ANALYSIS OF ADVERSE DRUG REACTIONS TO ANTIRETROVIRALS USE IN A SECONDARY HOSPITAL

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ABSTRACT

Although antiretrovirals (ARV) evidently extend the life expectancy of people living with HIV/AIDS (PLWH), their associated Adverse Drug Reactions (ADRs) are unavoidable, particularly in long-duration regimens. Several studies have reported a correlation between ADRs and adherence to ARV therapy. Meanwhile, ARV is the main determinant of achieving an immunological and virologic response. Pharmacists play the role of counselors in improving therapeutic outcomes including ADR management. This study aimed to analyze ADRs induced by ARV based on pharmacy documentation and to describe the frequency of PLWH follow-up visits over a two-year period. The study was conducted at Sleman Regional Hospital, an HIV/AIDS referral hospital in Yogyakarta. A cross-sectional design was used with saturated sampling, including all ARV use for HIV/AIDS. Data were collected from the pharmacy unit and patients' spontaneous reports. Prescribed ARV came from the electronic system, whereas ADR reports were from patients during voluntary consultation with the pharmacist or in PITC services. A total of 110 ARV were administered mostly to male patients aged 25-40 years. The most regimen was tenofovir+lamivudine+efavirenz (91%) with the highest frequency of follow-up visits ≤ 12 times (53%). The top three ADRs were dizziness (30%), nausea (11%), and headache (8%). Three of the four pediatric patients experienced ADRs, each with AZT-induced fatigue, bloating, and diarrhea in LPV/r monotherapy. Most of the patients did not maintain appointments for hospital visits. Further studies are recommended to analyze the causative factors of non-adherence, including the loss to follow-up group.

Keywords: Adverse Drug Reaction, Antiretroviral, Hospital, Indonesia

INTRODUCTION

The Joint United Nations Program on HIV/AIDS (UNAIDS) estimates that nearly 40 million of the world's population lives with HIV, the majority of which are of productive age. Meanwhile, in Indonesia, as of June 2022, data showed that the prevalence of AIDS had reached 519 thousand and was the highest in the Southeast Asian region (CNN Indonesia, 2022).

To date, antiretroviral therapy (ARV) remains the preferred therapy to suppress viral load, with the success of such therapy regimens determined by the starting time for ARV therapy, which definitely requires patient compliance (Antiretroviral Therapy Cohort Collaboration, 2017). Compliance with ARV use has been shown to correlate strongly with viral suppression and PLWH survival rates (Tchakoute *et al*., 2022). Besides the priority over compliance with ARV use, a major issue surrounding the use of antiretrovirals is the inevitable incidence of Adverse Drug Reactions (ADRs). Several studies have reported a correlation between the incidence of ADRs and decreased compliance with ARV therapy (Abadiga *et al*., 2020; Li *et al*., 2017).

Studies on ADRs have been conducted, and the most common clinical

manifestations are gastrointestinal effects, such as nausea, vomiting, elevated liver enzymes, rashes, and blood dyscrasias. However, most of these studies involved a limited number of patients and did not consider the role of hospital pharmacists in the analysis of ADR incidence (Arisudhana *et al*., 2018; Chowta *et al*., 2018; Pertiwi *et al*., 2020; Putra, 2021). Many studies have analyzed the role of pharmacists and their potential contribution to the management of HIV/AIDS patients who receive ARV therapy (Chatha *et al*., 2020; McCree *et al*., 2020; Shahi *et al*., 2023). Furthermore, 90% of the problems associated with ARV therapy can be resolved within six months based on pharmacist recommendations and interventions (Aderemi-Williams *et al*., 2021). A systematic review and meta-analysis of 25 studies concluded that pharmacist services improve compliance, viral load suppression, and CD4-T lymphocytes (Ahmed *et al*., 2022). Pharmacists are expected to be knowledgeable about all aspects of pharmacology and services for patients administered antiretrovirals, including compliance counseling and pharmacovigilance (Tseng *et al*., 2012). Therefore, the role of pharmacists in such patient groups should be developed, similar to the situation in Indonesia (Handayani *et al*., 2018).

