Antiretroviral treatment optimisation

Polly Clayden
HIV i-Base

Cape Town, 26 September 2014
Science evolved: smarter and better HIV treatment options are now available.
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 clinicaltrials.gov P Clayden and D Ripin.
The target product profile (TPP) 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
CADO-2: 10 year objectives

Naive patients

First-line

TAF/3TC/DTG

VF

Second-line

DRV/r + RPV or 2NRTIs

Patients currently on TDF/3TC/EFV or NRTI/NNRTIs

VF

DRV/r + DTG

New fixed dose combinations (FDCs) or single tablet regimens (STRs)
Single tablet regimens – target costs per person-year

- TAF/3TC/DTG $50
- TAF/3TC/EFV 400 $70
- DRV/r/DTG $250
Treatment optimisation trials – main objectives

- Evaluate long-term real life efficacy of first-line TAF/3TC/DTG vs TAF/3TC/EFV (including switch to second-line treatment)
- Establish new 400/100 mg OD dose of DRV/r (second-line)
- Establish DRV/r + DTG as single-tablet for second-line treatment
Efavirenz

- Many desirable characteristics for the TPP
- CNS side effects can leading to drug discontinuation
- ENCORE1 - 400 mg EFV non-inferior to 600 mg (standard dose) in treatment-naive patients at 48 weeks
  - Approx 3% fewer discontinuations in the 400 mg arm due to EFV-related side effects (rash, CNS, GI but not psychiatric)
  - 10% fewer patients reported these side effects.
- Comparable efficacy was achieved at reduced dose. Potential to reduced cost?
- Will the lower dose would be robust in the presence of rifampicin in TB/HIV co-infection? In pregnancy?

Puls R et al. 7th IAS Conference, July 2013
Dolutegravir

- 50 mg once-daily (in naive patients) non-boosted dose
- Very good efficacy
- Minimal toxicity
- Pregnancy category B
- Superior to EFV at 48 weeks in naive patients in phase III trials
- Potential to be low cost and co-formulated
- FDA/EMA approved with a broad indication for 12 years and above

FDA/EMA press statements. 2013
In the phase III trials

• Africans/Asians under-represented

• People with baseline NRTI or NNRTI resistance were not included (up to 10% in Africa/Asia)

• Women under-represented/no pregnant women

• No TB co-infection but there are PK interactions between DTG and TB medications
<table>
<thead>
<tr>
<th>Trial</th>
<th>New drug</th>
<th>Comparator</th>
<th>% women</th>
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<tbody>
<tr>
<td>STARTMRK</td>
<td>raltegravir</td>
<td>efavirenz</td>
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<tr>
<td>Single</td>
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<td>atazanavir/r</td>
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<td>STaR</td>
<td>rilpivirine</td>
<td>efavirenz</td>
<td>7%</td>
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Adapted from Sharon Walmsley
ARIA - dolutegravir in women

• Registrational trials for DTG mostly about 80% men
• ViiV is conducting a multinational phase IIIb study DTG+ABC+3TC versus ATV/r+TDF+FTC in 470 treatment naive women
• Sites in South Africa
• Pregnancy is an exclusion criterion

clinicaltrials.gov identifier:NCT01910402
Pregnancy

DTG 50 mg PK and safety third trimester and post partum in 25 women who become pregnant in DTG/ABC/3TC FDC study

clinicaltrials.gov identifier:NCT02075593
A phase I study in HIV negative volunteers of DTG with rifampicin and with rifabutin suggested that 50 mg twice daily is likely to be required with rifampicin (to overcome UGT1A1/CYP3A induction).

