Top Ten Advances in HIV Medicine/Looking Forward

Monica Gandhi MD, MPH
Professor of Medicine, UCSF
Medical Director Ward 86 HIV Clinic, San Francisco General Hospital
Learning Objectives
Upon completion of this presentation, learners should be better able to:

• Review recent advancements in the treatment and management of HIV disease, including updates from CROI 2019
• Appraise the latest data on ART and pregnancy given recent safety concerns
• Summarize the latest data in the prevention of HIV infection

Faculty and Planning Committee Disclosures
Please consult your program book or the conference App.

• Dr. Monica Gandhi has no real or apparent financial disclosures to report
• There will be no off-label/investigational uses discussed in this presentation.
Top 10 stories in HIV medicine

1. Re-commitment to end the HIV epidemic in the U.S.
2. New drugs for naïve and experienced patients approved this year
3. New drug for MDR-HIV this year
4. Injectable ART on horizon
5. New data on ART options with history of M184V (and other NRTI mutations)
6. ART in pregnancy – a new focus
7. PrEP expansion on the horizon
8. New PrEP options on their way
9. RAPID ART
10. Weight gain and co-morbidities

STORY #1: RE-COMMITMENT IN U.S. TO END THE HIV EPIDEMIC
Now is the time to end the HIV epidemic. We have a once-in-a-generation opportunity to eliminate new HIV infections in America.

- U.S. government committing to End the HIV Epidemic (EtHE) Feb 2019
- We have the tools to end the HIV epidemic
- 4 pillars: DIAGNOSE, TREAT, PROTECT, RESPOND

Major Geographic and Demographic Disparities for HIV Incidence in the U.S.
- 3007 counties in the United States
- During 2016-2017, > 50% of new HIV infections occurred in 48 counties, Washington, DC and Puerto Rico
- Majority of new HIV infections among Black/African American and Hispanic/Latino MSM; high incidence among transgender individuals and IDUs
- 7 mostly southern states have a disproportionate occurrence of HIV in rural areas

U.S. Areas with the Highest Burden of HIV Diagnosis

- Truly multi-agency HHS initiative: CDC, HRSA, Indian Health Services, NIH

75% reduction in new HIV diagnoses in 5 years and a 90% reduction in 10 years!

Diagnose all people with HIV as early as possible after infection.

Treat the infection rapidly and effectively to achieve sustained viral suppression.

Protect people at risk for HIV using potent and proven prevention interventions, including PrEP, a medication that can prevent HIV infections.

Respond rapidly to detect and respond to growing HIV clusters and prevent new HIV infections.

HIV HealthForce will establish local teams committed to the success of the Initiative in each jurisdiction.
“Removing social safety programs will undermine the administration’s strategy and will reduce likelihood of achieving the goal of the newly announced initiative…any policy that substantially increases the number of uninsured persons would lead to more difficulty accessing care and make achieving zero new cases nearly impossible.”

STORY #2: NEW MEDICATIONS APPROVED IN 2018 FOR EXPERIENCED AND NAIVE
**Bictegravir/TAF/FTC approved February 8, 2018**

**PROS**

- INSTI-based
- Well tolerated to date
- Single pill
- Small pill
- TAF/FTC as backbone so no pre-testing (e.g. no HLA-B5701)

**CONS**

- Data only in naïves and switch where no resistance in past (small 4030 study ongoing)
- Do not yet know signature mutations
- Can’t use bictegravir nor TAF with rifampin
- Still limited real-world data

**Gallant J. Lancet HIV 2017; Sax P. Lancet HIV 2017; Molina J. CROI 2018; Daar E. Lancet HIV 2018; Andreattra K CROI 2018; Andreattra K CROI 2019; Acosta R CROI 2019**

