EuResist Africa Network

Effectiveness of Protease-Inhibitor-based Second line Antiretroviral Therapy in sub-Saharan Africa

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Background and Objective

- There is limited data on the effectiveness of 2nd line antiretroviral therapy (ART) in sub-Saharan Africa (SSA). By WHO recommendations, 2nd line ART in SSA comprises a 2-NRTI backbone and a boosted Protease-Inhibitor.
- As treatment programs in SSA enter into their 3rd decade, such information is needed for strategic planning in developing alternative 2nd line therapies as well as preparations for 3rd line therapies.
- **The Objective of our study was to assess probability and determinants of 2nd line ART virological failure (VF) and re-suppression in SSA.**

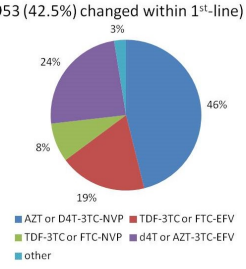
Methods

- Retrospective, multi-center study of 2nd line ART initiated 2005-2017 at four ART centers in Ethiopia (Asella, Adama), Ghana (Kumasi) and Uganda (Kampala).
- Main outcome measure was virologic failure (VF) defined as VL>1,000 copies/mL after >6 months on 2nd line therapy.
- Re-suppression = any VL<1,000 copies/mL after VF
- Predictors of VF and virologic re-suppression on 2nd line were evaluated using Cox Proportional Hazards regression and logistic regression models respectively.

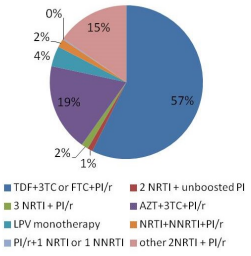
Description of the cohort (n = 2255)

- 2,255 subjects started 2nd line therapy at the 4 study sites, 61.6% being females, mean age 34.9 yrs.
- Switching from 1st line (56.4% NVP-based, 70.3% including thymidine-analogues) to 2nd line therapy occurred after a mean of 4.1 yrs.
- 2-nd line start instigated by toxicity (73.9%), clinical/immunological failure (8.9%) and virological failure (17.2%).
- Median calendar year at 2-nd line start: 2013 (IQR 2010-2015)

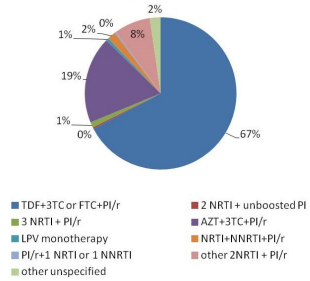
Last first line regimen
(953 (42.5%) changed within 1st-line)



Initial second line regimen

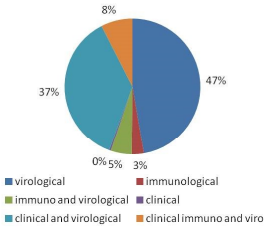


Last second line regimen (n = 2046)
(941 (43.9%) changed within 1st-line)



Description of failures in second line (n = 302)

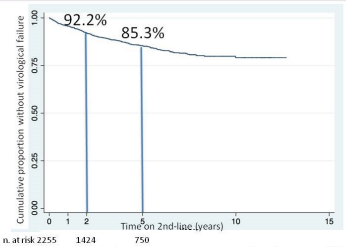
Type of failure (n=302)



WHO stage	At ART start	At 2nd line failure
1	11.0%	3.1%
2	27.0%	15.4%
3	41.3%	33.5%
4	20.6%	48.1%

- Out of 302 failures, there were 270 virologic failures (12.0% of the 2nd-line regimens), 43 (2.0%) immunologic failures, 125 (5.5%) clinical failures.

