Dose Optimisation of Antiretrovirals: a Feasible Approach to Expand HIV Treatment In Low and Middle Income Countries

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Background

- Out of 34 million people currently infected with HIV/AIDS, over 90% live in low and middle income countries

- Although around 9 million people have been started on antiretroviral treatment in these countries, at least additional 11 million people in low and middle income countries are eligible for treatment but are not receiving it

Background

- The vast majority of the 21 million people infected with HIV, but currently untreated, in developing countries will require antiretrovirals at some time in the future, if they are identified and tested

- In addition, there are an estimated 2.5 million new HIV infections every year

Background

- There is therefore a need to treat 20 million people with antiretrovirals in low or middle income countries within the next 5 years
- Funding is being cut and will be difficult to treat so many patients

Background

- Drug costs are accounting for as much as 60% of antiretroviral treatment program costs in many countries
- Active product ingredient production costs are the biggest driver of antiretroviral drug prices among generic manufacturers
- A given percentage reduction in dosage will translate into a virtually equivalent percentage reduction in drug pricing

Background

Even small reductions in the annual per-patient cost of treatment would lead to important reductions in the global cost of HIV treatment

Table 1. Annual costs of antiretroviral treatment per patient, in US dollars

Antiretroviral (dose)	Dose (mg)	UK price* Originator	Low-income country prices (MSF)	
			Originator	Generic
Nucleoside analogues				
Lamivudine (3TC)	300 OD	3193	79	24 (21–27)
Abacavir (ABC)	600 OD	4237	380	210 (170–256)
Zidovudine (ZDV)	300 b.i.d	3179	–	83 (75–100)
Stavudine (d4T)	30 b.i.d	3146	75	21 (19–30)
Tenofovir (TDF)	350 OD	4872	207	59 (57–73)
Emtricitabine (FTC)	200 OD	3122	–	72 (58–85)
TDF/FTC	300/200 OD	7994	319	98 (93–108)
TDF/3TC	300/300 OD	8065	–	75 (67–88)
ZDV/3TC	300/150 b.i.d	6085	386	103 (95–107)
Nonnucleosides				
Nevirapine	200 b.i.d	3055	219	35 (29–48)
Efavirenz	600 OD	3980	237	56 (44–97)
Etravirine	400 b.i.d	6109	438	–
Protease inhibitors				
Atazanavir/r	300/100 OD	6673	444	304
Lopinavir/r	400/100 b.i.d	5870	368	396 (371–402)
Darunavir/r	600/100 b.i.d	9498	969	1261
Integrase inhibitors				
Raltegravir	400 b.i.d	12363	675	–

b.i.d., twice daily; OD, once daily.
*Converted to US dollars at rate of 1.57.

From: Andrew Hill,
Curr Opin HIV AIDS 2013; 8: 34–40.

Have antiretroviral doses always been the same?

- The dose of zidovudine was reduced from 1,500 mg daily to 600 mg daily
- The dose of didanosine was reduced from 750 mg to 400 mg daily
- The dose of stavudine was reduced from 40 mg to 30 mg twice daily

How is the dose of an antiretroviral chosen?

- During the dose-selection phase of HIV drug development, clinical trials of 30-100 patients per arm are used to evaluate the efficacy and safety of several doses
- In most cases, these trials show similar levels of efficacy between a range of doses
- In these situations, pharmaceutical companies tend to progress with higher doses

Why to choose higher doses?

- To maximise the potential for long-term efficacy and possibly to ensure efficacy even when drug interactions lower the concentration of the new antiretroviral

Drawbacks of higher doses

- Choosing higher doses can compromise patient safety
- The higher doses are more expensive to manufacture

Efavirenz

- The DMP-005 trial of efavirenz was conducted in 1996-1997, was presented at the 5th CROI meeting in Chicago, February 1998, but was never published

- 137 naïve patients were randomized to 24 weeks of treatment with zidovudine plus lamivudine with efavirenz at doses of 200 mg, 400 mg or 600 mg once daily, or matching placebo

Efavirenz DMP-005 trial

- There was no difference in HIV RNA suppression rates between the three doses of efavirenz. These efficacy results were sustained to week 24

- 6 patients withdrew from the efavirenz 600 mg once daily arm owing to adverse events, versus none from the efavirenz 200 mg group

Slow efavirenz metabolizers

- Genetic analysis of patients receiving efavirenz showed that plasma drug levels could be up to three times higher for those with a certain CYP2B6 allelic variant, seen most often in Africans.[1]

- The CYP2B6*6 allele associated with slow efavirenz metabolizer phenotype is e.g. common in Batswana with a prevalence over 30%.[2]

[1] *Haas D et al. AIDS 2004; 18: 2391-400.*

[2] *Gross R et al. J Acquir Immune Defic Syndr 2008; 49: 336-37.*

Efavirenz drug levels

- In an analysis of 255 Dutch patients, females and those with low body weight had significantly higher efavirenz drug levels

