Gender Differences in Adverse Drug Reactions during HAART Therapy in HIV/AIDS Patients at a Tertiary Care Hospital Penang, Malaysia

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Abstract

Aims and objective: Current study is aimed to explore and observe adverse drug reactions occurrence of antiretroviral therapy and to examine the gender differences in treatment outcomes of HIV/AIDS patients during HAART therapy.

Method: An observational retrospective study of all patients on HAART therapy diagnosed with HIV infection from January 2007 to December 2012 was conducted at infectious disease department of Hospital Pulau Pinang, Malaysia. Patients socio-demographic, clinical and laboratory data was retrieved via self developed validated data collection form.

Results: Out of 743 patients 571 (76.8%) were male and 172 (23.1%) were female patients. A total number of 425 (57.2%) adverse drug reactions were reported among which 311 (73.1%) occurred in males and 114 (26.8%) in female patients, with a significant statistical relationship (*p*=0.02, OR=1.21). Out of total ADRs (57.2%) observed in both genders, a significant association was observed in Lipodystrophy (p=0.05), anemia (p=0.02), Peripheral Neuropathy (p=0.02) and pancreatitis (p=0.01). A total of 455 (79.6%) male and 139 (80.8%) female patients have improvement in CD4 cells count at the final follow up, a significant association (p=0.05) was observed among the mode of transmission and treatment outcome.

Conclusion: Overall, the ADRs observed in both gender emphasize the importance of developing safer HAART regimens and managing these adverse effects in a timely manner in order to avoid long-term health consequences.

Keywords: Gender; ADRs; Lipodystrophy; HAART; HIV/AIDS

Introduction

The rapid rollout of antiretroviral therapy (ART) in resource-limited settings over the last 7 years has ensured the treatment of millions of eligible HIV-infected individuals. ART responses in the majority of these individuals have been successful with robust changes in immunologic, clinical and virologic markers observed [1]. Due to increase in people receiving antiretroviral therapy (ART) the number of AIDS-related deaths has declined [2]. Since introduction of the ART, the disease has become in developing countries a chronic condition that can be managed for long term [3]. In recent years there is a growing awareness of the problems accompanying the use of HAART. In addition to drug resistance and difficulty of adhering to complex regimens, adverse effects associated with HAART have become a major concern [4]. In spite of ART benefits, adverse effects to these drugs have been pointed as one of the main reasons for discontinuation, switch and non-adherence [5]. From the previous studies, a study conducted in India resulted that in almost of 53.4% patients have developed at least one of the drug toxicity. The research conducted concluded that rash, peripheral neuropathy and anemia as the common adverse drug toxicities and that women are more likely to be experienced lactic acidosis [6]. Similarly in 2012 in Douala, Cameroon, a study revealed that, 66 (19.5%) of the 339 patients reported ADRs during HAART. Furthermore, authors suggest that caregivers should actively look for the HIV AIDS patients during HAART therapy and the introduction of newer generation drugs with low toxicity in resource constrained settings is mandatory [7].

In 2011, a study aimed to identify suspected adverse drug events on HAART therapy and showed 12.3% of ADRs prevalence. Further,

it was revealed that prevalence of ADRs was higher in males (12.43%) compared to females (11.30%) among which peripheral neuropathy and anemia were highly prevalent adverse drug reaction [8]. Moreover, a retrospective cohort study was conducted by Roman et al showed that the study done with Filipinos in 2011 was that 24% of patients experienced ADRs. The most common ADRs were anemia, rashes and lactic acidosis. Authors concluded that most of the ADRs were due to the use of Zidovudine and it will fewer in ADRs if Zidovudine is replaced by Tenofovir in the first line treatment of HAART therapy [9].

A study conducted in western Uganda was done to evaluate gender differences in treatment outcomes. Researchers evaluated 305 patients with HIV/AIDS and found that females were more likely to have viral suppression as compared to male patients. Females had a significantly higher baseline CD4 cell count at initiation of treatment compared to male gender [10].

