Antiretroviral treatment optimisation

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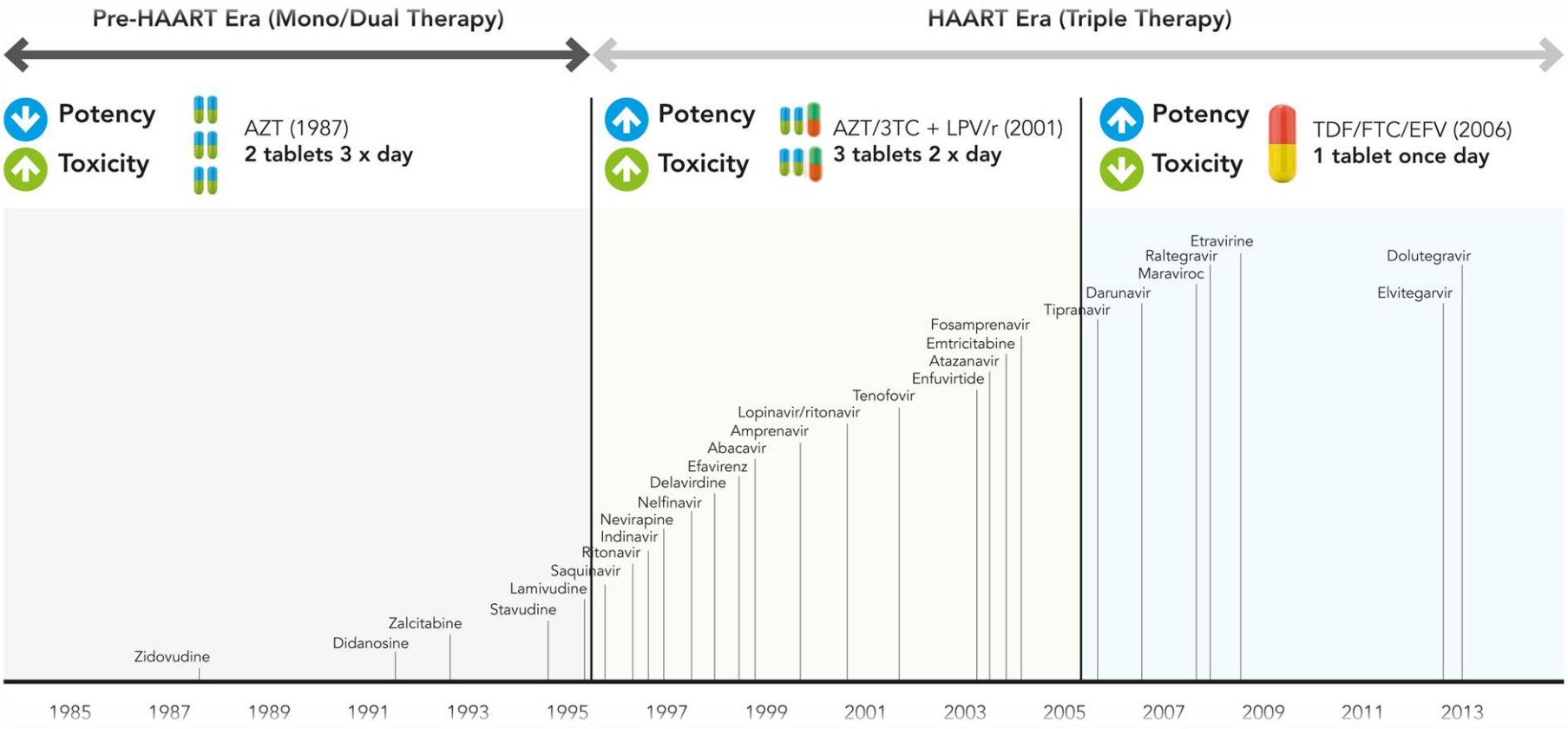
HIV i-Base

