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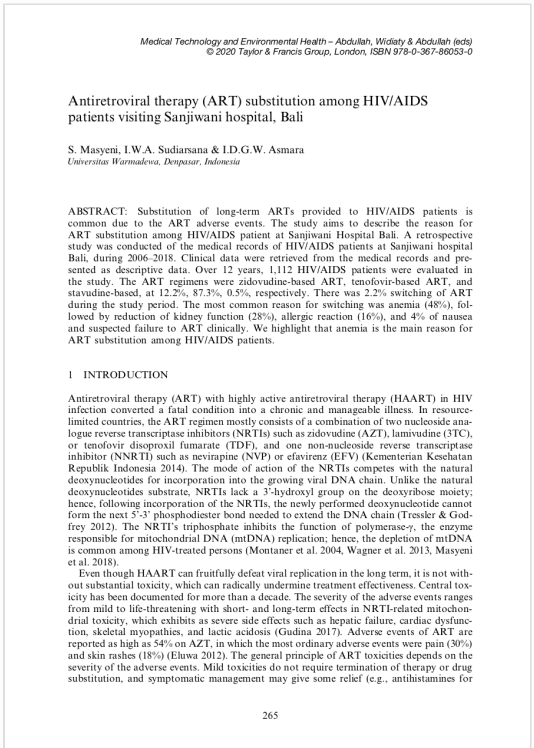

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Antiretroviral therapy (ART) substitution among HIV/AIDS patients visiting Sanjiwani hospital, Bali

S. Masyeni, I.W.A. Sudiarsana & I.D.G.W. Asmara
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ABSTRACT: Substitution of long-term ARTs provided to HIV/AIDS patients is common due to the ART adverse events. The study aims to describe the reason for ART substitution among HIV/AIDS patient at Sanjiwani Hospital Bali. A retrospective study was conducted of the medical records of HIV/AIDS patients at Sanjiwani hospital Bali, during 2006–2018. Clinical data were retrieved from the medical records and presented as descriptive data. Over 12 years, 1,112 HIV/AIDS patients were evaluated in the study. The ART regimens were zidovudine-based ART, tenofovir-based ART, and stavudine-based, at 12.2%, 87.3%, 0.5%, respectively. There was 2.2% switching of ART during the study period. The most common reason for switching was anemia (48%), followed by reduction of kidney function (28%), allergic reaction (16%), and 4% of nausea and suspected failure to ART clinically. We highlight that anemia is the main reason for ART substitution among HIV/AIDS patients.

1 INTRODUCTION

Antiretroviral therapy (ART) with highly active antiretroviral therapy (HAART) in HIV infection converted a fatal condition into a chronic and manageable illness. In resource-limited countries, the ART regimen mostly consists of a combination of two nucleoside analogue reverse transcriptase inhibitors (NRTIs) such as zidovudine (AZT), lamivudine (3TC), or tenofovir disoproxil fumarate (TDF), and one non-nucleoside reverse transcriptase inhibitor (NNRTI) such as nevirapine (NVP) or efavirenz (EFV) (Kementerian Kesehatan Republik Indonesia 2014). The mode of action of the NRTIs competes with the natural deoxynucleotides for incorporation into the growing viral DNA chain. Unlike the natural deoxynucleotides substrate, NRTIs lack a 3'-hydroxyl group on the deoxyribose moiety; hence, following incorporation of the NRTIs, the newly performed deoxynucleotide cannot form the next 5'-3' phosphodiester bond needed to extend the DNA chain (Tressler & Godfrey 2012). The NRTI's triphosphate inhibits the function of polymerase-γ, the enzyme responsible for mitochondrial DNA (mtDNA) replication; hence, the depletion of mtDNA is common among HIV-treated persons (Montaner et al. 2004, Wagner et al. 2013, Masyeni et al. 2018).