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The relationship between sex and ART outcomes has been well studied in developed countries, but less so in resource-limited settings. Findings from studies conducted in developed countries are inconsistent, with some data showing improved clinical and/or viroimmunologic outcomes among women [11,12], whereas others show better outcomes among men or no significant sex difference at all [13,14]. In resource limited settings, worse outcomes have been more consistently observed in men, including a higher risk of incident opportunistic infections, mortality, immunologic and virologic failure [15,16]. In developing settings, men are more likely to have more advanced HIV at disease presentation, which is thought to place them at higher risk of adverse outcomes and less likely to respond well to ART [10]. To our knowledge, there has been no published data regarding adverse drug reactions and improvement of CD4 cells outcomes associated with HAART in Malaysian HIV/AIDS patients among genders. Here, we explore the capacity of patients on long-term HAART to improve CD4 cell counts and the commencement of different adverse drug reaction between the two genders and at different CD4 cell count.

Methods

Study design

A retrospective cross-sectional observational study was conducted at infectious disease department of General Hospital Penang, Malaysia.

Ethical approval

The protocols were reviewed and approved by independent ethics committees and the National Medical Research Register (NMRR) in accordance to local regulations, notably regarding data protection. A letter of approval had been issued by NMRR for this study (**NMRR-13-1661-15774**). As the study had a retrospective design and the data were not collected directly from the patient but instead taken from records, there was no need for patient consent. Patient records/data were anonymized and de-identified prior to analysis.

Data collection

All the HIV infected patients on HAART therapy from January 2007 to December 2012 were included for the study. Pregnant women and children diagnosed with HIV were excluded from the study. The patient's record forms 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 and with initial CD4 cells count after every follow-up were recorded and observed during the study period.

Statistical analysis

Categorical data was reported numerically as numbers and percentage of the total while continuous data was reported using mean and standard deviations (SD). 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-value of 0.05 or below was considered statistically significant.

All statistical calculations were performed using SPSS statistical package (Version 20).

Results

A total of 997 patients were diagnosed as HIV infection between January 2007 and December 2012, of which 743 fulfilled our inclusion criteria. From the results a total of 314 (42.2%) patients had experienced

one or more ADRs out of which 235 (74.8%) were male patients and 79 (25.1%) were female. A statistically significant association (<0.001) was seen between weight and gender of the ADR patients in which most of the patients experienced ADRs were from weight group more than 50 kg. Statistically significant association was also observed among the smoking status (<0.001), alcoholic status (<0.001) and drug abusers (0.005) with gender in patients ADRs were occurred. Most of the ADRs were observed in 187 (78.2) male smoker patients and 218 (91.3%) male patients with no drug addiction (Table 1).

Overall 314 (42.2%) patients had experienced adverse drug reactions. A total number of 425 (57.2%) adverse drug reactions were reported among which 311 (73.1%) occurred in males and 114 (26.8%) in female patients. A statistical significant relationship was observed for gender and the occurrence of adverse drug reactions (p=0.002) (Table 1). Adverse drug reactions were also observed to be significantly associated with the patients mode of transmission (p=<0.001) and baseline CD4 cells count (p=0.03) (Table 2).

The statistical relation of ADRs with weight (p=<0.001) and marital

Socio-demographics	Male N=235 (%)	Female N=85 (%)	*p- value
Age (years)			
<30	17 (7.9)	10 (12.9)	
31-40	82 (35.1)	27 (34.1)	0.58
41-50	85 (35.6)	26 (32.9)	
>50	51 (21.3)	16 (20)	
Weight (kg)			
30-40 kg	04 (1.6)	08 (10.5)	**<0.001**
41-50 kg	82 (12.6)	28 (36.4)	
Above 50 kg	203 (85.7)	43 (52.9)	
Marital status			
Single	93 (38.7)	05 (8.2)	
Married	131 (56.5)	59 (71.7)	**<0.001**
Widow/Divorced	11 (4.7)	15 (20)	
Education status			
Primary	131 (53.3)	31 (38.8)	
Secondary	33 (15.8)	21 (25.9)	**0.05**
Graduation	20 (9.1)	04 (7.1)	
No education	51 (21.7)	23 (28.2)	
Employment level			
Employed	87 (36.3)	37 (45.9)	0.22**
Unemployed	146 (62.8)	42 (54.1)	
Student	02 (0.8)	00 (00)	
Smoking Status			
No	48 (21.7)	57 (74.1)	**<0.001**
Yes	187 (78.2)	22 (25.9)	
Alcoholic Status			
No	113 (47.4)	71 (87.1)	**<0.001**
Yes	122 (52.6)	08 (12.9)	
Drug Addiction			
No	218 (91.3)	79 (100)	**0.005**
Yes	17 (8.7)	00 (00)	
Heterosexual			
No	57 (25.6)	24 (32.9)	0.19
Yes	178 (74.3)	55 (67.1)	
Homo/Bi-sexual			
No	211 (87.3)	79 (100)	**0.001**
Yes	24 (12.6)	00 (00)	

