Adverse Effects of Highly Active Antiretroviral Therapy in Developing Countries

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Recent increases in access to highly active antiretroviral therapy (HAART) have made the management of drug toxicities an increasingly crucial component of human immunodeficiency virus (HIV) care in developing countries. The spectrum of adverse effects related to HAART in developing countries may differ from that in developed countries because of the high prevalence of conditions such as anemia, malnutrition, and tuberculosis and frequent initial presentation with advanced HIV disease. The severity of adverse effects may vary as a result of host genetics and diagnostic delays attributable to inadequate laboratory monitoring. This article reviews current knowledge about toxicities related to HAART in resource-limited regions, which are in the process of rapid treatment scale-up. We conclude that initiating HAART before advanced immunosuppression, titrating doses in single-pill drug combinations to differences in patients’ body weights, providing more intensive laboratory monitoring during the initial months of therapy, and providing access to less-toxic nucleoside reverse-transcriptase inhibitors may decrease the incidence of toxicities related to HAART in resource-limited regions.

Although the HIV-AIDS epidemic continues to spread in the developing world [1], reductions in the price of HAART for HIV-infected individuals in resource-constrained regions have made treatment increasingly accessible [2]. HIV care facilities in developing countries have witnessed dramatic decreases in mortality that are similar to those previously recorded in developed countries [3–5]. One by-product of increased access to HAART, however, is that management of antiretroviral drug-related toxicities is becoming an important component of HIV care in developing countries.

The spectrum of adverse effects associated with HAART may vary between developed and developing countries for several reasons. First, economic constraints limit the repertoire of accessible antiretroviral medications, making a handful of drugs responsible for most toxicities in developing countries [6]. Second, prohibitory laboratory monitoring costs may occasionally delay the diagnosis of specific toxicities, thereby increasing their severity. Third, comorbid conditions that are more prevalent in resource-limited regions, such as anemia and malnutrition; initial presentation with advanced immunosuppression; use of concomitant antituberculosis therapy (ATT); and use of herbal medications [7] may influence the incidence of adverse effects. Finally, host genetics may be associated with drug toxicities [8]; this is a relevant issue, because most antiretroviral drugs have been validated in developed countries (primarily in white populations) but are now being widely used in developing countries, where the vast majority of HIV-infected people live.

This article reviews research on the adverse effects associated with HAART in the context of rapid treatment scale-up, focusing on drugs predominantly used in resource-constrained regions. Two related challenges in the management of antiretroviral ther-
apy—coadministration of HAART with ATT and immune reconstitution syndrome (IRS)—will also be discussed.

**NUCLEOSIDE REVERSE-TRANSCRIPTASE INHIBITORS (NRTIs)**

**Stavudine**
Next to lamivudine, stavudine is the most commonly used NRTI, because of its relatively low cost [9, 10]. Stavudine is the NRTI that is most often associated with mitochondrial toxicity, which results in high rates of lipoatrophy, peripheral neuropathy, lactic acidosis, and pancreatitis [11].

*Peripheral neuropathy.* From 10% to 21% of persons exposed to stavudine developed peripheral neuropathy in developed countries [12, 13]. Although symptoms usually resolve after prompt discontinuation of stavudine therapy, persistent symptoms in a subset of patients may be problematic in developing countries, where many persons rely on physical labor for survival and usually do not have disability insurance.

Cohort studies from Cameroon, India, and Thailand found peripheral neuropathy rates that were similar to or, surprisingly, lower than those in developed countries [6, 14–16]. It is hard to establish whether these lower rates reflect underascertainment biases (e.g., short follow-up periods and insensitive screening tools). However, 56% of patients in a Malawian cohort developed peripheral neuropathy while receiving stavudine therapy [17]. The authors noted that one-third of their patients had a body weight <60 kg, for which a 30-mg dose of stavudine is recommended; however, only the 40-mg dose was available in the fixed-dose combination (FDC) used in the study. This highlights the necessity of the availability of FDCs with varied doses to minimize toxicity, especially in malnourished patients.

*Lipodystrophy and metabolic complications.* The prevalence of stavudine-associated lipodystrophy in western studies has reached as high as 50%–63% [18–20]. However, many of these studies included patients who also received protease inhibitors (PIs), which independently cause lipodystrophy. The risk has been shown to be greater for those initiating HAART with a low CD4 cell count [21, 22] and a low body mass index (BMI; calculated as the weight in kilograms divided by the square of the height in meters) [23]. Because stavudine-associated lipodystrophy commonly presents as lipoatrophy (i.e., fat loss in the cheeks, arms, and buttocks), malnutrition complicates its diagnosis. Careful assessment is needed to differentiate lipoatrophy from general wasting to prevent unnecessary modifications of therapy.

