Original Article

Adverse Drug Reactions in HIV/AIDS Patients at a Tertiary Care Hospital in Penang, Malaysia

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SUMMARY: In the current study we explored the occurrence of adverse drug reactions (ADRs) to antiretroviral therapy among human immune-deficiency virus (HIV)/AIDS patients. We concluded an observational retrospective study in all patients who were diagnosed with HIV infection and were receiving highly active antiviral therapy from Jan. 2007 to Dec. 2012 at Hospital Pulau Pinang, Malaysia. Patient socio-demographic details along with clinical features and susceptible ADRs were observed during the study period. Out of 743 patients, 571 (76.9%) were men, and 172 (23.1%) were women. Overall 314 (42.2%) patients experienced ADRs. A total of 425 ADRs were reported, with 311 (73.1%) occurring in men and 114 (26.8%) in women, with a significant statistical relationship (P value = 0.02, OR = 1.21). Overall 239 (56.2%) ADRs were recorded among Chinese, 94 (22.1%) in Malay, and 71 (16.7%) in Indian patients, which had a statistically significant association with ADRs (P = 0.05, OR = 1.50). Out of a total 425 among ADRs, lipodystrophy was recorded in 151 (35.5%) followed by skin rashes in 80 (18.8%), anemia in 74 (17.4%), and peripheral neuropathy in 27 (6.3%) patients. These findings suggest a need of intensive monitoring of ADRs in HIV treatment centres across Malaysia.

INTRODUCTION

Infection with the human immune deficiency virus (HIV) leads to AIDS, HIV is transmitted from person to person through sexual fluids, blood, and breast milk and those at the greatest risk of infection are intravenous drug users, sex workers, and men who have sex with men (1). According to a 2012 survey conducted by the World Health Organization, 31.4 to 35.9 million people worldwide are infected with HIV, of which about 0.8% were adults aged 15–49 years. More over survey also reports that new cases of HIV infection and deaths reported were 2.5 million and 1.7 million respectively till the end of 2011 (2). In Asia, already home to the world’s two most populous nations (China and India), an estimated 4.8 million people are living with HIV infection (3). In Malaysia, 79,855 cases of HIV have been reported by the end of 2011, with 71% of which were found in Malaysian ethnicity, followed by Chinese Malay (15%), Indian (8%), and all other ethnic populations (6%) (4). And approximately 3 million patients have access to highly active antiretroviral therapy (HAART) as of 2009 (5). In Malaysia, the number of HIV/AIDS patients receiving HAART has increased from 1,710 in 2003 to 6,207 in 2007 (6).

In 1996–1997 when antiretroviral therapy was first introduced, there was a mortality reduction of approximately 50% among people living with HIV/AIDS who were compliant with the ART regimen (7). The initial HAART therapy with three antiretroviral drugs has led to significant reduction in AIDS morbidity and mortality (8). Despite the efficacy of the HAART regimen, it involves a complex set of ART drugs that are associated with adverse drug reactions (ADRs), such as fat redistribution, dyslipidemia, and sexual dysfunction. These reactions are sufficiently severe in some patients so as to cause have non-compliance or discontinuation of ART (9,10). For instance, non-nucleoside reverse transcriptase inhibitors have been associated with rash and hepatotoxicity (11). Nucleoside reverse transcriptase inhibitors (NRTI’s) have been linked with hypersensitivity reactions, anemia, and neutropenia (12). Protease inhibitors meanwhile have been associated with hyperlipidemia, hyperglycemia, and gastrointestinal symptoms (13,14). Furthermore, increasingly complex drug therapies for HIV-infected patients increase the chances of ADR (15).

To our knowledge, there has been no published data regarding ADRs associated with HAART among Malaysian HIV/AIDS patients. The objective of this study was to explore the occurrence of ADRs among HIV/AIDS patients receiving HAART.

MATERIALS AND METHODS

We conducted a retrospective cross-sectional observational study at the Infectious Disease Department of General Hospital Pulau Pinang, Malaysia. All HIV-infected patients on HAART therapy between Jan. 2007 to Dec. 2012 were included in the study with two exceptions. HIV-positive pregnant women and HIV-positive children were excluded. Patient’ records were thoroughly reviewed and relevant data was noted on a validated data collection form. Demographic and clinical characteristics of patients that were susceptible to ADRs...
were recorded and observed during the study period. The reported ADRs were assessed for causality by using Naranjo’s algorithm scale (16). Categorical data was reported numerically as numbers and percentages of the total, while continuous data was reported using mean and standard deviations. Chi-square and Fischer’s exact tests were used to detect significance between categorical variables. Univariate analyses were also used for estimating further correlation between the ADRs and different variables. A $P \leq 0.05$ was considered statistically significant. All statistical calculations were performed using SPSS statistical package (version 20, Chicago, IL, USA).