*Chi Square test **Fisher exact test

Table 1: Gender base distribution of socio-demographic characteristics among ADR patients.

Characteristics	Total Patients N (%)	Patients with ADRs N (%)	Total ADRs N (%)	p-value *
Gender				
Male	571 (76.8)	235 (74.8)	311 (73.1)	**0.002**
Female	172 (23.1)	79 (25.1)	114 (26.8)	
Age Group				
<30	92 (12.3)	29 (9.2)	39 (9.1)	
31-40	257 (34.5)	107 (34.07)	145 (34.1)	0.51
41-50	254 (34.1)	112 (35.6)	149 (35)	
>50	140 (18.8)	66 (21)	92 (21.6)	
Weight Group				
30-40 kg	24 (3.2)	13 (4.1)	13 (3)	**<0.001**
41-50 kg	127 (17)	57 (18.1)	93 (21.8)	
>50 kg	592 (79.6)	244 (77.7)	319 (75)	
Marital Status				
Single	261 (35.1)	94 (29.9)	124 (29.1)	
Married	411 (55.3)	193 (61.4)	256 (60.2)	**<0.001**
Divorced	52 (6.9)	25 (7.9)	39 (9.1)	
Widowed	19 (2.5)	02 (0.6)	06 (1.4)	
Education Status				
Primary	350 (47.1)	159 (50.6)	214 (50.3)	
Secondary	201 (27)	60 (19.1)	80 (18.8)	**0.004**
Graduation	65 (8.7)	29 (9.2)	41 (9.6)	
No Education	127 (17)	66 (21)	90 (21.1)	
Employment Status				
Unemployed	263 (35.3)	114 (36.3)	156 (36.7)	0.34
Employed	465 (62.5)	198 (63)	267 (62.8)	
Student	15 (2)	02 (0.6)	02 (0.4)	
Mode of Transmission				
Heterosexual	546 (73.4)	230 (73.2)	299 (70.3)	
Homo/Bi-Sexual	83 (11.1)	30 (9.5)	38 (8.9)	**<0.001**
IDU's	56 (7.5)	20 (6.3)	32 (7.5)	
Unknown	58 (7.8)	34 (10.8)	56 (13.1)	
Baseline CD4 Cell Count				
<100	269 (36.2)	122 (38.8)	169 (39.7)	
100-200	146 (19.6)	72 (22.9)	92 (21.6)	**0.036**
200-350	290 (39)	105 (33.4)	145 (34.1)	
>350	38 (5.1)	15 (4.7)	19 (4.4)	

Table 2: Characteristics of HIV patients in Pulau Penang (n=743).

status (p=<0.001) of the patients was also found significant (Table 1). However, on further analysis unmarried patients (OR=1.57, p=0.005), divorced patients (OR=0.20, p=0.03) and patients who had unknown mode of transmission (OR=2.04, p=0.01) shows significant association with ADRs (Table 3).

Of total patients, 290 (39%) patients had baseline CD4 count between 200-350 cells/mm^3, while 269 (36.2%) patients had baseline CD4 count less than 100 cells/mm^3. There was a significant association (p=0.0001) between gender and baseline CD4 cells count (Table 4). Univariate analysis further demonstrated a significant relation (OR=1.42, p=0.05 and OR=0.66, p=0.008, respectively) with patients whose baseline CD4 count was <100 and 200-350 cells/mm^3 (Table 3).

