The Future of ART

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Disclosures

• none
ART in 2018

- Start ART at all CD4 cell counts
- 32 approved drugs
  - 5 broad mechanistic classes: NRTI, NNRTI, PI, INSTI, EI
- Up to 7 recommended first-line regimens worldwide
  - 1 standard strategy: 2 NRTI + [NNRTI, PI, or INSTI]
- ART Properties
  - Antiretroviral activity
  - Safety and tolerability
  - Convenience
  - Access and cost

Antiretroviral Drug Approval:
1987 - 2018

0 5 10 15 20 25 30 35
1987 1989 1991 1993 1995 1997 1999 2001 2003 2005 2007 2009 2011 2013 2015 2017

AZT ddI ddC d4T 3TC SQV RTV IDV NVP NFV DLV EFV ABC APV LPV/r TDF ENF ATV FTC FPV TPV DRV ETR RAL MVC RPV EVG TAF BIC IBA DOR
ART: What to Start? –
Recommended/Preferred: 2 NRTI + 3rd Drug

<table>
<thead>
<tr>
<th>Source</th>
<th>Recommended Drugs</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>IAS-USA 2018</td>
<td>TAF/FTC, TDF/FTC, ABC/3TC</td>
<td><a href="http://www.europeanaidsclinicalsociety.org/">www.europeanaidsclinicalsociety.org/</a></td>
</tr>
<tr>
<td>EACS 2017</td>
<td>TAF/FTC, TDF/FTC, ABC/3TC</td>
<td>UK 2016 update</td>
</tr>
<tr>
<td>UK 2016 update</td>
<td>TAF/FTC, TDF/FTC, ABC/3TC</td>
<td>WHO 2018 update</td>
</tr>
</tbody>
</table>

+ only with DTG; * performs less well/not recommended for baseline HIV RNA >100,000 and/or CD4 <200

Antiretroviral Activity
ART Trials: Virologic Responses
114 studies through 2012, 1-3 years of f/u: ITT analyses

Virologic Responses – Newer Studies

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>Study arm (N)</th>
<th>Regimen</th>
<th>HIV RNA &lt;50 at 48 wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>GS-US-380-1490</td>
<td>320</td>
<td>TAF/FTC/BIC</td>
<td>89%</td>
</tr>
<tr>
<td></td>
<td>325</td>
<td>TAF/FTC + DTG</td>
<td>93%</td>
</tr>
<tr>
<td>Sax Lancet 2017;390:2074</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GS-US-380-1489</td>
<td>316</td>
<td>TAF/FTC/BIC</td>
<td>92%</td>
</tr>
<tr>
<td>Gallant Lancet 2017;390:2063</td>
<td></td>
<td>ABC/3TC/DTG</td>
<td>93%</td>
</tr>
<tr>
<td>AMBER</td>
<td>362</td>
<td>TAF/FTC/DRV/c</td>
<td>91%</td>
</tr>
<tr>
<td>Eron AIDS 2018;32:1431</td>
<td>363</td>
<td>TAF/FTC + DRV/c</td>
<td>88%</td>
</tr>
<tr>
<td>GEMINI 1</td>
<td>356</td>
<td>DTG+3TC</td>
<td>90%</td>
</tr>
<tr>
<td>Cahn IAS 2018 #TUAB0106LB</td>
<td>359</td>
<td>TDF/FTC + DTG</td>
<td>93%</td>
</tr>
<tr>
<td></td>
<td>360</td>
<td>DTG+3TC</td>
<td>93%</td>
</tr>
<tr>
<td></td>
<td>359</td>
<td>TDF/FTC + DTG</td>
<td>94%</td>
</tr>
<tr>
<td>GEMINI 2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Virologic Responses – Comparative Studies

