What next?

ART new drugs, new studies

Francois Venter

Wits Reproductive Health & HIV Institute
Caveats

• Adult physician – but what interests the adults – soon in paeds
• Drugs identified at CADO and a few others
A widening menu of ARV use for treatment and prevention

Despite immediate increase from currently 17 million to 26 million people eligible for ART, the preventive effect will lead to decrease of number eligible after 2020.
The target product profile for optimal ARV candidates was defined at CADO in June 2010.

**Tolerability**
- Low incidence of side effects and toxicities
- Relationship to adherence

**Resistance**
- High barrier to resistance
- Forgiveness
- Context of regimen

**Convenience**
- Once-daily dosing (or less)
- Low pill burden
- No cumbersome testing reqs, Other (no lead-in dosing)
- For regimen eval: same dosing schedule for all drugs

**Special Popns**
- Pregnant women
- HIV/TB co-infected patients
- Children
- Hepatitis B and C

**Cost**
- Cost w/o dose reduction
- Potential cost w/ dose reduction
- Impact of programmatic cost
Think...

• Many HIV testing programmes performing well – issues such as TB and high VL less of an issue

• Pregnancy always an issue (? A separate tablet for men and women who can’t fall pregnant)
So what we got?
## Evolution of WHO ART Guidelines in Adults

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### Earlier initiation
- Earlier initiation
- Simpler treatment
- Less toxic, more robust regimens
- Better monitoring
## Evolution of WHO ART Guidelines in Adults

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- **Less toxic, more robust regimens**
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**HIV/AIDS Department**
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HIV/AIDS Department
With limited resources, a public health approach needs to balance both costs and effectiveness in order to maximize efficiencies.

Drugs that have been prioritized as having clinical superiority have shown dramatic price reductions over short periods of time even since CADO in 2010.

<table>
<thead>
<tr>
<th>Year</th>
<th>EFV</th>
<th>TDF</th>
<th>ATV/r</th>
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<tbody>
<tr>
<td>2006</td>
<td>$250</td>
<td>$250</td>
<td>$400</td>
</tr>
<tr>
<td>2010</td>
<td>$150</td>
<td>$100</td>
<td>$300</td>
</tr>
<tr>
<td>2012</td>
<td>$100</td>
<td>$100</td>
<td>$200</td>
</tr>
</tbody>
</table>

Price reductions:
- EFV: 77%
- TDF: 72%
- ATV/r: 21%
TDF + XTC + EFV

AZT + XTC + PI (lopinavir or atazanavir)

XTC, other nukes

Darunavir Raltegravir Etravirine
Currently available (or near-available) co-formulated antiretroviral agents and regimens

<table>
<thead>
<tr>
<th>Agent</th>
<th>Regimen</th>
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<tr>
<td>D4T/3TC</td>
<td>Dual NRTI</td>
</tr>
<tr>
<td>D4T/3TC/NVP</td>
<td>NNRTI + dual NRTI</td>
</tr>
<tr>
<td>ZDV/3TC</td>
<td>Dual NRTI</td>
</tr>
<tr>
<td>ZDV/3TC/ABC</td>
<td>Triple NRTI</td>
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<tr>
<td>LPV/RTV</td>
<td>Boosted PI</td>
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<tr>
<td>ATV/RTV</td>
<td>Boosted PI</td>
</tr>
<tr>
<td>DTG/ABC/3TC</td>
<td>INSTI + dual NNRTI</td>
</tr>
<tr>
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<td>Dual NRTI</td>
</tr>
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</tr>
<tr>
<td>TDF/FTC/EVG/COBI</td>
<td>Dual NRTI + INSTI + booster</td>
</tr>
</tbody>
</table>
ARVS REGISTERED/IN REGISTRATION PROCESS IN SOUTH AFRICA

The Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs/NtRTIs)

- Abacavir
- Didanosine
- Emtricitabine
- Lamivudine
- Stavudine
- Tenofovir
- Zidovudine

The Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

- Efavirenz
- Nevirapine
- Etravirine
- Rilpivirine

- Triomune, Atripla, Tripalvar, Complera

The Protease Inhibitors (PIs)

- Amprenavir
- Atazanavir
- Darunavir
- Indinavir
- Lopinavir
- Ritonavir
- Saquinavir

The Integrase Inhibitors (INSTIs)

- Raltegravir
- Dolutegravir

Fixed-drug combinations

- Combivir, Kivexa, Truvada

The HIV Entry Inhibitors

- Maraviroc
Antiretrovirals in the pipeline

Figure 1: The ARV pipeline contains several important products at late stages of development. Adapted from 2013 i-Base/TAG Pipeline Report and clinical trials.gov P Clayden and D Ripin
Pipeline Report
http://www.pipelinereport.org
Drug optimization

