Original Article

Determinants for zidovudine-induced anemia in HIV adult patients: A Thai multicenter study

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ABSTRACT

Objectives: This study was aimed to analyze the prevalence of zidovudine (AZT)-induced anemia, severity and determinants for the anemia in Thai human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) patients. **Materials and Methods:** A cross-sectional, multicenter study was carried out in HIV/AIDS adult out-patients who were taking AZT as part of the highly active antiretroviral therapy regimens, met relevant eligibility criteria and attended the eight antiretroviral clinics of community hospitals in Chumphon Province during January 2010-May 2012. Data on the prevalence and anemia characteristics were collected and analyzed. A binary logistic regression was performed to determine relevant factors with a significance level (α) of 0.05. **Results:** A total of 303 patients were included and nearly 71.6% of these started AZT + lamivudine + nevirapine as the primary regimen. Nearly half were male (48.8%) and the mean age was 39.5 years (standard deviation [SD] =8.6). Of 303 patients, 34 developed anemia that clearly started from 4 to 24 weeks after AZT-based therapy; the prevalence rate was 11.2%. With the AZT-induced anemia, patients mostly had the baseline CD4 count lower than 200 cells/mm^3 (64.7%), baseline body mass index (BMI) >18.5 kg/m^2 (61.8%) and baseline hemoglobin (Hb) in the range of 8.0-9.5 g/dL (85.3%); the mean Hb change from the baseline was 4.5 g/dL (SD = 3.2). The severity of anemia was mainly classified as grade 1 (55.9%) or 4 (32.4%). Four risk factors, i.e. baseline CD4 levels, Hb, BMI and duration of AZT use, significantly attributed to the anemia (P = 0.018, 0.004, 0.009 and 0.002, respectively). The risk of anemia could be predicted by 33.3% using the equation: Logit P_{anemia} = 6.186 + 1.666 × Baseline CD4 level-0.501 × Baseline Hb-0.225 × Baseline BMI + 2.338 × Duration of AZT therapy. **Conclusion:** HIV patients using AZT may experience mild-to-severe anemia with salient features. Four determining factors for the anemia should be closely monitored by pharmacists or health care professionals before altering the regimen.

INTRODUCTION

Approximately, 7 million people who live with acquired immunodeficiency syndromes (AIDS) can now access highly active antiretroviral therapy (HAART).[1] The increasing number of patients receiving HAART has led to a reduction in AIDS-related morbidity and mortality. However, some patients need to change HAART medicines owing to their toxicity.[1-3] Stavudine (d4T), for example, is a nucleoside reverse transcriptase inhibitor (NRTI) that has a long-term adverse effect with mitochondria toxicity; therefore, it is no longer recommended by the World Health Organization (WHO) as a preferred NRTI.[4,5] According to the WHO Guidelines, an NRTI is suggested as the first-line medicine for

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resource-limited countries, i.e., zidovudine (AZT) or tenofovir (TDF) plus lamivudine (3TC) and a non-nucleoside reverse transcriptase inhibitor (NNRTI).[6,7] The use of TDF is usually restricted due to its cost and reserved for patients who cannot use AZT for various reasons. Thus, AZT is now widely utilized as part of the HAART combination in many developing countries like Thailand.[8-10]

AZT has been used in human immunodeficiency virus (HIV)/AIDS patients for nearly 30 years, but it can cause anemia, which is considered as serious or life-threatening, compared with other adverse effects;[11-13] its side-effects are much less common with the use of low doses.[12] The drug-induced anemia may be mild, moderate, or severe depending on patient's conditions. The anemia may occur within 2-48 weeks from the treatment initiation, especially in the 1st 24 weeks, for which a health care team should closely monitor.[14,15] Several factors[16-20] such as gender, age, low CD4 count and low hemoglobin (Hb), attribute to this anemia, but they have not fully been investigated for the relationships. As the anemia also varies with regions, the goal of its management based on the WHO Guidelines[6] and guidance in resource-limited countries includes its diagnosis, monitoring for effectiveness and prevention of adverse drug effects. It might be ideal in practice if the risk of anemia could be predicted.