**RESULTS**

A total of 997 patients were diagnosed with HIV infection between Jan. 2007 and Dec. 2012, and 743 fulfilled our inclusion criteria. Out of 743 patients, 571 (76.9%) were men, and 172 (23.1%) were women. Overall, 314 (42.2%) patients experienced a total of 425 ADRs with 311 (73.1%) occurring in men and 114 (26.8%) in women. A statistically significant relationship was observed between patient sex and the occurrence of ADR ($P = 0.002$) (Table 1). In the multi-ethnic population of Malaysia, 239 (56.2%) ADRs were recorded in patients of Chinese ancestry, 94 (22.1%) in those of Malay, 71 (16.7%) in those of Indian ancestry, 21 (5.0%) in all other ethnicity with a statistically significant relationship ($P = 0.05$) (Table 1). On univariate analysis, a significant relation was observed only among patients of Indian ancestry ($P = 0.05$, OR = 1.50) (Table 2).

A total of 112 (35.7%) patients aged 41–50 experienced ADRs compared to 107 (34.1%) patients aged 31–40 years and 66 (21%) patients aged 50 years and above but no statistically significant relation between of ADR occurrence compared to other age groups (Table 1). However, further analysis showed that patients aged under 30 years ($P = 0.02$, OR = 0.59) had a statistically significant association with ADR occurrence compared to other age groups (Table 2). Among all 743 patients, 512 (68.9%) patients were smokers and 340 (45.8%) were alcoholic, both of which had a significant association with ADR occurrence ($P = 0.01$ and $P = 0.009$, respectively) (Table 1). Univariate analysis indicated that smokers (OR = 1.52, $p = 0.009$) and patients who were not alcoholics (OR = 1.48, $P = 0.008$) had significant associations with ADR occurrence (Table 2).

Of the 314 patients with recorded ADRs, 225 (71.7%) patients developed one ADR, 67 (21.3%) patients developed two ADRs, and 22 (7.0%) patients developed three ADRs. The most common HAART regimens used included first line therapies zidovudine (AZT) + lamivudine (3TC) + efavirenz (EFV) (41.8%), tenofovir (TDF) + emtricitabine (FTC) + EFV (34.2%), stavudin (D4T) + 3TC + nevirapine (NVP) (22.3%), and AZT + 3TC + NVP (21.2%), followed by second line therapies AZT + 3TC + lopinavir-ritonavir (LOP-RITO) (6.1%) and TDF + FTC + LOP-RITO (5.9%). Lipodystrophy (35.5%) was mostly associated with DT. However it also occurred in patients receiving AZT containing regimes. Skin rash (18.8%) was associated in patients receiving NVP and EFV containing regimes, while anemia (17.4%) was common in patients who received AZT containing regimes. A total of 425 ADRs were reported, including 151 (35.5%) for lipodys-

### Table 1. Characteristics of HIV patients in Pulau Penang ($n = 743$)

| Characteristic       | Patient with ADRs No. (%) | Total ADRs No. (%) | $P$ value |
|----------------------|---------------------------|--------------------|-----------|
| Sex                  |                           |                    |           |
| Man                  | 235 (74.8)                | 311 (73.2)         | 0.002$^1$ |
| Woman                | 79 (25.2)                 | 114 (26.8)         |           |
| Age group (yr)       |                           |                    |           |
| $\leq 30$            | 29 (9.2)                  | 39 (9.2)           |           |
| 31–40                | 107 (34.1)                | 145 (34.1)         | 0.51      |
| 41–50                | 112 (35.7)                | 149 (35.1)         |           |
| $\geq 51$            | 66 (21.0)                 | 92 (21.6)          |           |
| Ethnicity            |                           |                    |           |
| Malay                | 65 (20.7)                 | 94 (22.1)          |           |
| Chinese              | 179 (57.0)                | 239 (56.2)         | 0.05$^1$  |
| Indian               | 51 (16.2)                 | 71 (16.7)          |           |
| Others               | 19 (6.1)                  | 21 (4.9)           |           |
| Smoking status       |                           |                    |           |
| Smoker               | 200 (63.7)                | 269 (63.3)         | 0.01$^1$  |
| Non-smoker           | 114 (36.3)                | 156 (36.7)         |           |
| Alcohol use          |                           |                    |           |
| Alcoholic            | 126 (40.1)                | 162 (38.1)         | 0.009$^1$ |
| Non-alcoholic        | 188 (59.9)                | 263 (61.9)         |           |
| Drug abuse           |                           |                    |           |
| Drug abuse           | 18 (5.7)                  | 26 (6.1)           | 0.39      |
| Non-drug abuse       | 296 (94.3)                | 399 (93.9)         |           |

$^1$: Statistically significant.