Science evolved: smarter and better HIV treatment options are now available

Pre-HAART Era (Mono/Dual Therapy) vs. HAART Era (Triple Therapy)

- Potency
- Toxicity

1985: Zidovudine
1989: 2 tablets 3 x day
1991: Didanosine
1993: Stavudine
1995: Lamivudine
1997: Enfuvirtide
1999: Atraznavir
2001: AZT/3TC + LPV/r
2003: 3 tablets 2 x day
2005: TDF/FTC/EFV
2007: 1 tablet once day
2011: Etravirine
2013: Dolutegravir
2015: Raltegravir
2017: Maraviroc
2019: Elvitegravir
2021: Darunavir
What is there to fix???
XTC, other nukes

- TDF
- XTC
- EFV
- AZT
- PI (lopinavir or atazanavir)
- Darunavir
- Raltegravir
- Etravirine
Tenofovir has taken over the world!

- Well tolerated, FDCs galore, daily
- Cheap (only alternative that is cheaper is d4T)
- Hep B for free
### Recommended Regimens

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<td>DRV/RTV + TDF/FTC</td>
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### Alternative Regimens

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<td>EVG/COBI/TDF/FTC</td>
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## DHHS Guidelines: 2014 update

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### Recommended Regimens

| NNRTI based | ▪ EFV + \(\text{TDF/FTC or AZT/3TC}\) |

### Alternative Regimens

| NNRTI based | ▪ NVP + \(\text{TDF/FTC or AZT/3TC}\) |
Prescriptions over time

Rationale III: Evolution of d4T phase out in adults (2006-2012)

- **2007 amendment to 2006 WHO guidelines on d4T dose reduction**
- **2010 WHO guidelines recommendation on d4T phase out**
- d4T containing regimens as the most used 1st line regimen in the early years of ART scale up
- Significant reduction in the last years but 1.1 million patients have initiated d4T containing regimens in 2012
Changes in D4T, AZT & TDF use

Evolution in the APIs use in adults (2006-2012)

Between 2 to 4 million people using AZT containing regimen in 2012

WHO AMDS database, 2014 (preliminary data)
Is API production capacity a potential treatment bottleneck?

Situation of API production capacity for TDF and EFV with major API producers (WHO API manufacturer survey, May 2013)

<table>
<thead>
<tr>
<th>Major parameters</th>
<th>TDF</th>
<th>EFV</th>
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<tr>
<td>Number of API producers in 2012</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>API production capacity in 2012 (in metric tons)*</td>
<td>&gt;1,500</td>
<td>&gt;2,210</td>
</tr>
<tr>
<td>Estimated number of patients using regimens containing the API in end of 2012</td>
<td>3,500,000</td>
<td>3,700,000</td>
</tr>
<tr>
<td>Number of patients that could be treated in end of 2012</td>
<td>&gt;13,800,000</td>
<td>&gt;10,000,000</td>
</tr>
</tbody>
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(*) Data from some major manufacturers were not reported.

The manufacturers also mentioned that they are all in the process of increasing capacity.
Renal events in patients receiving TDF

- Complications data from large clinical trials generally reassuring re: safety of TDF

<table>
<thead>
<tr>
<th>Measures of Renal Function</th>
<th>Δ CrCl, mL/min*</th>
<th>Δ GFR, mL/min/1.73M²†</th>
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<tr>
<td><strong>GS 903 (Week 144 data)¹</strong></td>
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</tr>
<tr>
<td>TDF + 3TC + EFV</td>
<td>+2</td>
<td>-2</td>
</tr>
<tr>
<td>d4T + 3TC + EFV</td>
<td>+7</td>
<td>+9</td>
</tr>
<tr>
<td><strong>GS 934 (Week 48 data)²</strong></td>
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</tr>
<tr>
<td>TDF + FTC + EFV</td>
<td>-1</td>
<td>&lt; -1</td>
</tr>
<tr>
<td>ZDV/3TC + EFV</td>
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<td>&lt; -1</td>
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*CrCl calculated by Cockcroft-Gault formula;
†GFR calculated by Modification of Diet in Renal Disease formula.