Various studies with different design and settings have revealed different data on the prevalence and severity of AZT-induced anemia, but the overall characteristics of the anemia are still unclear. Although some HIV/AIDS researchers in Asia and Africa have partly explored the risk factors affecting the anemia caused by AZT, no prediction model has so far been created to help explain the risk associations and prevent this anemia. In addition, there is no evidence of the complete risk factors and applications of AZT disclosed from countries with scarce resources, including Thailand. It is therefore of paramount importance to explore this type of anemia thoroughly in terms of its characteristics and all relevant risk factors in HIV/AIDS patients.

Aim of the study

This pharmacoepidemiological study was aimed to analyze the prevalence of AZT-induced anemia, severity and determinants for the anemia in Thai HIV/AIDS patients receiving AZT-containing HARRT regimens.

MATERIALS AND METHODS

The cross-sectional, multicenter study was conducted in HIV/AIDS patients attending eight antiretroviral clinics of community hospitals in Chumphon Province, Thailand from January 2010 to May 2012. Since it was not feasible to find a control group in order to do an analytical study, the one-group pharmacoepidemiological study design was then selected. It was approved by the Ethics Review Board of each community hospital by the period of study. The severity of AZT-induced anemia was graded based on the AIDS Clinical Trials Group Criteria[21,22] by taking account of Hb levels, i.e., grade 1 (Hb: 8.0 to <9.5 g/dL), grade 2 (7.0-7.9 g/dL), grade 3 (6.5-6.9 g/dL) and grade 4 (<6.5 g/dL). The anemia prevalence was determined at the Hb level <9.5 g/dL during the follow-up period.[21,22]

Patients and eligibility criteria

Patients would be included in the study if they were HIV/AIDS adult out-patients aged 15 or over, received an AZT combination, could give oral or written consent and attended one of eight hospital's antiretroviral clinics. Exclusion criteria were: Patients who suffered from hematological disorders, or discontinued the AZT therapy. The sample size was estimated according to the anemia prevalence of 10% on average[11-13] – the required sample (N) $=4(Z_{crit})^2 p\,(1-p)/d^2$.[23] A sample of 138 was determined according to a 95% confidence interval with the expected width of 10%. Since a binary logistic regression analysis was also performed, it required roughly 200-300 subjects as assumed by the Wald test and case-control study.[24] On the whole, 300 patients were targeted to investigate the prevalence and logistic model.

Study tool

A data collection form was specially designed to collect the data. It included two parts. Part 1 was to gather patient's characteristics, i.e. gender, age, marital status, highest education, occupation, baseline body mass index (BMI) (or BMI prior to AZT therapy), smoking, alcohol consumption and AZT-based HAART regimen. Part 2 was involved in clinical data that embraced WHO AIDS clinical stage,[25] baseline CD4 count (or the recorded CD4 level before the AZT therapy), baseline and current Hb levels, concomitant use of co-trimoxazole, opportunistic infections and duration of the AZT therapy. Hematocrit was not included, as it renders little benefit for the anemia diagnosis. The data collection form was checked for face validity by two experts of the study team and rectified as suggested. The hard copies together with

an Excel format were then dispatched to eight clinics for data collection.

Study procedure

Each antiretroviral clinic, which was run by one HIV physician, one pharmacist, one nurse and assistant, performed routine patient care and treatment including one-stop service clinical care, counseling, laboratory testing (i.e. for blood glucose, renal function, liver function, lipid profile, complete blood count (CBC), CD4 count, viral load, drug resistance if needed) and monitoring for opportunistic infections and adverse drug effects. All antiretroviral were provided by the National AIDS Program and prescribed according to Thai National Guidelines 2010[26] and WHO Guidance.[1,8] Naïve patients or those switching from the d4T wash-out protocol received the first-line antiretrovirals that contain AZT at the daily dose of 500 mg if their body weight <60 kg and 600 mg if >60 kg. Most were prescribed a fixed-dose, combined pill (GPOvir Z 250®), which contains AZT 250 mg, 3TC 150 mg and nevirapine (NVP) 200 mg, to retain their adherence, but few received three 100 mg tablets twice a day or one 300 mg tablet twice a day, together with other medicines in the HAART regimens. According to the National Guidelines,[26] the medications together with monitoring schedules are shown in Table 1. For instance, HIV patients with Hb >8.0 g/dL can start with AZT-containing regimens and must change to d4T or TDF-based HAART if Hb <8.0 g/dL.

