CROI 2018 Update

Christian B. Ramers, MD, MPH, AAHIVS
Assistant Medical Director - Research/Special Populations
Family Health Centers of San Diego

Assistant Clinical Professor
UC San Diego School of Medicine

3/23/18
Disclosures

- **Speaker’s Bureau:** Janssen, Gilead, Merck, AbbVie
- **Scientific Advisor:** Gilead, Janssen, AbbVie
- **Grant/Research/Contracted Support:** CDC/HRSA, NWAETC, Pacific AETC, HealthHIV, Project ECHO, National Cancer Institute, Gilead Sciences
Learning Objectives

• Review the ‘tip of the iceberg’ of new research presented at CROI
• Discuss current state of HIV prevention and epidemiology
• List new innovations in HIV treatment
The SINGLE most interesting topic I’d like to hear about is:

A. Novel Anti-retroviral drugs for treatment and prevention
B. Status of Long-Acting injectable ART
C. Uptake of PrEP
D. HIV Vaccine research
E. HIV Cure research
F. Something else
No time to cover...
Maybe another time...

- How to fix the HIV care cascade (Del Rio, Mugavero, Dombrowski)
- Infectious complications of the Opioid epidemic (Hodder)
- Increased HIV transmission late in pregnancy (Heffron, Thompson)
- M184V in dual 3TC-containing ART switch (Gagliardini, #498)
- ‘Rapidly growing clusters’ HIV transmission, (young Latino MSM)
- Hepatitis C co-infection!!!
  - Recognition of sexual transmission and re-infection
  - Swiss HCVree study shows Treatment as Prevention in HCV works!
  - Salvage Rx for GLE/PIB relapsers (GLE/PIB+SOF+Riba)
- TDF in HBV-infected pregnant women (Jourdain, #131, ITAP study)
- Limited HIV Vaccine progress (one moving to human trials)
- Glimmer of hope in Cure research: 4 months after BNAb (PGT121)+TLR7 agonist GS-6290 provides ‘functional cure’ in monkeys
Anti-retroviral Therapy
ANDES: DRV/r+3TC vs. DRV/r+3TC/TDF

• 2-drug regimens being explored in switch and naïve indications

Virologic Suppression was similar (94% vs 94%)

No significant safety signals

Cahn P et al Abstract #489
EMERALD Virologic Rebound Subanalysis

- Switch study from in stable pts prior regimen to D/c/F/TAF

- Stratified by PI boosting with RTV or COBI

- 48 Wks: Primary Endpoint

- Randomized 2:1

- HIV-infected pts with stable HIV-1 RNA < 50 c/mL on boosted PI + FTC/TDF; any number of prior virologic failures on non-DRV-based regimens; either absence of documented DRV RAMs or no virologic failure on DRV; eGFR ≥ 50 mL/min (N = 1141)

- Switch to DRV/COBI/FTC/TAF 800/150/200/10 mg QD (n = 763)

- Continue Boosted PI + FTC/TAF (n = 378)

- Wk 96

- DRV/COBI/FTC/TAF Extension phase -> DRV/COBI/FTC/TAF Rollover phase

- eGFR, estimated glomerular filtration rate; RTV, ritonavir.

- Eron JJ et al Abstract #502
EMERALD: Virologic Rebound Through Wk 48 by Previous ART Experience

- Low virologic rebound rate across arms at Wk 48 regardless of number of previous VF or ARVs used

Cumulative Virologic Rebound Through Wk 48

- Overall Population
- Prior VF
- Number of Prior ARVs Used

- Switch to DRV/COBI/FTC/TAF
- Continued boosted PI + FTC/TDF

Pts With Virologic Rebound (%)