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**B/F/TAF Phase 3 Efficacy through Weeks 48 to 96**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Comparator</th>
<th>Efficacy</th>
<th>Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1489</td>
<td>Naïve</td>
<td>DTG/ABC/3TC (96 weeks data)</td>
<td>Non-inferior</td>
<td>0</td>
</tr>
<tr>
<td>1490</td>
<td>Naïve</td>
<td>DTG+FTC/TAF (96 week data)</td>
<td>Non-inferior</td>
<td>0</td>
</tr>
<tr>
<td>1844</td>
<td>Suppressed</td>
<td>DTG/ABC/3TC (48 weeks)</td>
<td>Non-inferior</td>
<td>0</td>
</tr>
<tr>
<td>1878</td>
<td>Suppressed</td>
<td>Boosted PI + 2 NRTIs (48 weeks)</td>
<td>Non-inferior</td>
<td>0 to INSTI but 1 L74V in PI arm</td>
</tr>
<tr>
<td>1961</td>
<td>Suppressed (women)</td>
<td>E/C/F/(TAF or TDF) ATV+RTV + FTC/TDF (48 weeks)</td>
<td>Non-inferior</td>
<td>0 to INSTI but 1 M184V in EFV arm</td>
</tr>
</tbody>
</table>

Have data from 2 naïve studies and in suppressed patients but not much data among patients with baseline resistance yet (more real-world practice will help define this, as will trials in patients with resistance like SAILING, VIKING with dolutegravir)

**Gallant J. Lancet HIV 2017; Sax P. Lancet HIV 2017; Molina J. CROI 2018; Daar E. Lancet HIV 2018; Kotyo CROI 2018; Wohl D; ID week 2018 LB4; Andreattra K CROI 2018**
Study 4030 (Acosta R CROI 2019)

- This study enrolled patients (n=545) with preceding NRTI, PI or NNRTI mutations (but suppressed on DTG/TAF/FTC) into DTG/TAF/FTC vs BIC/TAF/FTC
- 41 (14%) had preceding M184V by historical genotype and all maintained suppression at 12 weeks – both arms

**Bottom line:** We need more data on switching to BIC/TAF/FTC with history of genotypic resistance (no DAWNING, SAILING, VIKING for bictegravir)

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**DRV/cobi/TAF/FTC approved July 12, 2018**

**PROS**

- DRV has a high genetic barrier to resistance
- First PI single pill
- 10mg of TAF so no more 25mg TAF with DRV/cobi
- Works against NRTI-resistant virus (EMERALD)

**CONS**

- PI-based and has cobi booster
- DRV trough with DRV/cobi lower than with DRV/RTV
- Use a PI when you need a PI only, not 1st-line

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Orkin et al, Lancet HIV, 2018 and package insert; Eron et al. CROI 2018 abs 502; Kakuda T et al. JAC 2014
**Objective:** Assess efficacy (non-inferiority) and safety of switching to D/C/F/TAF vs. continuing boosted-PI + F/TDF regimens in suppressed pts

**Key inclusion criteria:**
- On stable bPI + F/TDF regimen for at least 6 months
- Viral load (VL) <50 for ≥2 months before screening
- Previous ART virologic failure (VF) allowed
- Absence of history of VF on DRV, and if historical genotype available, absence of DRV RAMs

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**EMERALD: D/C/F/TAF Switch (Wk 48)**

- Switch was non-inferior
- **Not strict criteria for switch study**
  - 58% had ≥5 prior ARV regimens
  - 15% had prior VF
  - No DAMs but could have resistance to TDF or 3TC
  - (Bictegravir switches – genotypic resistance to TDF/TAF/3TC/ABC excluded; SWORD or STRIVIVING DTG switch -resistance to any class excluded)
  - In few failures, NO resistance to any study drugs detected

- **D/C/F/TAF safe**- no benefit in renal biomarkers, but was benefit in bone biomarkers (96 week data similar - ID week 2018)

- Per package insert: 7 subjects had h/o TDF-associated resistance mutations; 53 had h/o 3TC (mainly M184). All suppressed
Doravirine (+/-TDF/3TC) approved August 30, 2018

**PROS**
- Well tolerated
- OK in hepatic and renal failure
- No food requirements
- Works against Y181C AND K103N (and G190A) containing viruses but in-vitro data, clinical data needed

**CONS**
- Lowish genetic barrier to resistance like all NNRTIs (emerging resistant mutation V106)
- Single pill combination is with TDF/3TC
- Can’t use with rifampin (can double dose with rifabutin)


**DRIVE AHEAD – think “head-to-head” with another NNRTI**

- DRIVE-AHEAD: randomized, double-blind, active-controlled phase III trial head to head with EFV in this trial – 48 weeks published\(^1\): 96 weeks at ID week 2018\(^2\)