Cape Town, 26 September 2014

Antiretroviral optimisation

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



Antiretrovirals in the pipeline

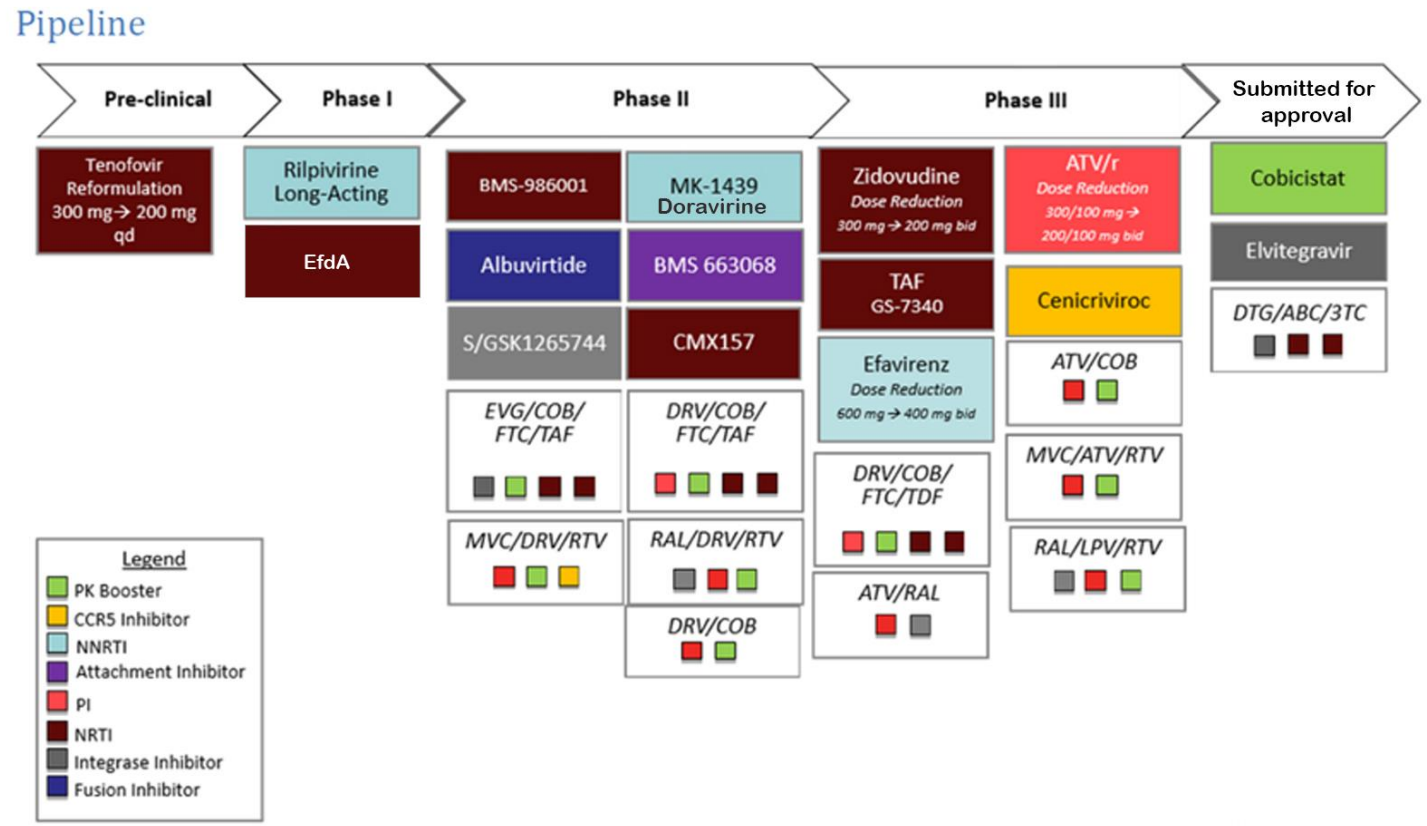
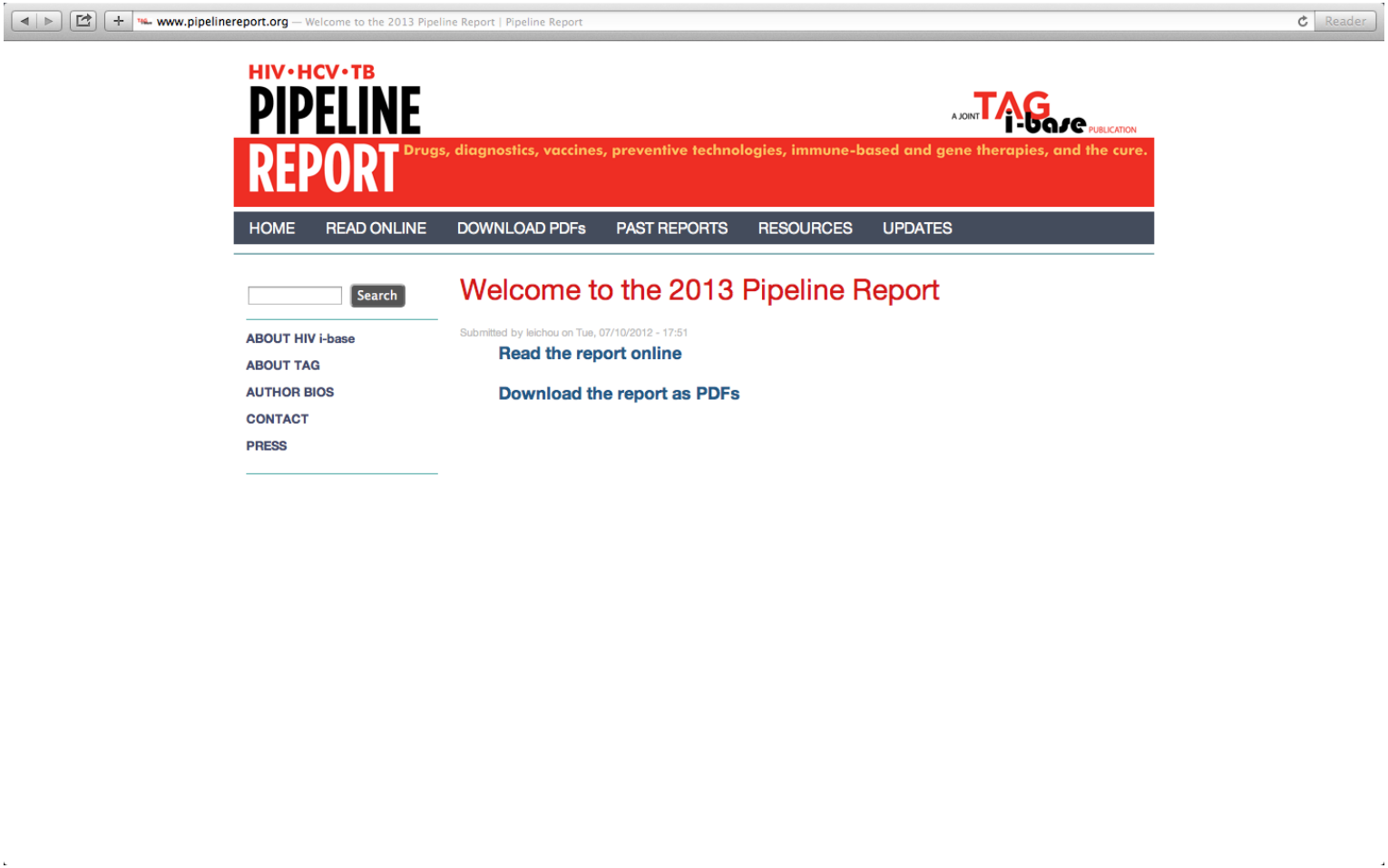


