Antiretroviral Toxicity Leading to a Medication Change in Multiple HIV Clinics in Resource Limited Settings

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Abstract

Background: Toxicities that led to antiretroviral substitution in a multi-country treatment program were described.

Methods: First line regimens included stavudine, lamivudine and nevirapine or efavirenz. Alternative therapy included zidovudine, tenofovir, efavirenz and lopinavir/ritonavir. Clinicians were trained to diagnose common antiretroviral side effects. Facilities had access to safety laboratory assays. Toxicity was detected clinically, and confirmed or monitored using specific laboratory assays where indicated.

Results: Between 2004 and 2006, among 6,520 patients in Uganda, Kenya and Zambia, initiating antiretroviral therapy, toxicity-related substitutions were observed for stavudine 24.6%, zidovudine 13%, nevirapine 6.6%, efavirenz 3.4%, lopinavir/ritonavir 2% and tenofovir 0.7%. Mean time to switch ranged from 25 days for Lopinavir/ritonavir, to 141 days for stavudine. Most common toxicities included neuropathy (stavudine), anemia (zidovudine), rash and liver toxicity (nevirapine).

Conclusions: Toxicity rates in the study were comparable to reports in Food and Drug Administration (FDA) label package inserts and other smaller published reports in Africa and Asia. These toxicity rates could be used to inform drug forecasting for resource-limited settings. Comparably high tolerability of tenofovir and efavirenz may support their preferential use.

Keywords: Antiretroviral agents; Drug tolerance; Low-income populations; Drug substitution; Public health

Background

Since 2004 there has been a substantial increase in access to combination antiretroviral therapy (cART) in low and middle income countries (LMICs). Over 6 million individuals were on cART by December 2010 [1]. Successful cART has been shown to be feasible and cost-effective in these settings, offering comparable mortality and morbidity benefits demonstrated in Western Europe and North America [2,3]. However achieving durable viral suppression in a majority of patients in LMICs remains a challenge, due in part to advanced disease at time of treatment initiation, interruptions in drug supply chain, drug interactions with frequently prescribed medications, and drug toxicities associated with guideline driven antiretroviral regimens. Antiretroviral intolerance and toxicity prevent adherence and predispose patients to fail HIV therapy [4]. In many LMICs faced with limited drug formulary the increased cost and complexity of care created by drug toxicity are additional strains to the health system [4-6]. Therefore the subsequent need to improve health providers capacity for early detection and competent management of adverse effects, the resulting need to improve laboratory capacity to detect serious side effects and demand to widen the antiretroviral formulary for appropriate switching of problem drugs further increases the costs of HIV care and treatment [7]. Therefore, selecting a drug regimen with the most favorable safety profiles and least complicated monitoring requirements would best support a public health approach to care where wide scale use of one regimen is driven by national treatment guidelines.

Furthermore, appropriate decisions on antiretroviral drug selection and the forecasting of alternative first line therapies should be based on evidence from the targeted treatment populations. Data on antiretroviral toxicity has largely been described for male patients in European and North America clinical research settings, and may not always be generalizable. For instance, Botswana women receiving thymidine analogues have a higher than expected incidence of mitochondrial toxicity [8]. There is a growing body of literature on the prevalence of toxicities in LMICs. By Grave et al. found that patients on zidovudine (AZT) and stavudine (d4T)-based therapy were more than twice, and more than five times likely, respectively to have a toxicity-driven regimen switch compared to those on tenofovir (TDF)-based regimens [9].

The aim of the study was to enhance the knowledge of antiretroviral toxicity, by determining the rates of toxicities leading to antiretroviral switches as part of routine clinical care in the United States President’s Emergency Plan for Aids Relief (PEPFAR) supported antiretroviral treatment programs. Toxicities that caused a drug change in 3 of the target sub-Saharan countries are described.

Methods

Study sites

AIDS Relief was a HIV treatment program supported by PEPFAR in ten countries, including Kenya, Uganda, Zambia, Nigeria, Tanzania, Ethiopia, Rwanda, South Africa, Guyana and Haiti. At the time of this analysis, the program supported 100,000 patients on cART and an estimated 250,000 individuals in palliative care. The program started in

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August 2004 initially by partnering with non-for-profit private health facilities largely located in rural and improvised locations. The facilities had physician and non-physician health providers. The study sites included were those in Kenya, Uganda and Tanzania.