Some data suggest that ethnic variability effects the incidence of lipodystrophy. White race may be an independent risk factor for the development of lipodystrophy [22, 24, 25]. Although a small South Korean cohort had a 3.5% rate of lipodystrophy [26], multiple subsequent east Asian cohorts have shown rates similar to those in western studies [27–29]. Only 17% of patients in 2 southeast Asian cohorts developed lipodystrophy, compared with 24.8% of patients in a Rwandan cohort and 46.1% in an Indian cohort [30–33].

The tendency of stavudine-associated lipodystrophy to affect facial features raises concerns that the widespread use of the drug in developing countries may increase stigma and decrease HAART adherence [31]. A study of 410 patients of Chinese ethnicity in Singapore found that lipodystrophy affected social relations for 23% of the patients and mood for 36% [27]. However, <1% of the patients wanted to discontinue therapy because of this toxicity. In contrast, a smaller study suggested that 14% of Brazilian patients considered therapy discontinuation because of this adverse effect [34]. Because toleration of lipodystrophy may be culturally specific, region-specific research may help determine the viability of stavudine use in different countries.

Although zidovudine sometimes causes lipodystrophy, stavudine is more strongly associated with this adverse effect [31, 35–37]. Therefore, one approach for reducing the incidence of lipodystrophy would be to substitute zidovudine for stavudine 6–12 months after HAART initiation, when lipodystrophy may begin to develop [35]. This allows antiretroviral roll-out programs to briefly take advantage of the lower cost and better initial tolerability of stavudine. Also, stavudine-containing HAART is associated with resolution of anemia in many patients within 6 months after initiation [38–41]. Because anemia is a relative contraindication for zidovudine use, stavudine therapy could bridge the way to zidovudine therapy by reducing the risk for anemia. Even after lipodystrophy develops, substituting another NRTI for stavudine may result in partial recovery [11, 42–44].

Of all the NRTIs, stavudine therapy has been most strongly associated with dyslipidemia and hyperglycemia in western studies [45–47]. Similar metabolic changes were present in patients in an Indian cohort treated with stavudine and zidovudine and in a cohort of patients of Chinese ethnicity treated with non-PI-containing HAART [27, 31]. As access to HAART increases, patients in developing countries may increasingly face the cardiovascular consequences of altered metabolism.

*Lactic acidosis.* Although relatively infrequent, multiple cohort studies [48–52] and case reports [53–58] from developing countries highlight concerns about timely diagnosis of life-threatening stavudine-induced lactic acidosis, for which women may be at a higher risk [49, 50, 52]. Pilot studies from Haiti and South Africa found that point-of-care testing with handheld devices measuring lactic acid levels (e.g., using finger stick blood samples) facilitated timely diagnosis of hyperlactatemia and prevented unnecessary regimen modifications in patients without increased serum lactate levels [59, 60]. Such devices may be beneficial as HIV care is decentralized to rural
locations, where lactic acid testing in laboratories may be unavailable.

Zidovudine

Myelosuppression. Anemia is common in developing countries, particularly among HIV-infected individuals [61–63], and generally worsens with disease progression [64–66]. High background levels of anemia may preclude zidovudine use in many patients. Zidovudine-related anemia usually occurs within 3 months after therapy initiation [6]. Risk factors include high zidovudine dosage, increased treatment duration, low CD4 cell count, and preexisting anemia [65, 67, 68]. Studies from Nigeria, Côte d’Ivoire, Haiti, and India have found rates of zidovudine-related anemia of 3%–12% [5, 6, 69–71].

A study from Côte d’Ivoire suggested synergistic toxicity between zidovudine and cotrimoxazole. Among 498 patients already receiving cotrimoxazole prophylaxis, the introduction of zidovudine-containing HAART resulted in one-half of the cohort developing severe neutropenia. Complete recovery occurred in nearly all patients after discontinuation of cotrimoxazole therapy, suggesting that this toxicity was attributable to a drug-drug interaction between these 2 myelosuppressive drugs [70].