Figure 1: The ARV pipeline contains several important products at late stages of development.
Adapted from 2013 i-Base/TAG Pipeline Report and clinical trials.gov P Clayden and D Ripin

Pipeline Report

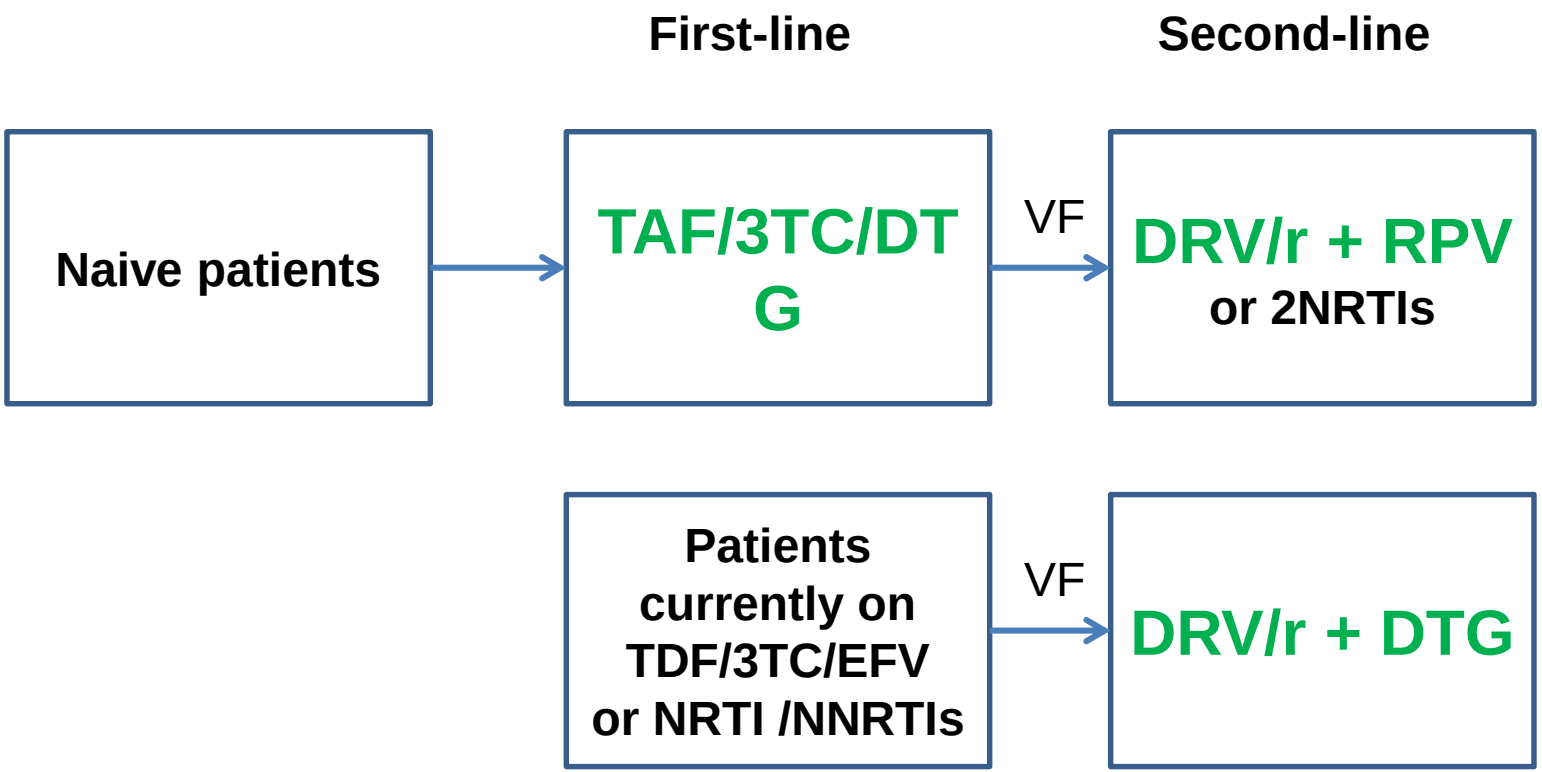
http://www.pipelinereport.org



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



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?

Leutscher PD et al. Scand J Infect Dis. February 2013
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

Walmsley SL et al. N Engl J Med. November 2013
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

Proportion of women in pivotal trials

Trial	New drug	Comparator	% women
STARTMRK	raltegravir	efavirenz	19%
Single	dolutegravir	efavirenz	16%
Spring-2	dolutegravir	raltegravir	15%
Flamingo	dolutegravir	darunavir/r	13%
Gilead 102	elvitegravir	efavirenz	22%
Gilead 103	elvitegravir	atazanavir/r	8%
ECHO	rilpivirine	efavirenz	23%
Thrive	rilpivirine	efavirenz	26%
STaR	rilpivirine	efavirenz	7%