1. Orkin CID 2018. 3. Squires K, ID week 2018
DRIVE-AHEAD: Key Efficacy Findings

**Wk 48 Virologic Efficacy**

<table>
<thead>
<tr>
<th>HIV-1 RNA &lt; 50 c/mL</th>
<th>HIV-1 RNA ≥ 50 c/mL</th>
<th>No Data in Window</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOR/3TC/TDF (84%)</td>
<td>EFV/FTC/TDF (81%)</td>
<td></td>
</tr>
<tr>
<td>PDVF</td>
<td>22 (6.0%)</td>
<td>14 (3.8%)</td>
</tr>
<tr>
<td>Genotyped</td>
<td>23</td>
<td>24</td>
</tr>
<tr>
<td>Primary NNRTI*</td>
<td>6 (1.6%)</td>
<td>12 (3.3%)</td>
</tr>
<tr>
<td>Primary NRTI*</td>
<td>5 (1.4%)</td>
<td>5 (1.4%)</td>
</tr>
<tr>
<td>Treatment difference: 3.5% (95% CI: -2.0% to 9.0%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Bottom line: No difference in efficacy**

DRIVE-FORWARD: NRTIs + Either Doravirine or DRV/RTV in Treatment-Naive Adults (PI = FORWARD)

- Multicenter, randomized, double-blind phase III study[^1]
  - Stratified by HIV-1 RNA (> vs ≤ 100,000 copies/mL) and NRTI selection (TDF/FTC or ABC/3TC)
  - ART-naive adults with HIV-1 RNA ≥ 1000 copies/mL within 45 days; no resistance to study drugs by genotype test (N = 766)

**Primary Analysis**

- **Wk 48**

  **Doravirine 100 mg QD + 2 NRTIs**
  - + DRV/RTV Placebo (n = 383)

  **DRV/RTV 800/100 mg QD + 2 NRTIs**
  - + Doravirine Placebo (n = 383)

*Investigator choice prior to randomization of open-label TDF/FTC or ABC/3TC.
†Option for eligible participants to receive doravirine + 2 NRTIs in extension phase.

- **Primary endpoint:** HIV-1 RNA < 50 copies/mL at Wk 48[^1]
  - Doravirine vs DRV/RTV: 84% vs 80% (difference: 3.9%; 95% CI: -1.6% to 9.4%)

[^1]: Molina JM, Lancet HIV 2018

Slide credit: clinicaloptions.com
DRIVE-FORWARD: Virologic Outcomes at Wk 96

**FDA Snapshot Analysis**

<table>
<thead>
<tr>
<th>HIV-1 RNA &lt; 50 copies/mL (%)</th>
<th>DOR + 2 NRTIs</th>
<th>DRV/RTV + 2 NRTIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>73.1</td>
<td>280/383</td>
<td>252/383</td>
</tr>
<tr>
<td>66.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**HIV-1 RNA < 50 copies/mL by Observed Failure Analysis, % (n)**

<table>
<thead>
<tr>
<th></th>
<th>DOR</th>
<th>DRV/RTV</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants</td>
<td>81.0 (342)</td>
<td>76.8 (323)</td>
</tr>
<tr>
<td>BL HIV-1 RNA, copies/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 100,000</td>
<td>85.6 (264)</td>
<td>79.7 (282)</td>
</tr>
<tr>
<td>&gt; 100,000</td>
<td>65.4 (78)</td>
<td>65.2 (72)</td>
</tr>
<tr>
<td>≤ 500,000</td>
<td>81.8 (325)</td>
<td>78.1 (311)</td>
</tr>
<tr>
<td>&gt; 500,000</td>
<td>64.7 (17)</td>
<td>36.4 (11)</td>
</tr>
<tr>
<td>BL CD4+ count, cells/mm³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 50</td>
<td>80.0 (5)</td>
<td>52.9 (17)</td>
</tr>
<tr>
<td>51-200</td>
<td>71.0 (31)</td>
<td>65.8 (38)</td>
</tr>
<tr>
<td>&gt; 200</td>
<td>82.0 (306)</td>
<td>79.9 (268)</td>
</tr>
<tr>
<td>NRTI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDF/FTC</td>
<td>80.3 (295)</td>
<td>76.3 (283)</td>
</tr>
<tr>
<td>ABC/3TC</td>
<td>85.1 (47)</td>
<td>80.0 (40)</td>
</tr>
</tbody>
</table>

*Discontinuation for lack of efficacy considered failure, other missing data excluded; n refers to total number of participants per subgroup.