Several studies suggesting a decrease in Creat clearance over time... and bone density issue
Renal safety of TDF: Systematic review and meta-analysis

• 17 studies included
• Median sample size was 517 participants
• There was
  – significantly greater loss of kidney function among the TDF recipients, compared with control subjects (mean difference in calculated CrCl, 3.92 mL/min; 95% CI, 2.13–5.70 mL/min)
  – a greater risk of acute renal failure (risk difference, 0.7%; 95% CI, 0.2–1.2)
  – no evidence that TDF-use led to increased risk of severe proteinuria, hypophosphataemia, or fractures
Effect of Baseline Renal Function on Tenofovir-Containing Antiretroviral Therapy Outcomes in Zambia

Lloyd Mulenga,1,2,3 Patrick Musonda,1,5 Albert Mwango,4 Michael J. Vinikoor,1,6 Mary-Ann Davies,7 Aggrey Mweemba,2 Alexandra Calmy,8 Jeffrey S. Stringer,1,6 Olivia Keiser,9 Benjamin H. Chi,1,6 and Gilles Wandeler4,10,11, for IeDEA-Southern Africa
Crude change in renal function during ART, by baseline renal function and treatment group

No renal impairment

Mild renal impairment

Moderate renal impairment

Severe renal impairment

Alternatives?

• AZT? More expensive, more toxic, low dose study in progress (200mg vs 300mg bd)
• ABC? Possible – limited by HLA testing, cost
• d4T – low dose study in progress (20mg bd vs TDF), anticipated results 2016; TDF cost has dropped, may have role in niche, fall-back, PEP
• Tenofovir alafenamide (TAF) and TDF-CHAI
Figure 9: The Tenofovir Chemical Family

The Tenofovir Family

TDF: Tenofovir Disoproxil Fumarate
TNF-ME: Monomer of tenofovir
TDF: tenofovir

dATP
Tenofovir alafenamide

• Better safety profile than TDF (10 or 25mg vs 300mg).
• Preliminary results promising – will it simply replace TDF? Less API, less toxicity (?co-formulations – estimated availability to LMIC 2020)
• TDF analogue – CHAI – 200mg vs 300mg: may be available
What next on TDF?

- d4T study will part-answer bone and renal worries; otherwise, just wait
- TAF likely to replace it; TDF-CHAI 200mg
- Lower doses AZT, d4T; ABC, other drugs unlikely to displace it
XTC, other nukes

- TDF
- XTC
- EFV

- AZT
- XTC
- PI (lopinavir or atazanavir)

- Darunavir
- Raltegravir
- Etravirine
Efavirenz

- Daily, cheap, co-formulated, huge experience base, TB (and most everything else)-friendly
- EFV side effects predictable, treatable, substitutions easy
- Everyone pretty happy re teratogenicity
- Etravirine – doesn’t address CNS side effects
- Do we chance on new drugs?

---

A randomized crossover study to compare efavirenz and etravirine treatment

BUT...

- Rash, hepatitis, gynaecomastia, lipids
- So they did ENCORE (Lancet 2013)– 400mg vs 600mg (?200mg to be done)
ENCORE-1 Trial: TDF/FTC + EFV 400mg or 600mg OD
HIV RNA <200 copies/mL at Week 48

Non-completer equals failure (FDA method)

Main ITT analysis
Outcome at Week 48

% HIV RNA <50, c/mL
Week 48

EFV400
EFV600
EFV400
EFV600

90.0%
86.0%
94.0%
92.0%

n=321
n=309
n=321
n=309

Puls et al. 7th IAS, Kuala Lumpur, July 2013 Abstract WELBB01
## ENCORE-1: drug-related adverse events

<table>
<thead>
<tr>
<th></th>
<th>EFV400 N=321</th>
<th>EFV600 N=309</th>
<th>Difference (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%) patients reporting AE</td>
<td>286 (89.1)</td>
<td>273 (88.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number (%) patients with study drug related AE</td>
<td>118 (36.8)</td>
<td>146 (47.2)</td>
<td>-10.5% (-18.2, -2.8)</td>
<td>0.008*</td>
</tr>
<tr>
<td>Number (%) patients stopping drug due to related AE</td>
<td>6 (1.9)</td>
<td>18 (5.8)</td>
<td>-3.96 (-6.96, -0.95)</td>
<td>0.010*</td>
</tr>
</tbody>
</table>

Puls et al. 7th IAS, Kuala Lumpur, July 2013 Abstract WELBB01
Issues with the EFV 400mg dose

If another drug interaction lowers EFV exposures further, could this compromise the efficacy of efavirenz?

- Pregnancy
- Rifampicin
Alternatives...