In Indonesia, pharmacist involvement is increasingly required through the PICT program (provider-initiated counselling and testing) adapted from the WHO and launched by the Indonesian Ministry of Health in 2010. Pharmacists provide therapeutic monitoring services and medication counseling to improve compliance and ADR management due to ARV use. However, many programs to date have demonstrated the role of pharmacists in providing services to undocumented patients with HIV, and there are a limited number of relevant studies that involve pharmacists as an accessible and valuable resource to assist in the management of patients with HIV (Horace, 2012). Therefore, this study aimed to analyze adverse drug reactions to antiretrovirals prescribed by counseling pharmacists and recorded in the documentation in one of the secondary hospitals owned by a local government in Indonesia, as well as to describe the follow-up visit routines of HIV/AIDS patients to visit the hospital.

RESEARCH METHODS

This retrospective cross-sectional study at Sleman Regional Hospital (RSUD Sleman) involved all HIV/AIDS patients of various age categories who were prescribed antiretrovirals over the 2019-2020 period. Data were collected from ARV prescriptions for both outpatients and inpatients at the pharmacy unit, pharmacy documentation, and patients' spontaneous reporting systems. Data on the prescriptions of drug regimens were obtained from the pharmacy electronic system, whereas reports on ADR incidents were based on the information provided by patients when consulting with the pharmacist as part of PITC services or on a voluntary basis. The pharmacy electronic system provided data on patients' name, gender, date of birth, prescribed ARV drug regimens, dosage, and schedule of follow-up visits. Patients were defined as the loss to follow-up group if they did not return to the hospital for at least 30 days from the date of their last appointment. The health insurance policy provided by the Indonesian government requires patients to control the disease every 30 days. In addition to administrative considerations, the need for routine therapy for chronic diseases such as HIV/AIDS requires patients to take medication regularly and be controlled every 30 days to monitor ARV therapy, especially ADR, which can be acute, chronic, or delayed. The documentation used at the research site was the drug therapy monitoring forms and ADR reporting forms (Supplementary 1 in the Indonesian version). The forms collected data on the manifestations of ADRs experienced by the patients, onset of ADRs, conditions upon experiencing ADRs (fully recovered/recovered with sequelae/not yet recovered/dead), and the names of all drugs taken by the patients. Univariate analysis was used to present data on demographic characteristics, prescribed ARV regimens, and frequency of patient follow-up visits over a two-year period of data retrieval using Microsoft Office 365 Excel. The incidence of ADRs for each ARV regimen is presented as a percentage. This research was approved by the Ethics Committee of the Sleman Regional Hospital (approval letter No. 180/1354).

RESULTS AND DISCUSSION

1. Characteristics and Patterns of Antiretroviral Use

This study was conducted in a public hospital owned by the regional government of Sleman Regency, a district with the largest population in the Province of Yogyakarta Special Region (DIY) in Indonesia, reaching 1.13 million people. Sleman Regional Hospital implemented the Provider-Initiated HIV Testing and Counseling Program (PITC) in 2014, or four years after the Ministry of Health of the Republic of Indonesia launched the program along with the guidelines for its implementation. The Sleman Regional Hospital has 16 pharmacists, but only one pharmacist is responsible as a medication counselor for patients with HIV/AIDS. ADR analysis of antiretrovirals in PLWH at Sleman Regional Hospital involved 110 patients, consisting of 99 outpatients and 11 inpatients. An overview of the distribution of the subject characteristics is shown in **Table I**.

Table I. Distribution of the Subject Characteristics

Characteristic	Total (%)
Gender	
Male	72 (65.45)
Female	38 (34.55)
Age category	
≤ 4	4 (3.64)
5-14	1 (0.91)
15-19	1 (0.91)
20-24	9 (8.18)
25-49	80 (72.72)
≥ 50	15 (13.64)
ARV regimen	
FDC (TDF 300 mg + 3TC 300 mg + EFV 600 mg)	101 (91.81)
NVP 200 mg + 3TC 150 mg + AZT 300 mg	3 (2.73)
EFV 600 mg + 3TC 150 mg + AZT 300 mg	1 (0.91)
AZT 100 mg	3 (2.73)
LPV/r 200 mg/50 mg	2 (1.82)
Frequency of monthly follow-up visits for 2 years	
≤ 12	58 (52.73)
13-18	19 (17.27)
19-23	27 (24.55)
24	6 (5.45)

The data showed that the incidence of HIV/AIDS in male patients was higher than that to female patients. This is in line with reports on HIV cases by sex distribution during the period 2008-2019 (Ditjen Pencegahan dan Pengendalian Penyakit Kemenkes RI, 2019). Similar findings were also shown in–2010-2015 data of Southeast Asian countries, including Indonesia (Pendse *et al*., 2016).