Molina JM, Lancet HIV 2018 (48 weeks); Molina JM IAS 2018 (Amsterdam) – 96 weeks

**DRIVE-FORWARD and DRIVE-AHEAD: 7 failed with resistance by week 48**

- Susceptibility analysis of the 7 doravirine-resistant clinical mutants from DRIVE-FORWARD and DRIVE-AHEAD phase III studies

### Fold Change by Virus

<table>
<thead>
<tr>
<th>NRTI</th>
<th>ZDV</th>
<th>d4T</th>
<th>ddl</th>
<th>ABC</th>
<th>FTC</th>
<th>3TC</th>
<th>TFP</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>A98G/F227C/M184V</td>
<td>0.1</td>
<td>0.7</td>
<td>1.2</td>
<td>2.7</td>
<td>&gt; 100</td>
<td>&gt; 100</td>
<td>0.5</td>
</tr>
<tr>
<td>A98G/V106I/H221Y/F227C/M184V</td>
<td>0.1</td>
<td>0.6</td>
<td>1.2</td>
<td>3.2</td>
<td>&gt; 100</td>
<td>&gt; 100</td>
<td>0.6</td>
</tr>
<tr>
<td>V106A/P225H/Y318F/K65R</td>
<td>1.0</td>
<td>1.4</td>
<td>1.8</td>
<td>2.4</td>
<td>7.7</td>
<td>12</td>
<td>1.6</td>
</tr>
<tr>
<td>V106I/F227C</td>
<td>0.2</td>
<td>0.7</td>
<td>1.0</td>
<td>0.7</td>
<td>2.8</td>
<td>3.1</td>
<td>0.3</td>
</tr>
<tr>
<td>V106I/H221Y/F227C/M184V</td>
<td>0.2</td>
<td>0.8</td>
<td>1.1</td>
<td>3.9</td>
<td>&gt; 100</td>
<td>&gt; 100</td>
<td>0.4</td>
</tr>
<tr>
<td>V106M/F227C/K65R/M184V</td>
<td>0.1</td>
<td>0.5</td>
<td>1.5</td>
<td>2.8</td>
<td>&gt; 100</td>
<td>&gt; 100</td>
<td>0.4</td>
</tr>
<tr>
<td>Y188L/M184V</td>
<td>0.5</td>
<td>0.8</td>
<td>1.6</td>
<td>2.9</td>
<td>&gt; 100</td>
<td>&gt; 100</td>
<td>0.8</td>
</tr>
</tbody>
</table>

**NNRTI**

<table>
<thead>
<tr>
<th>DOR</th>
<th>EFV</th>
<th>ETR</th>
<th>RPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>&gt; 93</td>
<td>9.0</td>
<td>2.8</td>
<td>3.8</td>
</tr>
<tr>
<td>&gt; 110</td>
<td>19</td>
<td>7.9</td>
<td>10</td>
</tr>
<tr>
<td>&gt; 210</td>
<td>4.8</td>
<td>0.7</td>
<td>1.0</td>
</tr>
<tr>
<td>&gt; 105</td>
<td>2.5</td>
<td>4.0</td>
<td>3.4</td>
</tr>
<tr>
<td>&gt; 96</td>
<td>1.7</td>
<td>1.5</td>
<td>1.2</td>
</tr>
<tr>
<td>&gt; 98</td>
<td>11.0</td>
<td>0.6</td>
<td>0.4</td>
</tr>
<tr>
<td>&gt; 181</td>
<td>&gt; 120</td>
<td>3.4</td>
<td>11</td>
</tr>
</tbody>
</table>


Bottom line on doravirine

- None of the NNRTIs are first-line in the U.S. Replacement of EFV/TDF/3TC with DOR/TDF/3TC internationally depends on cost
- In our setting
  - **Patients without resistance**: RPV/TAF/FTC used as alternative; DOR/TDF/3TC has TDF and not TAF
  - **Patients with resistance**: Etravirine or rilpivirine used in a TRIO like regimen (ANRS 139)\(^1\) which was ETR/DRV/r/RAL BID, modified is DTG/RPV/DRV/r and could use DTG/DOR/DRV/r if concerned about food but limited data of DOR in experienced (and no F227C, H221Y, P225H, V106)\(^2\)
  - Of note, ritonavir will increase doravirine exposure.\(^3\) Data indicates ability to give doravirine and dolutegravir together.\(^4\)