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>N</th>
<th>Regimen</th>
<th>VL &lt;50 (96 wks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTG 5257</td>
<td></td>
<td>2 NRTI + ATV/r</td>
<td>88%</td>
</tr>
<tr>
<td>Lennox Ann Intern Med 2014;161:461</td>
<td>605</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 NRTI + DRV/r</td>
<td>89%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 NRTI + RAL</td>
<td>94%*</td>
</tr>
<tr>
<td>SINGLE</td>
<td></td>
<td>ABC/3TC + DTG</td>
<td>80%*</td>
</tr>
<tr>
<td>Walmsley NEJM 2013;369:1807 + JAIDS 2015;70:515</td>
<td>414</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>TDF/FTC/EFV</td>
<td>72%</td>
</tr>
<tr>
<td>FLAMINGO</td>
<td></td>
<td>2 NRTI + DTG</td>
<td>80%*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 NRTI + DRV/r</td>
<td>68%</td>
</tr>
</tbody>
</table>

* = significant difference
Multi-Class Failure on TAF/FTC + DRV/r + DTG

VL 87K CD4 92

+ hx of failure on enfuvirtide!

HIV Entry Inhibitors

* = FDA approved

Adapted from Moore JP, PNAS 2003;100:10598-10602.
**Ibalizumab (IBA):**
**CD4 Post-Attachment Inhibitor**

- Monoclonal antibody; parenteral; binds to CD4 receptor
- **Phase 3**
  - Study pop: VL>1000, ART >6 mos, 3-class resistance, ≥1 sens. drug (N=40)
  - Study treatment: continue ART, add IBA 2000 mg day 7
    - day 14: 60% VL 1 log ↓
  -- Day 14 optimize background, continue IBA 800 mg q2 weeks
    - week 24: 43% VL <50

- extension to week 48 (n=27): 59% VL <50

Emu NEJM 2018;379:645
Emu IDWeek 2017 #1686

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**Fostemsavir (FTR): Oral Attachment Inhibitor**

- Prodrug of temsavir; inhibits CD4 binding by binding to gp120
- **Phase 1** dose-escalation: up to 1.5 log cps/ml ↓; ↓ baseline susceptibility in 12% of pts due to envelope polymorphisms
  
  Nettles JID 2012;206:1002

- **Phase 2b**: modestly rx-experienced, screened for susc (N=254); week 48: 61-82% VL <50; week 96: 61% VL <50 (MITT)
  
  DeJesus CROI 2016 #472 and Thompson Antivir Ther 2017;22:215

- **Phase 3**: heavily rx-experienced, NOT screened for susc (N=272 rand.; 99 non-rand.)
  - day 8: mean HIV RNA Δ: -0.2 (placebo) vs. -0.8 (FTR) log cps/ml
  - wk 24: VL <40: 54% (rand) vs. 36% (non-rand)

- FDA “breakthrough status” 2015; filing 2019-2020
HIV Maturation Inhibitors (MI)

BMS-955176/GSK3532795: virologic suppression, halted due to GI toxicity
Morales-Ramirez IAS 2017 #MOAB0103

HIV Capsid Inhibitor

Tse CROI 2017 #38
Safety and Tolerability

ART Trials: Discontinuations for Toxicity
114 studies through 2012, 1-3 years of f/u: ITT analyses

### Discontinuations for Adverse Events

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>Study arm (N)</th>
<th>Regimen</th>
<th>% d/c for adverse events at 48-96 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTG 5257</td>
<td>603</td>
<td>2 NRTI + RAL</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Lennox Ann Intern Med 2014</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPRING-2</td>
<td>411</td>
<td>2 NRTI + DTG</td>
<td>2%</td>
</tr>
<tr>
<td>Raffi Lancet Infect Dis 2013</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GS-US-292-0104/0111</td>
<td>866 867</td>
<td>TAF/FTC/EVG/c TDF/FTC/EVG/c</td>
<td>1% 2%</td>
</tr>
<tr>
<td>Wohl JAIDS 2016</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GS-US-380-1489</td>
<td>316 315</td>
<td>TAF/FTC/BIC ABC/3TC/DTG</td>
<td>0% 1%</td>
</tr>
<tr>
<td>Gallant Lancet 2017:390:2063</td>
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<td></td>
</tr>
</tbody>
</table>