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

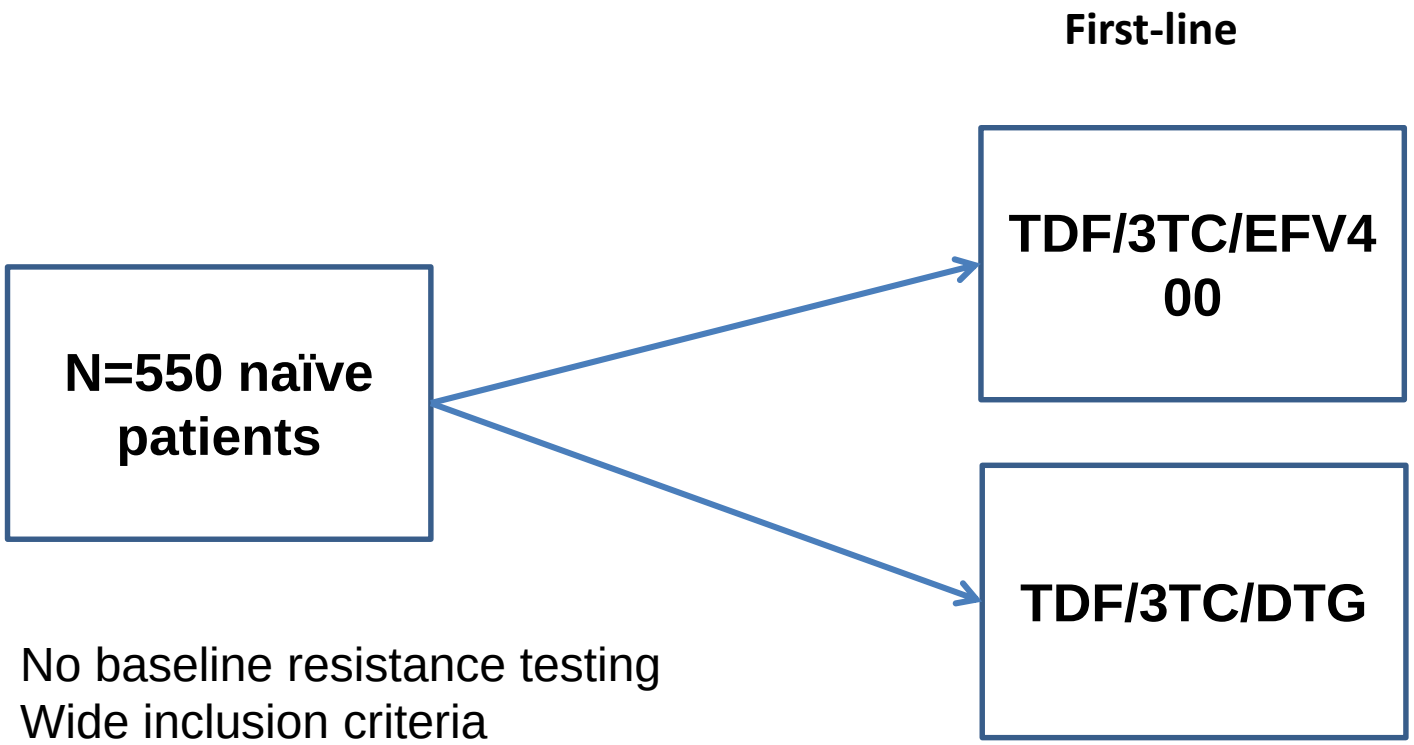
Tuberculosis

- 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



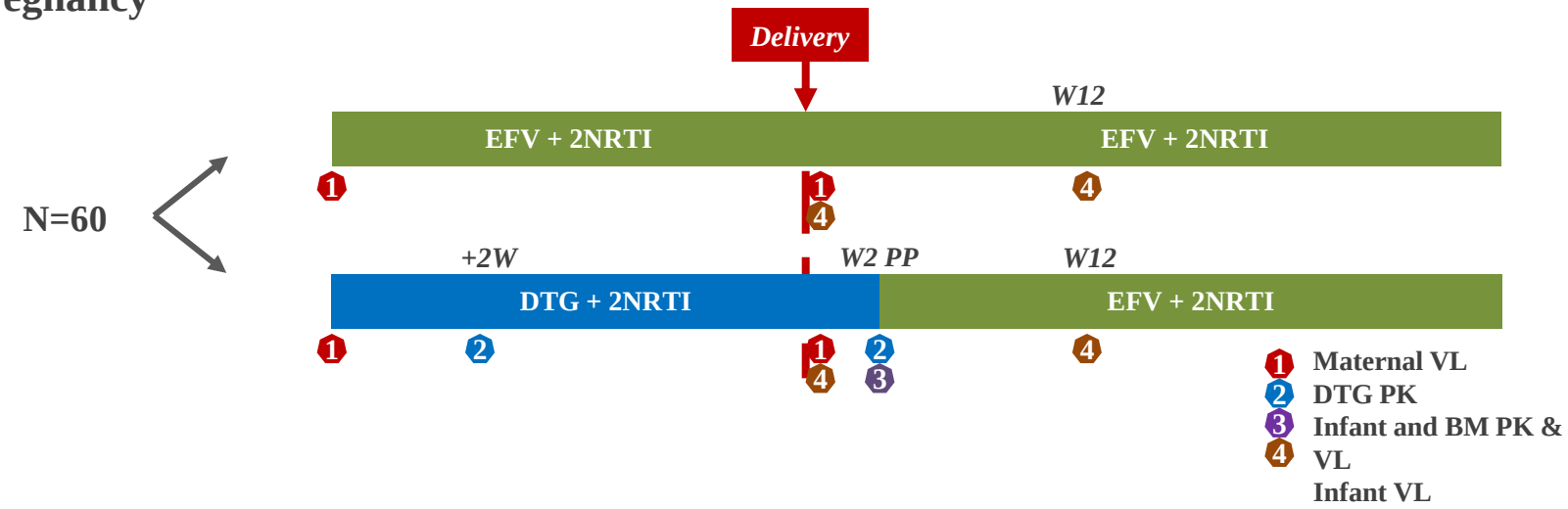
- No baseline resistance testing
- Wide inclusion criteria
- TB co-infection allowed
- Funded by ANRS/co-funding ad
  DTG supply still under discussion
- Starting 4Q2014

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**



- **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 breastmilk DTG levels**