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\(^1\)Yazdanpanah Y. CID 2009; \(^2\)Kumar P. DRIVE SHIFT trial, ID week October 2018; \(^3\)Khalilieh S et al. CROI 2017; \(^4\)Anderson MS et al. Clin Pharmacokinetics 2017

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**STORY #3: NEW MEDICATION APPROVED IN 2018 FOR MDR-HIV**
Ibalizumab monoclonal Ab approved March 6, 2018

- Binds CD4 receptor on T-cell, preventing attachment of gp120
- Phase 3 open-label single group study of 40 patients with MDR HIV, OBR
- At week 25, ibalizumab + OBR had mean decrease in VL $1.6 \log_{10}$ copies/ml from baseline (43% <50; 50% <200)
- 17 (43%) had co-administration investigational attachment inhibitor fostemsavir
- Diminished ibalizumab susceptibility in vitro in pts with VF
- For 16 patients who stayed on IBA by 96 weeks, 14 (88%) still VS

Emu B. NEJM Aug 2018; Emu CROI 2019 (abs 485)

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STORY #4: INJECTABLE ART ON HORIZON
FLAIR AND ATLAS - THE INJECTABLE STUDIES (PHASE 3 CABOTEGRAVIR/RILPIVIRINE TRIALS)

ATLAS: Adults with virologic suppression; 616 pts (33% women; 23% black); 50% NNRTI, 17% PI, 33% INSTI

No h/o VF in ATLAS
In both studies, no INSTI or NNRTI resistance except K103N

FLAIR: Naive adults; 566 pts (22% women; 18% black); On DTG/ABC/3TC x 16 weeks (and suppressed) first

Canada, France, Germany, Italy, Japan, the Netherlands, Russia, South Africa, Spain, UK, U.S.

Important additional information: 45% given at 4 weeks and 97% within 1 week of that
FLAIR AND ATLAS - FAILURES (3 in each study)

<table>
<thead>
<tr>
<th>Sex, Country, HIV-1 Subtype</th>
<th>Previous CAR</th>
<th>SVF Timepoint</th>
<th>Viral Load at SVF/CVF (c/mL)</th>
<th>SVF Timepoint RAMs (HIV-1 RNA)</th>
<th>Drug Sensitivity at SVF (Fold Change)</th>
<th>Baseline RAMs (PBMC/HIV-1 DNA; Day 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F, Russia, A/A1</td>
<td>3TC, AZT, LPv/rt</td>
<td>Week 8</td>
<td>79,166 / 25,745</td>
<td>E138A</td>
<td>L74I</td>
<td>RPV(2.4) CAB(0.8) DTG(0.9) E138E/A L74I</td>
</tr>
<tr>
<td>F, France, AG</td>
<td>3TC, AZT, NVP to 3TC, ABC, NVP</td>
<td>Week 12</td>
<td>695 / 268</td>
<td>V108l E138K</td>
<td>None</td>
<td>RPV(3.7) CAB(1.2) DTG(1.0) V108l E138K</td>
</tr>
<tr>
<td>M, Russia, A/A1</td>
<td>FTC, RAL, TDF to ABC, EFV, 3TC</td>
<td>Week 20</td>
<td>544 / 1841</td>
<td>E138E/K N155H L74I</td>
<td>None</td>
<td>RPV(6.5) CAB(2.7) DTG(1.2) L74I</td>
</tr>
</tbody>
</table>

Drug levels of 6 failures below population mean but within range of others who maintained suppression

<table>
<thead>
<tr>
<th>Sex, Country, HIV-1 Subtype, Viral Load Load (Baseline)</th>
<th>Baseline RAMs (HIV-1 RNA)</th>
<th>SVF Timepoint</th>
<th>Viral Load at SVF/CVF (c/mL)</th>
<th>SVF Timepoint RAMs (HIV-1 RNA)</th>
<th>Drug Sensitivity at SVF (Fold Change)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F, Russia, A1, 94K</td>
<td>NNRTI INSTI</td>
<td>Week 20</td>
<td>373 / 456</td>
<td>E138E/A K/T</td>
<td>L74I</td>
</tr>
<tr>
<td>M, Russia, A1, 23K</td>
<td>NNRTI INSTI</td>
<td>Week 26</td>
<td>287 / 209</td>
<td>K101E L74I</td>
<td>Q148R</td>
</tr>
<tr>
<td>F, Russia, A1, 20K</td>
<td>NNRTI INSTI</td>
<td>Week 48</td>
<td>488 / 440</td>
<td>E138K L74I</td>
<td>Q148R</td>
</tr>
</tbody>
</table>