DTG vs EFV, 50 mg DTG twice daily during TB treatment with rifampicin in 125 treatment naive participants 48 weeks

Dooley KE et al. J Acquir Immune Defic Syndr 2013
clinicaltrials.gov identifier: NCT02178592
NAMSAL

N=550 naïve patients

- No baseline resistance testing
- Wide inclusion criteria
- TB co-infection allowed
- Funded by ANRS/co-funding ad
  DTG supply still under discussion
- Starting 4Q2014

First-line

- TDF/3TC/EFV400
- TDF/3TC/DTG
**DoLPHIN**

**Dolutegravir PK in Pregnant HIV+ Women and their Neonates**
University of Liverpool/ Infectious Diseases Institute, Makerere University

- **Rationale:** Pharmacokinetics, interaction profile and efficacy of DTG make it an ideal agent for use in sub-Saharan Africa. Ethical imperative to actively evaluate use in pregnancy

**Study Design:**
- Women presenting 28-36 weeks gestation N= 60
- Randomised 1:1 to DTG vs EFV-based ART (2 NRTI backbone)
- **1° endpoint:** AUC$_{0-8}$ in 3rd trimester and 2 weeks postpartum
- **2° endpoints:** safety & tolerability; proportion with VL <50 at delivery; cord blood and breastfeeding DTG levels

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*Slide Saye Khoo*
Tenofovir disoproxil fumarate

- Tenofovir disoproxil fumarate (TDF) – prodrug of tenofovir
- Preferred as part of first-line treatment everywhere

BUT:
- Potential for long-term renal and bone toxicity
- High milligram dose (300 mg)
- CHAI is developing TDF(hx) – reformulation of the excipients to increase bioavailability - equivalent exposure with 200 mg
Tenofovir alafenamide

• Tenofovir alafenamide (TAF) – new prodrug of tenofovir under investigation
• Hoped to have better safety profile than TDF at lower dose
• More efficient cellular uptake than TDF - produces higher intracellular concentrations of tenofovir
• Lower plasma concentrations relative to TDF giving the potential for reducing the occurrence of toxicities
• Development programme prioritises FDCs – need information on unboosted dose
Darunavir

- PI-naive DRV/r 8:1 ratio (800/100 mg) once daily/treatment experienced patients 6:1 ratio (600/100 mg) twice daily
- Dose-ranging trials of DRV were only conducted in highly experienced patients – none in in PI naive patients
- In POWER 1 and 2 trials, doses ranging from 400/100 once daily to 600/100 twice daily were evaluated
- No correlation between dose and efficacy in people who were sensitive to DRV at baseline
- In PI-naive patients no correlation between PK of DRV and efficacy (two trials, over 1000 patients)
- Potential for 400/100 mg dose?

Katlama C et al. AIDS 2007
Haubrich et al. AIDS 2007
Darunavir

- No heat-stable co-formulated generic versions
- Not preferred second-line 2013 WHO guidelines
South Africa: DRV/r 400/100 OD trial

n=200
HIV RNA <50
on 2NRTI + LPV/r

2 NRTI + LPV/r 400/100 BD

2 NRTI + DRV/r 400/100 OD

Randomised, 48 weeks
South Africa (Francois Venter)
Funding approval phase
France: DRV/r 400/100 OD trial

- n=100
- HIV RNA <50
- on stable treatment
- 2 NRTI + DRV/r 400/100 OD

Single-arm, 48 weeks (Jean-Michel Molina)
Funding: approved by ANRS
Starting in 4Q2014
SL2: pilot study

- Treatment naive
- n=120
- (40 per arm)

Randomised, 48 weeks

Funding approval phase

- TDF/FTC + DRV/r 800/100 OD
- DTG + DRV/r 800/100 OD
- DTG + DRV/r 400/100* OD

* If PK from previous study is favourable
Pill A, Pill B: pivotal study

- NNRTI experienced
- n=1050 (350 per arm)

Randomised, 96 weeks
Africa, Asia

- 2NRTI + PI/r (Control)
- DTG + DRV/r 800/100 OD
- DTG + DRV/r 400/100 OD
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 for Universal Access
Low cost: $100 and $250 per person-year
Thank you

• Andrew Hill
• David Ripin
• Marco Vitoria
• Francois Venter
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