Even though HAART can fruitfully defeat viral replication in the long term, it is not without substantial toxicity, which can radically undermine treatment effectiveness. Central toxicity has been documented for more than a decade. The severity of the adverse events ranges from mild to life-threatening with short- and long-term effects in NRTI-related mitochondrial toxicity, which exhibits as severe side effects such as hepatic failure, cardiac dysfunction, skeletal myopathies, and lactic acidosis (Gudina 2017). Adverse events of ART are reported as high as 54% on AZT, in which the most ordinary adverse events were pain (30%) and skin rashes (18%) (Eluwa 2012). The general principle of ART toxicities depends on the severity of the adverse events. Mild toxicities do not require termination of therapy or drug substitution, and symptomatic management may give some relief (e.g., antihistamines for

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Even though HAART can fruitfully defeat viral replication in the long term, it is not without substantial toxicity, which can radically undermine treatment effectiveness. Central toxicity has been documented for more than a decade. The severity of the adverse events ranges from mild to life-threatening with short- and long-term effects in NRTI-related mitochondrial toxicity, which exhibits as severe side effects such as hepatic failure, cardiac dysfunction, skeletal myopathies, and lactic acidosis (Gudina 2017). Adverse events of ART are reported as high as 54% on AZT, in which the most ordinary adverse events were pain (30%) and skin rashes (18%) (Eluwa 2012). The general principle of ART toxicities depends on the severity of the adverse events. Mild toxicities do not require termination of therapy or drug substitution, and symptomatic management may give some relief (e.g., antihistamines for

a mild rash). Moderate or severe toxicities may require substitution with a drug in the same ART class but with a different toxicity profile, or with a drug in a different class, but do not require discontinuation of all ART. Severe life-threatening toxicities need cessation of all ARV drugs, and the commencement of proper supportive therapy until the symptoms are alleviated. Substitution of long-term ARTs provided to HIV/AIDS patients is common due to ART adverse events (Eluwa 2012).

However, only a little information is known about ART adverse events in many HIV programs in the public health sector of developing countries. The study aim is to describe the reasons for ART substitution among HIV/AIDS patients at Sanjiwani Hospital Bali.

2 METHODS

The current study was a hospital-based, retrospective observational study conducted at HIV care clinics in Gianyar Bali from 2006–2018. The hospital has an HIV clinic, staffed with health professionals trained in ART treatment and adherence counseling services. Clinical data were retrieved from the medical records and presented as descriptive data. The reasons for substitution were retrieved from the medical record. A data-gathering format was used to collect data on the demographic settings, the starting and changing regimens, the period of the initial therapy, CD4 count, World Health Organization (WHO) stage of the disease, and reasons for regimen substitution. Adverse drug reactions (ADR) are defined as the occurrence of adverse events such as diarrhea, nausea, vomiting, anemia, rash, fatigue, peripheral neuropathy, lipodystrophy, metabolic disturbances, or any other effect related to HAART. Substitution is defined as single or triple drug changes due to side effects and initiating another drug of the same class and/or another category.

3 RESULTS

A total of 1,094 medical records of HIV-infected patients at Sanjiwani Hospital were assessed in the study. Female patients account for the minority, (29%) and 7 (0.6%) of the female participants were pregnant. The median age of the participants was 32.5 (IQR 13) years old. Total CD4+ ≤100 cell/mm^3, CD4+ 101–200 cell/mm^3, CD4+ 201–350 cell/mm^3, CD4+ 351–499 cell/mm^3, and CD4+ ≥ 500 cell/mm^3 accounting for 347 (31.7%), 139 (12.7%), 173 (15.8%), and 37 (93.4%) respectively.

The first-line original ART consists of stavudine-based, tenofovir-based, and zidovudine-based ART. The stavudine ART is in combination with lamivudine and nevirapine or efavirenz, as well as the combination of TDF and ZDV. Characteristics of the participants are presented in Table 1. A majority of the patients were on the combination of tenofovir+lamivudine+efavirenz, the fixed-dose combination ART (738; 67.5%).