Cumulative probability of virological failure on 2nd-line ART



KM curve of time to virological failure with 2nd-line ART (n=270 of 2,255) with estimated proportion without VF at 1, 2 and 5 years

Time	Beg. Total	Fail	Survivor Function	Std. Error	[95% Conf. Int.]	
1	1830	88	0.9571	0.0045	0.9474	0.9650
2	1424	59	0.9223	0.0062	0.9092	0.9336
5	750	85	0.8535	0.0093	0.8342	0.8707

Results – predictors of 2nd line virological failure

Survival analysis: (Cox regression)

Variable	Univariable analysis		Multivariable analysis*	
	HR (95% CI)	P-value	aHR (95% CI)	P-value
Age (+1 year older)	0.98(0.96-0.99)	0.001	0.99 (0.97-1.00)	0.09
Calendar year of second line start	1.07 (1.02-1.13)	0.003	1.10 (1.05-1.16)	0.03
Rifampicin use in second line	2.40 (1.49-3.87)	<0.001	2.34 (1.44-3.78)	0.001
WHO stage at ART initiation				
4	Ref.		Ref.	
3	0.62 (0.46-0.83)	0.001	0.75 (0.56-1.00)	0.04
2	0.96 (0.55-1.04)	0.088	0.79 (0.57-1.10)	0.16
1	0.49 (0.29-0.85)	0.010	0.56 (0.32-0.96)	0.06
Reason for switch to 2nd line				
Toxicity/other/unknown			Ref.	
Clinical or immunological failure	0.08 (0.03-0.25)	<0.001	0.01 (0.03- 0.31)	<0.001
Virological +/- Clinical/Immunological failure	0.13 (0.05-0.31)	<0.001	0.13 (0.05-0.32)	<0.001
Ever changed within second line	0.68 (0.53-0.87)	0.002		

* Variables mutually adjusted and adjusted for ART site
Additional factors explored but not associated (p>0.10) at univariate analysis: sex, time from 1st-line initiation, type of 1st-line and 2nd-line regimen, , Ever changed within 1st-line, WHO stage at 2nd-line start.

Results – Re-suppression of VF while on 2nd line ART

- 144 of 270 (53.3%) patients with virological failure achieved VL <1,000 cps/mL while still on 2nd line
- Independent predictors of virologic re-suppression with aOR (95%CI) included experiencing any change within 2nd line; switching 2nd line before re-suppression; and more recent calendar year of 2nd line initiation.

Variables	Univariable analysis		Multivariable analysis*	
	OR (95% CI)	P-value	aOR (95% CI)	P-value
Age (+1 year older)	1.03 (1.00-1.05)	0.05	ne	
Sex (F vs M)	0.64 (0.39-1.04)	0.074	ne	
Initial 1st-line TDF-XTC-EFV vs ZDV/d4T-3TC-NVP	0.19 (0.07-0.53)	0.002	ne	
Initial 2nd-line TDF-XTC+PI/r	Ref.			
other 2NRTI+PI/r	4.03 (1.93-8.43)	<0.001	ne	
AZT+3TC+PI/r	0.33 (0.14-0.78)	0.012	ne	
VL at second line start	0.76 (0.55-1.05)	0.094	nc	
Ever changed within second line	2.23 (1.36-3.63)	0.001	nc	
HIV RNA at 2nd line failure (+1 log)			0.73 (0.51-1.05)	0.088
Switch of second line before re-suppression	0.10 (0.04-0.30)	<0.001	0.17 (0.04-0.82)	0.027
Calendar year of second line start (+1 more recent)	0.82 (0.75-0.89)	<0.001	0.84 (0.75-0.94)	0.002

Other factors explored but not associated: time from 1st-line initiation, WHO stage at 1st ART initiation and at 2nd-line failure , Ever changed within 1st-line, reason for starting 2nd-line, most recent 1st-line or 2nd- line regimen type, rifampin use
* Factors in the model are mutually adjusted; ne= not entered in the model, nc=not computed

Conclusions

- Effectiveness of 2nd line ART regimens in the analyzed SSA sites was good
- 2nd line ART was critically challenged by toxicity and/or interactions with TB therapy.
- Strategic priorities may include:
  - Improving tolerability of 1st line regimens
  - increasing the repertoire of 2nd line therapy in settings with high TB endemicity
  - improving regimens tolerability
  - setting 3rd line strategies for those failing existing 2nd line therapy.