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Background

The provision of HAART in resource-limited settings is characterised by limited numbers of first- and second-line regimens. While in developed countries the definition of viral failure and the decision to switch to a second-line regimen is guided by viral load (VL) monitoring (and resistance testing), many sites in resource-limited settings do not have access to VL monitoring.

Objectives

- To determine rates of switching from first-line antiretroviral combination regimens to second-line regimens
- To identify individual-level and program-level determinants of switching to second-line regimens
- To study the importance of viral load monitoring by comparing the WHO immunological and virological criteria for switching

Methods

Study Population

- Patients come from the ART in Lower Income Countries of the International Databases to Evaluate AIDS (ART-LINC of IeDEA), a large collaborative network of HIV/AIDS treatment programmes in 14 low and middle income countries in Africa, South America and Asia. All sites have access to CD4 monitoring, routine viral load (VL) monitoring is performed in 9 sites.
- Inclusion criteria:
 - 16 years or older
 - treatment-naïve
 - started HAART with NNRTI-based HAART regimen of at least 3 antiretroviral drugs
 - at least 6 months of follow-up

Definitions

- Second-line regimen was defined as a change from a NNRTI-based regimen to a PI-based regimen and a change of at least one NRTI after ≥ 6 months on HAART.
- Immunological criteria for switching (CD4 <100 cells/ μ l after 6 months on therapy or drop of CD4 to below baseline value or decline of at least 50% from on treatment peak value) and virological criteria for switching (HIV RNA > 10'000) were defined according to the WHO. Two consecutive values meeting the criteria were required.

Statistical Analysis

A) Primary outcome was switch to a second-line regimen. We used Kaplan-Meier and multivariable Weibull models with cohort as random effect. Time was measured from 6 months after start of HAART and analysis were adjusted for sex, age, CD4 and clinical stage, calendar period of starting HAART, availability of routine viral load monitoring and number of available drugs.

B) In cohorts with routine viral load monitoring immunological and virological WHO criteria for switching were compared.

Results

Study Population

Overall 20,113 patients from 17 sites were included in the analysis, 4495 (22%) from sites with routine VL monitoring. During 24,110 years of follow-up 576 patients switched after a median of 20 months (IQR 12-31). The switching rate overall was 23.9 per 1000 pyrs (95% CI 22.0-25.9) but ranged from 0 to 65 per 1000 pyrs across sites. At the time of the switch patients had similar CD4 cell counts and viral load values as at HAART initiation (table 1).

Table 1: Patients characteristics at start of first and second-line treatment initiation.

	Start of 1st line (n=20,113)	Start of 2nd line (n=576)
Female (%)	62%	57%
Age (med, IQR)	35 (30-41)	37 (32-43)
CD4 (med, IQR)	116 (53-186)	122 (48-202)
Log10 HIV RNA	5.0 (4.4-5.5)	5.1 (4.6-5.6)
Most common regimens	D4T 3TC NVP: 54% D4T 3TC EFV: 24% AZT 3TC EFV: 11%	AZT DDI LPV: 30% 3TC DDI IDV RTV: 10% ABC DDI LPV: 8%

Determinants of switching

Switching was associated with lower baseline CD4 counts, earlier calendar periods, lack of VL monitoring and the number of ARVs available (Table 2).

Table 2: Weibull regression for predictors of switching to second-line regimen (n=13,757)

Variable	Adjusted Hazard Ratio (95% CI)	P value
Year of starting HAART		
≤ 2002	1	< 0.001
2002-2004	0.51 (0.36-0.72)	
2005-2006	0.69 (0.45-1.06)	
Baseline CD4 (cells/μl)		
<25	1	< 0.001
25-49	0.75 (0.53-1.08)	
50-99	0.62 (0.45-0.86)	
100-199	0.43 (0.31-0.58)	
200-349	0.28 (0.18-0.45)	
≥ 350	0.21 (0.08-0.58)	
Routine VL testing available		
No	1	0.31
Yes	0.66 (0.29-1.48)	
Number of ARVs available in site		
8-10	1	0.22
11-13	1.88 (0.70-5.04)	
≥ 14	2.36 (0.88-6.31)	

The analysis was adjusted for all variables specified in the Methods section.

B) Immunological and virological WHO criteria compared

2520 patients from sites with routine VL monitoring and at least 2 CD4 cell counts after 6 months were included in this analysis. During 4569 person-years of follow-up 107 patients met the virologic criteria of whom 26 (24%) switched. 117 met the immunologic criteria and 26 (22%) switched. 293 patients switched without meeting immunologic or virologic criteria.

Table 3: WHO immunologic and virologic criteria compared.

Values within 1 year of WHO criteria	WHO Immunologic criteria fulfilled (n=117)
HIV Viral load	
> 10'000	52%
500-9999	11%
< 500	34%
Not available	3%
CD4 cell count	WHO virologic criteria fulfilled (n=107)
CD4 criteria for switching: +	56%
CD4 criteria for switching: -	44%

Discussion & Conclusions

- Few patients switched to second-line regimen but there was a considerable variability between sites.
- A low CD4 cell count was the most prominent predictor for switching.
- Physicians seem to be reluctant to switch therapy even if WHO criteria for switching are fulfilled. Patients who switched without virological or immunological indication probably switched because they fulfilled the clinical criteria for switching or due to adverse events. A limitation of our study is that most sites did not record information on causes of switching.
- About a third of patients with immunological failure had undetectable viral load values at that time. In contrast over 50% of virologic failures would not have been detected using WHO CD4 criteria alone. Routine viral load monitoring may therefore
 - prevent unnecessary switches and
 - identify failures that would be missed without VL monitoring

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