Adverse Drug Reactions among Patients Receiving Second-line ART in South Africa

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BACKGROUND

As first-line antiretroviral therapy (ART) programmes mature, an increasing number of patients are being switched to second-line regimens. Adverse drug reactions (ADRs) which result primarily from medicines toxicity and drug interactions may compromise the effectiveness of treatment programs through its potential impact on treatment adherence and retention. Understanding the timing and rate of ADRs among patients on second-line ART is important in preventing switches to more expensive third-line regimens, particularly in resource limited settings.

METHODS

This was a retrospective cohort study of HIV positive adult patients (≥18 years) who initiated standard second-line ART at a large urban clinic in Johannesburg, South Africa, from 01 April 2004 – 31 October 2015 (Figure 1).

The primary outcome was the development of a possible ADR defined as one of the following diagnosed conditions three to 12 months after initiating second-line ART: anaemia, dyslipidaemia, pain, skin conditions, neuropathy, diarrhoea, vomiting, gynecomastia/breast conditions, hepatitis, lactic acidosis, decreased kidney function/disease, headaches, glucose intolerance and psychiatric and sleep disorders.

Kaplan Meier survival analysis was used to determine ADR incidence in the first 12 months on second-line ART.

Person-time accrued from second-line treatment initiation to earliest of ADR, 12 months post second-line initiation or last clinic visit date.

Figure 1. Study cohort selection process

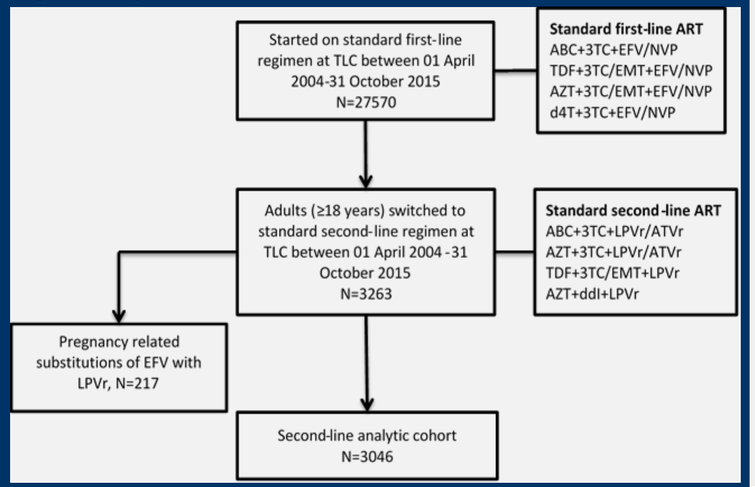


Figure 2. Initial second-line regimen by ART guideline periods of switch

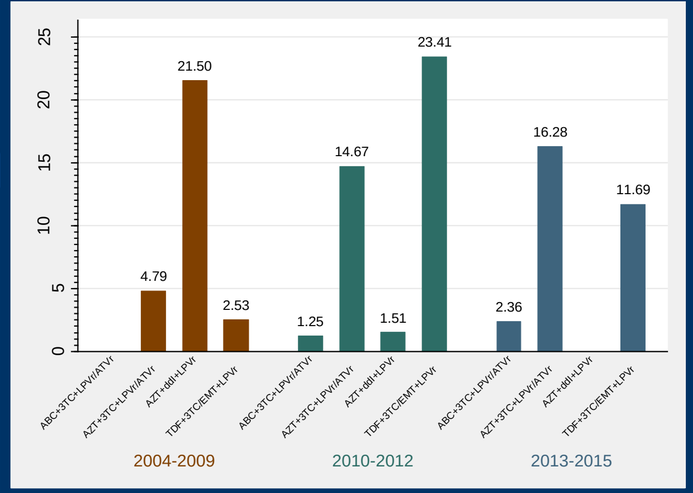
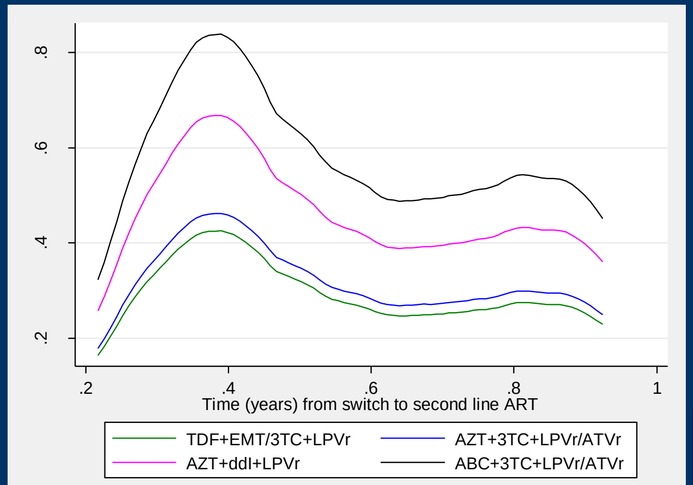


