ART Optimisation

Michelle Moorhouse
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Port Elizabeth
Disclosures

• Speaker fees and honoraria from Gilead Sciences, AbbVie, Cipla and Janssen, and has received conference sponsorship from BD, Gilead, Merck, Cipla and Mylan.

• Part of ART optimisation collaborations

• Funding from USAID, Unitaid and study drug donations from ViiV Healthcare and Gilead Sciences
An embarrassment of riches...

Pre-1995
- Mono, dual therapy – delayed progression

1995-early 2000s
- Suppressive

Now
- Focus on single, safe coformulated tablet, started ASAP

Future
- ‘Forgiveness’; focus on lab abnormalities > clinical ones; NCDs
HIV in South Africa, 2016

South Africa (2016)
- 7.1 million people living with HIV
- 18.9% adult HIV prevalence
- 270,000 new HIV infections
- 110,000 AIDS-related deaths
- 56% adults on antiretroviral treatment
- 55% children on antiretroviral treatment

Source: UNAIDS Data 2017
HIV in South Africa, 2016

One third of new infections in Eastern and Southern Africa

South Africa

- 7.1 million people
- 18.9% adult HIV prevalence
- 270,000 new HIV infections
- 110,000 AIDS-related deaths
- 56% adults on antiretroviral treatment
- 55% children on antiretroviral treatment

Source: UNAIDS Data 2017
Drug optimisation

Science evolved: smarter and better HIV treatment options are now available
## WHO guideline evolution

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>When to start</strong></td>
<td></td>
<td></td>
<td>CD4 ≤200</td>
<td>CD4 ≤350</td>
<td>CD4 ≤350</td>
<td>CD4 ≤500</td>
</tr>
<tr>
<td></td>
<td>CD4 ≤200</td>
<td>CD4 ≤200</td>
<td>CD4 ≤200</td>
<td>CD4 ≤350</td>
<td>CD4 ≤350</td>
<td>CD4 ≤500</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>− Consider 350</td>
<td>− Regardless CD4 for TB</td>
<td>− Regardless CD4 for TB</td>
<td>− Regardless CD4 for TB</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>− CD4 ≤350 for tuberculosis (TB)</td>
<td>− Regardless CD4 for HBV</td>
<td>− Regardless CD4 for HBV</td>
<td>− CD4 ≤350 as priority</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>− Regardless CD4 for TB, HBV PW and SDC</td>
<td>− CD4 ≤350 as priority</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>First-line ART</strong></td>
<td>8 options</td>
<td>4 options</td>
<td>8 options</td>
<td>6 options and FDCs</td>
<td>1 preferred option and FDCs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>− AZT preferred</td>
<td>− AZT preferred</td>
<td>− AZT or TDF preferred</td>
<td>− AZT or TDF preferred</td>
<td>− TDF and EFV preferred across all populations</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>− d4T dose reduction</td>
<td>− d4T phase out</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Second-line ART</strong></td>
<td>Boosted and non-boosted PIs</td>
<td>Boosted PIs</td>
<td>Boosted PI</td>
<td>Boosted PI</td>
<td>Boosted PIs</td>
<td></td>
</tr>
<tr>
<td><strong>Third-line ART</strong></td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>DRV/r, RAL, ETR</td>
<td>DRV/r, RAL, ETR</td>
<td></td>
</tr>
<tr>
<td><strong>Viral load (VL) testing</strong></td>
<td>No</td>
<td>No (desirable)</td>
<td>Yes (tertiary centers)</td>
<td>Yes (phase-in approach)</td>
<td>Yes (preferred for monitoring, use of PoC, DBS)</td>
<td></td>
</tr>
</tbody>
</table>

**Earlier initiation**

- **Greater number of options**

**Simpler treatment**

- **Encourage HIV DR to guide**

**Less toxic, more robust regimens**

- **Support for scale up of VL using all technologies**
Are we on target?

Global

70% [51 - 84%]

77% [57 - >89%]

82% [60 - >89%]

44%
Are we on target?

Global:
- 70% [51 - 84%]
- 77% [57 - >89%]
- 82% [60 - >89%]
- 44%

South Africa:
- 86%
- 65%
- 81%
- 45%

UNAIDS data 2017
Are we on target?

- Global:
  - 70% [51 - 84%]
  - 77% [57 - >89%]
  - 82% [60 - >89%]
Incidence still remains stubbornly high...

UNAIDS data 2017
SHIMS 2: HIV in Swaziland

- Assessment of HIV prevalence, incidence, and virologic suppression in nationally representative sample of individuals 15 years of age or older in Swaziland, 2016-2017 (N = 10,934)
  - Since 2011, national HIV prevention and treatment services expanded

- 2016 90-90-90 achievements: diagnosed, 84.7%; on treatment, 87.4%; virologically suppressed, 91.9%

**Comparison of 2011 (SHIMS 1) and 2016-2017 assessments of adults 18-49 years of age**

<table>
<thead>
<tr>
<th>Outcome, %</th>
<th>2011</th>
<th>2016-2017</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>32.1</td>
<td>30.5</td>
<td>0.103</td>
</tr>
<tr>
<td>Incidence</td>
<td>2.5</td>
<td>1.4</td>
<td>0.012</td>
</tr>
<tr>
<td>(44% decrease from 2011)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Virologically suppressed</td>
<td>34.8</td>
<td>71.3</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>(&gt; 100% increase from 2011)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PLWH on ART globally 2005-2015

19.5 million in 2016
Impact of HIV response on life expectancy

UNAIDS data 2017
Life expectancy

Near-normal expectancy for adults starting ART above 200 cells/mm$^3$

Increases in Adult Life Expectancy in Rural South Africa: Valuing the Scale-Up of HIV Treatment

Jacob Bor,¹,²* Abraham J. Herbst,¹ Marie-Louise Newell,¹,³ Till Bärnighausen¹,²

Adult life expectancy has increased from 49.2 years in 2003 to 60.5 years in 2011