Meanwhile, patients in the 25-49 age range (35 years old on average) were in the age category mostly diagnosed with HIV/AIDS and prescribed antiretrovirals, reaching 73%. These findings are consistent with a survey involving North American and European populations aged 25–29 years, an age range with the highest risk of developing HIV/AIDS (Govender *et al*., 2021). Productive age is the age of an individual who is sexually active or engaged in drug abuse, which can trigger a risk of contracting HIV/AIDS.

In addition, **Table I** shows that the greatest use of ARV regimens included three combinations of antiretrovirals comprising two drugs from the nucleoside reverse transcriptase inhibitor (NRTI) group and one from the non-nucleoside reverse transcriptase inhibitor (NNRTI) group, with a TDF + 3TC + EFV regimen in the form of a Fixed-Dose Combination (FDC) as the first-line therapy for HIV/AIDS treatment (Kemenkes Republik Indonesia, 2019). In line with the implementation of the National Health Security Program policy in Indonesia through BPJS services (Social Security Administrative Body), the antiretrovirals available in hospitals in accordance with the National Formulary are in tablet dosage form, with the potency of FDC (TDF 300 mg + 3TC 300 mg + EFV 600 mg), AZT 100 mg, LPV/r 200 mg/50 mg, NVP 200 mg + 3TC 150 mg/AZT 300 mg, and EFV 600 mg + 3TC 150 mg/AZT 300 mg. The duration of antiretroviral prescriptions followed the national policy of 30 days (Kemenkes Republik Indonesia, 2019). Furthermore, patients need follow-up visits to the hospital to redeem the prescriptions as well as for monitoring by health workers regarding patients' clinical condition and compliance.

The data in **Table I** also show that ARV regimens in the form of FDC preparations are the most commonly prescribed combinations to improve patient compliance. A study involving more than 7000 PLWH found that FDC regimens resulted in better compliance and a lower risk of hospitalization compared with a group of patients who received three or more pills per day (Sax *et al*., 2012). However, in certain situations, it is necessary to add other drugs to complete the regimen or to consider the patients' clinical conditions. Unfortunately, antiretroviral prescriptions in the FDC did not result in a high degree of compliance in this study. In addition, 94.55% of patients did not attend follow-up visits to the hospital, and almost 60% of patients made less than half the visit frequency they had to complete (<12 times in 2 years). As revealed in several studies, suboptimal adherence increases the risk of disease progression, drug resistance, viral load, and risk of transmission to death. This study found that in Indonesia, the ARV regimens in the FDC could not guarantee that PLWH will comply with treatment. A systematic meta-analysis of 125 studies with various age categories of PLWH concluded that various barriers related to treatment adherence existed in the group of patients who even received FDC of ARVs. These barriers include forgetfulness, travel, depression, and stigma (Shubber *et al*., 2016). This retrospective study did not include in-depth interviews with PLWH; therefore, this barrier could not be identified. This will be part of the recommendation for further research in Indonesia.

Compared with other studies that used the loss-to-follow-up (LFU) parameter, the non-compliance in this study was significantly higher, thus greatly affecting therapeutic failure. LFTU is defined as the cessation of ARV follow-ups for three months or more for various reasons. The use of more stringent parameters in this study, such as the frequency of monthly routine treatment, has likely made the findings much more significant than those of other studies (Berheto *et al*., 2014; Birhanu *et al*., 2020; Shiferaw *et al*., 2022).

As previously stated, only one pharmacist served as counselor. This affected the intensity and quality of the services provided to PLWH. All healthcare workers who have received a training program can act as counselors, especially in relation to medication compliance. In addition, intensive education about therapy, particularly in rural communities, remains important for ARV compliance (Molla *et al*., 2018; Shet *et al*., 2014). However, limited human resources in hospitals seem to be a key issue in Sleman Regional Hospital. This should be taken into account by both hospital management and the local government, particularly regarding the optimization of the counseling program in PITC by adding HIV/AIDS counselors and providing an information system that can better facilitate effective and efficient services. The profiles of the ARV regimens during the study period are presented in **Table II**.