### Table 2. Univariate analysis of patient demographics with ADRs

| Patient variable | Total ADRs No. (%) | OR$^1$ | 95% CI$^1$ | $P$ value |
|------------------|--------------------|--------|------------|-----------|
| Sex              |                    |        |            |           |
| Man              | 311 (73.2)         | 1.21   | 0.86–1.71  | 0.26      |
| Woman            | 114 (26.8)         |        |            |           |
| Age group (yr)   |                    |        |            |           |
| $\leq 30$        | 39 (9.2)           | 0.59   | 0.37–0.94  | 0.02$^2$  |
| 31–40            | 145 (34.1)         | 0.96   | 0.70–1.30  | 0.80      |
| 41–50            | 149 (35.1)         | 1.12   | 0.82–1.52  | 0.46      |
| $\geq 51$        | 92 (21.6)          | 1.27   | 0.88–1.48  | 0.19      |
| Ethnicity        |                    |        |            |           |
| Malay            | 94 (22.1)          | 0.94   | 0.66–1.34  | 0.74      |
| Chinese          | 239 (56.2)         | 0.78   | 0.58–1.05  | 0.10      |
| Indian           | 71 (16.7)          | 1.50   | 0.98–2.29  | 0.05$^2$  |
| Others           | 21 (4.9)           | 1.56   | 0.79–3.05  | 0.19      |
| Smoking status   |                    |        |            |           |
| Smoker           | 269 (63.3)         | 1.52   | 1.11–2.07  | 0.009$^2$ |
| Non-smoker       | 156 (36.7)         |        |            |           |
| Alcohol use      |                    |        |            |           |
| Alcoholic        | 162 (38.1)         | 1.48   | 1.10–1.99  | 0.008$^2$ |
| Non-alcoholic    | 263 (61.9)         |        |            |           |
| Drug abuse       |                    |        |            |           |
| Drug abuse       | 26 (6.1)           | 1.59   | 0.89–2.85  | 0.11      |
| Non-drug abuse   | 399 (93.9)         |        |            |           |

$^1$: OR, odds ratio; CI, confident interval.

$^2$: Statistically significant.
and body-mass index and fat composition or hormonal effects on prevalence might be because of the difference in body-

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The incidence rate of ADRs to HAART was (42.3%) in the current study. This rate was lower than the rate reported among the HIV-infected population in India (71.1%) (21), similar to the rate reported in Nigeria (54%) (22), and higher than the rate reported in Brazil (34.5%) (23), and as reported in a large cohort study of HIV infected adults in Switzerland (24). This suggests that the spectrum of ADRs to HAART vary from one country to another and between developed and developing countries. The variation in the rates may be explained by the differences in study methodology, HAART regimens prescribed, and study populations. Variations may be caused by concurrent medications used for treating opportunistic infections and other co-morbid conditions, or by the lack of available materials or equipment to easily identify ADRs compared to what is available in developed countries.

Among the various ADRs observed, lipodystrophy (35.5%) and skin rashes (18.8%) were the most common, followed by anemia (17.4%). A 2007 study found a similar percentage of lipodystrophy (34.2%) among Rwandan population of 409 adults (25) while Botswana study reported only 16% (26). A study in India, Kumarasamy et al. reported a 42% incidence of skin rashes, which was much higher than that in our study (18.8%). The same study reported an anemia incidence of 5.4% (27), a finding which is much lower compared to the findings from the current study 17.4%, as well as those found showed in Reddy et al. (23.7%) (17) and Singh et al. (15.8%) (28). Sharma et al. (21) reported a high occurrence of skin rashes (10%), and Bersoff-Matcha et al. (29) reported even higher rates: 26% among women and 22% among men. However, the incidence of skin rash in that report only reflects reactions from one specific drug, NVP. Peripheral neuropathy was observed in 6.3% of patients in the current study, a higher rate than the 1% reported by Divakar et al. (30) and much lower rate compared to the 22.2% rate reported by Sharma et al. (21). Peripheral neuropathy is a long-term adverse effect of D4T and some other antiretroviral drugs, developing only after 6 months of treatment. The current study was retrospective, while the duration of the study by Divakar et al. was just six months. This may explain why we observed a higher incidence of peripheral neuropathy.

Causality assessment of ADRs by the Naranjo scale showed that most of the ADRs were “Probable” (49.4%), “Possible” (41.6%), with 8% as “Definite”, and 0.9% as “Doubtful”. These results are in contrast to both with Reddy et al. where the majority of ADRs (63.7%) were reported as “Possible”, and with Mondayil et al. where the majority of ADRs were reported as “Definite”/“Probable” (18). The present study was conducted in only one ART center at the Government General Hospital of Penang, Malaysia. Results may exclude the actual number of HIV-infected patients who were on HAART and experienced ADRs.

In conclusion, the current study was an attempt to identify the most commonly reported HAART-induced
ADRs in Malaysia. Multiple patient variables including ethnicity, age group, and smoking status had significant associations with ADR occurrences. Results of the present study suggest that treating physicians can optimize treatment of HIV-positive patients receiving HAART, if they focus first on determining who is at risk for ADRs and taking the appropriate prophylactic measures to prevent them from occurring.

Conflict of interest None to declare.

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