Antiretroviral regimens

Combination Antiretroviral Therapy was initiated to eligible patients as defined in guidelines from the World Health Organization (WHO) and the respective countries. At the time of this analysis, these included patients with a CD4 cell count of <200/mm³, WHO stage IV disease and some with stage III disease. AIDS Relief provided a varied antiretroviral drug formulary. The first line therapies in most of the countries were d4T, lamivudine (3TC) and nevirapine (NVP). Efavirenz (EFV) was reserved for men, women outside the reproductive age group, and patients on concurrent rifampin therapy or with NVP toxicity. In Uganda, TDF could be used as first line therapy with 3TC and either NVP or EFV as indicated. All facilities were supplied with direct access to alternative therapy, including AZT, TDF, EFV and lopinavir-ritonavir (LPV/r). No additional protease inhibitors were available. TDF was not available in Zambia. A d4T dose of 30 milligrams was used for adult patients weighing less than 60 kilograms. NVP was excluded for patients with transaminase levels more than 2.5 times the upper limits of normal. TDF was excluded if the estimated creatinine clearance was less than 50 mL/min.

Monitoring and management of antiretroviral toxicity

Clinicians were trained to diagnose common adverse effects through didactic instruction and hands-on medical mentoring by experienced providers. All treatment facilities were supplied with access to safety laboratory assays including serum transaminases, amylase, glucose, creatinine, and plasma hematocrit. Viral load measurement, serum lactate acid level and lipids were not routinely available in most facilities. Programmatic intention to improve safety was for all patients prescribed cART to have serum creatinine, hematocrit and transaminase determination prior to starting therapy. Subsequent treatment toxicity was detected clinically, and confirmed or monitored using specific laboratory assays where indicated. Protocol driven laboratory assessment was not endorsed except that a repeat transaminase assay was to be performed if a patient initiating NVP had rash or any symptoms consistent with hepatitis. Longitudinal medical record systems created specifically for HIV care were established at each treatment facility. Clinical decisions and reasons to stop/switch cART were routinely documented on follow-up encounter forms.

Data collection and analysis

This was a retrospective cohort study. Information from the medical records was entered into the CAREWare® (international version, Jeff Murray’s Programming Shop, Inc., New Orleans, United States of America) electronic database. Outcomes data including mortality, periodic CD4 cell count determinations, retention status, adherence rates, opportunistic infections and antiretroviral drug-associated toxicities were routinely recorded for patient management, quality assurance and program evaluation. Clinician selection for determination of the reason for stopping or switching drugs because of 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”. Antiretroviral associated toxicities that led to a clinical decision to switch an antiretroviral drug between August 2004 and June 1, 2006, out of 6,520 patients in Uganda, Kenya and Zambia were described. The data were analyzed using STATA™ 9.2 Special Edition.

Results

6,520 records of patients who had initiated cART after August 2004 within the AIDSRelief program were analyzed (Table 1). 68% were female and the mean age was 37 years.

2388 (36.6%) patients sampled had a drug switch in the period, of whom 1164 (18%) were switched due to toxicity.

Drug toxicity was the most frequently listed reason for drug substitution (Figure 1). 61% of patients with dose-limiting toxicity leading to a switch were female.

Table 2 shows the proportions of patients switching due to toxicity for each drug. D4T had the most switches (24.6%) while tenofovir was the least frequently switched antiretroviral (Table 2).

Most documented switches due to NVP were due to rash, while rash and CNS adverse effects were the most documented reasons for EFV switch.

13 patients were switched due to lopinavir/ritonavir toxicity; 4 had

<table>
<thead>
<tr>
<th>Drug in initial therapy</th>
<th>Total started</th>
<th>Observed number and % switched due to toxicity</th>
<th>Median time to switch (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D4T</td>
<td>2149</td>
<td>530 (24.6%)</td>
<td>141</td>
</tr>
<tr>
<td>AZT</td>
<td>1453</td>
<td>261 (18.2%)</td>
<td>81</td>
</tr>
<tr>
<td>TDF</td>
<td>2938</td>
<td>22 (0.7%)</td>
<td>58</td>
</tr>
<tr>
<td>NVP</td>
<td>4288</td>
<td>285 (6.6%)</td>
<td>83</td>
</tr>
<tr>
<td>EFV</td>
<td>3657</td>
<td>124 (3.4%)</td>
<td>119</td>
</tr>
<tr>
<td>LPV/r</td>
<td>622</td>
<td>13 (2%)</td>
<td>25</td>
</tr>
</tbody>
</table>

Table 2: Numbers and proportions of patients switching therapy due to toxicity. The nucleos(t)ides (D4T, AZT, TDF) were switched among each other, and the non-nucleosides (NVP, EFV) were switched to each other or to LPV/r, as appropriate.
A higher proportion of men compared to women were switched due to toxicity, 706 (22%) vs. 458 (16%), respectively (p<0.001).