Table II. Description of the Antiretrovirals Use

Regimen	Age (years)	Gender	Total (%)
FDC (TDF+3TC+EFV)	23-60	Female	32 (29.09)
	19-64	Male	69 (62.72)
NVP+3TC+AZT	7 33	Female	2 (1.82)
	4	Male	1 (0.91)
EFV+3TC+AZT	28	Male	1 (0.91)
AZT	0	Female	1 (0.91)
	0	Male	2 (1.82)
LPV/r	30 44	Female	2 (1.82)

For PLWH, ARV therapy can be used as the first, second, and third lines. The first-line treatment included two drugs in the NRTI group and one in the NNRTI group. In the fixed-dose combination, TDF + 3TC (or FTC) + EFV taken once a day more rarely caused severe adverse drug reactions, which indicates a therapeutic and virological response compared with NNRTI once or twice a day or any guidelines containing PI. Other options for first-line treatment include AZT + 3TC + EFV, AZT + 3TC + NVP, or TDF + 3TC (or FTC) + NVP. This first-line option was recommended for adults as the category with the most significant findings in this study. Meanwhile, for children, the recommendations are AZT or TDF + 3TC (or FTC) and ABC + 3TC, with limitations that lead to the ongoing use of AZT + 3TC as the first-line ARV therapy in HIV-infected children. The therapy guidelines for toddlers are different from those for adults, since HIV infection during the perinatal period is faster in toddlers than in adults. The selection of ARVs for toddlers can include LPV/r syrup as first-line treatment. Meanwhile, second-line therapy is administered in cases of drug resistance and therapeutic failure (Kemenkes Republik Indonesia, 2019).

Four pediatric patients diagnosed with HIV/AIDS were prescribed an ARV regimen consisting of NVP + 3TC + AZT (n=2) and neonates (n=2) who received AZT monotherapy. The use of such therapy for 6 weeks has proven to be effective in preventing vertical HIV transmission in babies born to mothers who receive ARVs and whose blood HIV count is undetected (Kemenkes Republik Indonesia, 2019). Both AZT monotherapy and ARV combination regimens (NVP + 3TC + AZT) can be used as prophylactic therapies for neonatal patients. Furthermore, both have become dominant treatment trends for 25 years in the USA, based on two categories: monotherapy and combination regimen of 3-4 drugs (Williams *et al*., 2018).

With fewer children diagnosed with HIV, in-depth research on the choice and development of ARV regimens for pediatric patients is limited. Pharmacokinetic changes in pediatric patients are also challenging for drug development and research. The complex and multifaceted problem of non-adherence to treatment is a complicating factor in pediatric HIV treatment. This is related to this age group, which generally depends on the parents or adults who accompany them in treatment. In addition, the social stigma that still exists for those infected with HIV can be very difficult for a child and can cause a significant psychological burden (Lee *et al*., 2021). Meanwhile, large pill sizes for HIV regimens can be especially difficult for school-age children, particularly if dosing is required during school hours. In Indonesia, FDC ARV regimens are available and are expected to increase patient comfort. However, the hospital where this study was conducted did not provide the FDC, so the dispensing was using an adult regimen that was adjusted based on pediatric body weight. Recommendation for the government to facilitate the availability of FDC ARVs in every

health service, in addition to efficiency in dispensing time and practical reasons for administration.

In Indonesia, the current first-line therapy for PLWH has switched to dolutegravir, as recommended by the WHO in 2019 (Kemenkes Republik Indonesia, 2022; WHO, 2019). Recent studies have found that this drug provides a virologic response with a higher level of tolerance as first-line therapy for adult patients (Correa *et al*., 2020). Similarly, when administered to groups of children and adolescents with HIV-1, the pharmacokinetic profile of dolutegravir has been used as an approach to determine appropriate dosage regimens and dosage forms (Turkova *et al*., 2021; Waalewijn *et al*., 2022).

Additionally, there were concerning findings related to the frequency of follow-up visits that did not follow the predetermined schedule (once a month) in 104 patients (94.55%). Compared to other studies that used the loss-to-follow-up (LFTU) parameter, the non-compliance in this study was significantly higher, thus greatly affecting therapeutic failure. LFTU is defined as the cessation of ARV follow-ups for three months or more for various reasons. The use of more stringent parameters in this study, such as the frequency of monthly routine treatment, has likely made the findings much more significant than those of other studies (Berheto *et al*., 2014; Birhanu *et al*., 2020; Shiferaw *et al*., 2022). Optimizing the role of health professional teams, including pharmacists, is required to reduce the number of patients who do not comply with treatment.