Figure 3. Hazard of an ADR in the first 12 months on second line ART



RESULTS

Table 1. Predictors of an ADR event in the first 12 months on second line ART

Variables	Rate/100py (95%CI)	Adjusted Hazard Ratio (aHR)
Adverse drug reactions 6 months prior to second-line ART initiation		
No	21.1 (19.1-23.3)	1
Yes	60.7 (54.5-67.2)	2.5 (2.2-3.0)
Sex at second-line initiation		
Female	31.8 (29.1-34.8)	1
Male	27.2 (24.0-30.9)	0.7 (0.6-0.9)
Age at second-line initiation (years)		
18-30	35.4 (29.6-42.3)	1
30-40	28.0 (25.1-31.3)	0.9 (0.7-1.1)
≥40	30.7 (27.4-34.4)	1.0 (0.8-1.3)
CD4 cell count at second-line initiation (cells/mm³)		
0-199	42.9 (38.0-48.3)	1.4 (1.2-1.8)
200-349	29.7 (25.3-34.9)	1.2 (0.9-1.5)
≥350	23.8 (20.1-28.1)	1
BMI at second-line initiation		
<18.5	57.7 (46.5-71.6)	1.7 (1.3-2.2)
18.5-24.9	32.6 (29.3-36.3)	1
25-29.9	21.9 (18.6-25.9)	0.7 (0.6-0.8)
≥30	24.8 (20.4-30.0)	0.8 (0.6-1.0)
WHO stage at second-line initiation		
I/II	29.0 (26.4-31.9)	1
III/IV	36.7 (31.3-43.1)	1.2 (1.0-1.5)
Regimen at second-line initiation		
TDF+EMT/3TC+LPVr	23.7 (20.8-27.0)	1
AZT+3TC+LPVr/ATVr	25.7 (22.5-29.2)	1.2 (1.0-1.4)
AZT+ddI+LPVr	44.1 (38.7-50.3)	1.6 (1.3-1.9)
3TC+ABC+LPVr/ATVr	71.1 (54.2-93.3)	2.3 (1.7-3.2)
First-line regimen prior to switch		
ABC+3TC+EFV/NVP	58.5 (30.4-112.4)	1.6 (0.8-3.1)
TDF+EMT/3TC+EFV/NVP	24.7 (21.7-28.1)	1
AZT+3TC+EFV/NVP	29.1 (23.7-35.8)	1.2 (0.9-1.5)
d4T+3TC+EFV/NVP	34.2 (31.0-37.7)	1.3 (1.0-1.5)

BMI (Body Mass Index); WHO (World Health Organization); 3TC (Lamivudine); ABC (Abacavir); LPVr (Lopinavir/Ritonavir); ATVr (Atazanavir/Ritonavir); AZT (Zidovudine); ddI (Didanosine); TDF (Tenofovir); EMT (Emtricitabine); d4T (Stavudine); NVP (Nevirapine)

A total of 3046 patients initiated standard second-line ART. Of these patients, 24.0% (731/3046) had developed an ADR during the first 12 months of second line ART. Among the 731, 338 (46.2%) had experienced an ADR in the last 6 months of first-line ART.

The most frequent ADR were Anaemia (63.1%), renal insufficiency (10.9%), lipid conditions (7.0%), gastro-intestinal problems (6.4%). Overall ADRs occurred at a median time of 5.6 months (IQR: 4.1-8.3).

The highest ADR incidence was observed among patients receiving ABC+3TC+LPVr/ATVr or AZT+ddI+LPVr (Figure 2 & Table 1). While the lowest rate was observed among patients receiving TDF+EMT/3TC+LPVr.

The risk of experiencing an ADR in the first year on second-line ART was higher among those who experienced an ADR before switching to second line ART compared to those who did not, among females compared to males and among patients in staged III/IV compared to those in earlier disease staged. However, the risk of ADR decreased with increasing CD4 count and BMI at the time of switch to second line ART.

CONCLUSION

ADRs are fairly common among patients receiving second line ART. Patients who experienced an ADR while on first line ART remain at risk even after switching to second line ART. Patients switched to TDF based second line ART show lower rates of ADRs.

The ADRs occur within 6 months of second-line ART initiation. However, the declining incidence over time suggest that single/multi-drug substitutions may have taken place. Access to alternative second line drugs is key to ensuring greater ART adherence and retention.

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