Burger D et al. Br J Pharmacol 2006: 61: 148-54

Efavirenz and body weight

- The mean body weight for patients in the DMP-005 trial was higher than would be expected for an Asian or African naïve patient population, where efavirenz drug levels are also expected to be higher

Efavirenz dose reduction in HIV-infected patients

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DOI: 10.1111/j.1468-1293.2011.00964.x
HIV Medicine (2012), 13, 252–253

Clinical setting (Infectious Diseases Outpatient Clinic, University of Verona, Italy)

33 HIV-infected patients treated with two NRTIs plus EFV at reduced dose

Patients – 1

Group 1:

- Patients who reduced efavirenz to 400 mg after 33–119 months (mean 66.4) on full dose and when HIV-RNA was < 50 copies/mL

- EFV was reduced, due to sleep disturbances and on the basis of pharmacokinetic data, to 400 mg in all but one patient (switched to 200 mg)

Patients – 2

Group 2:

- Patients who had a mean 35.4 months (range 21–60) treatment duration and HIV-RNA < 50 copies/mL before efavirenz reduction to 400 mg by physicians in charge due to sleep disturbances and prior to knowing pharmacokinetic data

Patients – 3

Group 3:

- Patients naïve to antiretrovirals, with a pretreatment mean HIV RNA level of 104,529 copies/mL
- 4 patients were started on EFV 400 mg by the physicians in charge, 4 had decided to take only 400 mg and 2 only 200 mg despite being prescribed full dose
- The latter 6 patients informed physicians of their decision after few months on the reduced doses, and then PK analysis was performed

Results – 1

Only one virological failure has been observed thus far in the patients on reduced EFV dose

Results – 2

Characteristics of patients groups and pharmacokinetic data

Patients groups (No.)	Females / Males	Caucasians /Africans	Mean age (range)	Mean CD4 cells before EFV at reduced dose	Mean CD4 cell counts after EFV at reduced dose (months)	Mean (range) EFV Ctrough before reduced dose	Mean (range) EFV Ctrough 6 months after starting reduced dose
1 (16)	1/15	16/0	41 yrs (30–61)	694/µL	753/µL (33–37)	2380.5 ng/mL (1181–6585)	1569.1 ng/mL(193–3934)
2 (7)	2/5	6/1	48 yrs (27–68)	612/µL	722/µL (32–34)	3045.1 ng/mL (913–6872)	1049.1 ng/mL (402–2376)
3 (10)	4/6	10/0	48 yrs (34–67)	300/µL	814/µL (31–113)	N.A.	1579.9 ng/mL (1046–2163) *

*in 2 patients Ctrough was determined 69 and 72 months after starting EFV respectively

Failed patient in group 1

- After 27 months on a reduced efavirenz dose (400 mg), HIV RNA raised to 76 copies/mL
- Efavirenz increased to 600 mg
- HIV RNA < 40 copies/mL two weeks later
- Efavirenz decreased again to 400 mg after 10 months
- HIV RNA continues to be < 40 copies/mL two months later

Relationship between Minimum Effective Concentration and EFV efficacy – 1

- Although 10 patients (in groups 1 and 2) had efavirenz levels below Minimum Effective Concentration after dose reduction, only one virological failure has been observed over an up to 37 months follow-up period

Relationship between Minimum Effective Concentration and EFV efficacy – 2

- Previous studies also questioned relationship between plasma levels and efficacy
- The FOTO study* suggested that long-term maintenance phase of an efavirenz-containing fully suppressive first-line regimen could require lower pharmacological pressure

*Cohen CJ et al. Pilot study of a novel short-cycle antiretroviral treatment Interruption strategy: 48-week results of the five-days-on, two-days-off (FOTO) study. *HIV Clin Trials* 2007; 8: 19-23.

A daily dose of 400 mg efavirenz (EFV) is non-inferior to the standard 600 mg dose: week 48 data from the ENCORE1 study, a randomised, double-blind, placebo controlled, non-inferiority trial

Rebekah Puls for the ENCORE1 Study Group

Kirby Institute

Encore1 study design

A randomized, double-blind, placebo-controlled, non-inferiority clinical trial to compare the safety and efficacy of reduced dose EFV with standard dose EFV plus 2N(t)RTI in ART-naïve HIV-infected individuals over 96 weeks

Patient population

ART-naïve HIV-infected adults with no prior AIDS, plasma HIV-1 RNA (pVL) >1,000 copies/mL, 50 <$CD4^+$ T cells/µL <500, creatinine clearance ≥50 mL/min, no pregnancy or nursing mothers

Randomisation

I. TDF/FTC + 400 mg EFV qd

(2 x 200 mg EFV + 1 x 200 mg matched placebo)

II. TDF/FTC + 600 mg EFV qd

(3 x 200 mg EFV)

1:1 (400mg:600mg), stratified by clinical site and screening pVL

Conclusions

400 mg EFV was non-inferior to 600 mg EFV when combined with Truvada in a treatment-naive, HIV-infected adult population over 48 weeks

Evidence of reduced EFV-related side effects with lower dose

400 mg EFV should be considered for initial ARV treatment

In the ENCORE1 study, a significantly lower number of recipients of the efavirenz 400 mg regimen reported adverse events definitely or probably related to the study drug (118 [37%]) compared with efavirenz 600 mg (146 [47%]); p=0.008 .