2. Adverse Drug Reactions to Antiretrovirals

The number of adverse drug reactions at Sleman Regional Hospital was recorded from spontaneous reports by patients and documentation by pharmacists as the medication counselors who conducted PITC. The distribution of the incidence of adverse drug reactions to antiretrovirals is shown in **Table III**.

Table III. Description of ARV Adverse Drug Reactions

Reaction	Total (%)	ARV Regimen (n)
Dizziness	35 (30)	Regimen 1 (34); Regimen 3 (1)
Nausea	13 (11)	Regimen 1 (13)
Headache	9 (8)	Regimen 1 (9)
Fatigue	7 (6)	Regimen 1 (6); Regimen 4 (1)
Nausea, vomiting	5 (4)	Regimen 1 (4); Regimen 2 (1)
Fever	2 (2)	Regimen 1 (1); Regimen 2 (1)
Vertigo	2 (2)	Regimen 1 (2)
Bloating	2 (2)	Regimen 3 (1); Regimen 4 (1)
Cold	2 (2)	Regimen 1 (2)
Drowsiness	3 (3)	Regimen 1 (3)
Diarrhea	3 (3)	Regimen 1 (2); Regimen 5 (1)
Body ache and bone pain	2 (2)	Regimen 1 (2)
Itchy hands and feet	4 (3)	Regimen 2 (1)
Whole-body itching	2 (2)	Regimen 1 (2)
Itchy red spots	4 (3)	Regimen 1 (4)
Gnawing stomach pain	2 (2)	Regimen 1 (2)
Blood in the stool	1 (1)	Regimen 1 (1)
Heart palpitations	1 (1)	Regimen 1 (1)

Excessive dandruff	1 (1)	Regimen 1 (1)
Insomnia	5 (4)	Regimen 1 (5)
Nightmare	6 (5)	Regimen 1 (6)
Decreased appetite	2 (2)	Regimen 1 (2)
Neuropathy	1 (1)	Regimen 1 (1)
Leg and hand cramps	2 (2)	Regimen 1 (2)
Total	116 (100)	

*Regimen 1 = FDC (TDF + 3TC + EFV); Regimen 2 = NVP + 3TC + AZT; Regimen 3 = EFV + 3TC + AZT; Regimen 4 = AZT; Regimen 5 = LPV/r

Table III shows that the most unwanted reactions were dizziness, nausea, and headaches. These three reactions frequently occur in HIV patients who are treated with antiretroviral therapy, at the beginning of use or during therapy. This is in accordance with the results of some studies in which the most common nonspecific side effects related to the central nervous system were nausea, dizziness, and vertigo (Chimirri *et al*., 2013; Chowta *et al*., 2018; Menza, 2022; Tadesse *et al*., 2014). The regimen with the highest number of ADRs was FDC (TDF + 3TC + EFV). Similar findings were reported in a six-year retrospective study conducted in Ethiopia (Weldesenbet *et al*., 2022). In contrast, a study that analyzed 299 ADR reports found that a regimen consisting of NVP + 3TC + AZT (regimen 2) was three times more likely to cause ADRs than the TDF + 3TC + EFV regimen (Bhuvana *et al*., 2017; Rukmangathen *et al*., 2020). The number of patients dominantly using the TDF + 3TC + EFV regimen is likely to have led to the high number of ADRs observed for such regimens in this study. Differences in risk factors for experiencing ADR in addition to variations in patient phenotypes related to age, sex, other drugs used, and comorbidities are the cause of differences in ADR findings in several studies. In addition, genetic variation has also been shown to contribute to variations in the incidence of ADR in ARV use (Aceti *et al*., 2015; Pendse *et al*., 2016).

