PEOPLE FAILING FIRST-LINE REGIMENS REMAIN AT RISK FOR ADVERSE SECOND-LINE OUTCOMES

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BACKGROUND

- People living with HIV (PLHIV) who initiate first-line antiretroviral therapy (ART) with drug intolerance, transmitted drug resistance or poor adherence leading to treatment failure, require a switch to a second-line regimen. We assessed second-line treatment outcomes in the Thai National AIDS Program (NAP).

METHODS

- PLHIV aged ≥18 years starting first-line non-nucleoside reverse transcriptase inhibitor-based ART from 2008 to 2019, who switched to second-line protease-inhibitor (PI) based ART according to Thai guidelines at the time, were studied.
- Virological failure (VF) after second-line switch was viral load (VL) ≥1000 copies/mL; second-line failure was two consecutive VF episodes. Lost to follow-up (LTFU) was not attending clinic for >1 year.
- Second-line failure incidence was modelled with competing risks regression in those who had virological testing. Mortality in all participants was confirmed by National death registry linkage and associations assessed with Cox regression.

RESULTS

- Of 318,506 people initiating ART, 29,015 (9.1%) switched to a second-line regimen (Table 1). Most (61%) were male with median age of 37 (IQR 31-44) years, median switch CD4 count of 148 (IQR 49-296) cells/mm^3 and median duration on first-line ART of 1.6 (IQR 0.6 – 3.6) years.
- Main reasons for switching were VF/drug resistance (56%), clinical failure (24%) or adverse effects (14%).
- Second line regimens were ritonavir booster lopinavir (LPV/r) (95%), atazanavir (ATV) (3%), indinavir or other PIs (2%).

Main results:

* Over a median 4.1 (95%CI 2.3 – 6.2) years of follow-up, 16,404 (56%) PLHIV consistently had VL <50 copies/mL after switch

* Cumulative second-line failure incidence after 6 years was 9.8 (95%CI 9.4 – 10.2)%

* After switch, a total of 4,606 (16%) PLHIV died; 1,376 (5%) were LTFU but alive

* Second line failure was associated with female sex, switching in more recent years, younger age and lower CD4 cell counts at switch

* Mortality was associated with older age, switching in more recent years, lower switch CD4 counts, any viral load above 1,000 copies/mL or unknown VL (ineligible for testing due to recent switching), and LTFU

RESULTS (Continued)

- Associations with death second-line failure are shown in table 1.
- Death and LTFU rates were highest amongst those who recently switched and were not eligible for viral load testing.
- Forty percent and 20% of those who had 1 or ≥2 VL tests >1,000 copies/mL respectively, subsequently suppressed to <50 copies/mL.

DISCUSSION

- Consistent with the ACTG A5288 strategy trial, treatment failure was more common in women than men, implicating non-adherence due to intolerance, since 95% of the cohort were taking LPV/r-based regimens (*Godfrey et al, J Acquir Immune Defic Syndr (2020); 84(2):203-7*).
- That forty percent of PLHIV subsequently resuppressed after having one VL ≥1,000 copies/mL supports that non-adherence remains challenging in those switching from first-line regimens.

Table 1. Multivariable models showing adjusted sub-hazard ratios (aSHR) for factors associated with second-line failure (death and lost as competing risks), and adjusted hazard ratios (aHR) for mortality after second line switch. Models were adjusted for geographical region, treatment regimen and factors significant in univariable models at P <0.2.

Characteristic	Associations with second-line failure		Associations with mortality	
	aSHR(95% CI)	P	aHR(95% CI)	P
Female vs male	1.60 (1.46 - 1.75)	<0.001	0.95 (0.89 – 1.01)	0.098
Age at second-line initiation		<0.001		<0.001
18 – 24 years	2.96 (2.42 - 3.62)		0.46 (0.40 - 0.52)	
25 - 34 years	1.81 (1.52 - 2.15)		0.59 (0.54 - 0.64)	
35 - 49 years	1.17 (0.99 - 1.39)		0.74 (0.68 - 0.80)	
≥ 50 years	Reference		Reference	
Period of second-line switch		<0.001		<0.001
2008 - 2012	0.79 (0.69 - 0.90)		0.20 (0.18 - 0.22)	
2013 - 2016	0.79 (0.70 - 0.89)		0.36 (0.33 - 0.39)	
2017 - 2020	Reference		Reference	
Active OI at second-line switch			1.40 (1.27 - 1.55)	<0.001
Switch CD4 count (cells/mm^3)		<0.001		<0.001
< 200	1.48 (1.30 - 1.69)		1.75 (1.58 - 1.95)	
200 - 349	1.09 (0.93 - 1.26)		1.18 (1.04 - 1.34)	
≥ 350	Reference		Reference	
Unknown	0.93 (0.76 - 1.13)		1.23 (1.07 - 1.41)	
VL > 1000 copies/mL after switch				<0.001
0			Reference	
1			1.73 (1.58 - 1.89)	
≥2			1.52 (1.38 - 1.68)	
Not tested			6.40 (5.91 - 6.93)	
Lost to follow-up (vs in care)			44.0 (40.2 - 48.2)	<0.001

CONCLUSIONS

- In the Thai NAP, failure after switching to second line ART was approximately 10% at 6 years. Death and lost to follow-up occurred in 21% of the switch cohort.
- Second-line failure was higher in females, the majority of whom were taking LPV/r, and may relate to non-adherence due to intolerance.
- Death was associated with recent switching, LTFU, second-line failure and more severe immunosuppression at switch. This suggests switching should occur soon after detecting first line failure, and that more intensive follow-up, perhaps with newer technologies may reduce attrition in the period immediately after switching.

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