- Eron JJ et al Abstract #502

<table>
<thead>
<tr>
<th>Prior VF</th>
<th>0</th>
<th>≥ 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Population</td>
<td>n/N = 19/763</td>
<td>16/647</td>
</tr>
<tr>
<td>0</td>
<td>Δ 0.4 (-1.5, 2.2)</td>
<td>Δ 0 (-2.6, 2.0)</td>
</tr>
<tr>
<td>4</td>
<td>Δ 0.3 (-3.4, 3.1)</td>
<td>Δ 0.3 (-7.8, 5.9)</td>
</tr>
<tr>
<td>5</td>
<td>Δ 0.3 (-17.5, 2.7)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Δ 0.4 (-5.0, 3.9)</td>
<td></td>
</tr>
<tr>
<td>&gt; 7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of Prior ARVs Used</th>
<th>n/N = 8/378</th>
<th>3/160</th>
<th>1/56</th>
<th>1/30</th>
<th>5/211</th>
<th>2/101</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>19/763</td>
<td>16/647</td>
<td>3/116</td>
<td>0/53</td>
<td>5/69</td>
<td>1/30</td>
</tr>
<tr>
<td>4</td>
<td>7/316</td>
<td>3/160</td>
<td>2/98</td>
<td>1/56</td>
<td>5/69</td>
<td>2/101</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Δ indicates difference from baseline.
Bictegravir Switch from ABC/3TC/DTG

- Already been 3 large phase III trials showing non-inferiority to DTG-regimens (rx-naïve), ATZ/r or DRV/r regimens (rx-experienced)
- Study 380-1844: switch from suppressive ABC/3TC/DTG to B/F/TAF

Molina JM et al Abstract #22
Bictegravir Switch from ABC/3TC/DTG

- Switch to B/F/TAF was non-inferior to continued ABC/3TC/DTG
- No treatment emergent resistance in either arm
- Tolerability and Safety were excellent (similar lipid, bone, renal)

Molina JM et al Abstract #22
Switch From Suppressive PI- or INSTI-Based ART to BIC/FTC/TAF in Women

- Open-label, randomized, active-controlled phase III trial
  - Primary endpoint: Wk 48 HIV-1 RNA ≥ 50 c/mL (FDA snapshot; noninferior margin 4%)
  - Pts from Uganda (27%), Russia (24%), Thailand (22%), US (15%), Dominican Republic (12%)

- Median baseline values: age, 39-40 yrs; CD4+ cell count, 667-704 cells/mm³

- Regimen at randomization: EVG/COBI/FTC/TAF, 53%; EVG/COBI/FTC/TDF, 42%; ATV + RTV + FTC/TDF, 5%

* BIC/FTC/TAF 50/200/25 mg PO QD.

Slide credit: clinicaloptions.com

Kityo C, et al. CROI. 2018 Abstract 500
Switch From Suppressive PI- or INSTI-Based ART to BIC/FTC/TAF in Women

- Efficacy comparable overall and by subgroup analysis

MK-8591 (EFdA) is a novel, highly potent, long-acting NRTTI
- Active against a wide range of NRTI-resistant clones
- Multiple mechanisms of inhibition of Reverse Transcriptase
- Unlikely to have significant drug-drug interactions
- In vitro IC50 as low as 1.5 nM (~0.01 pmol/million cells)
- Long Half life in pre-clinical studies: ~120 hrs in healthy adults

Matthews R et al Abstract #26
Ibalizumab (Trogarzo)

- Humanized IgG4 mAb, CD4-directed attachment inhibitor
- IV loading dose 2 g, then 800 mg Q2 weeks
- Current study looked at Ibalizumab susceptibility in Treatment experienced patients with multi-drug resistant virus.

Resistance to other ART did not influence Ibalizumab susceptibility

Weinheimer et al Abstract #561
Abacavir and Cardiovascular Disease

- 2 human, 1 mouse model, and 1 in vitro (platelet) study all supporting association of ABC
- Swiss Cohort (n = 428): Coronary CT Angiograms. ABC only agent a/w with high risk plaque and CAD
- Platelet function study (n = 61) with switch from ABC/3Tc to F/TAF showed lower platelet reactivity after switch

- Switch to FTC/TAF associated with higher sGPVI levels persisting through

![Graph showing mean change in sGPVI (%) over weeks for FTC/TAF and ABC/3TC](image)

- Kovari H #670; Mallon PW #80
- Collado-Diaz V #674; Taylor KA #673
HIV Prevention
Which of the following is true about PrEP?