Discussion

For the most part the findings comparable to those from clinical trials in other similar care settings, and data reported in Food and Drug Administration (FDA) package labels from branded antiretrovirals (Table 4). In a similar study in primary care centers in Cape Town, South Africa, 71% of the study population (N=2679) were women, substitutions on d4T occurred in 21% of patients by 3 years, due to symptomatic hyperlactatemia (5%), lipodystrophy (9%) or peripheral neuropathy (6%). Substitutions due to AZT occurred in 8%, while those due to NVP occurred in 8% and EFV in 2%. TDF, however, was not part of the primary regimen in this study [10].

Although deaths directly attributed to cART toxicity are exceedingly rare [11] (in LMICs, most deaths in patients on cART occur early, in the first year, and are more often due to infections, wasting syndrome and malignancy [12], it increases costs and complexities of care. D4T was the most frequently implicated drug in toxicity-related switches. This is consistent with data from a Uganda study in which 84% of drug substitutions were due to d4T-related adverse effects [13].

The incidence of nucleoside analogue related lactic acidosis is approximately 0.57–8.5 per 1000 person years of antiretroviral therapy in developed country settings [26]. Lactic acidosis and hepatic steatosis have been particularly associated with d4T and didanosine (ddI), as well as female sex, older age and higher Body Mass Index (BMI) [27]. Other risk factors for d4T-associated lactic acidosis include pregnancy, renal insufficiency, low CD4 nadir and concomitant use of ribavirin, hydroxyurea, nephrotoxic agents and ddI [28]. The incidence is markedly higher in LMICs compared to other study groups, up to 19 per 1000 patient-years [29]. Less than 0.006% of the study patients had suspected lactic acidosis–comparable with other studies in similar settings. The rarity of the syndrome and the scarcity of appropriate laboratory confirmatory testing suggest that the data may underestimate the actual incidence, since lactic acidosis may go unrecognized clinically. 13% of patients who initiated d4T were switched due to peripheral neuropathy. 8-52% of patients on d4T experience neuropathy, especially in advanced HIV infection and in pre-existing neuropathy or with concomitant neurotoxic medications [30]. The study data does not account for grading of neuropathy, since patients with milder neuropathy may not have been switched. Early neuropathy may be missed except by more experienced and proactive providers. Similarly, the 1.9% rate of lipoatrophy/lipodystrophy (LAP/LDP) necessitating switch from d4T may underestimate the true

<table>
<thead>
<tr>
<th>Drug</th>
<th>D4T</th>
<th>AZT</th>
<th>TDF</th>
<th>NVP</th>
<th>EFV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxities</td>
<td>(n = 2149)</td>
<td>(n = 1433)</td>
<td>(n = 2938)</td>
<td>(n=4288)</td>
<td>(n=3657)</td>
</tr>
<tr>
<td>Lactic acidosis/ pancreatitis/ lipatrophy</td>
<td>57 (2.7%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral Neuropathy</td>
<td>279 (13%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Headache/ GI intolerance</td>
<td>0</td>
<td>6 (0.4%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>0</td>
<td>123 (6.6%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Renal toxicity</td>
<td>0</td>
<td>0</td>
<td>3 (0.1%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other/ Reason not Documented</td>
<td>194 (9%)</td>
<td>132 (6.2%)</td>
<td>19 (0.6%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total switched due to NRTI toxicity</td>
<td>530 (24.60%)</td>
<td>261 (18.20%)</td>
<td>22 (0.7%)*</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>18 (0.4%)</td>
<td>2 (0.05%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>92 (2.1%)</td>
<td>18 (0.5%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CNS</td>
<td>0</td>
<td>20 (0.5%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other/Reason not documented</td>
<td>175 (4.10%)</td>
<td>84 (2.30%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total switched due to NNRTI toxicity</td>
<td>285 (6.6%)</td>
<td>125 (3.4%)*</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*p<0.001

Table 3: Toxicity initiating switch for Reverse Transcriptase inhibitors.