Causes of death in South Africa

<table>
<thead>
<tr>
<th>Causes of death (based on ICD-10)</th>
<th>2013</th>
<th></th>
<th>2014</th>
<th></th>
<th>2015</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rank</td>
<td>Number</td>
<td>%</td>
<td>Rank</td>
<td>Number</td>
<td>%</td>
</tr>
<tr>
<td>Tuberculosis (A15-A19)**</td>
<td>1</td>
<td>41,904</td>
<td>8,8</td>
<td>1</td>
<td>39,495</td>
<td>8,3</td>
</tr>
<tr>
<td>Diabetes mellitus (E10-E14)</td>
<td>5</td>
<td>23,133</td>
<td>4,9</td>
<td>3</td>
<td>23,966</td>
<td>5,0</td>
</tr>
<tr>
<td>Cerebrovascular diseases (I60-I69)</td>
<td>4</td>
<td>23,158</td>
<td>4,9</td>
<td>2</td>
<td>24,131</td>
<td>5,1</td>
</tr>
<tr>
<td>Other forms of heart disease (I30-I52)</td>
<td>6</td>
<td>22,189</td>
<td>4,7</td>
<td>4</td>
<td>22,928</td>
<td>4,8</td>
</tr>
<tr>
<td>Human immunodeficiency virus [HIV] disease (B20-B24)</td>
<td>3</td>
<td>23,825</td>
<td>5,0</td>
<td>6</td>
<td>22,729</td>
<td>4,8</td>
</tr>
<tr>
<td>Influenza and pneumonia (J09-J18)</td>
<td>2</td>
<td>24,345</td>
<td>5,1</td>
<td>5</td>
<td>22,813</td>
<td>4,8</td>
</tr>
<tr>
<td>Hypertensive diseases (I10-I15)</td>
<td>7</td>
<td>17,104</td>
<td>3,6</td>
<td>7</td>
<td>18,319</td>
<td>3,9</td>
</tr>
</tbody>
</table>
HPTN 052: showed us treatment is the best prevention

Total HIV-1 Transmission Events: 39
(4 in immediate arm and 35 in delayed arm; $P < .0001$)

- Linked Transmissions: 28
  - Delayed Arm: 27
  - Immediate Arm: 1

- Unlinked or TBD Transmissions: 11

Single transmission in patient in immediate ART arm believed to have occurred close to time therapy began and prior to HIV-1 RNA suppression
ART coverage significantly decreased individual risk KwaZulu Natal, South Africa (2004-11)

- Africa Centre longitudinal surveillance cohort with community and individual data
- Between 2004 and 2011, 1395 HIV seroconversions and over 53,042 person-years of observation (crude HIV incidence rate of 2.63 (95% C.I. 2.50 to 2.77) per 100 person-years

Every % point increase in ART coverage among all HIV+ adults in a community, was associated with a 1.7% decline in the hazard of HIV acquisition ($p <0.001$)
START and TEMPRANO fixed “when to start” debate

### Table 1: Severe morbidity in TEMPRANO study at 30 months

<table>
<thead>
<tr>
<th></th>
<th>% events</th>
<th>n</th>
<th>Rate / 100 PY</th>
<th>adj HR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO ART</td>
<td>11.4%</td>
<td>111</td>
<td>4.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early ART</td>
<td>6.6%</td>
<td>64</td>
<td>2.8</td>
<td><strong>0.56</strong></td>
<td>0.0002</td>
</tr>
<tr>
<td>No IPT</td>
<td>10.7%</td>
<td>104</td>
<td>4.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPT</td>
<td>7.2%</td>
<td>71</td>
<td>3.0</td>
<td>0.65</td>
<td>0.005</td>
</tr>
</tbody>
</table>

### Table 1. Primary endpoint and its components in open DSMB report (15 May 2015)

<table>
<thead>
<tr>
<th></th>
<th>Early ART (arm A)</th>
<th>Deferred ART (arm B)</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>rate/100 PY</td>
<td>N</td>
</tr>
<tr>
<td>AIDS, serious non-AIDS, or death (primary)</td>
<td>41</td>
<td>0.60</td>
<td>86</td>
</tr>
<tr>
<td>AIDS or AIDS death</td>
<td>14</td>
<td>0.20</td>
<td>46</td>
</tr>
<tr>
<td>Serious non-AIDS or non-AIDS death</td>
<td>28</td>
<td>0.41</td>
<td>41</td>
</tr>
</tbody>
</table>

* PY = patient years, ** NS = non significant
Movement to “Treat All” happening

- 24% of all LMIC and 40% of fast-track countries have adopted Treat All
- By the end of 2016, more than half of all LMIC and 80% fast-track countries will have adopted Treat All

Uptake of WHO policy for initiation threshold among adults and adolescents living with HIV in low- and middle-income countries (LMIC) and fast-track countries (situation as of July 2016)

Lots more people will need treatment in the future...
WHO forecast for ARVs in LMIC: 2014–2018

Treatment for life

1. Expect a normal life expectancy:
   May et al. AIDS 2014

- UK CHIC: 21,388 people started ART 2000-2010

If 35 year old man started ART:

<table>
<thead>
<tr>
<th>CD4</th>
<th>Baseline</th>
<th>1 year ART</th>
<th>5 years ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;200</td>
<td>71</td>
<td>71</td>
<td>&amp; VL &gt; 50 54</td>
</tr>
<tr>
<td>200-349</td>
<td>78</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>&gt;350</td>
<td>77</td>
<td>81</td>
<td>&amp; VL &lt; 50 80</td>
</tr>
<tr>
<td>General population</td>
<td>78</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: If diagnosed, in care and on effective ART: life expectancy is normal

Great information to give to people newly diagnosed and encourage good adherence

Thanks: Julie Fox, Guys
What lifetime treatment means...

