance discontinued at Wk 24, developed DOR and FTC resistance

# Doravirine vs DRV + RTV: Safety

<table>
<thead>
<tr>
<th>AE, %</th>
<th>DOR (n = 383)</th>
<th>DRV + RTV (n = 383)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1 AE</td>
<td>80</td>
<td>78</td>
</tr>
<tr>
<td>Treatment-related AE</td>
<td>31</td>
<td>32</td>
</tr>
<tr>
<td>Serious AE</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Discontinuation for AE</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>AEs of clinical interest</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Rash*</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>▪ Neuropsychiatric†</td>
<td>11</td>
<td>13</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fasting Lipid Δ From BL to Wk 48, mg/dL</th>
<th>DOR (n = 383)</th>
<th>DRV + RTV (n = 383)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-c*</td>
<td>-4.51</td>
<td>9.92</td>
</tr>
<tr>
<td>Non-HDL-c*</td>
<td>-5.3</td>
<td>13.75</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>-1.37</td>
<td>17.9</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>-3.14</td>
<td>21.97</td>
</tr>
<tr>
<td>HDL-c</td>
<td>3.94</td>
<td>4.15</td>
</tr>
</tbody>
</table>

*P < .0001 for DOR vs DRV + RTV.

*Discontinued due to rash: n = 2 in DOR arm; n = 1 in DRV + RTV arm.
†No discontinuation for neuropsychiatric conditions.

Bictegravir + FTC/TAF vs DTG + FTC/TAF in Treatment-Naive Pts

- Bictegravir: investigational QD INSTI, active against most INSTI RAVs, low DDI potential, half-life ~ 18 hrs, no food requirement with dosing, primarily metabolized by CYP3A4 and UGT1A1
- Randomized, double-blind, active-controlled phase II trial
  - Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 24

Bictegravir + FTC/TAF vs DTG + FTC/TAF: Wk 24 and Wk 48 Efficacy (FDA Snapshot)

- No drug resistance detected in either arm through Wk 48

Difficult to conclude on safety from small study, but 4 fully enrolled phase III trials now evaluating efficacy, safety, tolerability of coformulated BIC/FTC/TAF

**Bictegravir + FTC/TAF vs DTG + FTC/TAF: Safety**

<table>
<thead>
<tr>
<th>Any Grade AE Occurring in ≥ 5% in Either Arm, %</th>
<th>BIC + FTC/TAF (n = 65)</th>
<th>DTG + FTC/TAF (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Nausea</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>Headache</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>URTI</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Chlamydial infection</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Back pain</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Furuncle</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Flatulence</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Costochondritis</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Hemorrhoids</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0</td>
<td>6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade 2-4 Lab Abnormality ≥ 5% in Either Arm, %</th>
<th>BIC + FTC/TAF (n = 64*)</th>
<th>DTG + FTC/TAF (n = 32*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatine kinase</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>AST</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>ALT</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>LDL</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Amylase</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Hematuria</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Glycosuria</td>
<td>2</td>
<td>6</td>
</tr>
</tbody>
</table>

*Pts with ≥ 1 post-BL laboratory assessment, excluding those not specified for all pts.

- Difficult to conclude on safety from small study, but 4 fully enrolled phase III trials now evaluating efficacy, safety, tolerability of coformulated BIC/FTC/TAF

Emerging Investigational Agents for Pts With MDR HIV

<table>
<thead>
<tr>
<th>Investigational Agent</th>
<th>Phase</th>
<th>MoA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fostemsavir[^1-3]</td>
<td>III</td>
<td>Prodrug; when metabolized binds gp120 to prevent CD4+ cell attachment, entry</td>
</tr>
<tr>
<td>Ibalizumab[^4,5]</td>
<td>III</td>
<td>Humanized anti-CD4 receptor mAb</td>
</tr>
</tbody>
</table>

AI438011: Fostemsavir + RAL + TDF in Treatment-Experienced Pts

- **Fostemsavir:** prodrug; proposed MoA: binding HIV-1 gp120 prevents viral attachment and entry into host CD4+ cells
- Randomized, active-controlled phase IIb study, blinded to dose
  - Primary endpoint: HIV-1 RNA < 50 c/mL at Wk 24

HIV-infected pts with exposure to ≥ 1 ARV for ≥ 1 wk; HIV-1 RNA ≥ 1000 c/mL; CD4+ ≥ 50 cells/mm³; virus susceptible to RAL, TDF, ATV, and fostemsavir IC₅₀ < 100 nM (N = 254)

- Fostemsavir 400 mg BID* PO + RAL + TDF (n = 50)
- Fostemsavir 800 mg BID* PO + RAL + TDF (n = 49)
- Fostemsavir 600 mg QD* PO + RAL + TDF (n = 51)
- Fostemsavir 1200 mg QD PO + RAL + TDF (n = 50)
- ATV/RTV 300/100 mg QD + RAL + TDF (n = 51)

*Fostemsavir dose changed to 1200 mg QD from Wk 48 to Wk 96.

