First-line Therapy with LPV/r vs NVP and 2 NRTIs in a Developing Country : Week 144 of a Randomized Trial



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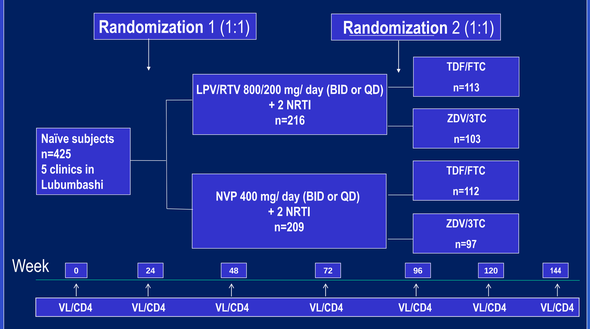
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Background

- WHO recommends 1 NNRTI + 2 NRTIs as first-line regimen in Resource-limited settings (RLSs) and boosted PI as second line regimen
- In RLSs , NNRTI-based regimen may result in emergence of more HIV drug resistance, because of a low genetic barrier.
- Therefore, in RLSs, the need to maximize the effectiveness of available first-line regimens and to sustain reduced morbidity and mortality remains a major challenge for ART programmes.
- The week 96 results of a prospective randomized trial comparing NVP-based regimens to LPV/r-based regimens as first-line therapy in Lubumbashi (Congo, DRC) showed more virologic failure (VL>1000c/ml) and more drug resistance mutations among patients on NVP (CROI 2012 abstract #K-1001)
- This is a report of the results of 144 weeks follow-up



Design of the study



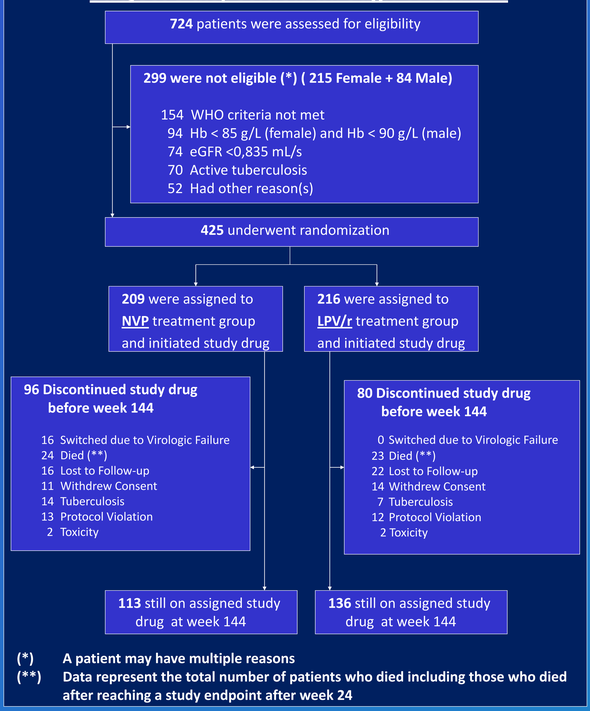
Primary endpoint

% of subjects with treatment failure at week 144 (ITT, Missing = Failure)

Treatment failure assessed after at least 24 weeks of therapy and defined as :

- ❑ Clinical failure:
  - ➢ occurrence (or relapse) of a WHO clinical stage IV or III event (including tuberculosis) or
  - ➢ death or
  - ➢ changing of therapy for toxicity
- ❑ Virologic failure:
  - ➢ HIV RNA > 1000 copies/ml (confirmed)

Subject's disposition through Week 144



(*) A patient may have multiple reasons

(**) Data represent the total number of patients who died including those who died after reaching a study endpoint after week 24