1. Less tolerance for nuisance SEs
2. Less focus on initiation period
3. ARVs and NCD risk factors
4. Interest in cure
5. Focus on costs
6. Longer acting
7. Harmony
8. Not acceptable to have “lesser” drugs in LMIC
The drugs rock

TDF + XTC + Efavirenz

Failure

AZT + 3TC + PI/r (LPV or ATV)

Failure

XTC, other nukes

Darunavir, Dolutegravir, Etravirine
ART trials

114 studies through 2012, up to 3 years of f/u: ITT analyses

Virologic responses

Safety and tolerability

Lee et al. PLoS One 2014
But there’s room for improvement

Some day drugs will be perfect
If we try
Some day drugs will be perfect
And no one will ever die
Some day risk will be zero
My, oh my
Some day pills will be magic
And they’ll taste of apple pie
First-line....

<table>
<thead>
<tr>
<th>Desirable Property</th>
<th>EFV/TDF/FTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>High resistance barrier</td>
<td>No</td>
</tr>
<tr>
<td>Well tolerated</td>
<td>Not initially</td>
</tr>
<tr>
<td>No lab tox monitoring</td>
<td>TDF creat</td>
</tr>
<tr>
<td>Safe in pregnancy</td>
<td>Yes</td>
</tr>
<tr>
<td>Low pill burden</td>
<td>Yes FDC</td>
</tr>
<tr>
<td>Once a day</td>
<td>Yes</td>
</tr>
<tr>
<td>Use with TB (rif)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Cost driver

Toxicity

Toxicity driver

Pill size

Low genetic barrier

Cost
Efavirenz’s warts...

Effavirenz

- Neuro-psychiatric
  - Ann Intern Med. 2005;143:714
- Suicide
- Metabolic
  - JAIDS 2012;60:33
  - Lancet Infect Dis 2012;12:111
  - Clin Infect Dis 2006;42:273
  - Lancet 2009; 374: 796
  - AIDS 2014;28(10):145
  - JAIDS 2011;57:2841
  - Karamchand Medicine 2016
- Bone mineral density
  - Dave PLoS ONE 10(12): e0144286.
- DILI
  - Sonderup AIDS 2016
- Late encephalopathy
  - Variava JAIDS 2017
**ENCORE1:**
Efficacy of 400 mg EFV vs. 600 mg

Non-inferiority comparisons at Week 96 HIV RNA viral load <200 copies/mL and <50 copies/mL by population and baseline HIV RNA strata

<table>
<thead>
<tr>
<th></th>
<th>EFV 400 mg (n/N)</th>
<th>EFV 600 mg (n/N)</th>
<th>Difference (95% CI)</th>
<th>P-value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients with HIV RNA &lt;200 c/mL at baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modified intention to treat</td>
<td>289/321</td>
<td>280/309</td>
<td>–0.6% (–5.2 to 4.0)</td>
<td>0.72</td>
</tr>
<tr>
<td>&lt;100,000</td>
<td>177/197</td>
<td>177/197</td>
<td>0% (–6.0 to 6.0)</td>
<td></td>
</tr>
<tr>
<td>≥100,000</td>
<td>112/124</td>
<td>103/112</td>
<td>–1.6% (–8.9 to 5.6)</td>
<td></td>
</tr>
<tr>
<td>NC=F</td>
<td>274/321</td>
<td>255/309</td>
<td>–1.6% (–8.9 to 5.6)</td>
<td>0.72</td>
</tr>
<tr>
<td>&lt;100,000</td>
<td>167/197</td>
<td>159/197</td>
<td>0% (–6.0 to 6.0)</td>
<td></td>
</tr>
<tr>
<td>≥100,000</td>
<td>107/124</td>
<td>96/112</td>
<td>–1.6% (–8.9 to 5.6)</td>
<td></td>
</tr>
<tr>
<td>Per protocol</td>
<td>273/279</td>
<td>254/257</td>
<td>–1.6% (–8.9 to 5.6)</td>
<td>0.72</td>
</tr>
<tr>
<td>&lt;100,000</td>
<td>166/170</td>
<td>158/160</td>
<td>–1.1% (–4.3 to 2.2)</td>
<td>0.97</td>
</tr>
<tr>
<td>≥100,000</td>
<td>107/109</td>
<td>97/97</td>
<td>–0.8% (–4.8 to 2.6)</td>
<td>0.97</td>
</tr>
<tr>
<td><strong>Patients with HIV RNA &lt;50 c/mL at baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modified intention to treat</td>
<td>277/321</td>
<td>170/197</td>
<td>–0.4% (–5.8 to 4.9)</td>
<td>0.83</td>
</tr>
<tr>
<td>&lt;100,000</td>
<td>166/170</td>
<td>158/160</td>
<td>0% (–6.8 to 6.8)</td>
<td></td>
</tr>
<tr>
<td>≥100,000</td>
<td>103/124</td>
<td>92/112</td>
<td>–1.2% (–9.8 to 7.4)</td>
<td>0.83</td>
</tr>
<tr>
<td>NC=F</td>
<td>264/321</td>
<td>161/197</td>
<td>–1.2% (–9.8 to 7.4)</td>
<td>0.83</td>
</tr>
<tr>
<td>&lt;100,000</td>
<td>154/197</td>
<td>92/112</td>
<td>3.6% (–4.4 to 11.5)</td>
<td>0.71</td>
</tr>
<tr>
<td>≥100,000</td>
<td>98/112</td>
<td>92/97</td>
<td>0.9% (–8.8 to 10.6)</td>
<td>0.71</td>
</tr>
</tbody>
</table>

**VL < 200 copies/mL:** 90% (400 mg) vs. 90.6% (600 mg)

**VL < 50 copies/mL:** 86.3% (400 mg) vs. 86.7% (600 mg)

ENCORE1 Study Group. Lancet 2014;383(9927):1474–82
## ENCORE1: Safety of 400 mg EFV vs. 600 mg EFV

96-week data from the randomised double-blind, placebo-controlled, non-inferiority ENCORE1 study in HIV-infected, ARV-naïve adults