ATLAS

Two injections, gluteal medius, intramuscular

Bottom line: CAB may not have genetic barrier of resistance that DTG has so give within 5 weeks and watch for results of ATLAS-2M
STORY #5: NEW DATA FOR ART CHOICES WITH HISTORY OF M184V (OR NRTI MUTATIONS)

DAWNING study- failed NRTI/NNRTI regimen and compare DTG vs LPV/r + 2 NRTIs

Open-label, randomized noninferiority phase IIIb study

Dolutegravir versus ritonavir-boosted lopinavir both with dual nucleoside reverse transcriptase inhibitor therapy in adults with HIV-1 infection in whom first-line therapy has failed (DAWNING): an open-label, non-inferiority, phase 3b trial

Primary endpoint at 48 wk: participants with VL <50 c/mL (ITT-E snapshot)
Baseline Resistance Profile and NRTI Background Regimen After Randomization

<table>
<thead>
<tr>
<th>Variable</th>
<th>DTG + 2 NRTIs (n=312)</th>
<th>LPV/r + 2 NRTIs (n=312)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any NRTI, n (%)</td>
<td>282 (90)</td>
<td>279 (88)</td>
</tr>
<tr>
<td>M184V only</td>
<td>77 (25)</td>
<td>85 (27)</td>
</tr>
<tr>
<td>M184V + ≥1 NRTI RAMs</td>
<td>184 (59)</td>
<td>167 (54)</td>
</tr>
<tr>
<td>K65R</td>
<td>96 (30)</td>
<td>92 (29)</td>
</tr>
<tr>
<td>K70E</td>
<td>33 (11)</td>
<td>37 (12)</td>
</tr>
<tr>
<td>1 TAM</td>
<td>54 (17)</td>
<td>63 (20)</td>
</tr>
<tr>
<td>≥2 TAMs</td>
<td>17 (6)</td>
<td>18 (6)</td>
</tr>
<tr>
<td>Any NNRTI, n (%)</td>
<td>296 (96)</td>
<td>295 (95)</td>
</tr>
<tr>
<td>1 major NNRTI RAM</td>
<td>68 (22)</td>
<td>62 (20)</td>
</tr>
<tr>
<td>≥2 major NNRTI RAMs</td>
<td>230 (74)</td>
<td>233 (75)</td>
</tr>
</tbody>
</table>

AZT + 3TC | 132 (42) | 121 (39) |
TDF + 3TC or FTC | 128 (41) | 134 (43) |
TDF + AZT | 41 (13) | 41 (13) |
ABC + 3TC | 7 (2) | 7 (2) |
Other | 9 (3) | 9 (3) |

RAM, resistance associated mutation; TAM, thymidine analogue mutation: XTC, 3TC or FTC.

>80% M184V; 30% K65R (note 95% NNRTI)
86% still used XTC; with K65R, lots of AZT
2 patients in DTG who failed had emergent INSTI resistance (G118R, R263K) but 3 patients with LPV who failed had no PI resistance

Bottom line for DAWNING

- DTG superior to PI (at least LPV/r) in maintaining virologic suppression with baseline NRTI resistance
- DTG maintains VS at 48 weeks in 85% of patients with M184V (didn’t have to be suppressed before switching like other examinations of this)
- Keep in mind everyone had genotypes here and HAD to have at least 1 active NRTI (so no DTG monotherapy of course!)
- We may not have a genotype when making such decisions
- Even DTG fails with some INSTI resistance; PIs generally do not
STORY #6: ART IN PREGNANCY – A NEW FOCUS

FDA Warning About Dolutegravir During Conception

FDA Drug Safety Communication: FDA to evaluate potential risk of neural tube birth defects with HIV medicine dolutegravir (Juluca, Tivicay, Triumeq)

Safety Announcement

The U.S. Food and Drug Administration (FDA) is alerting the public that serious cases of neural tube birth defects involving the brain, spine, and spinal cord have been reported in babies born to women treated with dolutegravir used to treat human immunodeficiency virus (HIV). Preliminary results from an ongoing observational study in Botswana found that women who received dolutegravir at the time of becoming pregnant or early in the first trimester appear to be at higher risk for these defects.