In this study, patients with Hb >9.5 g/dL were followed-up every 2 months for at least 12 months (or 48 weeks) and their CBC was checked every 6 months. Those with Hb <9.5 g/dL were monitored based on the schedule stated above. Pharmacists in eight clinics collected patients' data using the data collection form as planned.

Statistical analysis

The data from eight settings were centrally collated and checked for accuracy at Paknum-Chumphon Hospital.

Table 1: Medications and monitoring schemes for HIV patients with hemoglobin (Hb) levels

Hb (g/dL)	Medication	Monitoring
>9.5	AZT-based regimen	Check Hb every 2 months and CBC every 6 months
8.0-9.5	AZT-based regimen plus iron preparation	Check Hb every month and CBC every 2 months
<8.0	d4T or TDF-based regimen plus blood transfusion as appropriate	Check Hb and CBC every 1-2 weeks during the visit for blood transfusion

Hb=Hemoglobin, AZT=Zidovudine, CBC=Complete blood count, TDF=Tenofovir

All data were then entered into PASW Statistics 20 (SPSS-IBM Co., Chicago, IL, USA) and analyzed using descriptive statistics. The determinants for AZT-related anemia were calculated in 90% of patient cases, which were randomly selected by the software, by a binary logistic regression analysis. The rest 10% were used to test the logistic regression model. Regarding independent variables, 10 risk factors obtained from our pilot study and related literature were included in the analysis, i.e. gender, baseline CD4 level, baseline Hb, baseline BMI, duration of AZT-based therapy, smoking, alcohol intake, WHO AIDS clinical stage, concomitant use of co-trimoxazole and tuberculosis (TB) co-infection. A significance level(α) was set at 0.05.

RESULTS

At the outset, 321 patients were recruited, but 18 were excluded owing to their incomplete or unclear data, such as BMI and Hb levels. Thus, 303 patients were subsequently included in the study. Their characteristics are demonstrate in Table 2. Of these, nearly half were male (48.8%) and the mean age was 39.5 years (standard deviation [SD] =8.6); most were <40 years old. The majority were less educated

Table 2: Characteristics of patients receiving AZT-based HAART (*n*=303)

Characteristic	Number of patients (%)
Gender	
Female	155 (51.2)
Male	148 (48.8)
Age (years): Mean (SD)	39.5 (8.6)
<40	184 (60.7)
>40	119 (39.3)
Highest education	
None or incomplete primary school	15 (5.0)
Primary school	169 (55.8)
Secondary school	107 (35.3)
Higher than secondary school	12 (3.9)
Occupation	
Unemployed	32 (10.5)
Employed	143 (47.2)
Owned business	85 (28.1)
Fisherman or agriculturist	43 (14.2)
AZT-based HAART regimen	
AZT+3TC+NVP	217 (71.6)
AZT+3TC+EFV	43 (14.2)
AZT+3TC+IDV+RTV	13 (4.3)
AZT+DDI+IDV+RTV	14 (4.6)
AZT+TDF+LPV/r	16 (5.3)

AZT=Zidovudine, HAART=Highly active antiretroviral therapy, NVP=Nevirapine, 3TC=Lamivudine, EFV=Efavirenz, IDV=Indinavir, RTV=Ritonavir, DDI=Didanosine, TDF=Tenofovir, LPV/r=Lopinavir+ritonavir, SD=Standard deviation

with only primary and secondary levels (91.1%) and employed in private or government sectors (47.2%). All of them received one of five AZT-containing HAART regimens, but mainly the AZT + 3TC + NVP combination (71.6%). Some of them who became allergic to NVP were switched to efavirenz (EFV). In case of patients allergic to 3TC, it would be changed to didanosine or TDF. In addition, those who presented with NNRTI class allergies were switched to protease inhibitor base drugs, i.e., indinavir, ritonavir, or lopinavir + ritonavir.