### Adverse events and serious adverse events

<table>
<thead>
<tr>
<th>Adverse events (total = 3337)</th>
<th>EFV 400 mg (N=321)</th>
<th>EFV 600 mg (N=309)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of adverse events</td>
<td>1653 (49.5%)</td>
<td>1684 (50.5%)</td>
<td>0.42</td>
</tr>
<tr>
<td>Grade 1</td>
<td>1202 (73%)</td>
<td>1236 (73%)</td>
<td>-</td>
</tr>
<tr>
<td>Grade 2</td>
<td>381 (23%)</td>
<td>363 (22%)</td>
<td>-</td>
</tr>
<tr>
<td>Grade 3</td>
<td>62 (4%)</td>
<td>77 (5%)</td>
<td>-</td>
</tr>
<tr>
<td>Grade 4</td>
<td>8 (1%)</td>
<td>8 (1%)</td>
<td>-</td>
</tr>
<tr>
<td>Patients reporting adverse events</td>
<td>291 (91%)</td>
<td>285 (92%)</td>
<td>-1.6 (−2.8 to 5.9)</td>
</tr>
<tr>
<td>Patients with adverse event related to EFV*</td>
<td>126 (39%)</td>
<td>148 (48%)</td>
<td>−8.6 (−16.4 to −0.9)</td>
</tr>
<tr>
<td>Patients stopping EFV because of treatment-related adverse event*†</td>
<td>16 (13%)</td>
<td>34 (23%)</td>
<td>−10.3 (−19.2 to −1.4)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number of serious adverse events</td>
<td>32 (40%)</td>
<td>48 (60%)</td>
<td>-</td>
</tr>
<tr>
<td>Patients reporting serious adverse events</td>
<td>24 (8%)</td>
<td>32 (10%)</td>
<td>−2.9 (−7.3 to 1.5)</td>
</tr>
<tr>
<td>Patients reporting serious adverse event related to EFV*</td>
<td>2 (1%)</td>
<td>4 (1%)</td>
<td>−0.7 (−2.4 to 1.1)</td>
</tr>
</tbody>
</table>

*Definitely or probably related to EFV; †Relationship interaction p=0.046

EFV-related AEs: 39% (400 mg) vs. 48% (600 mg)
Discontinuations: 13% (400 mg) vs. 23% (600 mg)

ENCORE1 Study Group. Lancet 2014;383(9927):1474–82
Has the time come to abandon efavirenz for first-line antiretroviral therapy?

Francois Raffi¹*, Anton L. Pozniak² and Mark A. Wainberg³

Increasing primary resistance
Toxicity issues
Newer regimens more effective
High income countries no longer recommend EFV in first-line
“The integrase inhibitor era”

Shift To Integrase Inhibitor-based Therapy

Initial Antiretroviral Therapy

ART regimen type by year of initiation

Year of ART Initiation

1,773 patients initiating ART between 1996 and 2014 in the UCHCC, follow-up through 2015

Regimen Type
- NRTI only
- Other*
- NNRTI
- bPI**
- INSTI

bPI = LPV/r, DRV/r or ATV/r therapy
Other = includes unboosted PI and other bPI combinations

Courtesy of Thibaut Davy and Sonia Napravnik

Thanks Joe Eron
### Phase 3 studies of DTG-based ART in ARV-naive patients

- Randomised, non-inferiority phase 3 studies
- Primary endpoint: HIV-1 RNA < 50 copies/mL at week 48

<table>
<thead>
<tr>
<th>Study</th>
<th>ART-naive pts</th>
<th>Description</th>
<th>Treatment</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SPRING-2</strong></td>
<td>VL ≥ 1000 c/mL</td>
<td>(N = 822)</td>
<td>DTG 50 mg QD + 2 NRTIs*</td>
<td>411</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RAL 400 mg BID + 2 NRTIs*</td>
<td>411</td>
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<tr>
<td><strong>SINGLE</strong></td>
<td>VL ≥ 1000 c/mL</td>
<td>(N = 833)</td>
<td>DTG 50 mg QD + ABC/3TC QD</td>
<td>414</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>EFV/TDF/FTC QD</td>
<td>419</td>
</tr>
<tr>
<td><strong>FLAMINGO</strong></td>
<td>VL ≥ 1000 c/mL</td>
<td>(N = 484)</td>
<td>DTG 50 mg QD + 2 NRTIs*</td>
<td>242</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DRV/RTV 800/100 mg QD + 2 NRTIs*</td>
<td>242</td>
</tr>
</tbody>
</table>

*Investigator-selected NRTI backbone: either TDF/FTC or ABC/3TC.
SINGLE study: DTG vs. EFV

DTG + ABC/3TC for HIV-1 treatment in ARV-naïve adults with HIV infection: 96 and 114 week results from the randomised SINGLE study

Proportion of participants with HIV-1 RNA <50 c/mL

Difference in response
Week 96: 8.0% (95% CI, 2.3% to 13.8%); p=0.006
Week 114: 8.3% (95% CI, 2.0% to 14.6%); p=0.010

Walmsley et al. J Acquir Immune Defic Syndr 2015
Comparative efficacy and safety of first-line ART: A systematic review and network meta-analysis

Network of eligible comparisons between treatments

Kanter S, Lancet 2016
DTG in the real world...