Total switching of the ART was found in 26 (2.37%) patients. Ten out of 26 (38.46) cases of switching was ZDV-based as the original ART. Adverse events of ART were found in 22 (2.01%) patients. Types of adverse events included anemia 4 (18.18%), itching 10 (45.45%), a decrease of kidney function 7 (31.82), and gastrointestinal problems 1 (4.55%). The adverse effects of anemia and itching mostly relate to the combination of ZDV+3TC+NPV and another first-line ART, TDF+3TC+EFV is the most common ART of choice substitute for the previous ART. On the other hand, reduced kidney function may relate to TDF-based ART and change to ZDV-based ART. Some 50% of switching occurs in the first year of treatment (Figure 1).

The switching to second-line ART was found in 4 (0.36%) patients due to the suspicion of treatment failure, whether clinical failure (33.3%) or immunological failure (66.7%). The ART of choice for switching due to treatment failure is boosted lopinavir/ritonavir in combination with TDF+3TC.

Table 1. Characteristic of the participants (N = 1094).

Variable	Frequency	Percentage (%)
Gender		
Male	777	71.0
Age		
18–30	470	42.96
31–40	382	34.92
41–50	166	15.17
51–60	58	5.31
61–70	17	1.55
>70	1	0.09
Initial Body Weight		
Median (IQR)	55 (12)	
Initial CD4 (IQR)	136 (246)	
HIV stage (WHO)		
Stage 1	115	10.5
Stage 2	109	10.0
Stage 3	431	39.4
Stage 4	439	40.1

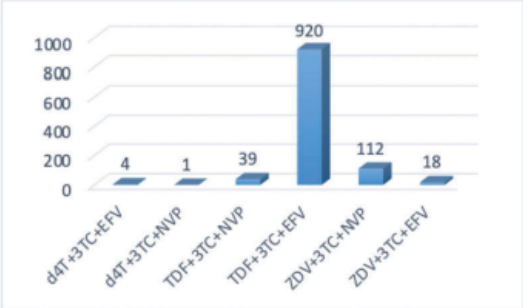

Figure 1. Profile of ART among the HIV-infected patients.

4 DISCUSSION

Acquired immunodeficiency syndrome (AIDS) caused by the human immunodeficiency virus (HIV) is a major global health problem (van Sighem et al. 2015). There are several studies of HIV infection in Bali due to subtype characteristics (Khairunisa et al. 2018), toxicity (Masyeni et al. 2018), adherence (Jiamsakul et al. 2014), and co-infection (Juliari 2018), which reflect the local epidemic of HIV infection. The main reasons for treatment conversion might be due to adverse events, poor adherence, a desire for pregnancy, or treatment failure (Haile & Berha 2019). The finding of high numbers of male patients who need ART substitution in the current study is supported by another study where they were found as high as 53.7%.

The median CD4 of the study participants is 136 cell/mm^3. This is in contrast with the finding of the previous study where they found the median CD4 of the patients was 201 cell/mm^3 (Zhang 2011). The discrepancy may associate with social demographics of the countries that affect the immune status of the patients. The study found toxicity (88%) as the most common reason to change the ART regimen. A concordance finding reported by other study found up to 72.73% ART changing due to toxicity (Assefa & Hussein 2014). This similar finding may be because the HIV sub-type is HIV-1, but we do not assess the genetic diversity of the patients.

The most common primary ART in the current study is a TDF-based regimen, which is in contrast with a previous study where the primary ART was zidovudine (ZDV) based (Sandeep 2014). In Indonesia, since 2014, the availability of TDF made it the ART of choice. Likewise, ZDV-adverse events such as anemia may cause a switch to another regimen in this study. Another study found that ART substitution is most commonly found due to NVP toxicities (Boulle 2007). This study found that toxicity due to NVP, although infrequent, may explain why the most common ART use at the hospital is TDF+3TC+EFV.

5 CONCLUSION

We highlight the most frequent ART substitution in the study was due to ART toxicities, instead of treatment failure. This finding may help physicians monitoring an ART-adverse event in improving the services for the patient's convenience.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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