Source: fda.gov/safety
Data Behind the FDA Warning

Prelim analysis of ongoing birth surveillance study in Botswana:

4 neural tube defects (NTDs) out of 426 infants born to women who **initiated** dolutegravir (DTG) prior to pregnancy & taking it at time of conception

Rate 0.94% vs. 0.12% with non-DTG ART at conception

Update from IAC 2018: estimated incidence **4/596 (0.67%)**


### Which drugs preferred, alternative in guidelines?

<table>
<thead>
<tr>
<th>NRTIs</th>
<th>NNRTIs</th>
<th>INSTIs</th>
<th>PIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine (AZT, ZDV) - Alternative</td>
<td>Efavirenz (EFV) - Alternative</td>
<td>Raltegravir (RAL)</td>
<td>Atazanavir/r (ATV/r)</td>
</tr>
<tr>
<td>Epzicom (ABC/3TC)</td>
<td>Rilpivirine (RPV) - Alternative</td>
<td>Dolutegravir (DTG) – After 1st trimester</td>
<td>Lopinavir/ritonavir (LPV) – Alternative</td>
</tr>
<tr>
<td>Truvada (TDF/FTC)</td>
<td></td>
<td></td>
<td>Darunavir/r (DRV/r)</td>
</tr>
</tbody>
</table>

**Single pill combinations**

- **Preferred** after 1st trimester
  - Triumeq (DTG/ABC/3TC)
  - Complera (RPV/TDF/FTC)
  - Atripla (EFV/TDF/FTC)

**Recommended**

- **RAL and ATV/r preferred**
- **EFV and ATV/r preferred**
### Other considerations in pregnancy

<table>
<thead>
<tr>
<th>ARV Class</th>
<th>ARV</th>
<th>Consideration</th>
</tr>
</thead>
</table>
| NNRTI (alternative SPCs) | Efavirenz            | • Primate studies raised concern about NTDs; not seen in human studies, deemed safe  
• Watch for intra-and postpartum depression |
|           | Rilpivirine          | • Don’t use if CD4 count <200 or HIV RNA >100,000  
• Heartburn? Can’t use PPI and stagger dosing with H2 blocker  
• PK lower in 2nd and 3rd trimester, unclear significance- use standard dose and monitor VL, be vigilant |
| INSTI     | Raltegravir          | • Change dose from 1200mg po daily to 400mg po BID in pregnancy  
• Separate doses from iron and don’t use aluminum/magnesium antacids  
• INSTIs reduce VL fast– can add to suppress; no clear class effects for NTDs |
|           | Dolutegravir         | • Not in 1st trimester; DTG/ABC/3TC only preferred SPC |
| PI        | Atazanavir + ritonavir | • PK changes not significant so use standard dosing, hyperbilirubinemia  
• Heartburn? Atazanavir concentrations lowered by PPIs, H2 blockers |
|           | Darunavir + ritonavir | • DHHS guidelines recommend darunavir 600 mg BID/ ritonavir 100 mg BID in pregnancy |

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**The ‘fundamental misconception’:**  
all women are always pregnable and therefore (through the magical operation of the mind characteristic of unconscious sexism) *always pregnant.*”  
- Vanessa Merton, *AJLM* 1993

**HIV:** Women represent 23% of participants in ARV research (median/study = 19%)  
Curno et al, *JAIDS* 2016

**Slide courtesy of Anne Lyerly MD**
Burden of justification

- Shifting burden – require justifying exclusion

STORY #7: PrEP EXPANSION ON HORIZON
PrEP expansion anticipated – USPSTF guideline coming

- 1.1 million individuals in U.S. at risk of HIV and should be offered PrEP (CDC)
- Number of PrEP users at end of 2028 estimated at 260,000-270,000 (AVAC, PrEPWatch 3/2019)

Under the ACA, if the USPSTF gives PrEP an A (or even a B), all insurers must offer it free as a preventative service.