Slide Saye Khoo

Tenofovir disproxil 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

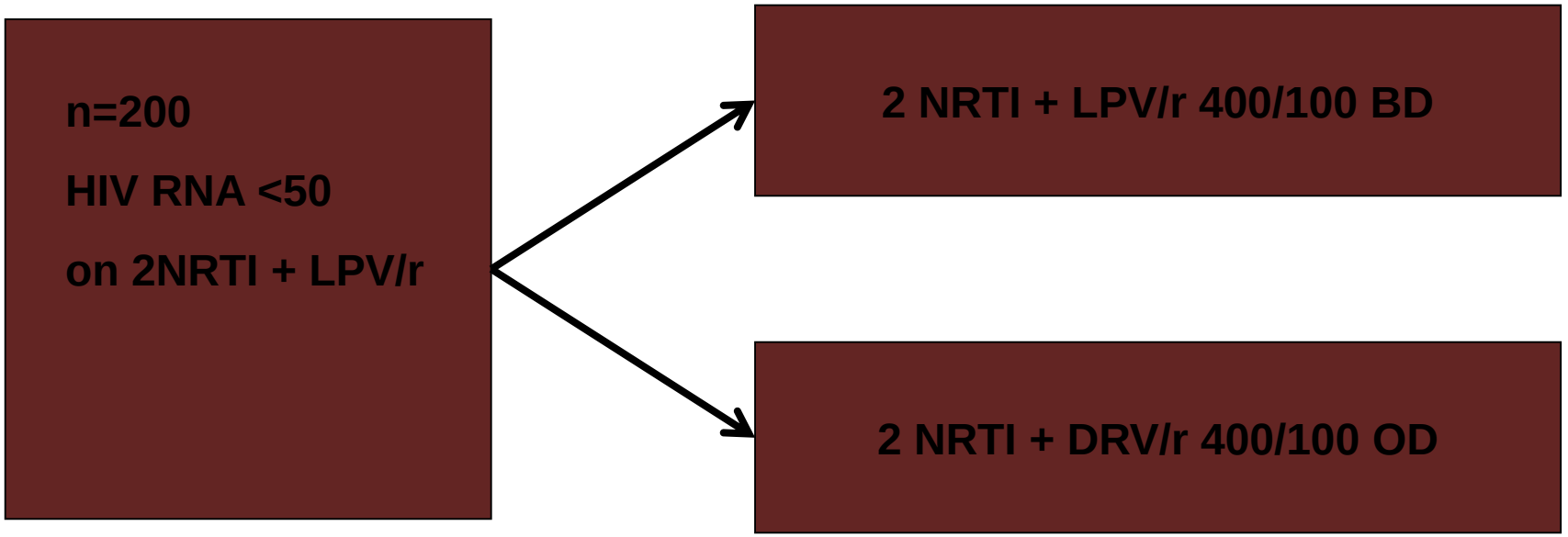
- PI-naive DRV/r 8:1 ratio (800/100 mg) once daily/ treatment experienced patients 6:1 ratio (600/100 mg) twice daily
- Dose-ranging trials of DRV were only conducted in highly experienced patients – none in in PI naive patients
- In POWER 1 and 2 trials, doses ranging from 400/100 once daily to 600/100 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 a. AIDS 2007
Haubrich et al. AIDS 2007

Darunavir

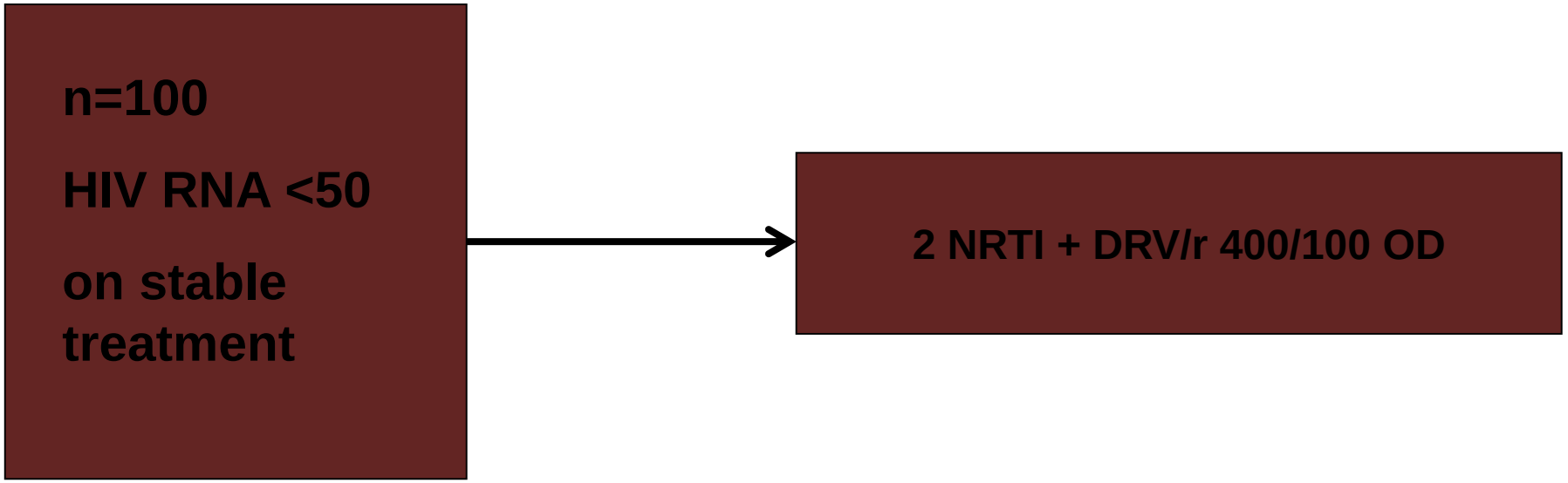
- No heat-stable co-formulated generic versions
- Not preferred second-line 2013 WHO guidelines