Cost savings for Efavirenz 400 mg dose

- Using a 400 mg dose of efavirenz would lower the cost by $16 per person per year in low income countries

- As several million people are likely to use efavirenz in low income countries, this dose reduction could translate to a cost saving of up to $70-130 million over 5 years

Lopinavir-ritonavir

- The Abbott 720 trial evaluated three doses of lopinavir/ritonavir in treatment naïve patients.
- The study population in this Phase 2 trial had a high baseline body weight and was composed predominantly of male Caucasians.

Murphy R et al. ABT-378/ritonavir plus stavudine and lamivudine for the treatment of antiretroviral-naïve adults with HIV-1 infection: 48 week results. *AIDS 2001; 15: 1-9.*

Abbott 720 trial of Lopinavir/Ritonavir

LPV/r Dose (BID)	200/100mg	400/100mg	400/200
N	16	51	33
Baseline CD4	471	335	275
Baseline HIV RNA	4.9	4.9	5.0
Race (% Caucasian)	75%	73%	66%
Gender (% male)	85%	94%	64%
48 Week Efficacy Data (ITT)			
Percent HIV RNA <400	100%	88%	73%
Percent HIV RNA <50	100%	75%	73%
48 week CD4 rise (mean)	+210	+250	+200

Lopinavir-ritonavir

- Strong efficacy of the 200/100 mg twice daily dose seen in PI-naïve patients
- 400/100 mg twice daily dose was chosen for Phase 3 development, in an attempt to target both PI-naïve and PI pre-treated patients with a single uniform dose
- Possibility of using a lower lopinavir/r dose for PI-naïve patients (including those failing first-line NNRTI-based ART in developing countries)

Lopinavir-ritonavir

- If the 200/50 mg twice daily dose could be established as efficacious, the cost of lopinavir/ritonavir could be lowered from $400 to $220 per person-year in African countries

Efficacy of lopinavir/ritonavir reduced dose (200/50 mg twice daily)

- Experience in six HIV-1-infected patients (4 women) on reduced dose of lopinavir/ritonavir followed in the Outpatient Clinic, Infectious Diseases Unit, University of Verona

Lattuada E, Lanzafame M, Vento S. Efficacy of Lopinavir-Ritonavir Reduced Dose in HIV-Infected Patients. *AIDS Patient Care and STDs 2011; 25: 455-56.*

Efficacy of lopinavir/ritonavir reduced dose (200/50 mg twice daily)

TABLE 1. BODY WEIGHT, BMI, HIV RNA LEVEL, AND CD4 CELL COUNT BEFORE STARTING HAART, DURATION OF LPV/R REDUCED DOSE, HIV RNA AT THE TIME OF SWITCH, AND HIV RNA AT LAST VISIT IN THE SIX PATIENTS STUDIED

Patient	*Weight (kg)*	*BMI*	*HIV RNA (copies/mL)*	*CD4⁺ Cells/μL*	*Months on reduced dose of LPV/r*	*HIV RNA (copies/mL) at the time of switch*	*HIV RNA (copies/mL) at the time of last visit*
1	43.0	17	23,659	301	24	<50	<50
2	66.0	23	55,268	156	16	<50	<50
3	77.3	24	116,435	257	18	NA	<50
4	75.2	23	192,540	240	9	<50	<50
5	45.2	19	6,064	388	10	NA	<50
6	56.5	17	78,769	172	7	<50	<50

BMI, body mass index; HAART, highly active antiretroviral therapy; LPV/r, lopinavir/ritonavir; NA, not applicable.

Atazanavir

- Potent protease inhibitor, currently administered at the dose of either 300 mg in combination with 100 mg of ritonavir or, less frequently, 400 mg once daily in treatment-naïve patients

- In HIV-1 infected Thai adults a pilot study of atazanavir/ritonavir at dose of 200/100 mg daily showed the same plasma atazanavir drug levels as in Caucasian patients given 300/100 mg daily of atazanavir/ritonavir*