Discontinuation due to neuropsychiatric AE

Factors associated with DTG discontinuation

<table>
<thead>
<tr>
<th></th>
<th>RH</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any AE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female, vs. male gender</td>
<td>2.81</td>
<td>1.46–5.41</td>
<td>0.002</td>
</tr>
<tr>
<td>Older age (&gt; 60 years), vs. younger age</td>
<td>2.88</td>
<td>1.56–5.34</td>
<td>&lt; 0.001</td>
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<tr>
<td>ABC with DTG initiated, vs. no ABC</td>
<td>2.63</td>
<td>1.61–4.29</td>
<td>0.0001</td>
</tr>
<tr>
<td>DTG start in 2016, vs. in 2014/2015</td>
<td>8.93</td>
<td>3.76–21.28</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td><strong>Neuropsychiatric AEs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female, vs. male gender</td>
<td>2.64</td>
<td>1.23–5.65</td>
<td>0.01</td>
</tr>
<tr>
<td>Older age (&gt; 60 years), vs. younger age</td>
<td>2.86</td>
<td>1.42–5.77</td>
<td>0.003</td>
</tr>
<tr>
<td>ABC with DTG initiated, vs. no ABC</td>
<td>2.42</td>
<td>1.38–4.24</td>
<td>0.002</td>
</tr>
<tr>
<td>DTG start in 2016, vs. in 2014/2015</td>
<td>11.36</td>
<td>4.31–29.41</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

ABC, abacavir; CI, confidence interval.

Hoffmann et al. HIV Medicine 2017; Libre et al. CROI 2017 abstract #615; Hsu et al. CROI 2017 abstract #664
DTG in the real world...

Factors associated with DTG discontinuation:
- Age with diabetes mellitus vs no diabetes
- Older age (<60 years) vs younger age
- Female vs male gender
- Neurocognitive AE

Discontinuation due to AE:
- DDVs
- RA
- DTC

Germany (2 cohorts), 1960 INSTI-based therapies

Discontinuation: discontinuation due to AE
First-line....

TDF + XTC + EFV

Cost driver: Toxicity
Toxicity driver:
Pill size
Low genetic barrier
Cost
Initial ART with E/C/F/TAF superior to E/C/F/TDF at Week 144

- Efficacy similar across 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 week 144: 1.4% in each arm

Studies 104/111: Week 144 safety outcomes

- Rate of discontinuation for AEs higher with TDF vs TAF regimen
  - 3.3% vs 1.3% ($P = 0.01$)
- 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%

<table>
<thead>
<tr>
<th>Renal events leading to discontinuation, n</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 first-line....

TAF + XTC + DTG

Safer
Cheaper

Safer
Need for second-line?
Cheaper
CLINICAL UPDATE

Cutting the cost of South African antiretroviral therapy using newer, safer drugs

W D F Venter,1 FCP (SA), MMed; B Kaiser,2 MPH, PharmD, BCPS; Y Pillay,3 PhD; F Conradie,4 MB BCh; G B Gomez,5 PhD; P Clayden,6 M Matsolo;7 C Amole,8 BA; L Rutter,7 BA; F Abdullah,9 MB ChB, FCPHM, BSc Hons (Epi); E J Abrams,10 MD; C P Casas,11 MSc; M Barnhart,12 MD, MPH; A Pillay,13 PhD; A Pozniak,14 ME; M Moorhouse,1 MB BCh; M Chersich,1 MB BCh, PhD; C Sc

1Wits Reproductive Health and HIV Institute, University of the
2Formerly UNITAID, Geneva, Switzerland
3HIV/AIDS, TB and Maternal, Child and Women's Health in

![Graph showing estimated crude savings on antiretroviral drugs](image)

Fig. 2. Estimated crude savings on antiretroviral drugs (assuming implementation of new regimen in 2019 - 2020). Cumulative savings compared with status quo (conservative = 300 000 annually, transition from old regimen to new over 3 years; moderate = new regimen, 400 000 annually, transition over 2 years; aggressive = new regimen, 500 000 annually, transition over 1 year).
## Comparison of current international guidelines for ART-naive

<table>
<thead>
<tr>
<th>Regimen</th>
<th>DHHS(^1)</th>
<th>EACS(^2)</th>
<th>BHIVA(^3)</th>
<th>IAS-USA(^4)</th>
<th>GeSIDA(^5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTG/3TC/ABC(^*)</td>
<td>Green</td>
<td>Green</td>
<td>Green</td>
<td>Green</td>
<td>Yellow</td>
</tr>
<tr>
<td>DTG + FTC/TDF</td>
<td>Green</td>
<td>Green</td>
<td>Green</td>
<td>Green</td>
<td>Green</td>
</tr>
<tr>
<td>EVG/COBI/FTC/TDF(^†)</td>
<td>Green</td>
<td>Green</td>
<td>Green</td>
<td>Green</td>
<td>Yellow</td>
</tr>
<tr>
<td>EVG/COBI/FTC/TAF(^‡)</td>
<td>Green</td>
<td>Green</td>
<td>Green</td>
<td>Yellow</td>
<td>Yellow</td>
</tr>
<tr>
<td>RAL + FTC/TDF</td>
<td>Green</td>
<td>Yellow</td>
<td>Green</td>
<td>Yellow</td>
<td>Yellow</td>
</tr>
<tr>
<td>ATV/RTV + FTC/TDF</td>
<td>Green</td>
<td>Yellow</td>
<td>Yellow</td>
<td>Yellow</td>
<td>Yellow</td>
</tr>
<tr>
<td>DRV/RTV + FTC/TDF</td>
<td>Green</td>
<td>Yellow</td>
<td>Yellow</td>
<td>Yellow</td>
<td>Yellow</td>
</tr>
<tr>
<td>EFV/FTC/TDF</td>
<td>Green</td>
<td>Yellow</td>
<td>Yellow</td>
<td>Yellow</td>
<td>Yellow</td>
</tr>
<tr>
<td>RPV/FTC/TDF(^§)</td>
<td>Green</td>
<td>Green</td>
<td>Green</td>
<td>Yellow</td>
<td>Yellow</td>
</tr>
</tbody>
</table>

---

*Only if HLA-B*5701 negative. †Only if CrCl ≥ 70 mL/min. ‡Only if CrCl ≥ 30 mL/min. §Only if baseline HIV-1 RNA < 100,000 copies/mL and CD4+ cell count > 200 cells/mm\(^3\).