Among 314 (42.2%) HIV patients, a total of 425 (57.2%) ADRs were recorded in which 311 (73.1%) ADRs were in male patients while 114 (26.8%) were observed in female patients. Lipodystrophy (35.5%) was observed 29% in male and 5.8% in female. A statistically significant

Characteristics	Univariate Analysis	
	OR (95% CI)	p-value*
Gender		
Male	1.21 (0.86-1.71)	0.26
Female		
Age Group		
<30	0.59 (0.37-0.94)	**0.02**
31-40	0.96 (0.70-1.30)	0.80
41-50	1.12 (0.82-1.52)	0.46
>50	1.27 (0.88-1.48)	0.19
Weight Group		
30-40 kg	0.68 (0.28-1.65)	0.40
41-50 kg	0.59 (0.26-1.34)	0.21
>50 kg	1.68 (0.74-3.82)	0.37
Marital Status		
Single	0.67 (0.49- 0.91)	**0.01**
Married	1.54 (1.14-2.07)	**0.004**
Divorced	1.28 (0.73-2.26)	0.38
Widowed	0.15 (0.03-0.67)	**0.01**
Education Status		
Primary	1.27 (0.95-1.71)	**0.09**
Secondary	0.48 (0.34-0.68)	**<0.001**
Graduation	1.11 (0.66-1.85)	0.68
No Education	1.60 (1.09-2.35)	**0.01**
Employment Status		
Unemployed	1.07 (0.79-1.45)	0.68
Employed	1.03 (0.76-1.39)	0.82
Student	0.20 (0.04-0.91)	**0.03**
Mode of Transmission		
Heterosexual	0.97 (0.70-1.36)	0.90
Homo/Bi-Sexual	0.74 (0.46-1.20)	0.23
IDU's	0.74 (0.42-1.30)	0.30
Unknown	2.04 (1.18-3.53)	**0.01**
Baseline CD4 Cell Count		
<100	1.21 (0.90-1.64)	0.19
100-200	1.42 (0.99-2.05)	**0.05**
200-350	0.66 (0.49-0.89)	**0.008**
>350	0.88 (0.45-1.72)	0.72

Table 3: Univariate analysis of ADRs with patient characteristics.

Baseline CD4 Count	Male (%)	Female (%)	p-value*
<100	229 (30.8)	40 (5.3)	
100-200	113 (15.2)	33 (4.4)	**0.0001**
200-350	201 (27)	89 (11.9)	
>350	28 (3.8)	10 (1.3)	
Final CD4 Count			
<100	50 (6.7)	08 (1.1)	
100-200	77 (10.3)	21 (2.8)	0.101
200-350	110 (14.8)	26 (3.5)	
>350	334 (44.9)	117 (15.7)	

Table 4: CD4 cells count in Gender of the study population.

association was observed in Lipodystrophy (p=0.05), anemia (p=0.02), peripheral neuropathy (p=0.02), pancreatitis (p=0.01) and diarrhea with gender (Table 5).

Among the total study population, 248 (92%) and 244 (84%) patients has a successful HAART therapy and their CD4 cells count

Adverse Drug Reactions	Number of ADRs N=425 (%)	Male	Female	p-value*
Vomiting	03 (0.7)	02	01	0.54
Diarrhea	06 (1.4)	02	04	**0.02**
Sleep Disorder	04 (0.9)	04	00	0.57
Dizziness	24 (5.6)	19	05	0.78
Rash	80 (18.8)	56	24	0.12
Lipodystrophy	151 (35.5)	126	25	**0.05**
Anemia	74 (17.4)	49	25	**0.02**
Peripheral Neuropathy	27 (6.3)	16	11	**0.02**
Itching	13 (3.05)	08	05	0.19
Pancreatitis	13 (3.05)	06	07	**0.01**
Weight loss	06 (1.4)	03	03	0.14
Lactic acidosis	08 (1.8)	06	02	0.90
Hepatotoxicity	07 (1.6)	05	02	0.66
Hepatic Steotasis	02 (0.4)	02	00	0.43
Blurred vision	05 (1.1)	05	00	0.59
Lethargy	02 (0.4)	02	00	0.43
Total Number of ADRs	425(57.2%)	311 (73.1%)	114 (26.8%)	

Table 5: Adverse drug reactions in gender of the study population.

