IMPACT OF A LOPINAVIR/RITONAVIR (KALETRA) BASED SECOND-LINE ANTIRETROVIRAL THERAPY REGIME ON LIPID AND LIPOPROTEIN PROFILES IN AN AFRICAN SETTING

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ABSTRACT

BACKGROUND: Most resource-constrained countries reserve boosted PIs (bPIs) for second-line following WHO recommendations. Lipid profiles at first-line clinical/immunological failure and following bPI-based second-line have not been studied in Africa.

METHODS: DART is a randomized trial comparing HIV/AIDS management strategies in Uganda/Zimbabwe in adults initiating first-line ART and switched to bPI-containing second-line at clinical (WHO 4), or, in those randomised to laboratory monitoring, immunological (CD4<100cells/mm³) failure. We evaluated fasting lipid profiles at second-line initiation and 48 weeks subsequently in stored samples from patients in Zimbabwe remaining on LPV/r (Kaletra/Aluvia) for ≥48 weeks. Lipid profiles determined were total cholesterol, triglyerides, HDL-C, LDL-C and VLDL-C. HDL-C and LDL-C were determined using homogenous methods.

RESULTS: 91 patients switched to second-line before 18 September 2006, of whom 66 (73%) had fasting samples at switch and ≥48 weeks, 14 (15%) died/were lost to follow-up <48 weeks, 10 (11%) interrupted for >14 days and 1 (1%) had no samples available. Of the 66 included patients (34 male), 57 (86%) received ZDV/d4T+3TC+TDF first-line, 6 (9%) ZDV/d4T+3TC+NVP, and 3 (5%) ZDV+3TC with TDF and NVP at different times. Initial second-line was NNRTI+LPV/r in 27 (41%), ddI+NNRTI+LPV/r in 33 (50%) and LPV/r+TDF+ddI/3TC/ZDV in the remaining 6 (9%). At second-line initiation median (IQR) total cholesterol, LDL-C, HDL-C and VLDL-C (mmol/L) were 3.3 (2.9-4.2), 1.8 (1.5-2.3), 0.7 (0.6-0.8) and 0.7 (0.6-1.1) respectively with triglycerides 1.0 (0.7-1.8). Levels were significantly increased after 48 weeks of Kaletra-containing second-line, by mean (SE) +2.0 (0.1), +1.1 (0.1), +0.5 (0.05) and +0.5 (0.05) respectively (all p<0.001); triglycerides also increased by +0.40 (0.16,p=0.01). At second-line initiation, 1 (2%) patient had grade 1 cholesterol (5.2-6.2mmol/L) and LDL-C (3.4-4.1mmol/L), and 1 (2%) grade 3 cholesterol (>7.8mmol/L) and grade 2 LDL-C (4.1-4.9 mmol/L); no triglycerides were elevated but 81% had HDL-C <0.9mmol/L and 60% cholesterol/HDL-C ratio <5. By 48 weeks, the prevalence of grade 1/2/3 cholesterol and LDL-C was 26 (39%) / 12 (18%) / 2 (3%) and 8 (12%) / 7 (11%) / 1 (2%) respectively, but only 14 (21%) had HDL-C<0.9mmol/L and 2 (3%) had grade 2 triglycerides; 66% had cholesterol/HDL-C ratio<5.

CONCLUSION: **Modest lipid elevations were observed in African patients mostly on LPV/r+NNRTI combinations. This may have long-term implications for total atherogenic risk assessment in patients on bPI-regimens in Africa.**

BACKGROUND

- DART was one of the first large scale ART randomised clinical trials in Africa. DART is comparing HIV/AIDS management strategies in 3316 adults initiating first-line ART in Uganda/Zimbabwe. Participants were randomised into two arms; a clinical monitoring arm and laboratory monitoring arm. Enrolment occurred during 2003/4 and follow-up is still on-going.
- Dyslipidaemia, which is a risk factor for cardiovascular morbidity, is a recognized metabolic complication of ART, particularly for regimens containing boosted protease inhibitors, NNRTIs and d4T. Most studies in this area have been carried out in developed countries and mainly included male HIV-infected patients.
- **There are few studies on the metabolic complications of ART in Sub-Saharan Africa which is witnessing an increasing number of patients being put on ART**

OBJECTIVE

The objective of this study was to evaluate lipid profiles in HIV-infected patients on lopinavir/ritonavir (LPV/r, Kaletra capsules) containing second-line ART regimens (mostly with NNRTIs) in the Zimbabwe DART centre