A. Other than FTC/TAF there are no additional agents in the pipeline
B. Large racial disparities in PrEP access exist in all regions of the US
C. Clinical trials show Dapivirine vaginal rings are more effective than PO FTC/TDF
D. Open-label extension studies tend to show worse adherence
HIV Prevention

- PrEP - Population level uptake
- Getting to Zero in San Francisco
- New Agents: Dapivirine Ring, MK-8591 and others
PrEP Uptake and Real World Efficacy

• Individual level PrEP efficacy well known (85-90%)
• New South Whales has 300-400 new diagnoses per year, highly concentrated (80% MSM) epidemic.
• Very close to 90-90-90 goals with engaged State level strategy
• F/TDF targeted towards high risk: STD, RAI, Crystal meth
• Target n = 3,700, enrolled >8,000
• ~30% drop-off overall
  • 3% after visit 1
  • 13% at 6 months
  • 14% at 12 months
• 32% reduction in recent HIV infections (149/yr → 102/yr)

Smith D et al Abstract #86
PrEP Estimates & Coverage

- CDC published estimates in 2015 of how many were expected to meet PrEP indications ~1.1 million, broken down nationally by risk

- Smith D et al Abstract #86
PrEP Estimates & Coverage

<table>
<thead>
<tr>
<th></th>
<th>MSM</th>
<th>HET</th>
<th>PWID</th>
<th>Total*</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 States, DC</td>
<td>814,000</td>
<td>258,000</td>
<td>73,000</td>
<td>1,145,000</td>
</tr>
<tr>
<td>Vital Signs estimate</td>
<td>492,000</td>
<td>624,000</td>
<td>115,000</td>
<td>1,232,000</td>
</tr>
<tr>
<td>Lower Limit of VS estimate</td>
<td>212,000</td>
<td>404,000</td>
<td>45,000</td>
<td>661,000</td>
</tr>
<tr>
<td>Upper Limit of VS estimate</td>
<td>772,000</td>
<td>846,000</td>
<td>185,000</td>
<td>1,803,000</td>
</tr>
</tbody>
</table>

“We believe the new estimates are a better reflection of the underlying geographic heterogeneity of HIV exposure risk”

Smith D et al Abstract #86
PrEP Estimates & Coverage

```
<table>
<thead>
<tr>
<th>Transmission risk group</th>
<th>Total</th>
<th>Black/African American</th>
<th>Hispanic/Latino</th>
<th>White, non-Hispanic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimated no.</td>
<td>Estimated no.</td>
<td>% of risk group total</td>
<td>Estimated no.</td>
</tr>
<tr>
<td>MSM</td>
<td>813,970</td>
<td><strong>309,190</strong></td>
<td>38.0</td>
<td><strong>220,760</strong></td>
</tr>
<tr>
<td>HET</td>
<td>258,080</td>
<td><strong>164,660</strong></td>
<td>63.8</td>
<td><strong>46,580</strong></td>
</tr>
<tr>
<td>Men</td>
<td>81,410</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Women</td>
<td>176,670</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>PWID</td>
<td>72,510</td>
<td><strong>26,490</strong></td>
<td>36.5</td>
<td><strong>14,920</strong></td>
</tr>
<tr>
<td>Total</td>
<td>1,144,550</td>
<td><strong>500,340</strong></td>
<td>43.7</td>
<td><strong>282,260</strong></td>
</tr>
</tbody>
</table>
```

“Of the 1.1 million persons at risk, 44% were Black, 25% Hispanic, and 27% White. Blacks and Hispanics together accounted for 2/3 of those with indications for PrEP use”

- Smith D et al Abstract #86
PrEP Estimates & Coverage

- 'Minimum' PrEP coverage calculations (excludes Kaiser, VA, Military) show striking racial/ethnic disparities.
- National coverage average is less than 10%

The size of the black population with PrEP indications relative to other races/ethnicities is sobering and indicates urgent need for action.

Smith D et al Abstract #86
Getting to Zero in San Francisco

- San Francisco has had a series of policy interventions since 2006 all focused on reducing new infections in the city.