Baseline Characteristics : NVP vs LPV/r

	NVP, n=209	LPV/r, n=216
Age (years), median (IQR)	38 (33-45)	38 (33-45)
Female	148 (70.8%)	157 (72.7%)
Previous exposure to NVP single dose for PMTCT	2	1
Black race	209 (100%)	216 (100%)
Weight (kg), median (IQR)	55 (50-62)	54 (49-62)
BMI (kg/m2), median (IQR)	21 (19-23)	20 (18-23)
WHO stage		
CD4+ cell count < 200 cells/µl	121 (58%)	128 (59%)
Stage III, n (%)	190 (90.9%)	202 (93.5%)
Stage IV, n (%)	10 (4.8%)	5 (2.3%)
CD4+ cell count (cells/µl)-median (IQR)	164 (84-253)	168 (84-253)
CD4+ cell count < 100 cells/µl	60 (28.7%)	61 (28.2%)
Plasma HIV RNA (log copies/ml), median (IQR)	5.17 (4.5-5.6)	5.13 (4.4-5.6)
Plasma HIV RNA > 100 000 copies/ml (%)	115 (55%)	115 (53%)
Clades (n)		
Clade C (%)	60.6	60.0
Clade A (%)	10.6	11.2
Clade G (%)	7.3	7.2
Clade K (%)	8.1	6.4
Other (%) (B,D,F,H,J,CRF01,CRF01_AE,CRF02_AG)	13.4	15.2
Hep B surface antigen, positive, n (%)	18 (8.6%)	22 (10.2%)
Hep C antibody, positive, n (%)	7 (3.3%)	8 (3.7%)
Hb, mmol/l, median (IQR)	6.8 (6.2-7.4)	6.8 (6.2-7.4)
eGFR (Cockcroft-Gault; ml/s), median (IQR)	1.17 (1.00-1.34)	1.12 (0.97-1.30)

Results

Treatment Outcome at week 144

ITT analysis, missing = failure	NVP n =209	LPV/r n = 216	Risk difference (95%)	P
Primary Endpoints				
▪ Clinical failure				
• New or recurrent WHO clinical stage III & IV event	11 (5.2%)	8 (3.7%)	-1.5 (-5.5 ; 2.4)	
• Death after 24 weeks	3 (1.4%)	3 (1.4%)	- 0 (-2 ; 2)	
• Changing of treatment for toxicity	2 (1.0%)	2 (0.9%)	- 0 (-1 ; 1)	
TOTAL	**16 (7.6%)**	**13 (6.0%)**	-1.6 (- 6.4 ; 3.2)	**p = 0.566**
▪ Virologic failure (plasma VL >1000 copies/ml)	**37 (17.7%)**	**20 (9.3%)**	- 8.4 (-14.79 ; - 2)	**p = 0.015**
All Therapeutic Failures	**53 (25.4%)**	**33 (15.3%)**	- 10.1 (-17.7 ; - 24.8)	**p = 0.011**
Other reasons off treatment (*)	**58 (27.8%)**	**61 (28.2%)**	0.4 (-8 ; 9)	**p = 0.915**
Total outcomes , n(%)	**111 (53.1%)**	**94 (43.5%)**	- 9.6 (-19.5 ; -0.0)	**p = 0.047**

(*) Deaths before week 24, TBC before week 24, Consent withdrawal, Protocol violation, Lost to follow-up, Missing data

Secondary endpoints at week 144

ITT analysis, missing = failure	NVP n =209	LPV/r n = 216	P
Secondary Endpoints			
▪ Plasma HIV RNA < 50 copies/ml	**114** (55%)	**118** (55%)	
▪ Mean CD4 increase from baseline (cells/µL)	**174** (IQR 102-330)	**251** (IQR 153-384)	**p= 0.0093**