METHODS

- Patients were switched to LPV/r-containing second-line ART at clinical failure (WHO 4 event) in those randomised to clinical monitoring only; or at clinical/immunological failure (CD4<100cells/mm³) in those randomised to clinical and laboratory monitoring
  - **most patients received LPV/r with NNRTIs following triple NRTI first-line regimens**
- 91 patients in DART-Zimbabwe were switched to second-line ART before 18 September 2006, of whom 66 (73%) had fasting samples at switch and ≥48 weeks. 14 (15%) died/were lost to follow-up before 48 weeks, 10 (11%) had interrupted ART for more than 14 days and 1 (1%) had no samples available.
- Serum lipids; total cholesterol (TC), triglycerides (TG), low density lipoprotein-cholesterol (LDL-C), and high density lipoprotein-cholesterol (HDL-C) were determined on the Beckman Coulter Synchron CX5 using Bechman Coulter reagents. The lipid profiles were measured at switch from first-line non-PI ART regimens and at ≥48 weeks on lopinavir/ritonavir based second-line regimens. **All samples were taken fasted.**
  - *TC* was measured using the cholesterol esterase/cholesterol oxidase method.
  - *TGs* were measured using lipase, and sequence of three coupled enzymatic steps using glycerolkinase, glycerophosphate oxidase triglyceride and horseradish peroxidase.
  - *LDL-C* was measured directly in a 2 step homogenous assay. The first step selectively solubilises non-LDL lipoprotein particles which are rendered non reactive. The second step solubilises LDL particles and the cholesterol moiety is determined as in the total cholesterol method.
  - *HDL-C* was measured directly using a reagent which selectively solubilises HDL particles. The HDL cholesterol is then determined as in the total cholesterol method.

RESULTS - ART received

First-line ART (N=66)	n (%)
ZDV/d4T+3TC+TDF	57(86%)
ZDV/d4T+3TC+NVP	6 (9%)
ZDV+3TC+TDF and ZDV+3TC+NVP*	3 (5%)

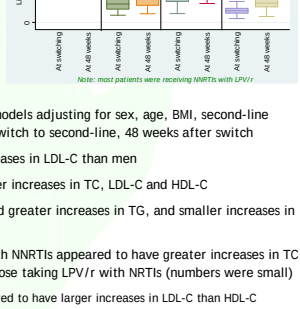
* substituted NVP->TDF for hepatotoxicity (2) or anti-TB therapy (1)

Second-line ART (N=66)	n (%)
LPV/r + EFV ±ddI**	9 (14%)
LPV/r + NVP ±ddI**	51 (77%)
LPV/r+TDF+ddI/3TC/ZDV†	6 (9%)

** 3/9 and 30/51 taking EFV and NVP respectively also took ddI as a 3rd drug
† patients took LPV/r+TDF and either ddI (n=1, for 7 months then substituting 3TC) or 3TC (n=3) or ZDV (n=2)

RESULTS - fasting lipid profiles

- At switch to second-line, women had significantly higher TC (+0.7, p=0.005), LDL-C (+0.5, p=0.003) and HDL-C (+0.1, p=0.03), but not vLDL-C or TG
  - no variation in lipid levels according to age or BMI at switch to second-line
  - patients who had received NVP first-line had higher HDL-C (+0.2, p=0.002) at switch than those who had received TDF and other NRTIs only
- Serum lipid (TC, triglycerides, LDL-C, and HDL-C) levels were statistically significantly increased ≥48 weeks after switching to LPV/r containing second-line ART regimens (mostly with NNRTIs) (median (IQR) in Figure 1 to right, mean (SD) in Table below)



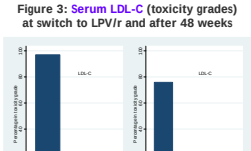
- In multivariable regression models adjusting for sex, age, BMI, second-line regimen and lipid levels at switch to second-line, 48 weeks after switch
  - women had greater increases in LDL-C than men
  - older patients had greater increases in TC, LDL-C and HDL-C
  - those with higher BMI had greater increases in TG, and smaller increases in HDL-C
  - patients taking LPV/r with NNRTIs appeared to have greater increases in TC, LDL-C and HDL-C than those taking LPV/r with NRTIs (numbers were small)
    - ★those taking EFV appeared to have larger increases in LDL-C than HDL-C
    - ★those taking NVP appeared to have similar increases in LDL-C than HDL-C