Efficacy, Safety of Fostemsavir + RAL + TDF

At Wk 96, 90% of pts had HIV-1 RNA < 50 copies/mL in both fostemsavir and ATV/RTV arms in observed analysis[1]

— No significant differences in virologic efficacy regardless of race, sex, age, BL HIV-1 RNA, BL CD4+ cell count, or IC$_{50}$ subgroups[1]

— Fostemsavir generally well tolerated, with higher rates of grade 2-4 treatment-emergent AEs (37% vs 9%) and d/c for AEs (10% vs 3%) for ATV/RTV arm vs fostemsavir arm[2]

**TMB-301: Ibalizumab in Pretreated Pts Infected With Multidrug-Resistant HIV**

- **Ibalizumab**: humanized mAb to CD4 receptor that blocks HIV entry into CD4+ T-cells
  - FDA breakthrough and orphan drug designations
- Single-arm, open-label phase III trial
  - Primary endpoint: $\geq 0.5 \log_{10} \text{HIV-1 RNA decrease at Day 14}$

**Pts with HIV-1 RNA > 1000 copies/mL; on ART $\geq 6$ mos, on stable ART $\geq 8$ wks; resistant to $\geq 1$ ARV from 3 classes, sensitive to $\geq 1$ ARV for OBR (N = 40)**

**Control Period**: Day 0-7

- **Ibalizumab**: 2000 mg IV Day 7 (loading dose)
- Continue Failing ART Days 0-14

**Primary Endpoint**: Day 14

- **Ibalizumab**: 800 mg IV Day 21, Q2W (maintenance dose)
- Switch to OBR Day 14

# TMB-301: Efficacy

<table>
<thead>
<tr>
<th>Virologic Outcome</th>
<th>Ibalizumab + OBR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 14</strong></td>
<td></td>
</tr>
<tr>
<td>$\geq 0.5 \log_{10}$ HIV-1 RNA decrease, %</td>
<td>83*</td>
</tr>
<tr>
<td>$\geq 1.0 \log_{10}$ HIV-1 RNA decrease, %</td>
<td>60</td>
</tr>
<tr>
<td>Mean HIV-1 RNA decrease, $\log_{10}$</td>
<td>1.1</td>
</tr>
<tr>
<td><strong>Wk 24</strong></td>
<td></td>
</tr>
<tr>
<td>$\geq 1.0 \log_{10}$ HIV-1 RNA decrease, %</td>
<td>55</td>
</tr>
<tr>
<td>$\geq 2.0 \log_{10}$ HIV-1 RNA decrease, %</td>
<td>48</td>
</tr>
<tr>
<td>HIV-1 RNA &lt; 50 copies/mL, %</td>
<td>43</td>
</tr>
<tr>
<td>HIV-1 RNA &lt; 200 copies/mL, %</td>
<td>50</td>
</tr>
<tr>
<td>Mean HIV-1 RNA decrease from BL, $\log_{10}$</td>
<td>1.6</td>
</tr>
</tbody>
</table>

*Primary endpoint; $P < .0001$ vs 3% at end of control period.
TMB-301: Safety

• 9 pts reported 17 serious AEs\textsuperscript{[1]}
  – 1 drug-related serious AE (IRIS) resulted in discontinuation
• 9 other pts discontinued
  – Death (n = 4; liver failure, Kaposi sarcoma; end-stage AIDS, lymphoma)
  – Consent withdrawal (n = 3)
  – Lost to follow-up (n = 2)
• No cases of anti-ibalizumab antibodies
• Phase III TMB-311 study ongoing; extension for pts from TMB-301; accepting new pts\textsuperscript{[2]}
• IM dosing may be viable as administration route as compared with IV dosing\textsuperscript{[3]}

# Additional Investigational Agents Reported at CROI 2017: Preclinical and Phase I

<table>
<thead>
<tr>
<th>Agent</th>
<th>MoA or Formulation</th>
<th>Phase</th>
<th>Dosing/ Administration</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>GS-CA1[^1]</td>
<td>HIV capsid inhibitor</td>
<td>Pre-clinical</td>
<td>Extended release, suitable for SC of solid depot formulation</td>
<td>Potent ART with orthogonol resistance profile to existing ART; potential for long-acting formulation due to low aqueous solubility, high stability</td>
</tr>
<tr>
<td>GS-9131[^2]</td>
<td>NRTI</td>
<td>Pre-clinical</td>
<td>Potential for once daily dosing</td>
<td>Potent ART active against NRTI RAMs K65R, L74V, M184V alone or in combination; minimal loss of susceptibility with 4 or more TAMs</td>
</tr>
<tr>
<td>MK-8591[^3]</td>
<td>Nucleoside Reverse Transcriptase Translocation Inhibitor (NRTTI)</td>
<td>I</td>
<td>10 mg QW PO; potential for extended duration</td>
<td>Comparable MK-8591 levels in animal rectal, vaginal tissue to TDF levels in tissues of human subjects highlights potential prophylaxis utility</td>
</tr>
<tr>
<td>GS-PI1[^4]</td>
<td>PI</td>
<td>Pre-clinical</td>
<td>Potential for unboosted, QD dosing</td>
<td>Potent ART with high barrier to resistance, including &lt; 2-fold loss in potency against major PI RAMs, and 10-fold to 40-fold longer in vivo half life vs ATV or DRV</td>
</tr>
</tbody>
</table>

### Additional Investigational Agents Reported at CROI 2017: Phase II

<table>
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<tr>
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<tbody>
<tr>
<td>TMC278 LA[1]</td>
<td>LA injectable RPV (IM)</td>
<td>II</td>
<td>1200 mg IM Q8W</td>
<td>▪ Potential as injectable, long-acting PrEP</td>
</tr>
<tr>
<td>Elsulfavirine[2]</td>
<td>Prodrug of new NNRTI VM1500A</td>
<td>IIb</td>
<td>Combined therapy: 20 mg elsulfavirine + FTC/TDF PO QD</td>
<td>Less toxic alternative to EFV for initial ART</td>
</tr>
<tr>
<td>UB-421[3]</td>
<td>Anti-CD4 receptor mAb</td>
<td>II</td>
<td>10 mg/kg QW IV or 25 mg/kg Q2W IV</td>
<td>▪ Possible ART alternative for maintenance therapy in virologically suppressed pts</td>
</tr>
</tbody>
</table>