



# ART-Associated Toxicities Leading to a Switch in Medication: Experience in Uganda, Kenya, and Zambia

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## ABSTRACT

- Background:** The AIDSRelief care and treatment program is a PEPFAR supported program. We report the antiretroviral associated toxicity which was associated with a change in treatment reported between August, 2004 and June 1, 2006, out of 6,520 treated patients in Uganda, Kenya, and Zambia.
- Methods:** A standardized medical record format is utilized across the three countries. Only drug associated toxicities leading to a clinical decision to change an antiretroviral medication are recorded within the medical record and subsequently abstracted into the CareWare electronic database. The frequencies of associated toxicities were aggregated across the three countries regardless of what regimen the drug was in combination with.
- Results:** A total of 1,164 patients experienced a toxicity which resulted in a drug switch. Of 2,149 patients treated with D4T, 24% switched due to an associated toxicity including neuropathy, lipatrophy, pancreatitis, or lactic acidosis. Of the 1,433 patients treated with AZT, 13% switched due to anemia or GI intolerance. Of the 2,938 treated with TDF, 0.7% switched due to renal insufficiency. Of the 4,288 patients treated with NVP, 6.6% switched due to rash or hepatic toxicity. Of the 3,657 patients treated with EFV, 3.4% switched due to CNS intolerance, rash, or hepatic toxicity. Of the 622 patients treated with LPV/r, 2.0% switched due to metabolic abnormalities, liver toxicity, or diarrhea.
- Conclusion:** Toxicities reported in our program are similar to other published reports in Africa. The comparably low toxicity rates of Tenofovir and Efavirenz support the preferential use of these agents for a "public health" approach over the current predominately used agents. Limitations of the study include an underestimation of toxicities and reliance on provider diagnosis and discretion to change therapy.

## OBJECTIVE

Appropriate decisions on antiretroviral drug forecasting and the selection of first line therapy should be based on evidence from the targeted treatment populations.

- Although toxicity is a major limitation both for the short term and long term durability of antiretroviral therapy, little data exists on the expected rates of antiretroviral therapy toxicity outside of the US and Europe to guide these decisions.
- We aimed to routinely and systematically compile information on the rates and reasons of dose limiting toxicity in routine clinical care in our PEPFAR supported antiretroviral treatment programs.

## INTRODUCTION

AIDSRelief is a care and treatment program supported by the President's Emergency Plan for AIDS Relief working in 9 countries. The program started the treatment of patients with antiretroviral therapy in August, 2004. Outcomes data including mortality, lost to follow up, and antiretroviral drug associated toxicities leading to a change in treatment are recorded for quality assurance and evaluation. Here we report the antiretroviral associated toxicities reported between August, 2004 and June 1, 2006, out of 6,520 treated patients in Uganda, Kenya, and Zambia in which data was obtained.

## METHODS

- Longitudinal medical record systems geared towards HIV care and treatment were established at each treatment facility.
- Clinical decisions to stop or switch antiretroviral therapy and the reason for the decision were routinely captured on all patient visits on "follow-up" encounter forms.
- Information from medical records were subsequently entered in the Care Ware (international version) electronic database. Continuous data quality improvement activities were utilized.
- All treatment facilities were supplied with access to routine safety labs including AST, ALT, HCT, Hb, creatinine, amylase, and serum glucose. Ability to monitor for lactic acid and serum lipids was not readily available.
- All treatment facilities were supplied with direct access to alternative first line therapy, AZT, TDF, EFV, and LPV/r. TDF was not available in Zambia, and was predominately used as first line in Uganda.
- Clinician selection of the reason for stopping or switching drugs for toxicity or intolerance was guided through an evidence based "menu" of options, including "other" as a choice. Clinicians had the ability to write in an alternative reason not on the "menu".
- Data was analyzed using STATA 9.2 Special Edition.

## RESULTS

Demographics of Treated Population	N=6520	(%)
Female	4434	(68%)
Age (mean)	37	
Patients with Dose Limiting Toxicity	N=1164	(%)
Female	706	(67%)
Age (mean)	36	
Days on Regimen Prior to Toxicity (mean)	153	

All Clinical Reasons for Therapy Switch		
	N	(%)
Clinical Failure	240	(3.6)
Drug Interaction	324	(4.9)
Patient Preference	31	(0.4)
Poor Adherence	40	(0.6)
Pregnancy	94	(1.4)
Toxicity	1164	(18.0)
Unlisted	495	(7.6)
<b>Total</b>	<b>2388</b>	<b>(36.6)</b>

Drugs	Total Started	Observed % Switched Due to Toxicity	Median time to toxicity (days)
D4T	2149	24.6%	141
AZT	1433	13.2%	81
TDF	2938	0.7%	58
NVP	4288	6.6%	83
EFV	3657	3.4%	119
LPV/r	622	2.0%	25

D4T Attributable Toxicity		
	N	(%)
Lactic Acidosis	13	(2.4)
Lipatrophy	40	(7.5)
Pancreatitis	4	(0.7)
Peripheral Neuropathy	279	(53.0)
Other/Reason not documented	194	(36.0)
<b>Total</b>	<b>530</b>	

AZT Attributable Toxicity		
	N	(%)
Headache	2	(0.01)
Neutropenia	1	(0.50)
Anemia	123	(61.5)
Nausea/Vomiting	6	(0.03)
Other/Reason not documented	132	(66.0)
<b>Total</b>	<b>190</b>	

TDF Attributable Toxicity		
	N	(%)
Renal Toxicity	3	(13.6)
Other/Reason not documented	19	(86.0)
<b>Total</b>	<b>22</b>	

NVP Attributable Toxicity		
	N	(%)
Hepatotoxicity	18	(6.3)
Rash	92	(3.2)
Other/Reason not documented	175	(5.5)
<b>Total</b>	<b>285</b>	

EFV Attributable Toxicity		
	N	(%)
Hepatotoxicity	2	(1.60)
CNS	20	(16.1)
Rash	18	(14.5)
Other/Reason not documented	84	(67.7)
<b>Total</b>	<b>124</b>	

LPV/r Attributable Toxicity		
	N	(%)
Nausea/Vomiting	4	(30.7)
Diarrhea		Not documented
Other/Reason not documented	9	(69.2)
<b>Total</b>	<b>13</b>	

## DISCUSSION/LIMITATIONS

Limitations of the study include an underestimation of toxicities and reliance on provider diagnosis and discretion to change therapy.

- Our analysis covered only a 20 month time period. This could significantly underestimate time dependent metabolic complications associated with D4T toxicity, as well as AZT, TDF, and LPV/r.
- We chose only to capture toxicities which led to a clinical decision to stop or switch drugs. We did not attempt to have clinicians "grade" toxicities, thus there is no uniform definitions as would be seen in clinical trials.
- Decisions to stop or switch drug were purely based on clinical experience and knowledge, and we saw differences in toxicity rates between different treatment sites, with less use of alternative first line drugs associated with less experienced clinicians.
- The majority of patients started therapy with CD4 counts well below 200c/mm<sup>3</sup>, which may have contributed to the lower than expected NVP toxicity rates observed.

## CONCLUSION

Toxicities reported in our treatment programs, are similar to other published reports in Africa and India. The comparably low toxicity rates of Tenofovir and Efavirenz support the preferential use of these agents for a "public health" approach over the current predominately used agents.

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