Among patients who discontinue stavudine therapy because of toxicity, those who cannot substitute zidovudine therapy because of persisting anemia may be left with no options, because these are the least expensive NRTIs in resource-limited regions [9, 10]. This highlights the need for increased access to NRTIs with different toxicity profiles, such as tenofovir and abacavir, in developing countries.

NONNUCLEOSIDE REVERSE-TRANSCRIPTASE INHIBITORS (NNRTIs)

Nevirapine

Nevirapine is the most commonly used NNRTI in developing countries because of its lower cost, compared with efavirenz [9, 10].

Hypersensitivity rash. Hypersensitivity rash occurred in 16%–20% of patients in studies in developed country [68, 72, 73]. Two US studies that disaggregated data by ethnicity found that mostly persons of Mexican origin and some persons of South American origin were at a higher risk [74, 75]. Data do not suggest a higher risk of rash among other ethnic groups, with most studies in developing countries finding rates similar to or lower than those in developed countries. Cohorts from Haiti, India, Thailand, and Malawi found nevirapine-associated rash rates of 3%–26% [5, 6, 15–17, 76]. Female patients may be at an increased risk for nevirapine-associated rash [76–79].

Initiating patients on a lower lead-in dosage of nevirapine of 200 mg once daily, followed by escalation to the full 200-mg twice-daily dosage after 2 weeks, helps prevent severe rashes, such as Stevens-Johnson syndrome [72]. The use of FDCs in developing countries does not enable clinicians to titrate nevirapine therapy initiation. Without appropriate physician education, the use of the full nevirapine dose in FDCs for patients beginning HAART may increase the incidence of life-threatening rashes. Although nevirapine therapy can safely be replaced with efavirenz therapy for those who experience adverse reactions, because there is little evidence of rash cross-toxicity between the 2 drugs [76, 80], this substitution is often precluded by the higher cost of efavirenz in developing countries [10].

Hepatotoxicity. The incidence of drug-related hepatitis in US and European trials has ranged from 1% to 10% [72, 81–83]. Cohorts from Haiti, Thailand, India, Zambia, and Malawi found similar rates of nevirapine-associated hepatotoxicity, ranging from <1% to 7% [5, 6, 15–17, 84].

A South African study reported a 17% incidence of serious hepatotoxicity (i.e., alanine aminotransferase and aspartate aminotransferase levels >5 times the upper limit of normal) among 385 patients receiving nevirapine-based regimens, compared with no cases of hepatotoxicity among 83 patients receiving efavirenz-based regimens [85]. Female patients with a BMI <18.5 had a 50% incidence of serious hepatotoxicity. Leith et al. [86] argued that the mean CD4 cell count of 398 cells/µL at treatment initiation in this cohort may explain this elevated hepatitis rate. A retrospective analysis of prior studies found a 12-fold increased risk of severe hepatotoxicity in women with CD4 cell counts >250 cells/µL, compared with women with CD4 cell counts <250 cells/µL (resulting in a “black box” warning for nevirapine [87]); the risk for men increased at CD4 cell counts >400 cells/µL [86, 88, 89]. Of note, studies from Thailand and Zambia have not found this association between nevirapine-induced hepatotoxicity and CD4 cell count [84, 90]. The authors of the South African study argued that race and BMI, rather than baseline CD4 cell count, accounted for the high hepatotoxicity rate [91], because studies have found decreased nevirapine clearance in individuals with a low BMI, of black race, or with particular pharmacogenetic profiles [92, 93]. Thai ethnicity may also be a risk factor for nevirapine-associated hepatotoxicity [89]. Additional research is needed to clarify the complex relationship between race/ethnicity, baseline CD4 cell count, and the risk of nevirapine-induced hepatitis.

A Thai study found that 17 (18.6%) of 91 patients receiving nevirapine therapy developed serious hepatitis [94], which may be explained by the high prevalence of hepatitis B virus (HBV) and hepatitis C virus (HCV) coinfection in this cohort. Similar to findings in western studies [95], HBV-infected patients in this study had a higher hepatotoxicity rate (57.4%) than did HBV-uninfected patients, and patients with HCV had a hepatotoxicity rate of 72.2%. Conversely, long-term nevirapine use
may increase the rate of progression to cirrhosis in HBV-HCV coinfected patients [96]. The authors of the Thai study, therefore, suggest that nevirapine use might be contraindicated in regions where HBV-HCV coinfection screening is unavailable and where background prevalence is >10% [94]. Prevention of nevirapine-associated liver toxicity, therefore, requires attention to multiple factors prior to HAART initiation, including female sex, high CD4 cell count at initiation, low BMI, low albumin level [85], HBV-HCV coinfection, use of ATT, and, possibly, race/ethnicity.