- Integrase inhibitors
- Rilprivine
What about: Dolutegravir

- Wunderkind of the moment
- 50 mg once-daily (in naïve patients)
- Very good efficacy
- Minimal toxicity
- Pregnancy category B
- Superior to EFV at 48 weeks in naïve patients—SINGLE study (compared ABC/3TC/DTG with TDF/FTC/EFV.) – but safer, not virologically better
- Potential to be low cost and coformulated
- Some concerns about resistance claims, creat clearance

FDA press statement. August 2013
Elvitegravir

- Integrase inhibitor
- Requires boosting
  - ritonavir
  - Cobicistat
- Co-formulated with a booster, TDF and FTC
- Renal monitoring, drug interactions

- QUAD-Stribild
Raltegravir

• Integrase inhibitor, very well tolerated, price dropping
• Very heavily studied
• , ?can do once daily ?TB friendly
• For this and the other integrase inhibitors – what do we do in 3rd line? New 2nd line?
What about: Rilpivirine

- Novel NNRTI, low mg dose, possible very low cost
- Single day dosage
- Co-formulated with TDF and FTC as Complera
- Not OK with TB, high VL
TDF + XTC + EFV

AZT + XTC + PI (lopinavir or atazanavir)

XTC, other nukes

Darunavir, Raltegravir, Etravirine
AZT

• Current low dose study in progress – but in first line
• ???any role for AZT in future???
TDF + XTC + EFV

AZT + XTC + PI (lopinavir or atazanavir)

XTC, other nukes:
Darunavir, Raltegravir, Etravirine
Darunavir in 2nd line

- ‘Best PI’ – better side effects
- If we get the dose down from 800/100...
- ? 600/100 ?400/100 – lower cost, less side effects
- BUT – will the virological potency be maintained?
- Studies planned
(Short term) future dream?

- (photo credit John Mellors)
Pill "A" to Pill "B" – two single tablet regimens?

- Pill "A"  
  TDF/3TC/EFV400  
  $100

- Pill "B"  
  DRV400/r/DTG  
  $250

- Two pills, used in sequence
- Simple treatment rule – task shifting
- No overlapping drug resistance
- Mass generic production
- Low cost: $100 and $250 per person-year
What about the children?

- Granules and sprinkles – lpv/rit, raltegravir, others
- Low dose d4T planned – ABC/TDF concerns
<table>
<thead>
<tr>
<th>FDC</th>
<th>Doses</th>
<th>Status and comments</th>
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</thead>
<tbody>
<tr>
<td>AZT/3TC/NVP</td>
<td>60/30/50 mg</td>
<td>Available</td>
</tr>
<tr>
<td>ABC/3TC/NVP</td>
<td>60/30/50 mg</td>
<td>Alternate 1st line.</td>
</tr>
<tr>
<td>ABC/3TC/EFV</td>
<td>120/60/100 mg</td>
<td>Preferred 1st line &gt;3 to 10 years</td>
</tr>
<tr>
<td>TDF/3TC/EFV</td>
<td>75/75/150 mg</td>
<td>Preferred 1st line &gt;10 years</td>
</tr>
<tr>
<td>AZT/3TC/LPV/r</td>
<td>30/15/40/10 mg</td>
<td>Preferred 1st line &lt;3 years. Preferred second line &gt;3 years.</td>
</tr>
<tr>
<td>ABC/3TC/3TC/LPV/r</td>
<td>30/15/40/10 mg</td>
<td>Preferred 1st line &lt;3 years.</td>
</tr>
<tr>
<td>Trial</td>
<td>New drug</td>
<td>Comparator</td>
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<tr>
<td>------------</td>
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<td>------------</td>
</tr>
<tr>
<td>STARTMRK</td>
<td>raltegravir</td>
<td>efavirenz</td>
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<tr>
<td>Single</td>
<td>dolutegravir</td>
<td>efavirenz</td>
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<tr>
<td>Spring-2</td>
<td>dolutegravir</td>
<td>raltegravir</td>
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<tr>
<td>Flamingo</td>
<td>dolutegravir</td>
<td>darunavir/r</td>
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<tr>
<td>Gilead 102</td>
<td>elvitegravir</td>
<td>efavirenz</td>
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<tr>
<td>Gilead 103</td>
<td>elvitegravir</td>
<td>atazanavir/r</td>
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<tr>
<td>ECHO</td>
<td>rilpivirine</td>
<td>efavirenz</td>
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<tr>
<td>Thrive</td>
<td>rilpivirine</td>
<td>efavirenz</td>
</tr>
<tr>
<td>STaR</td>
<td>rilpivirine</td>
<td>efavirenz</td>
</tr>
</tbody>
</table>

Thanks Polly Clayden, adapted from Sharon Walmsley
Conclusions

• New drugs likely to be in play in our area
• Big changes likely in second line
• EFV 600mg - ?if will be displaced
SAVE THE DATE
24 – 27 SEPTEMBER 2014

- Excellent local and international speakers
- Lively debates
- Skills building sessions
- Presentations on the latest on treatment, prevention, basic science and ethics to mention a few

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