Buchbinder S et al, Abstract #87
Getting to Zero in San Francisco

- 2014 launched a ‘collective impact’ model to integrate City-wide PrEP, Rapid ART, and Linkage/engagement/retention in care

Buchbinder S et al, Abstract #87
Getting to Zero in San Francisco

- Drilling down on PrEP use shows race/ethnicity disparities

- Buchbinder S et al, Abstract #87
Getting to Zero in San Francisco

- Qualitative study of African American MSM in an STD clinic showed a surprisingly low self-perception of risk

Buchbinder S et al, Abstract #87
Expansion of RAPID Protocol in SF

- 2017: WHO endorses immediate ART, yet DHHS ’investigational’
- Since 2015, SF Getting to Zero initiative rolled out RAPID protocol
  - All new diagnoses linked within 5 days
  - At first care visit after baseline lab draw, ART Should be started (unless risk for fatal IRIS)
  - Starting regimen: FTC/TDF or FTC/TAF + Boosted DRV or INSTI: (ELV/c, RAL, or DTG)

<table>
<thead>
<tr>
<th>Metric</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosed (%)</td>
<td>399</td>
<td>329</td>
<td>295</td>
<td>265</td>
</tr>
<tr>
<td>In Care (%)</td>
<td>372 (93)</td>
<td>318 (97)</td>
<td>282 (96)</td>
<td>258 (97)</td>
</tr>
<tr>
<td>Started ART (%)</td>
<td>311 (78)</td>
<td>276 (84)</td>
<td>244 (83)</td>
<td>215 (81)</td>
</tr>
<tr>
<td>ART included INSTI (%)</td>
<td>145 (47)</td>
<td>203 (74)</td>
<td>195 (80)</td>
<td>159 (74)</td>
</tr>
<tr>
<td>Met RAPID definition (%)*</td>
<td>23 (6)</td>
<td>45 (14)</td>
<td>50 (17)</td>
<td>80 (30)</td>
</tr>
</tbody>
</table>

* Both linked < 5 days and started ART < 1 day after linkage

- Bacon, O et al, Abstract #93
Expansion of RAPID Protocol in SF

- Although some slight variation by race/ethnicity and age, improvements were seen across groups.

<table>
<thead>
<tr>
<th>Metric</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
<th>△ 2013-16</th>
</tr>
</thead>
<tbody>
<tr>
<td>In Care within 1 year (%)</td>
<td>372 (93)</td>
<td>318 (97)</td>
<td>282 (96)</td>
<td>258 (97)</td>
<td></td>
</tr>
<tr>
<td>Diagnosis to care (days)</td>
<td>8</td>
<td>7</td>
<td>7</td>
<td>5</td>
<td>-38%</td>
</tr>
<tr>
<td>1st Care Visit to ART (days)</td>
<td>27</td>
<td>17</td>
<td>6</td>
<td>1</td>
<td>-96%</td>
</tr>
<tr>
<td>ART to VL&lt;200c/mL (days)</td>
<td>70</td>
<td>53</td>
<td>50</td>
<td>38</td>
<td>-46%</td>
</tr>
<tr>
<td>Diagnosis to VL&lt;200 c/mL (days)</td>
<td>134</td>
<td>92</td>
<td>77</td>
<td>61</td>
<td>-54%</td>
</tr>
</tbody>
</table>

Bacon, O et al, Abstract #93
FTC/TAF

• Currently Oral FTC/TDF is the only approved agent for PrEP
• F/TAF approved for HIV Treatment
  • 10-fold more active against HIV in vitro
  • 25 mg dose yields 4-7-fold higher TFV/DP levels in PBMC and 90% lower plasma exposure than 300 mg TDF
  • Significantly reduced bone/renal exposure
• DISCOVER Trial fully enrolled (92 sites, 5,000 MSM and TG women), F/TDF vs. F/TAF, anticipated completion 2/2019
• Current study used PO F/TAF in comparable doses, then pigtail macaque SHIV challenge
  • 6/6 infected in placebo arm
  • 1/6 infected in F/TAF arm

Massud I et al Abstract #85
Dapivirine Vaginal Ring for PrEP

- CROI 2016: phase III proof of concept trials
  - MTN-020/ASPIRE Study; IPM 027/The Ring study
- CROI 2018: open-label extension
  - all HIV-/non-pregnant eligible, no placebo
  - MTN-025/HOPE Study; IPM 032/DREAM

- Baeten J et al, Abstract #143LB
- Rosenberg Z et al, Abstract #144LB
Dapivirine Vaginal Ring for PrEP

For PrEP, open-label extensions provided key information beyond what was learned in phase III trials, moving the field towards demonstration and scale-up:

- **Phase III trials**
  - Proof-of-concept
  - HIV-1 protection 44-75%
  - iPrEx, Partners PrEP

- **Open-label extensions**
  - Greater adherence & HIV-1 protection (100% with 4+ doses/wk)
  - iPrEx OLE

- **Demonstration**
  - Very high adherence, very low HIV-1
  - PROUD, Partners Demo

The dapivirine ring is just embarking on this pathway. Today’s results are the first from an open-label evaluation.