Efavirenz

Neuropsychiatric disorders. Neuropsychiatric disorders are the most concerning adverse effects associated with efavirenz therapy with regard to tolerability and adherence. In western cohorts, one-half of patients have these symptoms at initiation of efavirenz therapy, but these symptoms usually resolve within 1 month [97]. People of African descent with a variant of hepatic enzyme CYP2B6 may experience slower clearance of efavirenz from plasma and increased neurotoxicity [98–100].

A study from Haiti supports this data on ethnic differences. The study found that 46 (10%) of 452 patients discontinued efavirenz therapy because of persistent neurotoxicity [5]; this rate is higher than that found in US studies [97]. A study from Côte d’Ivoire also found a high neurotoxicity rate (69%) after initiation of efavirenz therapy [101, 102]. In contrast to the Haitian study, these symptoms resolved in most patients by the third month of therapy, with only 1 patient of 808 patient-months of follow-up discontinuing therapy because of neurotoxicity. Additional research clarifying the influence of ethnicity on efavirenz plasma levels may lead to dose adjustments, which may decrease rates of neurotoxicity in particular populations.

OVERLAPPING TOXICITIES OF HAART AND ATT

Dean et al. [103] highlighted the problem of overlapping toxicities when they found a high incidence (54%) of adverse events in a cohort of 188 patients coinfected with HIV and tuberculosis. These toxicities (table 1), which occurred at a higher rate than in previous control groups of HIV-infected patients treated with ATT in the pre-HAART era, led to interruption of HAART or ATT regimens in one-third of patients [103]. Nevirapine has multiple overlapping toxicities with ATT drugs, especially rifampicin [104]. A Thai study indicated that patients receiving ATT while receiving nevirapine therapy had a 7.4-fold increased risk of developing hepatitis and a 3-fold increased risk of developing a rash [105].

One small cohort found a high incidence (55%) of peripheral neuropathy in patients receiving both stavudine and isoniazid therapies [106], and another study found peripheral neuropathy to be the most common toxicity in a cohort of patients coinfected with HIV and tuberculosis [103]. Patients receiving both drugs should be closely monitored and should receive supplemental pyridoxine therapy to reduce the risk of isoniazid-related neurotoxicity. Finally, as patients begin to experience failure of first-line, NNRTI-based regimens (with tuberculosis being the most common infection marking clinical failure), overlapping toxicities associated with ATT and PIs, such as hepatitis, will become increasingly important in developing countries.

IRS

IRS, a paradoxical worsening of clinical status after HAART initiation, is increasingly recognized as an adverse consequence of antiretroviral therapy [107–111]. Developing countries may have a higher incidence of IRS as a result of a higher burden of opportunistic infections and frequent therapy initiation in patients with low CD4 cell counts, both of which are risk factors for IRS [112–116]. For example, HIV-infected patients receiving care from Medicins Sans Frontieres programs in sub-Saharan Africa, southeast Asia, and Central America had a median CD4 cell count of 48 cells/µL at HAART initiation, placing many at a high risk for IRS [117].

Unlike in developed countries, tuberculosis is the most common pathogen involved in IRS in resource-limited countries. Indian and Thai studies found IRS rates of 15% and 13%, respectively, among patients coinfected with HIV and tuberculosis after the initiation of HAART [118, 119]. Such cases are difficult to differentiate from cases of multidrug-resistant

**Table 1. Overlapping toxicities associated with antiretroviral and antituberculosis drugs.**

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Antiretroviral drugs</th>
<th>Antituberculosis drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis</td>
<td>Nevirapine, protease inhibitors</td>
<td>Rifampicin, isoniazid, pyrazinamide, ethionamide</td>
</tr>
<tr>
<td>Rash</td>
<td>Nevirapine, efavirenz, abacavir</td>
<td>Rifampicin, isoniazid, quinolones</td>
</tr>
<tr>
<td>Anemia, neutropenia</td>
<td>Zidovudine</td>
<td>Rifampicin, isoniazid</td>
</tr>
<tr>
<td>Nausea, vomiting</td>
<td>Zidovudine, ritonavir, indinavir</td>
<td>Rifampicin, pyrazinamide, quinolones, ethionamide</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>Stavudine, didanosine, zalcitabine</td>
<td>Isoniazid, ethambutol, cycloserine</td>
</tr>
<tr>
<td>CNS symptoms</td>
<td>Efavirenz</td>
<td>Streptomycin, quinolones, cycloserine</td>
</tr>
</tbody>
</table>