---

3. BHIVA Guidelines. 2015.
But... not in WHO guidelines

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Preferred first-line options</th>
<th>Alternative first-line options</th>
</tr>
</thead>
<tbody>
<tr>
<td>IAS (2014)</td>
<td>11</td>
<td>16</td>
</tr>
<tr>
<td>DHHS (2015)</td>
<td>05</td>
<td>07</td>
</tr>
<tr>
<td>EACS (2015)</td>
<td>06</td>
<td>13</td>
</tr>
<tr>
<td>WHO (2015)</td>
<td>01</td>
<td>05</td>
</tr>
</tbody>
</table>
Why aren’t these drugs used?

- Not preferred options in WHO guidelines
- Many drugs are not registered and no co-formulations are available
- Limited data on use in TB (almost all new drugs)
- Limited data on use in pregnancy (almost all new drugs)
- Costs: abacavir, all integrase inhibitors – hope for dolutegravir
ADVANCE (NCT03122262)

Number = 1110*
≥12 years, ≥40 kg

- Non inferiority of 2 new combinations to current treatment
- Open label, randomised, single site study over 48 weeks
- * n=1110, with 90-120 in age group 12-18 years
New drugs in TB and pregnancy
New approaches in RLS

Things to consider:

- Efficacy
- Affordability
- Tolerability
- Compatibility: TB and hepatitis
- Optimising ART in RLS
- Minimal risk of failure
- No food restrictions
- FDC

New approaches:

- New(er) drugs
- Same drugs
  - Different doses
  - Different combinations
    (dual therapy)
  - Different formulations
    (injectables, implantables)
- And new classes, immunoglobulins

Vitoria M. Antivir Ther 2014
Reduced drug regimens in ARV-naïve patients

- DTG + 3TC (Paddle)
- DTG + RPV (SWORD)
- DTG + 3TC (GEMINI & TANGO) (ACTG 5353 & ASPIRE) (Lamidol)

- CABT LA + RPV LA (LATTE-2)
- CABT LA + RPV LA (FLAIR & ATLAS)

- ISTI + NNRTI
- ISTI + 3TC

Courtesy J Arribas
Dolutegravir monotherapy in ART-naive

- N = 9 pts who refused NRTIs and initiated DTG monotherapy
- All pts had baseline HIV-1 RNA < 100,000 copies/mL
- No baseline NRTI, NNRTI, PI, or INSTI resistance


<table>
<thead>
<tr>
<th>Pt</th>
<th>Baseline HIV-1 RNA, copies/mL</th>
<th>After 4 Wks’ DTG</th>
<th>At Last Visit</th>
<th>Baseline CD4+ Cell Count, cells/mm³</th>
<th>At Last Visit</th>
<th>Mos on DTG</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20,400</td>
<td>Undetectable</td>
<td>Undetectable</td>
<td>248</td>
<td>600</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>18,400</td>
<td>Undetectable</td>
<td>&lt;20</td>
<td>335</td>
<td>471</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>90,500</td>
<td>31</td>
<td>Undetectable</td>
<td>356</td>
<td>527</td>
<td>7</td>
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<tr>
<td>4</td>
<td>39,000</td>
<td>35</td>
<td>Undetectable</td>
<td>350</td>
<td>623</td>
<td>7</td>
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<tr>
<td>5</td>
<td>43,300</td>
<td>&lt;20</td>
<td>Undetectable</td>
<td>329</td>
<td>613</td>
<td>7</td>
</tr>
<tr>
<td>6</td>
<td>17,500</td>
<td>45</td>
<td>&lt;20</td>
<td>229</td>
<td>400</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>18,200</td>
<td>&lt;20</td>
<td>Undetectable</td>
<td>785</td>
<td>879</td>
<td>6</td>
</tr>
<tr>
<td>8</td>
<td>16,900</td>
<td>Undetectable</td>
<td>Undetectable</td>
<td>214</td>
<td>309</td>
<td>8</td>
</tr>
<tr>
<td>9</td>
<td>52,000</td>
<td>&lt;20</td>
<td>Undetectable</td>
<td>345</td>
<td>484</td>
<td>6</td>
</tr>
</tbody>
</table>
Second-line

- TDF
- XTC
- Efavirenz

Failure:

- AZT
- 3TC
- PI/r (LPV or ATV)

Cost and toxicity:

- Darunavir
- Raltegravir
- Etravirine
Safety issues with PIs

LPV/r
- GI upset
- Lipids
- Hepatitis
- Dysglycaemia

ATV/r
- Jaundice
- Lipids (low potential)
- Renal stones
- Hepatitis

DRV/r
- Rash
- GI upset
- Hepatitis
How do we make PIs safer?

• New molecules
• Prodrugs of current PIs
  • Improve bioavailability
  • Reduce side effects
• New formulations of existing PIs
• Different pharmacokinetic boosters
• Use existing PIs in a different ways
  • Lower doses
  • Different combinations e.g. nuke sparing
Second-line: the future

- TDF + XTC + Efavirenz
  - Failure

- AZT + 3TC + DRV, DTG, RPV, doravirine, other
  - Failure

- XTC, other nukes

- Darunavir
- InSTI
- Etravirine
Key eligibility criteria: on first-line 2 NRTIs + NNRTI regimen for ≥ 6 months, failing virologically (HIV-1 RNA ≥400 c/mL on 2 occasions); no primary viral resistance to PIs or INSTIs

Stratification: by HIV-1 RNA (≤ or >100,000 copies/mL), number of fully active NRTIs in the investigator-selected study background regimen (2 or <2)

Primary endpoint: proportion with HIV-1 RNA <50 c/mL at Week 48 using the FDA snapshot algorithm (12% noninferiority margin)
DTG + 2 NRTIs is superior to LPV/RTV + 2 NRTIs with respect to snapshot in the ITT-E (<50 c/mL) at Week 24, *P* < 0.001

- **CI**, confidence interval; **ITT-E**, intent-to-treat exposed; **PP**, per protocol.