*Avihingsanon A et al. *Clin Pharmacol Ther 2009 ;85: 402-08.*

Studies of reduced (optimised) doses of antiretrovirals

Antiretroviral agent	Reference	Method	Doses studied	Outcome	Conclusion
Zidovudine	Volberding et al. 1990	Randomised, double-bind study	1,500 mg daily vs 500 mg daily vs placebo	Progression to AIDS lower in the 500 mg and in the 1,500 mg than in the placebo group	Lower dose showed equal efficacy and improved safety
Stavudine	Hill et al. 2007	Meta-analysis	30 mg twice daily vs 40 mg twice daily	Lower rates of peripheral neuropathy and lipoatrophy with lower dose	Lower dose showed equal efficacy and improved safety
	McComsey et al. 2008	Randomised ,open-label study	20 mg twice daily vs 40 mg twice daily, and 15 mg twice daily vs 30 mg twice daily	Improvement in mitochondrial indices with lower doses	Lower dose showed equal efficacy and improved safety
Efavirenz	Hicks et al. 1998	Double-blind, placebo-controlled phase 2 clinical trial	600 mg vs 400 mg vs 200 mg daily	No difference between the proportion of patients with HIV-RNA <400 copies/mL at 24 weeks for all three doses	Lower doses of efavirenz equally efficacious
	ENCORE 1	Double-blind, placebo-controlled clinical trial	600 mg vs 400 mg daily	Ongoing 96 week study begun in August 2011	N.A.
	Lanzafame et al. 2012	Clinical cohort with pharmacokinetic analysis	400 mg daily	HIV-RNA persistently < 50 copies/mL with improved safety	Viral efficacy with improved safety

Studies of reduced (optimised) doses of antiretrovirals

Antiretroviral agent	Reference	Method	Doses studied	Outcome	Conclusion
Atazanavir	Avihingsanonet al. 2009	Pharmacokinetic analysis of Thai patients	300 mg plus 100 mg of RTV vs 200 mg plus 100 mg of RTV daily	Same efficacy and plasma atazanavir drug levels as seen in Caucasians on 300/100 mg daily	200 mg plus 100 mg of ritonavir dosing sufficient in Thai patients
	Giola et al. 2008	Pharmacokinetic analysis of Caucasian patients	300 mg plus 100 mg of RTV vs 200 mg plus 100 mg of RTV daily	Same efficacy of standard dose of atazanavir (300/100 mg daily)	Reduction of side-effect (hyperbilirubinemia) and persistence of viral control
Darunavir	Lanzafame et al. 2011	Clinical case series with pharmacokinetic analysis	600 mg of darunavir plus 100 mg of ritonavir daily	HIV-RNA persistently < 50 copies/mL	Viral efficacy of lower dose
Lopinavir	Murphy et al. 2001	Prospective, randomised, double-blind trial	400 mg plus 100 mg vs 200 plus 100 mg of RTV	100% of patients on lower dose had suppressed viral load (HIV-RNA < 50 copies/mL) vs 50% on higher dose	Better virological outcome probability related to greater tolerability of lower dose than standard dose
	Hill et al. 2009	Pharmacokinetic meta-analysis	200/50 mg twice daily vs 200/150 mg twice daily vs 400/100 mg twice daily	200/150 mg twice daily dose of lopinavir/ritonavir showed similar lopinavir plasma levels to the standard dose	Higher ritonavir dose can increase plasma concentration of lopinavir
	Ramautarsing et al. 2012	Pharmacokinetic analysis of Thai patients	200/50 mg twice daily	Most Thai patients had inadequate lopinavir plasma concentrations but undetectable HIV-RNA at week 12	Reduced lopinavir and ritonavir doses do not allow adequate lopinavir plasma concentrations
	Lattuada et al. 2011	Clinical case series with pharmacokinetic analysis	200/50 mg twice daily	Viral efficacy at 12 months even though not all patients had adequate lopinavir plasma concentrations	Reduced lopinavir and ritonavir doses allow persistent control of viral replication

Table 3. Ongoing dose-optimization trials

Clinical trial	Sample size	Treatment arms	Inclusion	Countries
ENCORE-1	$n = 572$	TDF/FTC/EFV 400 mg OD TDF/FTC/EFV 600 mg OD	Naive	Worldwide
LASA	$n = 560$	2 NRTI/ATV/r 200/100 mg 2 NRTI/ATV/r 300/100 mg OD	Switch	Thailand
WRHI 001	$n = 1068$	d4T 20 mg b.i.d. + 3TC/EFV TDF + 3TC/EFV	Naive	South Africa Uganda, India

b.i.d., twice daily; OD, once daily; WRHI, Witswatersland Reproductive Health Institute.

From: Andrew Hill,
Curr Opin HIV AIDS 2013; 8: 34–40.

Table 4. Potential cost savings from dose-optimisation trials, for Universal Access

	Current algorithm		Future option		Cost saving	
Costs	Person	Worldwide	Person	Worldwide	Person	Worldwide
First-line treatment	TDF/3TC/EFV		TDF/3TC/EFV 400			
Costs (12 m treated)	$131	$1.57 billion	$115	$1.38 billion	$16	$192 million
Second-line treatment	ZDV/3TC/ATV/r		ATV/r 200/50 + DTG			
Costs (3 m treated)	$407	$1.22 billion	$240	$720 million	$167	$501 million
Total costs/year:		$2.79 billion		$2.10 billion		
Total savings/year:						$693 million

From: Andrew Hill,
Curr Opin HIV AIDS 2013; 8: 34–40.