Characteristics	Total patients N (%)	Successful N (%)	Unsuccessful N (%)	p-value*
Gender				
Male	571 (76.8)	455 (79.6)	116 (20.3)	0.74
Female	172 (23.1)	139 (80.8)	33 (19.1)	
Age Group				
<30	92 (12.3)	78 (84.7)	14 (15.2)	
31-40	257 (34.5)	198 (77)	59 (23)	0.20
41-50	254 (34.1)	210 (82.6)	44 (17.3)	
>50	140 (18.8)	108 (77.1)	32 (22.9)	
Weight Group				
30-40 kg	24 (3.2)	22 (91.6)	02 (8.3)	0.26
41-50 kg	127 (17)	98 (77.1)	29 (22.9)	
>50 kg	592 (79.6)	474 (80.1)	118 (19.9)	
Marital Status				
Single	261 (35.1)	210 (80.4)	51 (19.5)	
Married	411 (55.3)	323 (78.5)	88 (21.4)	0.51
Divorced	52 (6.9)	44 (84.6)	08 (15.3)	
Widowed	19 (2.5)	17 (89.4)	02 (10.6)	
Mode of Transmission				
Heterosexual	546 (73.4)	445 (83.3)	101 (18.4)	
Homo/Bi-Sexual	83 (11.1)	67 (80.7)	16 (19.2)	**0.05**
IDU's	56 (7.5)	37 (66)	19 (33.9)	
Unknown	58 (7.8)	45 (77.5)	13 (22.4)	
Baseline CD4 Cell Count				
<100	269 (36.2)	248 (92)	21 (08)	
100-200	146 (19.6)	101 (69.1)	45 (30.8)	**<0.001**
200-350	290 (39)	244 (84)	46 (16)	
>350	38 (5.1)	01 (02)	37 (98)	

Table 6: Treatment outcome of HAART therapy based on CD4 cells count recovery.

increased whose baseline CD4 cells count were less than 100 cells/mm3 and 200-350 cells/mm³ respectively. However 37 (98%) patients HAART therapy were failed whose CD4 cells count was more than 350 cell/mm³ at baseline. Out of 546 (73.4%) patients who were diagnosed as heterosexual, 445 (83.3%) patients have successful HAART therapy. Moreover, 67 (80.7%) patients whose mode of transmission were

homo/bi-sexual and 37 (66%) patients injecting drug users also have positive response to HAART therapy. Statistically significant relation was observed among the patients mode of transmission (p=0.05) and baseline CD4 cells count (<0.001) with treatment outcome of HAART therapy (Table 6).

Discussion

The results of the current study showed that 42.6% patients experienced ADRs, out of which 31.9% were male and 10.7% were female patients with a higher rate in both adult male and female patients of age group 31-50 years. In contrast, most of the previous studies result in higher prevalence of ADRs among female than male patients [17-19], however the observation support the result of higher prevalence rate of ADRs in age group 31-50 years of patients [17,20]. The results of ours study may be due to majority of the male patients in the current study.

ADRs occurrence was high in married patients in both male and female patients. However, higher prevalence rate of 71.7% was observed in female married patients. These results are supported by the study conducted in Ethiopia [21]. The reason may be that majority of the HIV infected female patients were married. Majority of the male (53.3%) and female patients (38.8%) have at least a primary education. The same results were found in some African studies [22,23] as well as supported by previous study conducted in Malaysia [24]. This is most likely due to compulsory primary school education policy practice in Malaysia. Majority of the male patients (62.8%) that had experienced ADRs were unemployed and 54.1% of female patients are housewives. This result is supported by the previous study conducted in Uganda [10] which is in contrast with the study conducted in Malaysia [25].

The risk factor among ADRs group of patients were mostly heterosexual both in male (74.3%) and female (67.1%), however heterosexuality was slightly higher among male patients and other risk factor like homosexuality and IDU's were overall in male patients. These results are supported by the study previously conducted in France, Uganda and Berlin, Germany [26-28]. Current study shows that majority of the patients of both male and female genders have their sexual risk factor and IDU's and also majority of the overall patients have developed HIV infection through heterosexual, homo/bisexual and injecting drug use behavior. It may be due to the increasing awareness in sexuality and poor socioeconomic characteristics in Malaysia.

