Randomized Comparison of Three Second Line ART Regimens in Africa: the 2 Lady Study

Poster 541LB

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ABSTRACT

Background: Access to antiretroviral therapy (ART) has increased significantly in the last decade: 9.7 million people were on ART at the end of 2012, 2.9% only on second line. WHO recommends the use of a ritonavir boosted Protease Inhibitor (PI/b) containing regimen in patients failing a Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)-based first line, but evidence for the choice of combination is lacking.

Methodology: A 48 weeks, randomized, open label, non-inferiority trial in 3 African cities (Yaoundé - Cameroon, Bobo Dioulasso - Burkina Faso, Dakar - Senegal) comparing efficacy and safety of 3 second line regimens:

Arm A: tenofovir (TDF)/emtricitabine (FTC) + lopinavir/ritonavir (LPV/r), reference arm,
Arm B: abacavir (ABC) + didanosine (ddI) + LPV/r,
Arm C: TDF/FTC + darunavir/ritonavir (DRV/r).
Patients were eligible if above 18 years, failed a first line NNRTI based ART (confirmed HIV-1 RNA≥1 000 copies/mL), showed good adherence (≥80%) and signed informed consent. Efficacy was defined as a HIV-1 RNA <50 copies/mL at 48 weeks and was analysed in both intention to treat (ITT-FDA snapshot) and per protocol (PP). Sample size was calculated for a power of 80% to show non inferiority with a margin of 15% and two-sided 95% confidence intervals.

Results: From January 2010 to October 2012, 454 patients were randomized. Participants were mainly women (72%), had been on ART for a median duration of 49 months (IQR 33- 69), had a median CD4 count of 183 cell/mm3 (IQR 87 - 290) and a median plasma HIV-1 RNA (VL) of 4.5 log10 (IQR 4 - 5.1). All but 6 had resistance to at least one first line drug and 95% to 2 classes.
At week 48 (cf table), 294 (65.2%) of the 451 analysed participants had an HIV-1 RNA<50 copies/mL, while 275 (83.2%) and 410 (90.9%) had a VL below 200 and 1 000 copies/mL respectively.
Primary results in ITT showed a difference of 5.6% (IC95% -5.1; 16.4) and 6.1% (IC95% -4.5; 16.7) between the reference arm A and arms B and C respectively, excluding non-inferiority. In multivariate analysis, VL ≤ 100 000 copies/ml at baseline was independent predictor of viral suppression.
No difference among arms was observed in median CD4 gain (+127 cells/uL), mortality or severe adverse events. No Protease mutations were observed in patients failing second line.

Conclusions: Despite multiple NRTI mutations, PI/b based second line regimens showed satisfactory results. However, results for patients with high viral load at switch to second line are of special concern. The WHO recommended regimen remains a valid option

INTRODUCTION

Access to antiretroviral therapy (ART) has increased significantly in the last decade: 9.7 million people were on ART at the end of 2012, 2.9% only on second line. WHO recommends the use of a ritonavir boosted Protease Inhibitor (PI/b) containing regimen in patients failing a Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)-based first line.

The evidence for the latest recommendation on second line is graded as low despite the review of randomized clinical trials. The main concerns are serious issues with indirectness: study population from high-income settings, majority of treatment-experienced (including PI-experienced) participants and the choice of NRTI backbone which is often optimized by the use of resistance testing before switch: conditions quite unlike in low and middle income countries.

In this study, we wanted to compare efficacy and safety of one of the recommended WHO second line combinations, LPV/r with the TDF/FTC backbone with two alternative regimens: one with LPV/r plus ABC and ddI, and the other with a newer bPI, DRV/r with TDF/FTC with the advantage of a once daily dosing. The trial conducted in RLS where viral monitoring is not yet widely available could provide evidence for the public health approach.

METHODS

A randomized, parallel, open label, multicentre, 48 weeks non inferiority trial to compare efficacy and safety of three PI based second line antiretroviral (ARV) combinations.

Four study sites: the Central and Military Hospitals of Yaoundé in Cameroon
the Fann Hospital of Dakar, in Senegal and the Day Hospital of the University Hospital of Bobo Dioulasso, in Burkina Faso.



Eligibility Criteria

✓aged above 18 years,
✓HIV-1 positive group M,
✓failing an NNRTI-based first line ART after at least 6 months of treatment (defined as a confirmed HIV-1 RNA above 1.000 copies/mL) after at least one month of adherence support,
✓no changes in combination in the last three months.