Prevalence and characteristics of AZT-induced anemia

Table 3 presents the salient features and risk factors of anemia potentially caused by AZT in the HAART regimens. Of 303 patients, 34 developed anemia; the prevalence rate was 11.2%. They primarily developed anemia after taking the medicine for 4 weeks up to 48 weeks (or 1-12 months), but few experienced it within 4 weeks (0.7%). This tendency is clearly presents in Figure 1. Most of the patients suffered from mild anemia (grade 1 with Hb 8.0-9.4 g/dL; 55.9%), which were successfully treated by hematinic drugs, e.g., ferrous supplement (FBC®) one tablet 3 times daily and folic acid 5 mg daily. Then monitor patient's Hb and other anemic signs and symptoms without altering AZT. However, some patients experienced severe, life-threatening anemia (grade 4 with Hb <6.5 g/dL; 32.4%) that required blood transfusion and switching from AZT to TDF or another NRTI, like abacavir. The remainder was moderate cases that were managed by blood transfusion and monitoring for the anemia conditions. Since there is no specific guidance for AZT-induced anemia management, all antiretroviral clinics simply followed the National Guidelines, i.e. changing AZT to other antiretroviral drugs if Hb <8.0 g/dL or in patients with anemia grades 2-4.

Most of the patients had the baseline CD4 count lower than 200 cells/mm^3 (64.7%), baseline BMI >18.5 kg/m^2 (61.8%) and baseline Hb in the range of 8.0-9.5 g/dL (85.3%) with the mean of 11.6 g/dL (SD = 1.7); the mean Hb change from the baseline was 4.5 g/dL (SD = 3.2). Patients with AIDS stages 2-3 (76.5%) chiefly suffered from the anemia. Their average BMI was within the normal limit, but a bit lower than those without the anemia (19.5 + 3.0 vs. 21.3 + 3.3 kg/m^2). The majority of them did not smoke cigarettes/cigars, consume alcohol or take co-trimoxazole at the same time. Apart from that, few had opportunistic infection, i.e., TB, candidiasis, or herpes zoster, when they developed this anemia.

Table 3: Characteristics and risk factors of AZT-induced anemia

Characteristic	Number of patients (%)		
	Patient with anemia (*n*=34)	Patient without anemia (*n*=269)	Total (*n*=303)
Severity of AZT-induced anemia			
Grade 1: Hb 8.0-9.4 g/dL	19 (55.9)	-	-
Grade 2: Hb 7.0-7.9 g/dL	3 (8.8)	-	-
Grade 3: Hb 6.5-6.9 g/dL	1 (2.9)	-	-
Grade 4: Hb<6.5 g/dL	11 (32.4)	-	-
Duration of AZT taken (weeks): Mean (SD)	10.8 (9.9)	21.19 (14.6)	20.0 (14.6)
<4	2 (5.9)	2 (0.7)	4 (1.3)
4-24	11 (32.3)	22 (8.2)	33 (10.9)
25-48	12 (35.3)	63 (23.4)	75 24.8)
>48	9 (26.5)	182 (67.7)	191 (63.0)
Baseline CD4 count (cells/mm^3): Mean (SD)	201 (219)	331 (260)	317 (259)
<200	22 (64.7)	94 (34.9)	116 (38.3)
>200	12 (35.3)	175 (65.1)	187 (61.7)
Baseline Hb (g/dL): Mean (SD)	11.6 (1.7)	12.9 (2.0)	12.8 (2.0)
>9.5	5 (14.7)	269 (100.0)	274 (90.4)
8.0-9.5	29 (85.3)	-	29 (9.6)
Hb change after AZT therapy (g/dL): Mean (SD)	4.5 (3.2)	0.4 (1.6)	0.9 (2.1)
WHO AIDS clinical stage			
Stage 1	7 (20.6)	155 (57.6)	162 (53.5)
Stage 2	16 (47.1)	54 (20.1)	70 (23.1)
Stage 3	10 (29.4)	36 (13.4)	46 (15.2)
Stage 4	1 (2.9)	24 (8.9)	25 (8.2)
Baseline body mass index (kg/m^2): Mean (SD)	19.5 (3.0)	21.5 (3.3)	21.3 (3.3)
<18.5	13 (38.2)	44 (16.4)	57 (18.8)
>18.5	21 (61.8)	224 (83.6)	245 (80.9)
Smoking-Yes	7 (20.6)	73 (27.1)	80 (26.4)
Alcohol intake-Yes	3 (8.8)	54 (20.1)	57 (18.8)
Concomitant use of co-trimoxazole	16 (47.1)	96 (35.7)	112 (37.0)
Opportunistic infections			
Tuberculosis-Yes	5 (14.7)	61 (22.7)	29 (9.6)
Candidiasis-Yes	8 (23.5)	15 (5.6)	23 (7.6)
Herpes zoster-Yes	2 (5.9)	5 (1.9)	7 (2.3)