Virologic results and drug resistance mutations (1) at Week 144

	NVP, n =209	LPV/r, n =216	P
Number of patients with VF, n (%)	37 (17.7%)	20 (9.3%)	**p = 0.015**
Genotype available at VF	26 (70.2%)	13 (65%)	
Any resistance-associated mutation at baseline, n (*)	3	0	
Resistance-associated mutation at VF, n(%)	23 (88.4%)	0	**p < 0.0001**
NNRTI-associated mutation, n (%)	23 (88.4%)	0	**p < 0.0001**
K103N	17 (65.3%)	0	
Y181C/V	11 (42.3%)	0	
Other (**)	13 (50.0%)	0	
N(t)RTI-associated mutation, n (%)	19 (73.0%)	3 (23.0%)	**p = 0.0055**
M184V/I	18 (69.2%)	3 (23.0%)	**p = 0.0154**
K65R	7 (26.9%)	0	**p = 0.073**
Thymidine analogue associated mutation (***)	4 (15.3%)	0	
N(t)RTI along with NNRTI associated mutation, n (%)	18 (69.2%)	0	**p < 0.0001**
Major protease mutation, n	0	0	
Any protease mutation, n (%)	0	1 (7.6%)	

(1) According to IAS-USA, 2011 list.

(*) NNRTI mutations: K103N, Y181C, V108I ; N(t)RTI mutations: M184V, L120W.

(**) Other NNRTI mutations: K101E, V106I/L, V108I/L, Y188C, G190A, F227L, M230L, P236H

(***) Thymidine analogue associated mutations: 41L, 67N, 70R,210W, 215F/Y, 219Q/E

% of patients with adherence ≥ 95%

Population	NVP	LPV/r	P
All Patients	77.4	73.6	**P = 0.909**
Patients with virologic failure	54	50	**P = 0.788**
Patients without virologic failure	79	76	**P = 0.604**

Results

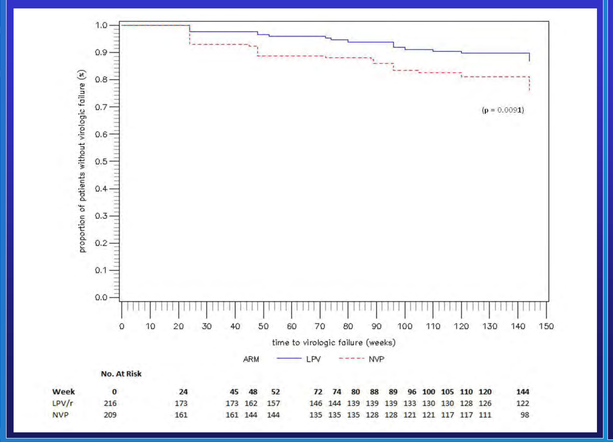
Safety analysis through 144 weeks – NVP vs LPV/r

NVP vs LPV/r-based regimens	NVP n=209	LPV/r n=216	P
Patients with at least one clinical adverse event , n (%)	34 (16.3%)	63 (29.2%)	**P= 0.002**
Adverse events leading to study drug discontinuation,n (%)	2 (0.9%)	2 (0.9%)	**P= 1.000**
Clinical events (grade 1 - 4), n (%)			
Rash	8 (3.8%)	0	**P= 0.003**
Vomiting	15 (7.2%)	31 (14.4%)	**P= 0.017**
Diarrhea	0	35 (16.2%)	**p < 0.0001**
Nausea	20 (9.6%)	40 (18.5%)	**P= 0.008**
Laboratory abnormalities (grade 3 - 4)			
Hepatic aminotransferase (>5.1 x ULN)	9 (4.3%)	4 (1.9%)	**P= 0.167**
Haemoglobin (< 4.65 mmol/L)	20 (9.6%)	18 (8.3%)	**P= 0.734**
Total cholesterol (>300 mg/dL)	2 (1.0%)	1 (0.5%)	
Triglycerides (>750 mg/dL)	0	0	
eGFR (< 0.50 mL/s)	3 (1.4%)	3 (1.4%)	**P= 1.000**
Median change in eGFR from baseline (ml/s)	+ 0.34 IQR (0.11 ;0.64)	+ 0.19 IQR (-0.01 ; 0.48)	**P= 0.0044**