Patients were excluded if they had:

✓previous exposure to study products (except lamivudine/emtricitabine),
✓renal or hepatic failure,
✓severe AIDS related disease or were on tuberculosis treatment,
✓positive pregnancy test .

Primary Objective

Comparison of viral efficacy measured at week 48 and defined as the proportion of patients with HIV-1 RNA < 50 copies/ml

Interventions

•Group A: ritonavir boosted lopinavir (co-formulated lopinavir 200 mg/ritonavir 50 mg 2 tablets twice a day) with tenofovir/emtricitabine (*Truvada*® 1 tablet per day)
•Group B: didanosine (enteric coated capsule of 250 or 400 mg based on body weight) with abacavir (600 mg tablets) once a day with boosted lopinavir twice a day
•Group C: darunavir 400 mg (2 tablets) boosted with ritonavir (100 mg tablet) and tenofovir/emtricitabine (*Truvada*®) all taken with food once a day.

Procedures

Randomization was stratified by study site and screening viral load (≤ 5.000 copies/mL or above 5.000 copies/mL). Randomization sequence was computer generated in block of six and was concealed to study personnel.
Participants attended protocol visits at randomization and then at week 4, 12, 24, 36 and 48. At each visit, participants were assessed clinically and blood sample for efficacy and safety were taken.

Statistical analysis

Primary endpoint was analyzed in both intention to treat (ITT-FDA snapshot) and per protocol (PP). Sample size was calculated on the hypothesis of 80% response (50 copies/ml) at 48 weeks, for a power of 80% to show non inferiority with a margin of 15% and two-sided 95% confidence intervals.

RESULTS

Between January 2010 and September 2012, 584 patients were assessed for eligibility. Finally 454 patients were randomized (304 in Cameroon, 91 in Burkina Faso and 59 in Senegal), three were excluded from modified intent-to-treat analysis: 2 withdraw before study drug administration and 1 was excluded for protocol violation. Baseline characteristics are summarized in Table 1.

Table 1: Baseline characteristics of participants

	Group A n=152	Group B n=145	Group C n=154	Total n=451
Women, n (%)	113 (74%)	105 (72%)	106 (69%)	324 (72%)
Age, median (Q1-Q3)	38 (34-45)	38 (33-47)	36 (32-45)	38 (32-46)
Weight, median (Q1-Q3)	64 (55-71)	65 (55-75)	65 (58-71)	65 (56-72)
BMI, median (Q1-Q3)	22.9 (20.4-25.4)	22.9 (21.0-27.3)	23.6 (21.5-25.9)	23.1 (21.0-26.0)
WHO classification at ART initiation				
1	16	33	26	75 (17%)
2	41	26	27	94 (21%)
3	74	67	76	217 (48%)
4	21	19	25	65 (14%)
ART duration , median (Q1-Q3)	50 (31-68)	52 (37-68)	45 (32-69)	49 (33-69)
HBs Ag positive, n (%)	13 (9%)	9 (6%)	16 (10%)	38 (8%)
VL $\log_{10}$, median (Q1-Q3)	4.4 (4.0-5.0)	4.6 (4.1-5.1)	4.5 (4.0-5.1)	4.5 (4.0-5.1)
VL≥ 100 000 copies/ml, n (%)	36 (24%)	42 (29%)	44 (29%)	122 (27%)
CD4, median (Q1-Q3)	199 (92-318)	195 (100-288)	153 (81-261)	183 (87-290)
Resistance (n=446) Stanford algorithm (done retrospectively)				
Resistance to at least one second line drug received	147 (98%)	30 (21%)	148 (97%)	325 (73%)
ABC only	NA	3	NA	-
ddI only	NA	7	NA	-
ABC + ddI	NA	20	NA	-
FTC only	135	NA	128	-
TDF only	0	NA	0	-
FTC + TDF	12	NA	20	-

At week 48 in ITT (see table 2), 294 (65.2%) of the 451 analyzed participants had an HIV-1 RNA<50 copies/mL, while 275 (83.2%) and 410 (90.9%) had a VL below 200 and 1 000 copies/mL respectively.
Primary results in ITT showed a difference of 5.6% (IC95% -5.1; 16.4) and 6.1% (IC95% -4.5; 16.7) between the reference group A and groups B and C respectively, excluding non-inferiority (see fig.1 below)
In multivariate analysis, VL < 100 000 copies/ml at baseline and adherence above 95% were independently associated with viral suppression.