- Grant et al., NEJM 2010; Baeten et al., NEJM 2012; Grant et al., Lancet ID 2014; McCormack et al. Lancet 2016; Baeten et al., PLoS Med 2016

- Baeten J et al, Abstract #143LB
- Rosenberg Z et al, Abstract #144LB
Dapivirine Vaginal Ring for PrEP

- CROI 2016: phase III proof of concept trials
  - MTN-020/ASPIRE Study; IPM 027/The Ring study
- CROI 2018: open-label extension
  - all HIV-/non-pregnant eligible; no placebo arm
  - MTN-025/HOPE Study; IPM 032/DREAM

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>ASPIRE (Phase III)</th>
<th>HOPE (Open-Label)</th>
<th>Ring Study (Phase III)</th>
<th>DREAM (Open-label)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uptake (n)</td>
<td></td>
<td>1299/1407 (92% uptake)</td>
<td></td>
<td>900</td>
</tr>
<tr>
<td>Adherence*</td>
<td>77%</td>
<td>89%</td>
<td>83%</td>
<td>96%</td>
</tr>
<tr>
<td>HIV Incidence**</td>
<td>4.5/100 p-y (3.7-5.5)</td>
<td>1.9/100 p-y (1.0-3.4)</td>
<td>4.1/100 p-y (0.49-0.99)</td>
<td>1.88/100 p-y (0.9-3.2)</td>
</tr>
</tbody>
</table>

- *measured by residual dapivirine concentration in ring (at least 4 mg difference)
- **in Phase III trials this is placebo incidence

- Baeten J et al, Abstract #143LB
- Rosenberg Z et al, Abstract #144LB
Dapivirine Vaginal Ring for PrEP

- The HIV-1 incidence observed to date in MTN-025/HOPE compares favorably to that seen in prior open-label extension studies, for example iPrEx OLE:

  EXPECTED
  HIV-1 incidence 4.1

  OBSERVED
  HIV-1 incidence 1.9

  iPrEx placebo
  HIV-1 incidence 3.9

  iPrEx OLE
  HIV-1 incidence 2.0

  iPrEx OLE
  HIV-1 incidence 0.0

  high adherence

HIV incidence in iPrEx OLE among the subset with high PrEP adherence was zero. Similar adherent subset analyses are not yet available for MTN-025/HOPE.

- Baeten J et al, Abstract #143LB
- Rosenberg Z et al, Abstract #144LB
Griffithsin/Carrageenan FDI

- Goal to develop Multi-Purpose Prevention Technologies (MPT’s)
  - Incurable STI’s, large global burden; HIV: 38 million, HPV: 347 million women, HSV-2 472 million
- GRFT/CG Fast Dissolving Insert (FDI)
  - GRFT - small lectin derived from red algae, not absorbed
  - Picomolar anti-HIV activity (blocks entry), no X-resistance
  - CG - polysaccharide also from algae, potent anti-HPV
  - GFRT/CG combination improves anti-HSV/HPV activity
- Macaque vaginal SHIV challenge
- Mouse vaginal HSV-2 model
- Mouse vaginal HPV-16 model
- No pH change or Inflammation

- GRFT/CG Human gel study underway

- Derby N, et al Abstract #84
MK-8591

MK-8591 (EFdA) is a novel, highly potent, long-acting NRTTI

- Because of favorable pharmacokinetics, weekly dosing is being explored
- Current study is a dose-finding study for once weekly oral administration

- Previously 3.9 mg/kg dosing completely protective (10 mg/week)
- 1.3 mg/kg and 0.43 mg/kg protective
- 0.10 mg/kg allowed 2/8 animals infected (still 7-fold more protected compared to placebo)

Markowitz M et al Abstract #89LB
Summary

- PrEP coverage is only ~10% of those in need with deep racial disparities across all regions
- Getting to Zero initiatives (PrEP, linkage/retention, rapid ART start) starting to decrease HIV incidence.
- Several new/varied agents in ART and PrEP pipeline