

# High Rates of Non-Fatal Toxicities in a 24 Month Cohort Receiving Publicly Funded HAART in South Africa

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## BACKGROUND

Publicly funded antiretroviral therapy (ART) commenced in South Africa in April 2004. In accordance with the World Health Organization recommendations for ART in resource-limited settings, seven antiretrovirals are available through the national program. The first line regimen consists of either efavirenz (EFV) or nevirapine (NVP) with stavudine (d4T) and lamivudine (3TC). The second line regimen, recommended for virological failure consists of lopinavir/ritonavir (LPV/r), didanosine (ddI), and zidovudine (AZT). Individual drug switches are permitted for toxicity.

ART toxicities significantly impact outcomes. Toxicities may result in significant morbidity and mortality, affect adherence, interfere with other medications (TB therapy), and necessitate regimen changes. Specific toxicities include peripheral neuropathy, lipodystrophy, gynecomastia, pancreatitis, lactic acidosis, dyslipidemia, and hypersensitivity.

Few studies have been published on long-term toxicities of patients receiving government funded ART in South Africa. Cohorts from Khayelitsha and McCord Hospital indicate that peripheral neuropathy and lipodystrophy are the most common toxicities necessitating an ART regimen change, and that overweight women may be at increased risk of lactic acidosis. In order to better define the long-term side effects of a d4T-containing first-line regimen and their impact on clinical management, we performed a retrospective record review of patients followed for two years on publicly funded ART in South Africa.

## METHODS

We performed a retrospective record review to describe the effects of two years of treatment at a large, urban, publicly funded South African clinic. Patients were ART-naïve, non-pregnant adults initiated on treatment between April and July of 2004 at the Johannesburg Hospital HIV clinic. A total of 305 patients were available for review.

The following variables were recorded:

- socioeconomic demographics
- incidence of pre- and post-ART opportunistic infections
- serial clinical and laboratory parameters (weight, CD4 cell count, and hemoglobin)
- side effects of treatment and regimen changes.

Clinically significant side effects necessitating regimen changes were corroborated with pharmacy records. Data was systematically extracted by a chart reviewer (EW). Incidence was calculated in person-years of follow-up from ART initiation until the first censoring event, which included 24 months of follow-up, last known clinic visit, date of transfer of care, or date of death. Defaulters were defined as patients who failed to attend within six weeks of their last scheduled clinic visit or pharmacy medication appointment. Patient disposition was determined by active case finding through the use of a dedicated case manager and searching of death records. Data were expressed as means ( $\pm$  standard deviation).

The study was approved by The University of the Witwatersrand Ethics Committee.

## RESULTS

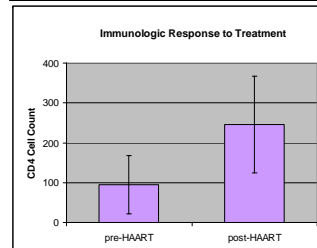
### Characteristics of the Cohort

**Table 1.** Characteristics of 305 HIV-infected patients initiated on ART, Johannesburg Hospital HIV clinic, April – July, 2004

Characteristic	Value	Characteristic	Value
Age (yr)	36±6.6	TB status – no of patients (%)	
Female patients – no of patients (%)	212 (70)	Never TB	155 (51)
Black race – no of patients (%)	276 (96)	Ongoing TB therapy at ART initiation	44 (14)
Unemployed status – no of patients (%)	204 (70)	TB therapy completed before ART initiation	80 (26)
Marital status – no of patients (%)		TB therapy initiated post-ART	18 (6)
Single	181 (59)	Duration since HIV diagnosis (yrs)	3.4±4.6
Married	61 (21)	Initial ART regimen – no of patients (%)	
Divorced / Separated	11(4)	1A: (d4T, 3TC, EFV)	301 (99)
Widowed	10 (3)	Other	4 (1)
Cohabiting	13 (4)	Disposition – no of patients (%)	
Education level – no of patients (%)		Still followed	225 (74)
None	10 (3)	Defaulted	57 (19)
0-7 yrs	48 (16)	Transferred	6 (2)
8-12 yrs	176 (58)	Died	17 (6)
>12 yrs	17 (6)		

\*Plus-minus values are means  $\pm$  SD

### Response to HAART

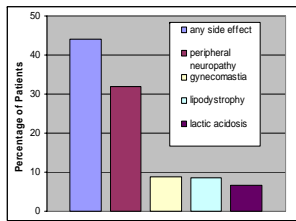


**Fig 1: Immunologic response to ART in a cohort of 305 patients.** Over an average treatment period of 1.5 years, mean CD4 count increased from 95±73 to 245±121 cells/mm<sup>3</sup>.

### Toxicities associated with d4T-containing ART first-line regimen

44.1% of patients experienced one or more treatment related side effect, yielding an incidence rate of 30.3 events/100 patient-years.

19.7% of patients changed regimens due to toxicities. Regimen changes occurred after 14.5±7.4 months of therapy.



**Fig 2. High rates of ART toxicity in patients initiated on d4T-containing regimen.** 135 (44.1%) patients experienced one or more treatment related side effects. The most common side effects were peripheral neuropathy (n=97, 31.8%), gynecomastia (n=27, 8.9%), lipodystrophy (n=26, 8.5%) and lactic acidosis (n=20, 6.6%).

During the follow-up period there were 17 (6% of all treated patients) deaths, 2 of which were attributed to fatal toxicities of ART.

## SUMMARY OF RESULTS

Mean duration of follow-up was 1.49±0.58 years, with a total of 445 patient-years of follow-up. Mean CD4 cell count increased from 95±73 to 245±121 cells/mm<sup>3</sup>, with 81.3% of patients having at least one documented undetectable viral load after ART initiation.

135 (44.1%) patients experienced one or more treatment related side effect, yielding an incidence rate of 30.3 events/100 patient-years. The most common side effects were peripheral neuropathy (n=97, 31.8%), lipodystrophy (n=26, 8.5%), gynecomastia (n=27, 8.9%), and lactic acidosis (n=20, 6.6%).

Treatment limiting side effects necessitated ART regimen change in 60 (19.7%) of patients. On average, regimen changes occurred after 14.5±7.4 months of therapy. During the follow-up period there were 17 (6%) deaths, 2 of which were attributed to fatal toxicities of ART (1 to lactic acidosis, and 1 to fulminant hepatitis).

## CONCLUSIONS

Although publicly funded ART treatment in South Africa is associated with low mortality and favorable clinical and immunologic responses, significant non-fatal adverse effects – lipodystrophy (including lipodystrophy and gynecomastia), lactic acidosis and peripheral neuropathy – necessitated a regimen change in one-fifth of patients initiated on d4T/3TC/Etz.

In response to increasing data showing d4T associated toxicities in the developing world, WHO guidelines for ARV treatment in resource-limited settings have been revised to recommend removing d4T from first-line regimens wherever possible. Our findings support these revised WHO guidelines that caution against the toxicities of d4T-containing regimens.

## FUTURE DIRECTIONS

We are in the process of analyzing the data collected from this cohort and answering additional research questions. In particular, we are interested in analyzing serial weights and correlating them to virologic and immunologic treatment responses. The value of weight as an indicator of treatment response is of interest in resource-limited settings, where efforts to minimize laboratory testing may have significant impact on publicly funded ART programs.

## REFERENCES

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