		TC (mmol/L)		LDL-C (mmol/L)		HDL-C (mmol/L)		vLDL-C (mmol/L)		TG (mmol/L)	
	n (%) or median (IQR)	mean(sd)	p	mean(sd)	p	mean(sd)	p	mean(sd)	p	mean(sd)	p
Initiation of second-line	65 (100%)	3.4 (1.0)		1.8 (0.7)		0.7 (0.2)		0.9 (0.4)		1.4 (1.0)	
48 weeks later	65* (100%)	5.4 (1.2)		2.8 (0.9)		1.2(0.4)		1.3 (0.6)		1.9 (1.3)	
Change	65* (100%)	+2.0(1.1)	<0.001	+1.1 (0.8)	<0.001	+0.5(0.4)	<0.001	+0.5 (0.7)	<0.001	+0.4(1.3)	0.01
Multivariable regression model for change in lipid parameter**											
At 2nd line ‡		effect (se)	p	effect (se)	p	effect (se)	p	effect (se)	p	effect (se)	p
Sex: female	32 (48%)	+0.4 (0.3)	0.14	**+0.5 (0.2)**	**0.04**	+0.1 (0.08)	0.26	-0.2 (0.1)	0.17	-0.07 (0.3)	0.81
Age: per 10 years	38 (34-43)	**+0.4 (0.2)**	**0.02**	**+0.3 (0.1)**	**0.06**	**+0.1 (0.06)**	**0.02**	+0.02 (0.1)	0.81	-0.04 (0.2)	0.87
BMI: per 2 units	21 (17-26)	+0.02(0.03)	0.47	+0.02(0.03)	0.41	**-0.02(0.01)**	**0.08**	+0.02 (0.02)	0.43	**+0.08†(0.04)**	**0.07**
NVP	50 (77%)	**+1.3 (0.4)**	**0.004**	+0.6 (0.3)	0.10	**+0.6 (0.2)**	**<0.001**	+0.5 (0.3)	0.10	+0.4 (0.6)	0.43
EFV	9 (14%)	**+1.6 (0.5)**	**0.003**	**+0.9 (0.4)**	**0.03**	**+0.4 (0.2)**	**0.02**	+0.5 (0.3)	0.14	+0.4 (0.6)	0.57
ddI	34 (52%)	-0.04 (0.3)	0.88	-0.1 (0.2)	0.54	-0.1 (0.1)	0.21	+0.1(0.1)	0.35	+0.2 (0.3)	0.54

* excluding 1 patient missing sample at 2nd line initiation ** all models adjusted for baseline lipid level † BMI at week 48 (rather than second-line) as this was a better predictor ‡ reference category: man aged 40 years with BMI 25 at switch, receiving LPV/r plus NRTIs (no NNRTI) without ddI as their second-line regimen

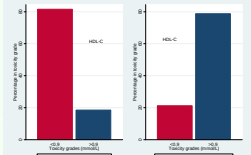
- At switch to LPV/r based second-line regimens (mostly with NNRTIs), 96% of patients had grade 0 **serum TC** levels (<5.2 mmol/L). At ≥48 weeks after switch, 26(39%), 12(18%), 2(3%) patients had grades 1, 2 and 3 **serum TC** levels respectively (**Figure 2**)

Figure 2: Serum TC (toxicity grades) at switch to LPV/r and after ≥48 weeks



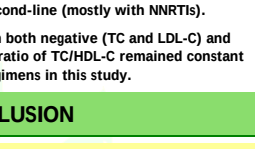
- At switch to LPV/r based second-line regimens (mostly with NNRTIs), 96% of patients had grade 0 **serum LDL-C** levels (<3.4 mmol/L). At ≥48 weeks after switch, 8(12%), 7(11%), 1(2%) patients had grades 1, 2 and 3 **serum LDL-C** levels respectively (**Figure 3**)

Figure 3: Serum LDL-C (toxicity grades) at switch to LPV/r and after 48 weeks



- At switch to LPV/r based second-line regimens (mostly with NNRTIs), 56 (85%) patients had low serum **HDL-C** levels <0.9 mmol/L. At ≥48 weeks after switch, only 14 (21%) still had low serum HDL-C levels <0.9 mmol/L (**Figure 4**).
- At switch to LPV/r based second-line regimens (mostly with NNRTIs), none of the patients had raised **triglycerides**; at ≥48 weeks after switch, 2(3%) had grade 2 toxicity.
- There was no significant change in **TC/HDL-C ratio** after ≥48 weeks of second-line LPV/r based second-line therapy (mostly with NNRTIs)
  - 39 (60%) had TC/HDL-C<5 at switch to second-line, compared to 44 (66%) after 48 weeks

Figure 4: Serum HDL-C at switch to LPV/r and after ≥48 weeks



DISCUSSION

⇨**Similarly to other studies, serum lipids (TC, TG, LDL-C, HDL-C) increased significantly following switch to boosted PI (LPV/r) containing second-line regimens.**

★**However, most patients in our study were taking LPV/r with NNRTIs as their second-line regimen, following 3NRTIs first-line**

★**Most patients were taking NVP with LPV/r: given the small numbers caution is needed in interpreting comparisons with EFV or no NNRTIs**

⇨**At switch, only a few patients had TC and LDL-C levels considered associated with increased cardiovascular disease risk; this proportion increased to 60% and 22% respectively after 48 weeks of LPV/r based second-line (mostly with NNRTIs).**

⇨**Changes in TG levels during LPV/r second line ART were not clinically significant.**

⇨**At switch, few patients (15%) had levels of serum HDL-C considered protective for cardiovascular disease. This proportion increased to 79% after 48 weeks of LPV/r-based second-line (mostly with NNRTIs).**

⇨**Although there was an increase in both negative (TC and LDL-C) and positive (HDL-C) risk factors, the ratio of TC/HDL-C remained constant after exposure to LPV/r-based regimens in this study.**

CONCLUSION

Lipid elevations were modest in African patients on second-line therapy with LPV/r (mostly with NNRTIs). Assessment and management of the total atherogenic risk of the increasing number of patients on LPV/r based second-line therapy in Sub-Saharan Africa requires further study.

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