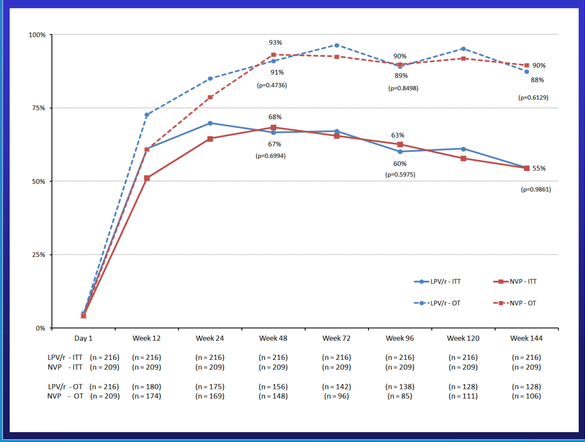
Safety analysis through 144 weeks-Backbone comparison

Backbone comparison	TDF/FTC n=225	ZDV/3TC n=200	P
Patients with at least one clinical adverse event , n (%)	40 (15.1%)	56 (28%)	**P= 0.015**
Adverse events leading to study drug discontinuation, n (%)	1 (0.4%)	7 (3.5%)	**P= 0.029**
Clinical events (grade 1 - 4), n (%)			
Rash	6 (2.7%)	2 (1.0%)	**P= 0.291**
Vomiting	18 (8.0%)	28 (14%)	**P= 0.060**
Diarrhea	19 (8.4%)	15 (7.5%)	**P = 0.858**
Nausea	17 (7.6%)	42 (21%)	**p < 0.0001**
Laboratory abnormalities (grade 3 - 4)			
Hepatic aminotransferase (>5.1 x ULN)	8 (3.6%)	3 (1.5%)	**P= 0.230**
Haemoglobin (< 4.65 mmol/L)	15 (6.7%)	19 (9.5%)	**P= 0.290**
Neutropenia (< 0.750 x 10^9/L)	3 (1.3%)	13 (6.5%)	**P= 0.0085**
Total cholesterol (> 300 mg/dL)	1 (0.4%)	2 (1.0%)	
Triglycerides (> 750 mg/dL)	0	0	
eGFR (< 0.50 mL/s)	2 (0.9%)	3 (1.5%)	**P= 0.670**
Median change in eGFR from baseline (ml/s)	+0.21 IQR (0.04;0.56)	+0.27 IQR (0.05;0.50)	**P= 0.959**

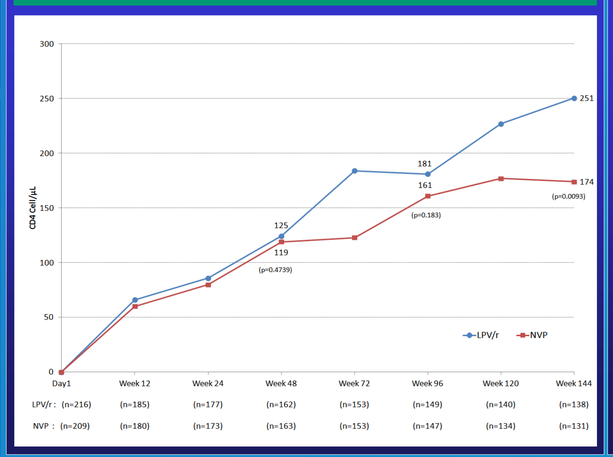
Virologic failure through 144 weeks



% of patients with VL<50 copies/ml (ITT, M=F)



CD4 Median Change from Baseline (ITT, M=F)



eGFR Median Change from Baseline through 144 weeks



Conclusion

- In a resource-limited setting after 144 weeks of follow-up NNRTI-NRTI first-line regimen is associated with more virologic failure, more drug resistance mutations and a lower immunologic response than a PI-based regimen.
- In Africa there are important gaps in service delivery and program performance that contribute to :
  - ♦ sub-optimal adherence,
  - ♦ substandard antiretroviral regimen and
  - ♦ acquired drug resistance

  In such settings a boosted-PI strategy could be a better first-line option.
- Cost-effectiveness of such strategy should be evaluated.