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tuberculosis, as highlighted in 2 Indian case reports [120, 121]. Other reported presentations of IRS that may be more common in developing countries include exacerbations of leprosy [122, 123], leishmaniasis [124, 125], and Mycobacterium bovis infection (acquired through bacille Calmette-Guérin vaccination) [126].

CONCLUSIONS

This review illuminates a few common trends in HAART-related toxicities that are relevant to developing countries. First, initiation of antiretroviral therapy at advanced stages of AIDS has implications beyond the obvious risk of morbidity and mortality due to opportunistic infections. Low CD4 cell count at treatment initiation is a risk factor for multiple adverse effects, including stavudine-induced peripheral neuropathy [127, 128], lipodystrophy [21, 22], and lactic acidosis [11, 129]; zidovudine-induced myelosuppression [67]; didanosine-induced pancreatitis [130]; and IRS [113]. Moreover, the high burden of opportunistic infection in patients with low CD4 cell counts increases overlapping toxicities between HAART and opportunistic infection treatments—a problem of particular concern for patients receiving ATT. Therefore, earlier HAART initiation, before the development of a low CD4 cell count and opportunistic infection, may reduce the incidence of adverse effects. Increased access to HIV testing services, with the aim of engaging more patients in long-term follow-up, may help achieve this goal. Second, although fixed-dose combinations of HAART are highly effective and increase adherence [14, 16], they may lead to increased toxicity when used improperly. Roll-out programs should ensure that FDCs are available in doses that are appropriate for a patient’s body weight, as well as allow for a run-in period of a lower dose of nevirapine.

Third, most adverse effects can be ascertained through an appropriate clinical examination for specific symptoms and signs, including neuropsychiatric problems (due to efavirenz-related toxicity), fatigue with conjunctival pallor (due to zidovudine-related anemia), and peripheral wasting (due to stavudine-related lipodystrophy). Implementation of protocols for regular clinical screening of patients, especially during the initial months of therapy, may help detect toxicities earlier. As suggested by a Kenyan study, early detection may also be facilitated by training family or community volunteers to identify toxicities [131]. In addition, facilities for laboratory monitoring of specific toxicities are a crucial component of scale-up of antiretroviral therapy. Current World Health Organization guidelines recommend liver enzyme and hemoglobin investigations only when patients are symptomatic [9]; however, because most cases of nevirapine-related hepatitis and zidovudine-induced anemia occur during the initial months of therapy, more intensive laboratory monitoring during this time may prevent severe toxicity.

Finally, by reducing antiretroviral drug options, toxicities may have a significant socioeconomic impact on low-income patients in developing countries. In studies from Haiti and South India, adverse effects were the primary reason for therapy modification [5, 132]. Currently, most government roll-out programs in resource-constrained regions provide few or no second-line drugs [133, 134]. Therefore, increased access to less-toxic first-line drugs and less-expensive second-line drugs is needed to cope with this issue. Specifically, patients will benefit if government programs ensure access to tenofovir or abacavir therapy for the small subset of patients who experience adverse reactions associated with both stavudine and zidovudine therapies, as well as with PIs for patients who cannot tolerate both nevirapine and efavirenz.

Although few data are available on tenofovir, abacavir, and PI use in developing countries, these medications can be anticipated to have their own specific benefits and complications in resource-limited regions. A multisite trial in Africa found tenofovir therapy to be associated with a 1.3% rate of significant nephrotoxicity, which was comparable to other regimens [135]. Because abacavir therapy may cause a hypersensitivity rash, abacavir use may possibly complicate diagnosis of nevirapine-induced rash in patients initiating both medications. As previously noted, PI use may be problematic in patients receiving ATT, not only because of overlapping hepatotoxicity, but also because of drug-drug interactions with rifampicin [136].

Despite the problems associated with toxicities, the distribution of HAART in developing countries should not be discouraged, especially when these life-saving medications remain unavailable to the majority of patients in need [2]. However, excellent clinical follow-up is simultaneously required to manage the morbidity associated with HAART.

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