Table 2: Results in ITT and PP for different thresholds of viral load and difference between groups at week 48

	A n (%)	B n (%)	C n (%)	Total n (%)	A-B, % (95% CI)	A-C, % (95% CI)
ITT, Total	152	145	154	451		
VL < 50 copies/mL	105 (69.1%)	92 (63.4%)	97 (63.0%)	294 (65.2%)	5.6% (-5.1 ; 16.4)	6.1% (-4.5 ; 16.7)
VL < 200 copies/mL	130 (85.5%)	118 (81.4%)	127 (82.5%)	375 (83.2%)	4.1% (-4.3 ; 12.6)	3.1% (-5.1 ; 11.3)
VL < 1000 copies/mL	142 (93.4%)	129 (89.0%)	139 (90.3%)	410 (90.9%)	4.5% ([-2.0 ; 10.9)	3.2% (-3.0 ; 9.3)
PP, Total	149	135	148	432		
VL < 50 copies/mL	105 (70.0%)	92 (68.2%)	97 (65.5%)	294 (68.1%)	2.3% (-8.4 ; 13.1)	4.9% (-5.7 ; 15.5)
VL < 200 copies/mL	129 (86.6%)	117 (86.7%)	127 (85.8%)	373 (86.3%)	-0.1% (-8.0 ; 7.8)	0.8% (-7.1 ; 8.6)
VL < 1000 copies/mL	141 (94.6%)	128 (94.8%)	139 (93.9%)	408 (94.4%)	-0.2% (-5.4 ; 5.0)	0.7% (-4.6 ; 6.0)

Figure 1: Difference in VL <50 copies/mL at week 48 stratified by baseline VL and analytical population

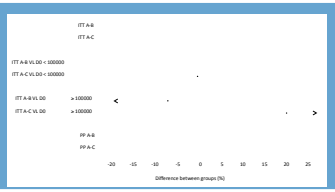
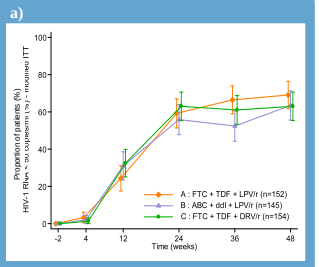


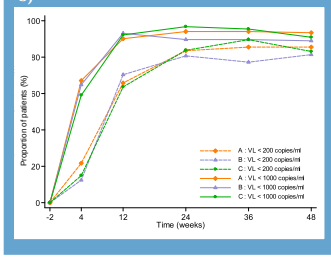
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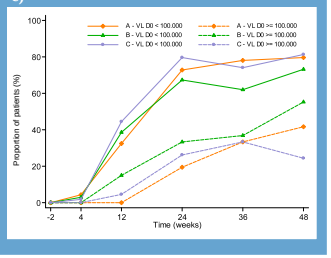
a)Proportion of patients in each group with VL<50 copies/ml in ITT with CI95%

b)Proportion of patients with VL< 200 and 1.000 copies/ml in ITT in each group

c)Proportion of patients with VL<50 copies/ml stratified for baseline VL < or ≥ 100.000 copies/ml in PP.







Median gain in CD4 over 48 weeks was of 127 cell/mm3 (IQR 72-203) with no significant difference among groups.

We did not observe any differences among groups for death, serious adverse events, AIDS defining events (table 3). Despite differences in pill number and daily dose, adherence was similar among groups.

Table 3: Mortality, SAE and AIDS events

	A n=152	B n=145	C n=154	Total n=451	P
Death, n(%)	1 (1%)	2 (1%)	3 (2%)	6 (1%)	0.7
Serious Adverse Events, n(%)	17 (11%)	22 (15%)	19 (12%)	58 (13%)	0.6
AIDS defiiing events, n(%)	17 (11%)	23 (16%)	30 (19%)	70 (16%)	0.13

CONCLUSION

In limited resource countries where viral load is not routinely available patients are diagnosed with first line failure late when many mutation have already appeared.
Despite this, the boosted PI containing second lines show satisfactory results for the majority of patients. The recommended WHO option (TDF + FTC + LPV/r) remains a valid option, but some concern exists for patient with high VL at failure for whom special strategies should be investigated.
In our study we were unable to show non inferiority of two possible alternative second lines (ABC + ddI + LPV/r, FTC + TDF + DRV/r) possibly due to lack of power in relation to the less then expected success rate for a VL threshold of 50 copies/ml in patients with multiple resistances.

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