AZT=Zidovudine, Hb=Hemoglobin, SD=Standard deviation, WHO=World health organization, AIDS=Acquired immune deficiency syndrome

Determinants for AZT-induced anemia

Risk factors involved in the anemia potentially induced by the AZT treatment are summarized in Table 4. Data obtained from 270 out of 303 or roughly 90% were used to determine a binary logistic model, which was tested in the rest. of 10 variables, only

four determining factors, i.e., baseline CD4, baseline Hb, baseline BMI and duration of AZT use, were significantly associated with the anemia caused by AZT (P = 0.018, 0.004, 0.009 and 0.002). The risk of anemia, or natural logarithm for the odds of AZT-induced anemia, could be predicted by 33.3% using the equation:

$$\text{Logit } P_{anemia} = 6.186 + 1.666 \times \text{Baseline CD4} - 0.501 \times \text{Baseline Hb} - 0.225 \times \text{Baseline BMI} + 2.338 \times \text{Duration of AZT treatment}$$

where $\text{Logit } P_{anemia}$ = ln (odds of anemia) = ln (prob [anemia]/prob [no anemia])

Baseline CD4: 0 for <200 cells/mm^3 and 1 for >200 cells/mm^3

Baseline Hb: actual value >8.0 g/dL

Baseline BMI: actual value >12.9 kg/m^2

Duration of AZT use: 0 for <12 weeks and 1 for >12 weeks.

The duration of 12 weeks was chosen as a cut-off point, for it better helped determine the anemia and the mean period of AZT therapy in this study was 11 weeks or so. Figure 2 depicts the relationship of patients' baseline CD4, anemia severity (grades 1-4) and the prevalence

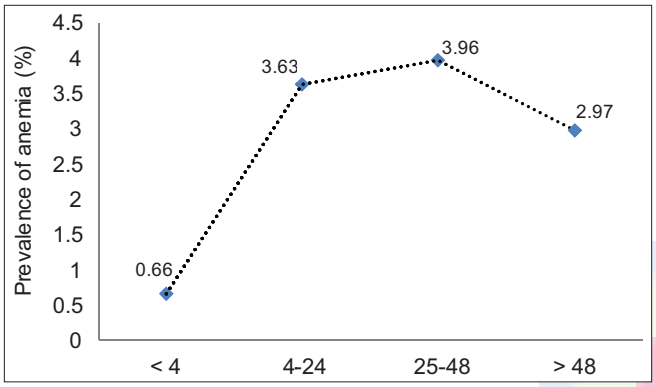

Figure 1: Zidovudine (AZT)-induced anemia detected in various periods of AZT-based therapy

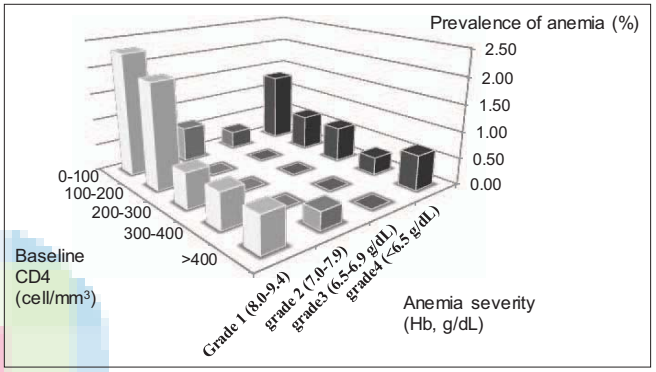

Figure 2: Relationship of patients' baseline CD4, anemia severity with grades 1-4 and the anemia prevalence

Table 4: Determining factors for AZT-induced anemia based on a binary logistic regression model (*n*=270)