Table 4: Comparison of discontinuation rates associated with antiretrovirals in various major trials/ package insert data.
incidence, since clinicians may have missed early LAP/LDP, or may not readily switch in mild LAP/LDP partly in the setting of a limited drug formulary. Dual-energy X-ray Absorptiometry (DEXA) for diagnosis of LAP/LDP is not readily available in LMICs, but patients’ self-report correlates well and can be incorporated for early diagnosis [31].

8.6% of patients starting AZT in this study were discontinued due to anemia, comparable to other studies [15,32]. The lower 1.1% rate quoted in the package insert is derived from an evaluation with a now infrequently used 500 mg/d adult dose in largely asymptomatic patients with higher BMI [16].

TDF induced renal dysfunction occurs more often in patients with pre-existing renal dysfunction, with low BMI, age greater than 50 years, concomitant use of other nephrotoxic drugs, and most consistently with low CD4 cell count and presence of diabetes [33]. TDF-related nephrotoxicity causing infrequent drug switch (0.7% of patients initiating a TDF-based regimen) is consistent with data from other studies [34]. Longer-term studies through 144 weeks suggest no clinically relevant renal disease or adverse events associated with TDF, and better tolerability compared to other nucleoside analogues [35,36]. The association with low BMI suggests that renal toxicity may be dependent on drug exposure. In countries which utilize thymidine analogues in their first line regimens, second line regimens often include TDF with LPV/r, by which interaction the TDF exposure increases some 30%; increasing renal toxicity may therefore be observed with time [37]. In this analysis, urinalysis or serum phosphate testing were not routinely performed; the rate of renal tubular dysfunction therefore remains undetermined. Further, the cohort is comprised largely of patients younger than 50 years of age, which may further contribute to lower renal toxicity rates.

Rates of switch appear lower for EFV and NVP, compared to other studies, perhaps owing to lack of ‘routine’ laboratory monitoring of liver chemistry or missed clinical diagnosis, but are consistent with findings of higher toxicity-switch rates due to NVP, especially related to liver and skin effects [10,18]. Dose-limiting EFV-related neurocerebellar symptoms, found in the study, albeit lower, are also comparable to other studies in similar settings [38].

The switches from LPV/r suspected toxicities occurred relatively early—after a mean of 25 days on therapy—suggesting that gastrointestinal intolerance rather than metabolic abnormalities could have contributed. This 2% rate of switch compares with the 2-4% in other studies, but may have been under-estimated by missed diagnosis of lipid/glycemic complications and LAP/LDP [25].

Limitations of the Study

Decisions to stop or switch drug were purely based on clinical experience and knowledge; differences in reported toxicity rates between different treatment sites and use of alternative first line drugs appeared to vary with clinician experience. Role of co-administered medications was not evaluated. A significant number of reasons for switch were not described. This analysis covered only a 20 month time period, and combined with a lack of routine periodic laboratory monitoring (lipids, lactate, creatinine and blood glucose/glycated hemoglobin) it may exclude time dependent metabolic complications associated with d4T, LPV/r, AZT, EFV and perhaps TDF. Only toxicities which led to a clinical decision to stop or switch drugs are described—there was no attempt to have clinicians “grade” toxicities with uniform definitions as would be seen in clinical trials. The majority of patients started therapy with CD4 counts well below 200 cells/μL, which may have contributed to the lower than expected NVP toxicity rate, and perhaps to the higher toxicity rates observed with d4T. Finally, the relatively younger median age of the sample may exclude age-dependent toxicity of TDF. Additionally the higher proportion of men switched for toxicity compared to women deserves further evaluation.

Conclusions

Toxicities reported in this study are comparable to other published reports in Africa and Asia and resemble those seen in registration trials and other clinical trials with some notable exceptions that can be attributed to clinical scenarios commonly seen in resource limited settings [10]. These findings may be used for drug forecasting, and could be considered by national AIDS programs in updating national treatment protocols. In LMICs therefore, the comparably high efficacy and tolerability rates of TDF and EFV support the preferential use of these agents for a “public health approach” over D4T, AZT and NVP, and may be more applicable in the strategy in which less experienced/non-physician providers may be initiating the majority of antiretroviral therapy.

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