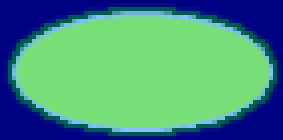
Tenofovir

- Pharmacokinetic parameters of tenofovir are dose proportional and reductions in plasma HIV-1 RNA are dose-related at doses of 75 to 300 mg daily

- It could be worthwhile to test tenofovir at a reduced dose of 225 or 250 mg daily

Pill "A" to Pill "B" – two single tablet regimens?

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



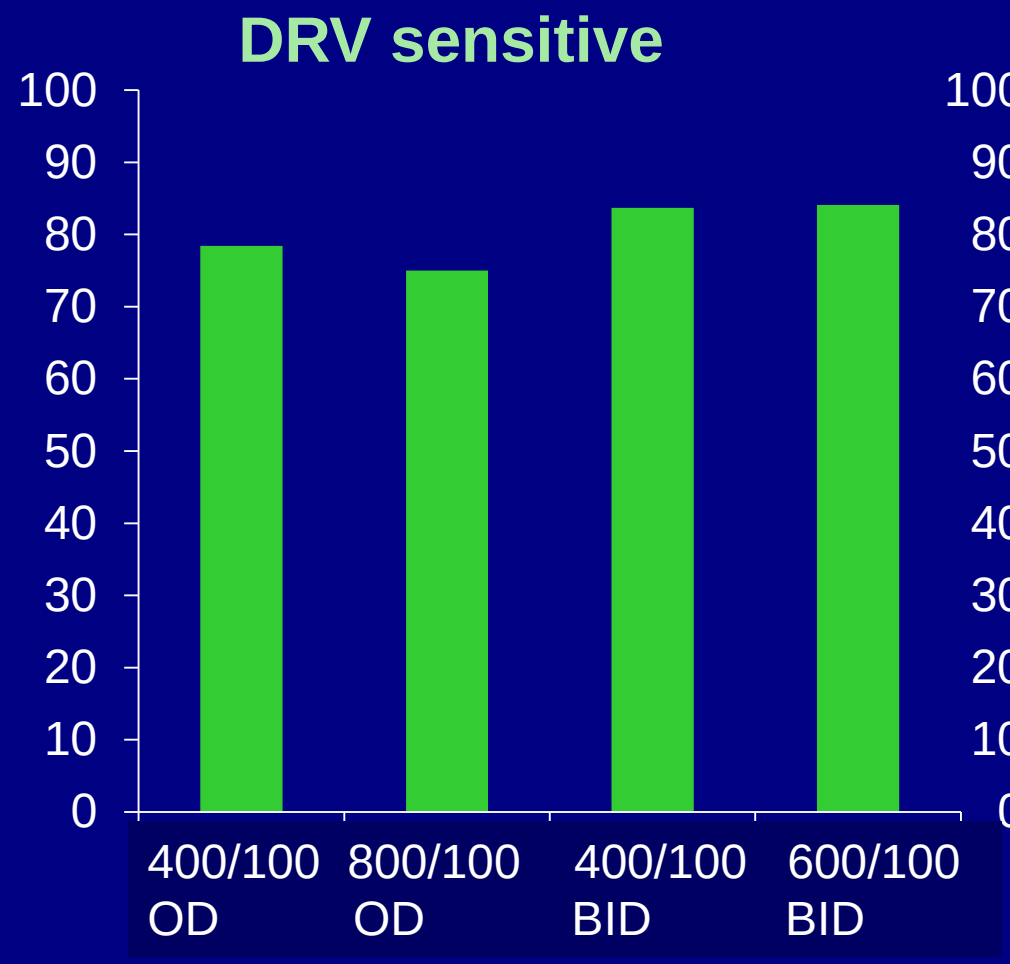
Pill "B" DRV400/r/DTG $250

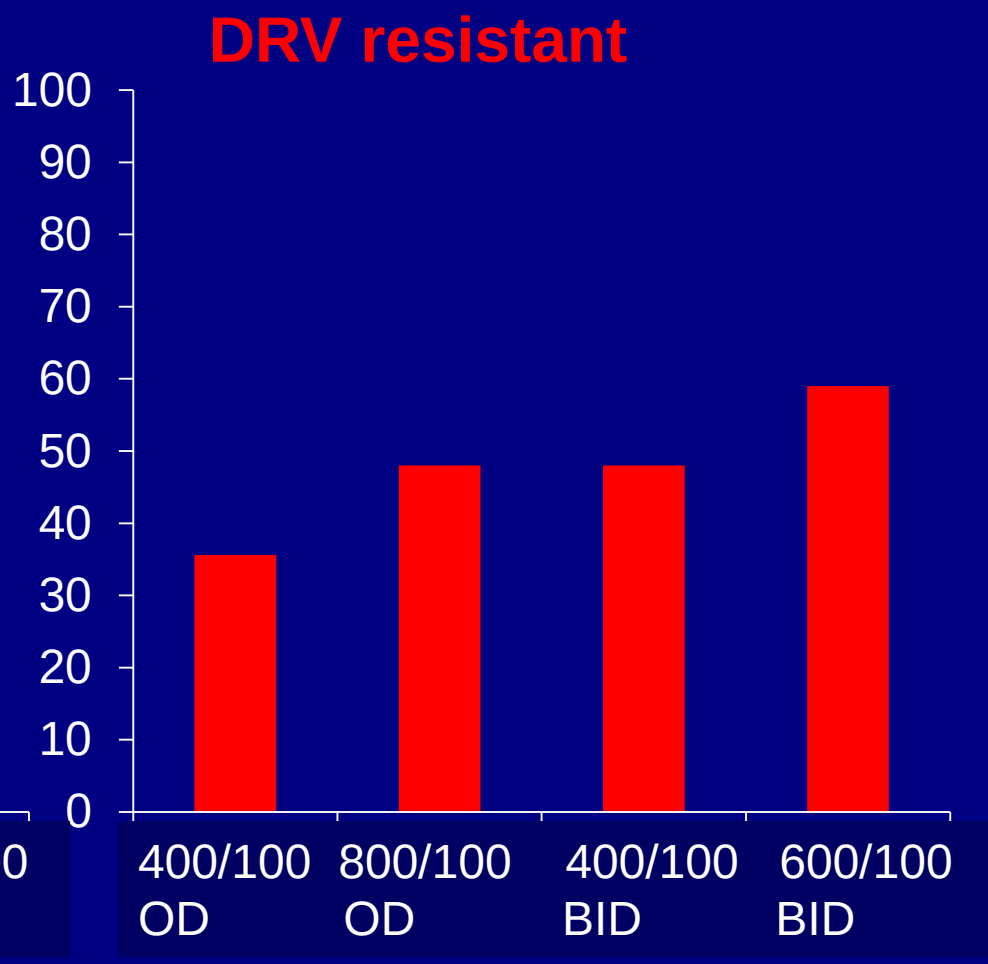
- Two pills, used in sequence
- Simple treatment rule – task shifting
- No overlapping drug resistance
- Mass generic production
- Low cost: $100 and $250 per person-year

DRV/r: can we switch to a 400/100 mg OD dose?

- FDA approved dose of DRV/r is 600/100 mg BID for PI pre-treated patients, 800/100 mg OD for PI naïve patients (ODIN)
- Non-dose proportional PK: Cmin for 400/100 mg OD is only 33% lower than for 800/100 mg OD (POWER 1 and 2 trials)
- In the POWER trials, doses of 400/100 mg OD to 600/100 mg BID were equally effective for patients sensitive to DRV. Dose-response only seen for DRV resistant patients.
- No dose-finding studies have ever been run in PI naïve patients
- Pilot study shows efficacy for 600/100 mg OD, other trials being started

POWER trials: %HIV RNA >1 log reduction at Week 24, by dose and baseline DRV resistance





Katlama C et al AIDS 2007, 21: 395-402
Haubrich et al AIDS 2007, 21: F11-F18

DRV/r 600/100 OD + 2NRTIs: 12 naïve patients

Patient	RNA BL	RNA FU	Time	DRV Cmin
Naïve	85,501	<50	20 months	2866
Naïve	115,853	<50	19 months	3140
Naïve	334,500	<50	10 months	3627
Naïve	154,000	<50	24 months	2553
Naïve	87,350	<50	18 months	3824
Naïve	88,110	<50	19 months	1700
Naïve	34,793	<50	12 months	1268
Naïve	4,526	<50	18 months	3732
Naïve	235,520	<50	20 months	2019
Naïve	7,251	<50	15 months	2818
Naïve	63,244	<50	16 months	4562
Naïve	397,932	<50	5 months	no data