Meanwhile, pediatric patients who received AZT monotherapy experienced fatigue and bloating, while another child given LPV/r had diarrhea. A five-year cohort study involving 174 pediatric patients in a tertiary hospital also found gastrointestinal disorders to be the most clinical manifestations due to ARV use, with the incidence of diarrhea induced by the use of a regimen that contained lopinavir (Ray *et al*., 2023). In general, ADR based on WHO severity classification are divided into levels 1, 2, 3, and 4, with level 4 being the most severe. However, in some cases, levels 3 and 4 require substitution therapies. Management strategies must be individualized for each child, taking into account the level of the ADR severity, viral suppression status, and the available ARV options (NIH Office of AIDS Research Advisory Council (OARAC), 2023). Several studies of ADR due to the use of ARVs in pediatric patients found the majority of ADRs to be in categories 2 and 3 (Abdela *et al*., 2019; Oumar *et al*., 2023). However, another study found that more than 50% of patients with ARV had ADR with a severity category of 1. All patients with ADR level 1 recovered completely without intervention, whereas 90.5% of patients with ADR level 2 also recovered without any regimen substitution. These findings can be used to educate patients' families to improve adherence, which is the biggest problem in the use of ARVs, including in pediatrics (Dash and Rose, 2023). With the limitations of studies of ADRs due to ARVs in pediatric groups with HIV/AIDS as opposed to those in adult patients, including studies of long-term ADRs, particular attention should be paid to improving the quality of life of pediatric patients.

This study found that some patients experienced more than one ADRs. This could have affected their willingness to continue the treatment. Some studies have shown that the incidence of ADRs strongly correlates with a decrease in the level of patient compliance

with taking ARVs (Abadiga *et al*., 2020; Rajesh *et al*., 2012). Meanwhile, treatment compliance is necessary to determine the success of therapy by viral suppression (Bezabhe *et al*., 2016; Tchakoute *et al*., 2022). The data collection for the incidence of ADRs on a voluntary basis or via scheduled reports as part of the PITC program has made this study different from many other studies that were predominantly conducted by research team members who were unfamiliar to the patients.

However, the identification of ADRs based on patients' voluntary reports on the symptoms they have experienced can be confused with the clinical conditions associated with HIV/AIDS symptoms, such as fever. In this case, the data obtained allows overestimation to occur. However, with self-reporting, patients feel more comfortable because there is no coercion, which allows them to give in-depth reports to their counselors as opposed to documented ADRs, such as those using interview sheets or Naranjo algorithm worksheets.

A limitation of this retrospective study was the absence of medical records. The Research Ethics Committee of Sleman Regional Hospital has required that, for specific patients such as PLWH, access to patients' medical records must be completed with informed consent from all patients. Meanwhile, the majority of HIV/AIDS patients in Indonesia to date are very private due to the possible social pressure they face, making access to communicating with patients or their families extremely difficult. Only some patients could be quite open but only with their counselors or particular non-governmental organizations (NGOs). Consequently, the ADRs were only identified based on pharmacist documentation, including the patients' spontaneous reports to the counseling pharmacist. In addition, retrospective data collection allows only limited data acquisition and is prone to bias because it merely relies on existing documents or notes and does not use medical records or the Naranjo algorithm form. In Sleman Regional Hospital, counseling services for PLWH are implemented when a patient is diagnosed with HIV/AIDS before receiving ARV treatment (pre-ARV), two months after receiving an ARV regimen, if patients undergo a change in drug regimens based on a doctor's decision, in re-education for LFU (Lost to Follow-up) patients, and in services upon patient request. Therefore, this study could not completely describe the incidence of ADRs associated with the use of ARVs, including the incidence of severe ADRs that require confirmation with objective data, such as laboratory data or a doctor's examination. Prospective studies involving collaboration between hospital PICT counselors and NGOs are required to improve disclosure of ADR incidents. Further investigation and analysis of the factors influencing noncompliance with PLWH follow-up visits are also recommended to create strategic programs that can improve the clinical outcomes of patients with HIV/AIDS.

CONCLUSION

Dizziness (30%), nausea (11%), and headache (8%) were the three most reported types of ADRs in HIV/AIDS patients prescribed antiretrovirals. Meanwhile, three out of four pediatric patients experienced ADR, with each patient experiencing fatigue, bloating due to AZT, and diarrhea in LPV/r therapy. In addition, more than 90% of patients did not routinely seek treatment over a two-year period. Optimizing the role of health workers, including hospital pharmacists, as medication counselors is necessary to improve treatment compliance. The causative factors of non-compliance with follow-up visits among PLWH, including in the loss-to-follow-up groups, and the provision of varied approach models should be further studied as a strategy to manage optimal therapy for HIV/AIDS patients.

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