South Africa: DRV/r 400/100 OD trial



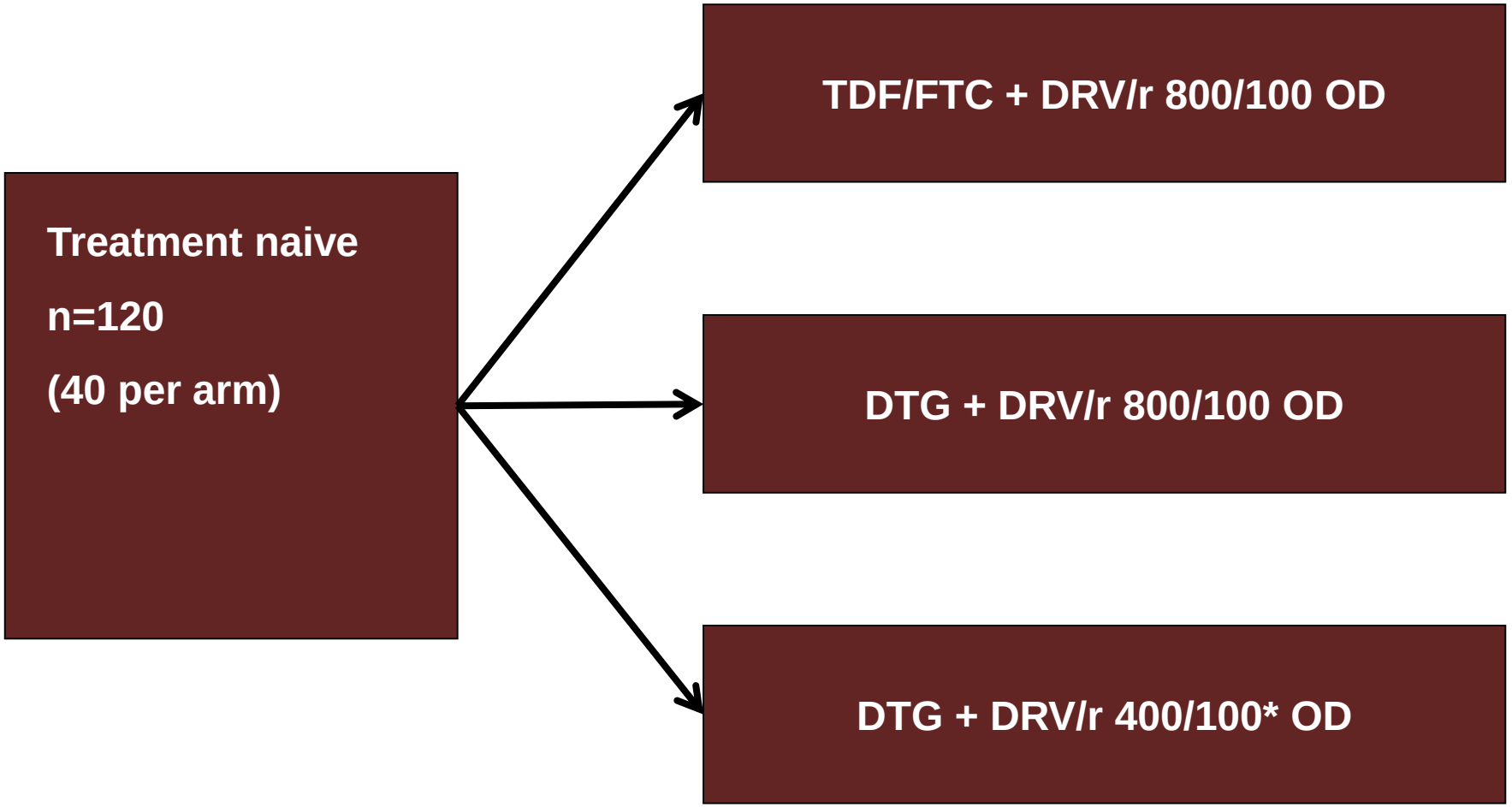
Randomised, 48 weeks
South Africa (Francois Venter)
Funding approval phase

