

Early and Late Toxicities of the First-Line Antiretroviral Regimen in Johannesburg, South Africa

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Background

Concern has emerged about toxicities of d4T-containing regimens used in the global antiretroviral roll-out. While d4T will be increasingly phased out, its low cost and inclusion in fixed-dose combinations ensures its continued widespread use. Understanding the time to onset of ARV toxicities in a Southern African population is critical for clinical management and may help guide planned drug substitutions.

Methods

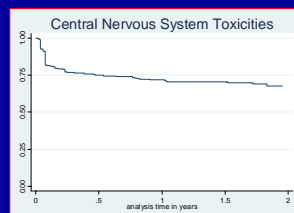
This is a retrospective review of the first 303 consecutive non-pregnant, adult patients initiated on publicly funded HAART at Johannesburg Hospital ARV clinic from April-June 2004. Time-to-event analysis was performed for five toxicities observed during the first 24 months of follow-up. For each toxicity, incidence rates were calculated during the first and second year of treatment and expressed in events per person-year (95% CI).

Table 1. Baseline Characteristics of 303 consecutive antiretroviral naïve patients who were started on HAART at Johannesburg General Hospital from April 2004 to June 2004

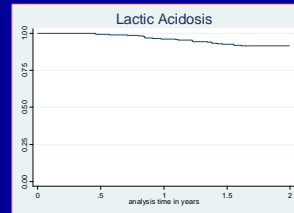
| | |
|-------------------------------------------------------|--------------------|
| Female, n (%) | 210 (69) |
| Median age, years (range) | 35 (20-67) |
| Race, n (%) | |
| Black | 274 (95) |
| White | 5 (2) |
| Coloured | 5 (2) |
| Asian | 3 (1) |
| Mean baseline weight, kg (SD) | 62 (13) |
| Median baseline CD4 count, cells/u/l (range) | 90 (1-341) |
| Median baseline viral load, 1000 copies/mL (range) | 190000 (0-2100000) |
| History of Tuberculosis prior to HAART initiation | |
| TB treatment completed before initiating HAART, n (%) | 80 (26) |
| TB treatment ongoing when HAART initiated, n (%) | 43 (14) |
| Pre-existing Peripheral Neuropathy, n (%) | 18 (6) |
| Initial Regimen | |
| d4T/3TC/EFZ, n (%) | 301 (99) |
| d4T/3TC/NVP, n (%) | 2 (1) |

Figure 1. Survival analysis for five toxicities over 24 months of follow-up. Three distinct side-effect profiles were observed: early, constant, and late onset of toxicity.

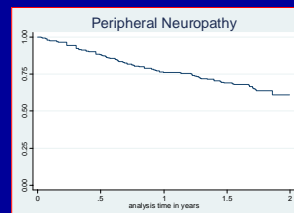
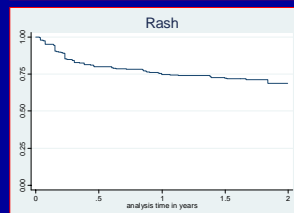
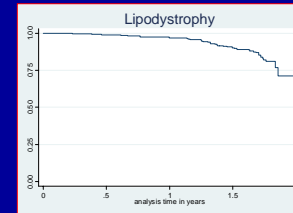
Early onset toxicities



Constant onset toxicities



Late onset toxicity



Early toxicities were CNS side-effects and rash. CNS toxicity was greater in year 1 (0.41; 0.33-0.50), than in year 2 (0.05; 0.02-0.11). Similarly, rash peaked in year 1 (0.32; 0.25-0.41) compared to year 2 (0.07; 0.04-0.14).

Constant onset of toxicity from year 1 to year 2 was seen in peripheral neuropathy (0.27; 0.21-0.32) versus 0.21 (0.14-0.31) and lactic acidosis (n=20; 0.04; 0.02-0.07) versus 0.06 (0.03-0.12).

Late onset of toxicity was characteristic of lipodystrophy, with a significantly lower incidence in year 1 (0.03; 0.02-0.06) than in year 2 (0.21; 0.15-0.31).

Table 2. Incidence of toxicities, overall and by year of treatment, in a cohort of 303 consecutive antiretroviral naïve patients initiated on HAART at Johannesburg General Hospital from April 2004 – June 2004 and followed for 24 months.

| Toxicity | Events | Overall incidence (95% CI) ^a | Incidence in year 1 (95% CI) | Incidence in year 2 (95% CI) |
|------------------------------------|--------|-----------------------------------------|------------------------------|------------------------------|
| CNS toxicity ^b | 88 | 0.28 (0.22-0.34) | 0.41 (0.33-0.50) | 0.05 (0.02-0.11) |
| Rash | 80 | 0.23 (0.19-0.29) | 0.32 (0.25-0.41) | 0.07 (0.04-0.14) |
| Peripheral Neuropathy ^c | 88 | 0.25 (0.20-0.31) | 0.27 (0.21-0.35) | 0.21 (0.14-0.31) |
| Lactic Acidosis | 20 | 0.05 (0.03-0.07) | 0.04 (0.02-0.07) | 0.06 (0.03-0.12) |
| Lipodystrophy ^d | 40 | 0.10 (0.07-0.13) | 0.03 (0.02-0.06) | 0.21 (0.15-0.31) |

^a All incidences are expressed as event per person-year

^b Includes headache (36), dizziness (43), insomnia (6), bad dreams (10), sensory disturbances (5) and psychosis (2). Patients may have reported more than one simultaneous CNS side effect.

^c Includes only patients with new cases of peripheral neuropathy after initiating antiretroviral therapy. Patients with preexisting peripheral neuropathy are excluded.

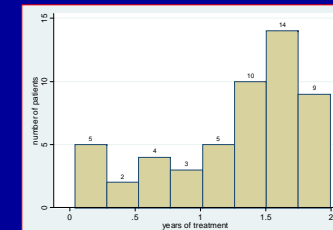
^d Includes lipodystrophy and breast enlargement

Clinical Significance of the Toxicities

303 patients were followed for 431 patient years. During the 24 month period of observation, 60 patients (19.8%) switched from their initial antiretroviral regimen. Of the 60 regimen changes, 52 (87%) were due to treatment-related toxicities: 22 (42%) lipodystrophy, 19 (37%) peripheral neuropathy, 9 (17%) lactic acidosis, 3 (6%) CNS side-effects, and 1 (2%) rash. More than one simultaneous reason for change was possible.

Figure 2. Timing of first regimen change.

Of the 52 patients who switch their first-line regimen due to side effects, 14 (27%) switches occurred in year one of treatment and 38 (73%) occurred in year two.



Conclusions

d4T-specific toxicities (peripheral neuropathy, lipodystrophy, and lactic acidosis) appear to be significant and cumulative. Other toxicities (CNS side effects and rash) appear within the first year and rarely necessitate regimen change. Physicians should anticipate increasing rates of toxicities during the second year of treatment with d4T containing regimens. Low cost alternatives with lower toxicities are urgently needed.