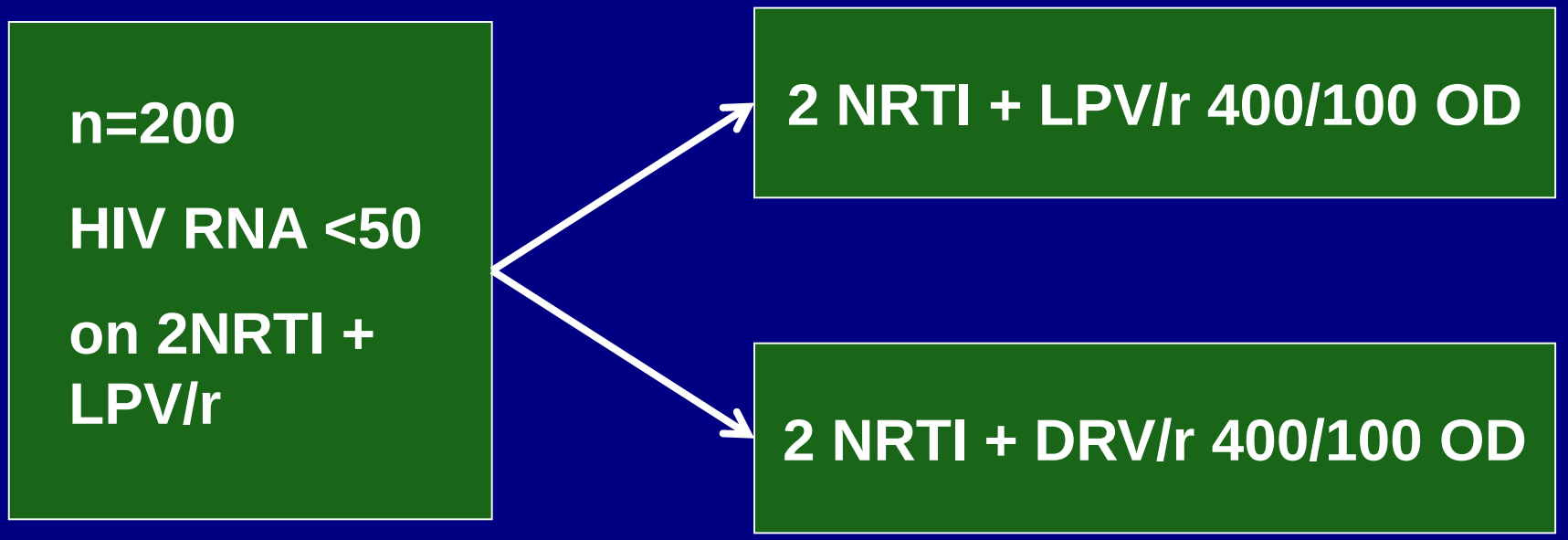
Lanzafame et al, EACS, Brussels 2013 [abstr PE8/11]

DRV/r 600/100 OD+2NRTIs: 7 pre-treated patients

Prior ARV's	RNA BL	RNA FU	Time	DRV Cmin
TDF/FTC/FPV/r	33,250	<50	55 months	2143
ZDV/3TC/TDF	15,226	<50	55 months	4518
TDF/FTC/FPV/r	586	<50	43 months	844
TDF/FTC/ATV/r	8,450	<50	38 months	no data
TDF/FTC/LPV/r	11,426	<50	38 months	no data
TDF/FTC/FPV	119	<50	22 months	no data
TDF/FTC/FPV/r	112	<50	20 months	no data

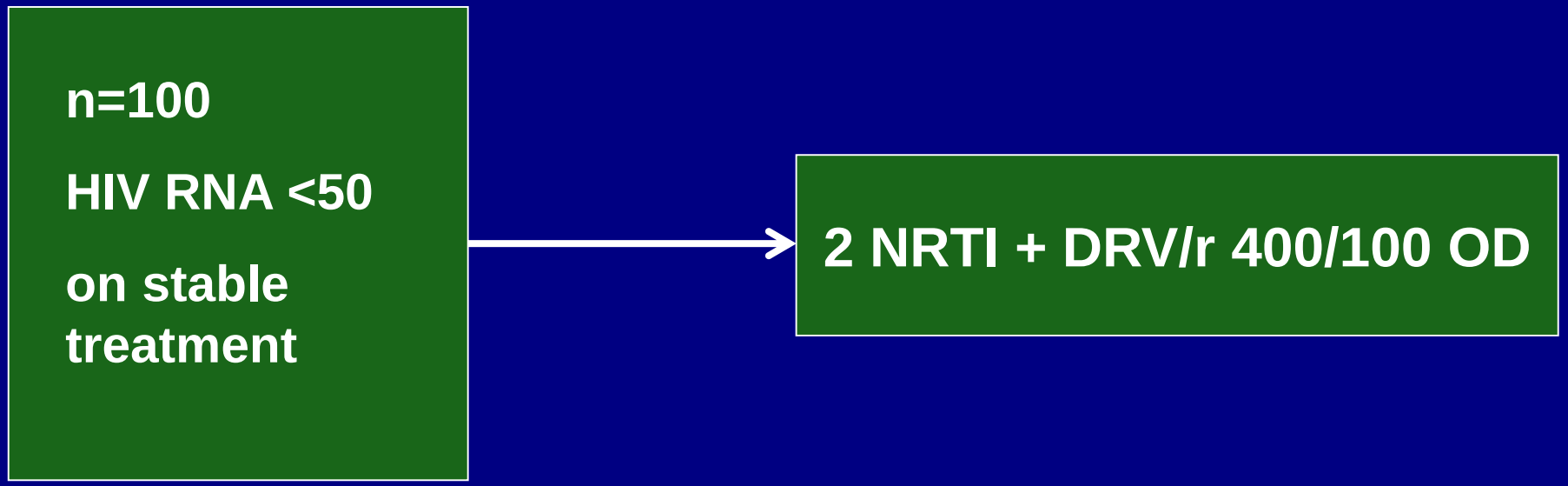
Lanzafame et al, EACS, Brussels 2013 [abstr PE8/11]