Factor	Detail (code)	Regression data				
		B	*P* value	Exp (B)	95% confidence interval	
Constant	-	6.186	0.039*	485.788	-	-
Gender	Female (0) Male (1)	0.158	0.781	1.172	0.384	3.571
Baseline CD4 count (cells/mm^3)	≤200 (0) >200 (1)	1.666	0.018*	5.292	1.325	21.135
Baseline hemoglobin (g/dL)	Actual value	−0.501	0.004*	0.606	0.430	0.852
Baseline body mass index (kg/m^2)	Actual value	−0.225	0.009*	0.798	0.675	0.944
Duration of AZT therapy	<12 weeks (0) >12 weeks (1)	2.338	0.002*	10.361	2.291	46.864
AIDS clinical stage	Stage 1-2 (0) Stage 3-4 (1)	−0.001	0.999	0.999	0.313	3.190
Smoking	Yes (1) No (0)	0.674	0.315	1.964	0.527	7.311
Alcohol intake	Yes (1) No (0)	0.350	0.624	1.419	0.350	5.757
Co-trimoxazole use	Yes (1) No (0)	0.555	0.413	1.742	0.461	6.581
Tuberculosis co-infection	Yes (1) No (0)	0.389	0.593	1.476	0.354	6.161
Nagelkerke R^2	-	0.333	-	-	-	-

*P<0.05 (statistically significant). AZT=Zidovudine, AIDS=Acquired immune deficiency syndrome

of anemia. It was likely that patients with low CD4 had a tendency of developing anemia with slightly higher prevalence rates after receiving AZT treatment.

DISCUSSION

The findings reflected the use of AZT-based HAART in middle-aged patients with the low socio-economic status, which were consistent with overall HIV/AIDS patients in Thailand.[9] The combination of AZT + 3TC + NVP was the preferred regimen in community hospitals, as it was tolerable and widely used by community hospitals. Ideally, a TDF-based regimen, such as, TDF + 3TC + EFV, is the most appropriate and tolerate one, but in Thailand it is still reserved for HIV patients and requires specialist's approval on a case-by-case basis. Some patients however needed to switch to others owing to adverse drug reactions or drug resistance. Brokering and Qaquish[22] pointed out anemia and its management in patients receiving HAART regimens are vital to HIV management and need to be monitored by multidisciplinary team. Two antiretrovirals are particularly of concern, i.e., AZT and d4T. Compared with d4T, the odds ratio of AZT inducing anemia is 1.693[27] or 2.51,[6] or the risk is roughly 2-3 times. Nevertheless, this study just looked at only AZT and its combinations, but not d4T that is rarely employed now.

The AZT-induced anemia is rather unique and should be properly managed.[20,28] The exact mechanism of the anemia is still unknown. It was hypothesized that AZT may suppress erythropoiesis or inhibit erythroid stem cells, thus causing pure red-cell aplasia (i.e. decreased reticulocyte counts and Hb levels without hemolysis or blood loss), increasing mean corpuscular volume (MCV) and elevating erythropoietin levels.[13,29] This could partially explain why iron supplements, folic acid (or vitamin B_{12}), or blood transfusion can be used to manage the anemia based on its severity. Apart from that, it remains unclear as to whether the anemia is a Type A adverse drug reaction (dose-dependent), as some patients receiving a low dose also need blood transfusion.[29] In this study, the prevalence of AZT-induced anemia was 11.2%, which was in accordance with other studies that reported 4.0-21.9% of anemic cases.[11-13] It should be noted that 29 out of 34 patients with AZT-induced anemia experience mild-to-moderate anemia (Hb: 8.0-9.5 g/dL). The initial anemia was different from the AZT-induced type, which was later identified and confirmed by low reticulocytes and Hb, increased MCV and high erythropoietin levels. However, in this study the reticulocyte counts and MCV were performed for all patients to confirm AZT-induced anemia but not all recorded. Thus, the incomplete data could not be presented. Owing to the lack of facilities in the community hospitals, erythropoietin levels were not measured.

Most patients experienced grade 1 anemia (6.3%), possibly because they could be clearly identified during their visits. However, some with serious events (grades 3-4; 3.9%) were later detected on account of patients' conditions. This could be partly explained by the patient's education background and fast anemic onset. Although the association between the anemia severity and the education level was not presented here, it was likely that patients with low education were not fully aware of their anemia and came to the antiretroviral clinics quite late with high anemic grades. Moreover, in some cases the anemia quickly developed; thus severe anemia was just detected. Regarding the prevalence of severe anemia, it was higher than the one reported in Zambia (2.2%),[14] but lower than those in India (7.1-8.0%) and Australia (14.5%),[17,19] possibly due to patient variations and study design.