Aboud et al. IAS 2017; Paris, France. Slides TUAB0105LB.
Snapshot outcomes at Week 24: ITT-E and PP Populations

- DTG + 2 NRTIs is **superior** to LPV/RTV + 2 NRTIs with respect to snapshot in the ITT-E (< 50 copies/mL) at Week 24, *P* < 0.001
  
  - CI, confidence interval; ITT-E, intent-to-treat exposed; PP, per protocol.

Aboud et al. IAS 2017; Paris, France. Slides TUAB0105LB.
The Doodle study

- Number = 470
- VL < 50 copies/mL
- On PI/r-based ART
- ≥ 12 years, ≥ 40 kg

1:1

DTG 50 mg + TDF 300 mg + FTC 200 mg

PI/r + TDF 300 mg + FTC 200 mg

<table>
<thead>
<tr>
<th>Screen</th>
<th>Enrolment</th>
<th>Visit 1/2</th>
<th>Visit 3</th>
<th>Visit 4</th>
<th>Visit 5</th>
<th>EOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day -60 to -1</td>
<td>Week 0</td>
<td>Week 4/8</td>
<td>Week 12</td>
<td>Week 24</td>
<td>Week 36</td>
<td>Week 48</td>
</tr>
</tbody>
</table>

Randomisation

Primary endpoint
Or something completely different?

Dolutegravir plus Rilpivirine in Suppressed Heavily Pretreated HIV-Infected Patients


Background. Patients with previous multiple virological failures are frequently suppressed with complex, toxic regimens. We aimed to explore the role of dolutegravir (DTG) 50 mg plus rilpivirine (RPV) 25 mg once daily in fully suppressed patients with a history of repeated treatment failures.

Methods. Ongoing cohort study. Heavily pretreated patients with multiple virological failures and resistance mutations who were on complex suppressive therapy were switched to a QD dual regimen with DTG + RPV. Patients were excluded if resistance to integrase inhibitors (INI) or RPV was shown. Follow-up visits were scheduled at 4, 12, 24, and 48 weeks after switching. The main outcome variable was persistence of undetectable viral load.

Liver toxicity

Liver enzymes at baseline and 48 weeks:

- Bilir: 1.10 vs 0.68
- AST: 44 vs 27
- ALT: 52 vs 27
- GGT: 78 vs 78
- AP: 94 vs 84

All P < 0.05

Lipid profile

- TG: Baseline 133 vs 173 at 48w (P = 0.01)
- LDL: Baseline 123 vs 115 at 48w (P = 0.13)
- HDL: Baseline 45 vs 49 at 48w (P = 0.94)
- CT: Baseline 202 vs 188 at 48w (P = 0.04)

Renal function

Creatinine (Cr) and CKD-EPI at Baseline, 4w, 24w, and 48w:

- Baseline: 85, 75, 76, 76
- CKD-EPI: 1.11, 1.2, 1.18, 1.24

Conclusions

- Switching to a simple, dual regimen of DTG plus RPV in heavily pretreated, multiply failed, suppressed HIV-infected patients, is safe and highly efficacious.
What if...

TDF + XTC + Efavirenz

AZT + 3TC + PI/r (LPV or ATV)

TAF + XTC + DTG
Ambition versus reality

Global

90% [51–84%]

90% [57–>89%]

90% [60–>89%]
Even in settings with good testing & ART coverage, treatment cascades still show important leakages...

Cascade of HIV care – Sub-Saharan Africa

- Breakpoint 1: undiagnosed HIV positive
- Breakpoint 2: living with HIV
- Breakpoint 3: in care

Cascade of HIV Care – Brazil, 2013

- Breakpoint 1: undiagnosed HIV positive
- Breakpoint 2: living with HIV
- Breakpoint 3: in care

Cascade of HIV care – United States

- Breakpoint 1: living with HIV
- Breakpoint 2: in care
- Breakpoint 3: treatment

Cascade of HIV care – Russia

- Breakpoint 1: undiagnosed HIV positive population
- Breakpoint 2: treatment guidelines recommend ART in CD4 < 350
- Breakpoint 3: adherence to ART

Cascade of HIV care – British Columbia (CA)

- Breakpoint 1: living with HIV
- Breakpoint 2: in care
- Breakpoint 3: treatment

Hill et al. CROI 2015 [abstr 1118]

Thanks: Andrew Hill
Will 90-90-90 do it?

Mind the Gap

UNAIDS Target for 2020

Diagnosed

On Treatment

90%

90%

Virally Suppressed

90%

Today’s targets leave a prevention gap.

Ending the AIDS epidemic by 2030 takes comprehensive targets and action.

AVAC Report 2014/15: Prevention on the Line
www.avac.org/report2014-15/graphics
Will 90-90-90 do it?

- Combination prevention: 90%
- Diagnosed: 90%
- On ART: 90%
- Virally suppressed: 90%
Rich countries too

Projected UK ARV costs, if branded drugs used (8% growth/year)

Does not include:
PreP
HCV treatment

Thanks: Andrew Hill
Review

Reframing HIV care: putting people at the centre of antiretroviral delivery

Chris Duncombe¹, Scott Rosenblum¹, Nicholas Hellmann², Charles Holmes³, Lynne Wilkinson⁴, Marc Biot⁴, Helen Bygrave⁴, David Hoos⁵ and Geoff Garnett¹

The levers of tiered care

- ART initiation/refills
- Clinical monitoring
- Adherence support
- Laboratory tests
- OI treatment
- Psychosocial support

Summary

Service intensity

Service frequency

People

Health worker cadre

Service location

- HIV clinic/hospital
- Primary care clinic
- Other clinic
- Community
- Home

Figure 1 Four levers to tailor or adapt care to people’s needs (service frequency, location, intensity and cadre).
WHERE'S WALLY?
Men are less likely than women to have suppressed viral loads

UNAIDS data 2017
Still too many people start ART late

% people starting ART with CD4 < 100
Testing, testing...