**STORY #8: NEW PrEP OPTIONS ON THEIR WAY**
DISCOVER: Daily FTC/TAF vs FTC/TDF for PrEP

- International, randomized, double-blind phase III noninferiority trial

- Primary endpoint: HIV incidence when 100% of pts completed Wk 48 and 50% complete Wk 96, evaluated as rate ratio with noninferiority margin < 1.62

- At BL: TGW, 1% to 2% (75 individuals total); Hispanic/Latinx, 24% to 25%; white, 84%; ≥2 condomless anal sex (receptive) events past 12 wks, 58% to 60%; recreational drug use past 12 wks, 67%; taking FTC/TDF PrEP, 16% to 17%

*Defined as ≥2 episodes of condomless anal sex within past 12 wks or rectal gonorrhea, chlamydia, syphilis within past 24 wks.

Hare. CROI 2019. Abstr 104LB.

DISCOVER- Efficacy outcomes

Hare. CROI 2019. Abstr 104LB.
Bottom line on TAF/FTC for PREP

- Few HIV infections in this efficacy trial (so did not reach endpoint at 48 weeks of “numbers averted” expected) but likely TAF/FTC and TDF/FTC are equally effective for MSM
- Only 75 TGW in this study of 5200 so hard to make comment and no cisgender women
- Safety at 48 weeks – bit better, renal/bone issues resolve after d/c of PrEP so unclear significance
- Not yet FDA approved, concern for coverage
- Expert opinion: Patients with renal insufficiency (e.g. CrCl 30-60 ml/min)

STORY #9: RAPID ART AND LONGER TERM DATA
ART should be initiated as soon as possible after diagnosis, including immediately after diagnosis, unless patient is not ready to commit to starting therapy.

Since the long-term clinical benefits of same-day ART initiation have yet to be proven in the United States, this approach remains investigational.

Example: Ward 86 RAPID Start Program

- 3 RCTs in resource-limited settings (Haiti, Africa) showed earlier initiation of ART associated with higher rates of early virologic suppression[^1-^3]
- US programs (Atlanta, New Orleans); Ward 86 HIV Clinic in SF started 2013[^4]
  - Patients referred from testing sites, offered same-day or next-day intakes, and received multidisciplinary evaluation, support, and insurance enrollment/optimization
  - Patients provided ART starter packs and close follow-up (call within 1-2 days; appts within 1-2 wks)
  - Demographics and labs extracted from the medical record
  - Subsequent HIV-1 RNA levels obtained from public health surveillance data
  - Kaplan-Meier curves summarized distribution of times to first virologic suppression; virologic suppression rates at last HIV-1 RNA measurement recorded were calculated

Ward 86 RAPID Analysis

- Retrospective analysis on 216 out of 225 patients (96%) referred to RAPID program from 2013-2017
  - Reasons for not starting rapid ART: declined, 4; not started by clinician, 3; excluded from analysis, 2*

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>Retrospective Cohort (N = 216)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age at HIV diagnosis, yrs (range)</td>
<td>30.0 (16-61)</td>
</tr>
<tr>
<td>Women/transwomen, n (%)</td>
<td>17 (7.9)/1 (0.5)</td>
</tr>
<tr>
<td>Race/ethnicity, %</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>25 (11.6)</td>
</tr>
<tr>
<td>Latinx/Hispanic</td>
<td>58 (26.9)</td>
</tr>
<tr>
<td>White</td>
<td>79 (36.6)</td>
</tr>
<tr>
<td>Health challenges, %</td>
<td></td>
</tr>
<tr>
<td>Substance use disorder</td>
<td>51.4</td>
</tr>
<tr>
<td>Major mental health disorder</td>
<td>48.1</td>
</tr>
<tr>
<td>Homeless/unstable housing</td>
<td>30.6</td>
</tr>
<tr>
<td>Median CD4+ cell count, cells/mm³</td>
<td>441 (3-1905)</td>
</tr>
<tr>
<td>Median HIV-1 RNA, copies/mL</td>
<td>37,011 (0 to &gt; 10 million)</td>
</tr>
</tbody>
</table>

*Excluded because no HIV-1 RNA measurements performed after initiating ART.

Coffey. AIDS. 2019

Ward 86 RAPID ART Program:
Time to Virologic Suppression, 2013-2017

Coffey. AIDS. 2019
STORY #10: MANAGING CO-MORBIDITIES AND WEIGHT GAIN

More weight gain may be associated with INSTIs but more data needed and risk factors for obesity multifactorial and need managing

Koethe. CROI 2019
Thank you to Harry Lampiris MD, Renslow Sherer MD, ACTHIV committee, Ward 86 and Diane Havlir MD