The AZT-induced anemia clearly presented after 4 weeks of AZT-based therapy and the high prevalence started from 4 to 24 weeks (or 1-6 months), which was congruent with other studies indicating the occurrence of anemia in 24 weeks.[7,11,14,19] Some late-onset anemia, namely >1 year, which was unraveled by few studies,[17,30] also took place in this study. With respect to Hb, it tended to drop from the mean baseline of 11.6 g/dL (SD = 1.7) with the percentage mean change of 38.8%. This result was partly confirmed by Zhou *et al*. that revealed Hb declines by 0.5 g/dL in 12 weeks, 0.4 g/dL in 24 weeks and 0.2 g/dL in 48 weeks.[17] They also found if baseline Hb declines from 13 to 10 g/dL, the anemia will rise from 7% to 58%. Although there was no deceased patient in this study, Giganti and his team[14] asserted the risk of death caused by AZT-impacted anemia was 5.4%, 4.6% and 4.5% for the Hb levels of <8.5, 8.5-10 and >10 g/dL, respectively. In addition to Hb, most patients with anemia (64.7%) had CD4 counts <200 cells/mm^3, which was aligned with the study of Claster *et al*.[21] i.e., 83.7%. As the anemic patients were mostly diagnosed as AIDS stages of 2-3, they were particularly prone to anemia. This trend was similar to the results of the meta-analysis in numerous resource-limited countries.[17]

Regarding other risk factors, the majority of patients had BMI above 18.5 kg/m^2, few opportunistic infections with co-trimoxazole therapy and moderate life-styles. This might signify the certain degree of health in this patient group and implied the anemia due to AZT could possibly happen in patients with various health status and HIV conditions. This complexity was emphasized by the logistic regression model that was able to predict the anemia risk by solely 33.3% based on the four significant factors, i.e. baseline CD4, baseline Hb, baseline BMI and the period of AZT use. The result was slightly different from several studies in India and Australia[15-17,30] that found only three determinants from association tests, i.e. the baseline CD4, baseline BMI and duration of AZT usage within 24 weeks. In contrast, the study of Agarwal *et al*.[11] did confirm female gender, but not CD4 or BMI, is associated with the anemia and that of Kirragga *et al*. focused on the TB co-infection as a risk factor.

In order to interpret the risk of AZT-anemia, all four determining factors of a patient, either attributes or actual values, must be substituted in the logistic equation and then take an antilog for the natural logarithmic value to yield an odds of anemia. If the odds was >1.0, then the patient receiving the AZT-based HAART combination would be at risk of anemia. An implication for this equation was if a patient with low CD4 (<200 cell/mm^2), low Hb (e.g., 8.0-9.4 g/dL), or low BMI had to take the medicine, an intensive monitoring for the 1st 12 weeks, especially for CBC, would be required.

Limitations of the study

As each antiretroviral clinic had the small number of HIV/AIDS patients, it took longer time for the patient recruitment than originally planned. Although all patients' data were carefully collected, some incomplete files still existed for various reasons. This led to excluding some cases from the study. Moreover, a subgroup analysis for patients using AZT 250 mg and 300 mg was not performed, as it was not powered enough to do so. With the analysis of two doses, the study could however provide the actual AZT usage (low internal validity) but high external validity in terms of generalizability.

CONCLUSION

This study could investigate AZT-induced anemia in terms of its prevalence, specific features, severity and determining factors in Thai HIV/AIDS patients taking AZT-based HARRT combinations. The findings would be of help to health care professionals, especially in countries with resource scarcity, to understand more about this type of anemia and its management, as part of a pharmacovigilance program. In addition, local guidelines for the management of AZT-induced anemia can be developed based on the results of this study. According to the binary logistic regression model, it is necessary to monitor the anemia closely in patients with low levels of CD4, Hb and BMI especially within the 1st 12 weeks and routinely carried out over the period of AZT treatment. If the anemia does occur, it should be managed accordingly. More pharmacoepidemiological studies are needed to explore the adverse effects of other antiretrovirals in HAART combinations in order to provide optimum pharmaceutical care for HIV/AIDS patients.

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