South Africa: DRV/r 400/100 OD trial



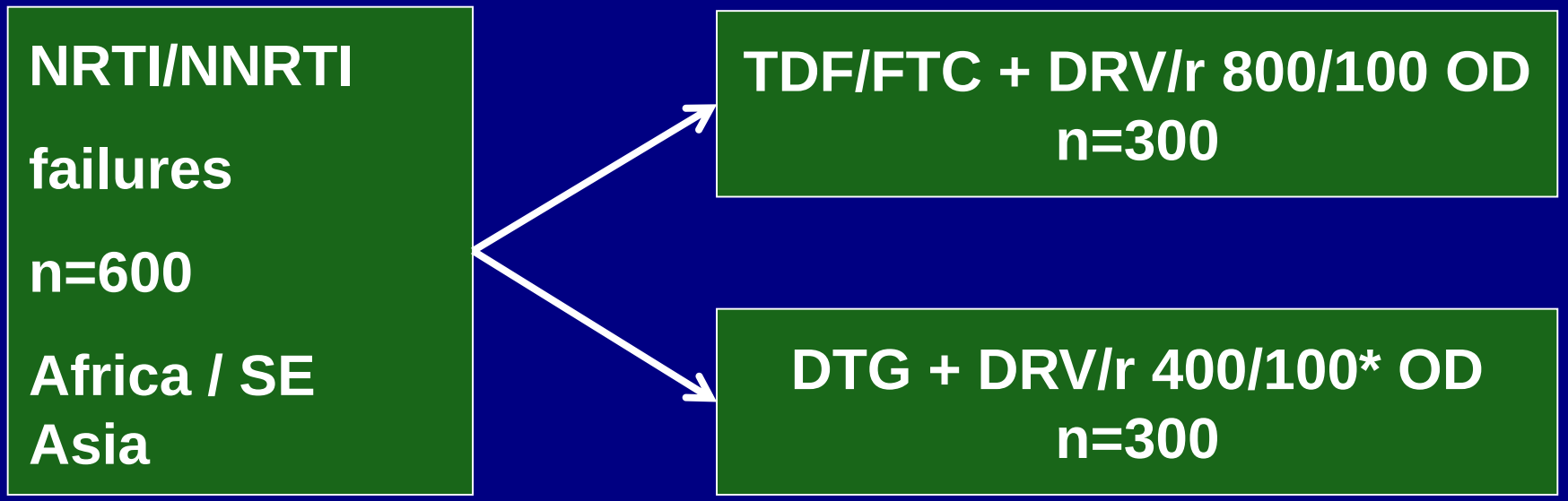
Randomised, 48 weeks
South Africa (Francois Venter)
Funding approval phase

France: DRV/r 400/100 OD trial



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

SL2: Registration study



*or 50mg booster?

Randomised, 96 weeks
Target countries introducing viral load – identify VFs
Powered for non-inferiority: FDA, PEPFAR and WHO approval

Theoretical concerns with lower (optimised) doses of antiretrovirals

- Higher risk of treatment-emergent drug resistance
- Under-exposure leading to virological failure
- Reduced forgiving of nonadherence compared with the standard dose
- Less ability to withstand drug-drug interactions which lower exposures

Advantages of lower (optimised) doses of antiretrovirals

- Reduction in adverse events
- Improved tolerability
- Better quality of life
- Better adherence to treatment

Tropical Medicine and International Health doi:10.1111/tmi.12008

VOLUME 00 NO 00

Editorial

Dose reduction of antiretrovirals: a feasible and testable approach to expand HIV treatment in developing countries

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keywords antiretrovirals, efavirenz, darunavir, lopinavir/ritonavir, stavudine, drug cost

It is urgent to implement reasonably large, well-powered non-inferiority trials comparing lower doses and the currently used ones, and we think that it would be in the best interest even of drug companies and regulatory agencies to propose and fund such trials, as it is ultimately more convenient to access a wider patient population.
These trials should also consider economic data, in order to analyse real life-based models, and would also allow to reconsider currently established relationships between plasma levels and efficacy of antiretrovirals questioned by some studies (Langmann et al. 2002).

Conclusion

Dose optimisation of antiretrovirals should be further explored as a strategy to improve tolerability and decrease costs especially in low and middle income countries