In the present study, the prevalence of ADRs was high in males as compared to female patients, same as the findings in Lihite et al. [29]. In contrast to our finding, Rajesh et al. [30] has found high prevalence of ADRs in females, when compared to males. The reason for differences in prevalence of ADRs among gender might be due to difference in body mass index and fat composition or hormonal effects on drug metabolism. In our study most of the patients were aged between 31-40 years and 41-50 years; therefore we might have detected majority of ADRs from this group of patients. An ADRs observed in adults was similar to Mehta et al. [31], however Melmon [32] has reported large percentages of ADRs in geriatric and pediatric populations. Few studies from resource-limited settings have directly assessed the relationship of sex on HIV outcomes in response to ART, or factors associated with sex disparities in treatment outcomes. In a recent study from India [33], comparing sex differences in HAART outcomes, women had significantly higher CD4 cell counts after the completion of HAART therapy. In the present study a similar results (80.8%) were observed, though there was not any significant association (p=0.78) observed between the gender and treatment outcome. In two similar studies from

rural Uganda, women were more likely to have a lower mortality than men as well a higher rate of viral suppression, although the findings did not quite reach statistical significance [10,34]. In countries where there is considerably more data on the relationship between sex and HAART outcomes, most studies have found no sex differences in response to treatment [14,15] with a few showing more favorable responses in women [35,36]. Previous studies have identified age [37,38] and low baseline CD4 counts [39] as risk factors for incomplete CD4 cell recovery. However, the present study suggest an association of the mode of transmission to be the risk factor (p=0.05) which may be due to difference in the study design, duration of the study and inclusion criteria of the study.

Sex discrepancies in treatment outcomes are thought to result from differences in both biologic and behavioral factors including antiretroviral metabolism, antiretroviral adherence and retention in care. Furthermore, Men have also been found to have a significantly higher rate of loss to follow-up and non-adherence to ART, with one study showing a direct correlation with HIV outcomes [34].

It has also been proposed that men respond less well to treatment because they are less adherent to care and ART [40]. There are few studies from resource-limited settings that have examined sex differences in adherence to ART and its association with treatment outcomes. In Zambia, no association was observed between sex and adherence to medications, defined as the number of antiretroviral doses taken out of the number of doses prescribed using pharmacy pick up records and pill counts [41].

In conclusion, results from this study lend further evidence of less favorable outcomes among both HIV-infected men and women. In this study, two important and potentially modifiable factors, level of immunosuppression at ART initiation and adverse drug reaction associated with HAART therapy significantly contribute to inferior outcomes in HIV patients, suggesting biologic differences between sexes may play a larger role. In developing settings, women continue to be the focus of healthcare interventions and these study findings should prompt HIV programs to now pay greater attention to men. Longer term studies of sex disparities in treatment outcomes should be conducted to help determine the most effective interventions to close this sex gap.

Conclusion

Overall, the high frequency of metabolic complications observed in both women and men emphasizes the importance of developing safer HAART regimens and managing these side effects in a timely manner in order to avoid long-term health consequences associated with such toxicities.

Our study shows that both male and females in Penang, Malaysia on HAART have better treatment outcomes. The good clinical ART outcomes observed under standardized treatment protocols suggest that simply expanding access to treatment can have positive outcomes and also suggests that barriers to seeking and accessing treatment are being reduced. Therefore, it would be important to undertake a larger study to confirm the observed differences between genders in treatment outcomes.

Study Limitations

The study was conducted retrospectively by collecting any available data without gathering any information directly from the patient, due to this reason it was not possible to assess the disease severity and exact ADRs experienced by the patients. In addition some of the data were missing hence could not be added to further improve the strength of the findings.

Study Implications

Systemic procedure for updating patient's profile in the hospital can be useful so that any crucial data of patient's demographic characteristics, socioeconomic status, physical examination, etc., can be easily gathered. A large sampled prospective study would be essential to re-evaluate the findings of the present study focusing on various aspects of patient demographics, clinical parameters and ADRs in particular.

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