### Safety and Tolerability: Newer Approaches

- **Lower doses:**
  - **ENCORE 1** (2 NRTI + EFV 400 mg vs. 600 mg)
    Double-blind randomized, study of initial ART (N=630) → demonstrated non-inferiority   Puls Lancet 2014;383:1474
  - **WRHI 052**  Venter IAS 2018 #TUAB0107LB
    Switch study of pts on LPV/r >6 months, VL <50, no hx of other PI use (N=300)
    - Randomized to continue LPV/r or switch to DRV/r 400/100 qd
    - VL <50 at wk 48 (ITT) 95.4% (LPV) vs. 96.7% (DRV)  
      $\Delta +1.2\%$ (95% CI: -3.7, +6.2%)  
    - Conclusions:  
      - DRV/r 400/100 non-inferior + “significantly cheaper”  
    - Other studies in progress: **ATV 300 mg**
Safety and Tolerability: Newer Approaches

- **Newer drugs:**
  - tenofovir alafenamide (TAF)
  - TAF vs. TDF: Similar virologic efficacy
    - 1733 pts on [TAF or TDF]/FTC/EVG/c  *Sax* Lancet 2015;385:2606

  - Switch TDF $\rightarrow$ TAF improved renal/bone markers
    - 1443 pts on TDF with GFR $\geq$ 50 cc/min  *Mills* Lancet ID 2016;16:43
    - 663 pts on TDF with GFR $\geq$ 50 cc/min  *Gallant* Lancet HIV 2016;3:e158
    - 242 pts on TDF (65%) or not (35%) with eGFR 30-69  *Pozniak* JAIDS 2016;71:530

Newer Approaches: 2-Drug Regimens

- **PI/r + 3TC (or FTC)**
  - DUAL (switch; DRV/r): *Pulido* Clin Infect Dis 2017;65;2112
  - ANDES (DRV/r): *Sued* IAS 2017 #MOAB0106LB

- **PI/r + integrase inhibitor**
  - NEAT-001 (DRV/r + RAL) *Raffi* Lancet 2014;384:1942

- **NNRTI + integrase inhibitor**
  - SWORD (switch; RPV + DTG) *Libre* Lancet 2018;391:839
  - ETRAL (switch; ETR + RAL) *Katlama* IAS 2017 #MOPEB0314
  - FLAIR (CAB + RPV) (in progress)
2-Drug Regimen: DTG + 3TC

- **PADDLE Study** Cahn JIAS 2017;20:1; Figueroa IAS 2017 #MOPEB0287
  - Treatment-naïve individuals with HIV RNA 5-100K (N=20)
  - 2-drug regimen of DTG + 3TC
  - Results: All suppressed VL <50 by week 8
    - 18/20 (90%) remained suppressed through week 96

- **ACTG 5353** Taiwo CID 2018;66:1689
  - Treatment-naïve, HIV RNA up to 500K (N=120)
  - 90% <50 copies/ml at week 24 (FDA snapshot analysis)

- **GEMINI 1 and 2** Cahn AIDS 2018 #TUAB0106LB
- **Switch studies**

**2-Drug ART: DTG + 3TC vs. DTG + TDF/FTC**

Randomized, double-blind, parallel-group, multicenter, non-inferiority (≥10%) studies

Study population: Rx-naïve, no baseline drug resistance, VL 1000-500K (N=1433)

<table>
<thead>
<tr>
<th>48 week virologic outcome</th>
<th>Adjusted treatment difference (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEMINI-1 DTG + 3TC (N=356)</td>
<td>DTG + TDF/FTC (N=358)</td>
</tr>
<tr>
<td>GEMINI-2 DTG + 3TC (N=360)</td>
<td>DTG + TDF/FTC (N=359)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GEMINI-1</th>
<th>DTG + TDF/FTC</th>
<th>DTG + 3TC</th>
</tr>
</thead>
<tbody>
<tr>
<td>90.93</td>
<td>93.94</td>
<td></td>
</tr>
<tr>
<td>4.2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>2.6</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>6.7</td>
<td>2.9</td>
<td></td>
</tr>
</tbody>
</table>

2% withdrawal for adverse events in each group; improved renal/bone markers in 2-drug gp

Conclusion: DTG + 3TC is non-inferior to DTG + TDF/FTC with respect to proportion <50 at Wk 48 (snapshot, ITT-E population)

Cahn AIDS 2018 #TUAB0106LB
**Newer Approaches**

- **Less frequent dosing**
  - RAL daily formulation Cahn *Lancet HIV* 2017;4:e486