- First 90 possibly the hardest
- Innovative operational testing strategies needed beyond:
  - Facility based testing
  - Community based testing
  - ? Self testing
  - ? workplaces ? key populations ? schools
Self testing

RESEARCH ARTICLE
‘I Know that I Do Have HIV but Nobody Saw Me’: Oral HIV Self-Testing in an Informal Settlement in South Africa

Guillermo Martínez Pérez1*, Vivian Cox2, Tom Ellman3, Ann Moore2, Gabriela Patten2, Amir Shroufi1, Kathryn Stinson2, Gilles Van Cutsem1, Maryrene Ibeto1*
Major Programmatic Outcome: ART Initiation ≤ 90 Days

377 ART eligible patients enrolled

190 standard patients
- 54 did not initiate ≤ 90 days (28%)
- 2 initiated ≤ 180 days
- 52 did not initiate

136 initiated ≤ 90 days (72%)

187 rapid patients
- 5 did not initiate ≤ 90 days (3%)
- 1 initiated ≤ 180 days
- 4 did not initiate (all lost during TB workup)

182 initiated ≤ 90 days (97%)

Risk difference 25% (95% CI 19 to 33%)
Crude relative risk 1.36 (95% CI 1.24 to 1.49)
Conclusions

It is possible to initiate nearly all eligible patients on ART (75% on the same day) and improve overall health outcomes.

36% ART Initiation

26% Viral Suppression
## Effect Modification by Site and by Age and Sex

<table>
<thead>
<tr>
<th>Initiated ≤ 90 days and retained and suppressed by 10 months</th>
<th>Standard arm</th>
<th>Rapid arm</th>
<th>Crude relative risk [95% CI]*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full sample</td>
<td>96/190 (51%)</td>
<td>119/187 (64%)</td>
<td>1.26 (1.05-1.50)</td>
</tr>
<tr>
<td><strong>Site</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary health clinic</td>
<td>46 (43%)</td>
<td>67 (64%)</td>
<td><strong>1.50 (1.15-1.95)</strong></td>
</tr>
<tr>
<td>Hospital-based HIV clinic</td>
<td>50 (61%)</td>
<td>52 (63%)</td>
<td>1.04 (0.82-1.32)</td>
</tr>
<tr>
<td><strong>Age and sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male &lt; 35</td>
<td>12/32 (38%)</td>
<td>32/45 (71%)</td>
<td><strong>1.90 (1.17-3.08)</strong></td>
</tr>
<tr>
<td>Male ≥ 35</td>
<td>31/53 (58%)</td>
<td>28/45 (62%)</td>
<td>1.06 (0.77-1.47)</td>
</tr>
<tr>
<td>Female &lt; 35</td>
<td>28/60 (47%)</td>
<td>32/53 (60%)</td>
<td>1.29 (0.91-1.83)</td>
</tr>
<tr>
<td>Female ≥ 35</td>
<td>25/45 (56%)</td>
<td>27/44 (61%)</td>
<td>1.10 (0.78-1.57)</td>
</tr>
</tbody>
</table>

*Effect observed in study; p-values for interaction terms for absolute risk differences were not significant*
Implementation of community-based adherence clubs for stable antiretroviral therapy patients in Cape Town, South Africa

Anna Grimsrud¹, Joseph Sharp¹, Cathy Kalombo⁹, Linda-Gail Bekker²,⁴ and Landon Myer⁷

Community-Based Adherence Clubs for the Management of Stable Antiretroviral Therapy Patients in Cape Town, South Africa: A Cohort Study

Anna Grimsrud, MPH, PhD,* Maria Lesosky, PhD,†† Cathy Kalombo, MBChB,‡ Lida-Gail Bekker, PhD,§§ and Landon Myer, PhD*
VL monitoring: a rate-limiting step

National policy on routine viral load for monitoring antiretroviral therapy and level of implementation for adults and adolescents (situation as of July 2016)

The evolving HIV treatment paradigm


HIV-1 discovered

ZDV monotherapy

ZDV/3TC

Triple-Drug Therapy

Single-Tablet Regimens

Long Acting Injectable?

The Integrase Era

3TC=lamivudine; ZDV=zidovudine

Joe Eron
Plenty in the pipelines...

- **Integrase Inhibitors**
  - Dolutegravir (approved)
  - GS-9883 (Phase III)

- **N(t)RTI**
  - TAF (approved)
  - EFdA (4'-ethynyl-2-fluoro-2'-deoxyadenosine) (Phase I-II)

- **NNRTI**
  - Doravirine (Phase III)

- **Maturation Inhibitors**
  - BMS 955176 (Phase II)

- **Attachment inhibitors**
  - BMS 663068 -> 626529 (Phase III)

- **Broadly neutralizing monoclonal antibodies**

New Targets: e.g. LEDGF, combination entry, additional maturation sites, HIV-1 RNA processing
Antiretroviral Therapy: The Next Generation?

- Implantable (and removable) combination antiretrovirals

- Vectored delivery of combinations of antibody-based therapy or protein based therapy

*Recombinant AAV (rAAV) features*

- Transfects both dividing & non-dividing cells
- No host-genome integration & Stable Expression
- Ease to produce at high viral titer (Helper Free)
- Do not elicit significant immune response in vivo
- Can be used for in vivo gene deliveries

And nanoparticles
Conclusion

• Exciting new drug innovations
• Dolutegravir and new integrase inhibitors likely to revolutionise treatment for patients
• TAF may help dramatically reduce prices
• Difficult to predict for second-line, but so many options!
• Injectables/implantables – exciting medium term
• ART alone is not enough
Acknowledgements
Save the Date

XXVI INTERNATIONAL WORKSHOP ON HIV DRUG RESISTANCE AND TREATMENT STRATEGIES
6 - 8 November 2017 Johannesburg, South Africa

6 – 8 November 2017
26th International Workshop on HIV Drug Resistance and Treatment Strategies
Johannesburg, South Africa
www.HIVresistance2017.co.za

24 – 27 October 2018
4th Southern African HIV Clinicians Society Conference
Johannesburg, South Africa
www.sahivsoc2018.co.za