France: DRV/r 400/100 OD trial

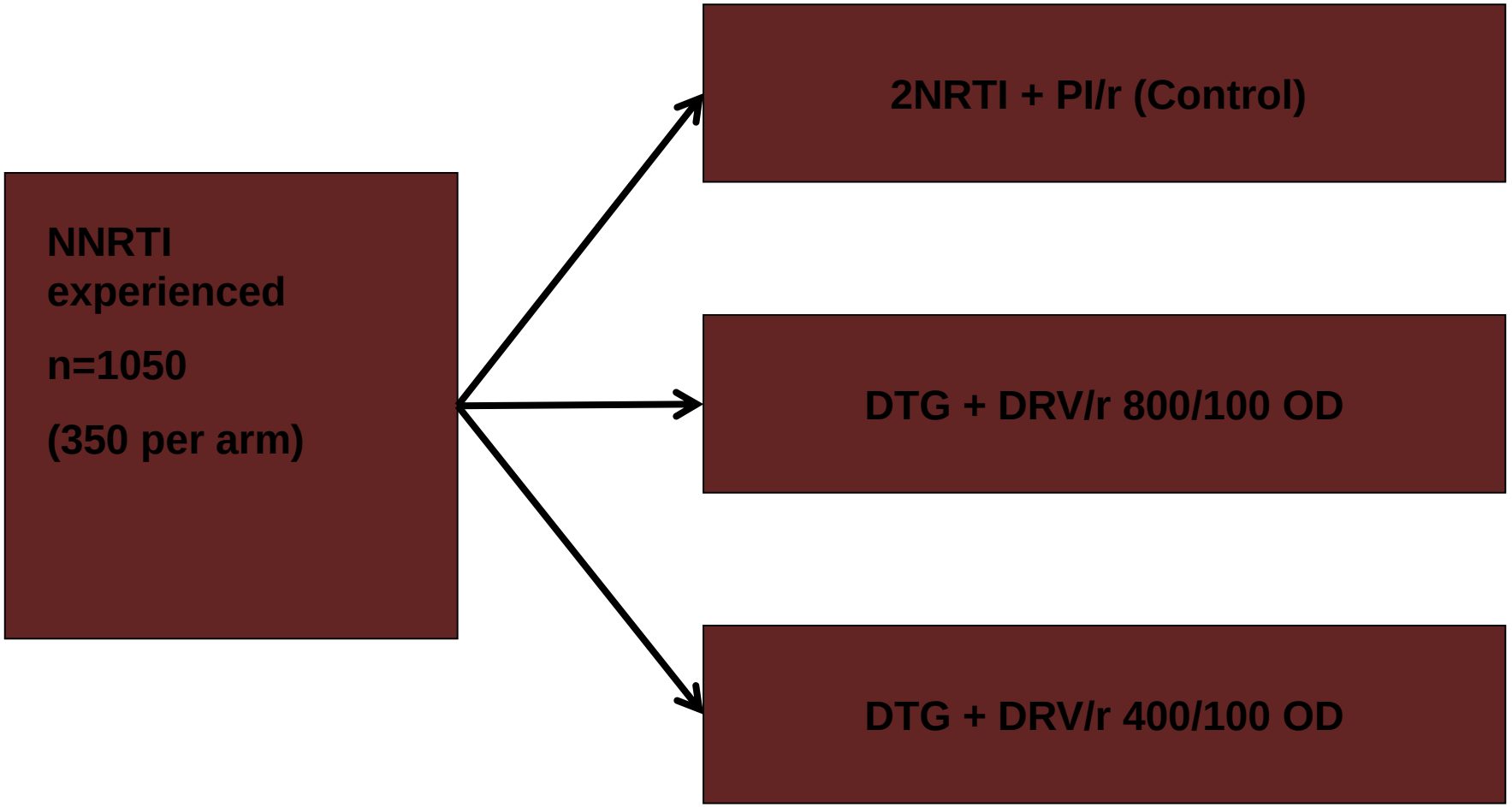


Single-arm, 48 weeks (Jean-Michel Molina)
Funding: approved by ANRS
Starting in 4Q2014

SL2: pilot study



Pill A, Pill B: pivotal study



Randomised, 96 weeks
Africa, Asia

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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