- **Newer co-formulations**
  - ATV/c and DRV/c
  - TAF/FTC/DRV/c *Eron AIDS* 2018;32:1431

- **New Injectable Drugs**
  - RPV LA Jackson *Clin Pharmacol Ther* 2014;96:314
  - Cabotegravir (CAB) Spreen *JAIDS* 2014;67:481

**LATTE-2: IM CAB + IM RPV**

- Randomized, open-label, phase 2b, non-inferiority study
- Study population: ART-naïve (N=309)
- Study rx: PO CAB + ABC/3TC X 4 wks, then randomized 2:2:1
- Results (HIV RNA <50 at 96 wks)
  - **IM CAB + IM RPV q8 wks** – 94%
  - **IM CAB + IM RPV q4 wks** – 87%
  - **PO CAB + ABC/3TC** – 84%
- Injection site reactions were nearly universal
  - 97%+ were mild or moderate; lasted a median of 3 days
  - 2 pts (<1%) d/c due to ISR
- Conclusions: IM non-inferior (comparable) to PO; well-tolerated
  *Eron IAS 2017 #MOAX0205LB; Margolis *Lancet* 2017;390:1499
- Phase 3 studies evaluating IM q8, q4 wks: ATLAS; ATLAS-M
**MK-8591 (EFdA)**

- 4’-ethynyl-2-fluoro-2’-deoxyadenosine; EFdA
- Non-obligate chain terminator
- Inhibits RT by preventing translocation (NRTTI)
- ½ life 150-160 hours(!)
- Potent antiviral activity (PBMC EC50 = 0.2 nM) with broad coverage (HIV-1, HIV-2, MDR strains)
- Accumulates in LN, vagina, rectum (animals) Grobler CROI 2017 #435
- Low-dose and parenteral formulations with long ½ lives

**Long-Acting Subdermal Implants: MK-8591 in Animal Studies**

Drug-eluting implants, both bioerodible and non-erodible

- **a** PLA - polyactic acid
- **b** PCL - polycaprolactone
- **c** EVA - ethylene vinyl acetate

**NHP**

Barrett AAC 2018 (epub)
Long-Acting Subdermal Implants: Tenofovir Alafenamide (TAF) in Dogs

Access and Cost
Aiming for the 2020 treatment target

Number of people living with HIV accessing antiretroviral therapy, global, 2000–2017 and 2020 target


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ART: Cost

Table 1. Target prices for key first-line combination treatments in low or low-middle income countries

<table>
<thead>
<tr>
<th>Combination treatment</th>
<th>Estimated price per patient-year</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF/3TC/ATV/r</td>
<td>$279</td>
<td>13</td>
</tr>
<tr>
<td>TDF/FTC/ELV/COBI</td>
<td>$184</td>
<td>14</td>
</tr>
<tr>
<td>ABC/3TC/DTG</td>
<td>$179</td>
<td>14</td>
</tr>
<tr>
<td>TDF/FTC/EFV600</td>
<td>$144</td>
<td>13</td>
</tr>
<tr>
<td>TDF/3TC/EFV600</td>
<td>$130</td>
<td>13</td>
</tr>
<tr>
<td>TDF/3TC/EFV400</td>
<td>$100 to $110</td>
<td>13</td>
</tr>
<tr>
<td>IAF/3TC/DTG</td>
<td>$60</td>
<td>14</td>
</tr>
<tr>
<td>DTG/3TC</td>
<td>$46</td>
<td>14</td>
</tr>
</tbody>
</table>

Vittoria JIAS 2016;19:20504
Future of ART: Conclusions

• Antiretroviral Therapy
  – Activity    excellent; need MDR-active drugs
  – Safety/tolerability   excellent
  – Convenience   excellent; newer formulations
  – Affordability     improved
  – Accessibility   improved  WHO Goal: “30 by 20”

Acknowledgments

• Weill Cornell Medicine
  – Cornell HIV Clinical Trials Unit (CCTU)
  – Division of Infectious Diseases

• AIDS Clinical Trials Group (ACTG)
• HIV Prevention Trials Network (HPTN)
• NIH, NIAID, Division of AIDS

• The participant volunteers!
• David Cooper – mentor and friend!