

Antiretroviral Side Effects on Adherence in People Living with HIV/AIDS

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ABSTRACT

Background: Antiretroviral therapy is a lifelong treatment in people living with HIV/AIDS (PLWHA). Adherence is the key to the effectiveness of antiretroviral therapy. The administration of antiretroviral has some side effects that may affect patient adherence.

Purpose: This study aimed to examine the impacts of antiretroviral side effects on adherence in PLWHA.

Methods: This study used a correlational research design. The samples were 78 patients receiving antiretroviral therapy at the tropical disease and infection polyclinic in a hospital in Semarang. Purposive sampling was used to recruit the samples. Data on side effects of antiretroviral were obtained based on the patients' reports, while data on adherence of pill consumption were obtained through the calculation of pills using pill count adherence rate. The collected data were analyzed using the Fisher's exact test.

Results: Results showed that the side effects of antiretroviral therapy influenced the antiretroviral adherence ($p < 0.001$). Most of the side effects of antiretroviral reported by participants were nausea and dizziness. Some participants also reported weakness, difficult to concentrate, and diarrhea.

Conclusion: The side effects of antiretroviral had negative impacts on patients' antiretroviral therapy adherence. Therefore, nurses and health care providers of PLWHA should be able to recognize and give concern on antiretroviral side effect management.

Keywords: Adherence; antiretroviral; PLWHA; side effect

BACKGROUND

HIV/AIDS is still a global health problem since it was discovered. The report of Joint United Nations Program on HIV/AIDS (UNAIDS) in 2015 shows that the number of people living with HIV/AIDS (PLWHA) in the world reaches 36.7 million people with 2.1 million newly infected with HIV and 1.1 million deaths due to AIDS (UNAIDS, 2016). Indonesia is among the 12 countries in the Asia Pacific region with the fastest spread of HIV cases since 2001 up to 2015 (UNAIDS, 2016). In Indonesia PLWHA receiving antiretroviral therapy reached 130,577 people, consisting of adults (93.5%) and children (6.5%). Most of them were still on antiretroviral therapy (50.5%), while 2.6% were unknown, 15.6% were died, 8.7% were out, 2% stopped, 20.6% were lost to follow up (Directorate General of Disease Control and Environmental Health, 2016). The

number of PLWHA in Semarang City was 2,926 who were eligible for antiretroviral therapy and 987 people were still on antiretroviral therapy (Semarang City Health Office, 2015).

Antiretroviral can reduce the risk of HIV transmission, inhibit worsening of opportunistic infections, reduce the amount of virus (viral load) to be undetectable (Directorate General of Disease Control and Environmental Health, 2011). Treatment with antiretroviral is associated with a number of adverse events that have short-term and long-term consequences. The patients' perception that the medication has side effects may cause patients to be non-adherent to the treatment. Factors affecting non-adherence to medication among patients are complex. Few studies found that the side effects of treatment were associated with poor adherence and in spite of antiretroviral benefit, adverse effects are commonly the main reasons for skipping medication (Al-Dakkak et al., 2013).

Some studies reported high incidence of antiretroviral side-effects primarily at initial initiation of ART (Masenyetse, Manda, & Mwambi, 2015; Teklay, 2013). Other studies have shown that patients reporting higher adverse reactions to antiretroviral are more likely to be non-adherent to their antiretroviral regimen. This suggests that adverse reactions may cause treatment interruption and replacement in the prescribed regimen. High adherence (>95%) in antiretroviral is needed to avoid viral resistance to antiretroviral drugs, treatment failure, and lost to follow up (Ministry of Health Republic of Indonesia, 2012; UNAIDS, 2016).

Adherence is an important determinant of successful antiretroviral therapy (Teklay, 2013). Most patients get first-line antiretroviral which can be obtained freely while the type of antiretroviral given is based on the patient's condition. The side effects experienced by the patients are various with varying levels of adherence. Severe side effects of antiretroviral may have significant impacts on adherence. Even though nursing interventions have been given but there are still many inadequacies in the consumption of antiretroviral drugs due to the side effects of therapy. It is critical to understand the impacts of antiretroviral side effects on adherence in PLWHA.

PURPOSE

This study aimed to examine the impacts of antiretroviral side effects on adherence in PLWHA.

METHODS

Design and sample

This study used a correlational research design. The samples were 78 participants who were recruited by purposive sampling. The inclusion criteria were; patients aged >18 years, at 1st and 2nd clinical stages, use first-line antiretroviral therapy, and CD4 cell count >200 cells/mm³ when initiating therapy. Upon enrollment and during follow-up visits, data on socio-demographic factors were collected, including the number and doses of antiretroviral, durations of antiretroviral used, age, and employment status. Antiretroviral side effect symptoms were collected using the questionnaires. Participants were asked to bring their medication bottles to each study visit. Using a pill-count form, data on the

name, number of remaining pills in the bottle, and number of prescribed pills of each antiretroviral medication were collected at each visit.

Ethical consideration

The study was conducted at the tropical and infection disease polyclinic in a hospital in Semarang for 5 weeks in 2017. This study was reviewed and approved by the medical research ethics committee of the Faculty of Medicine, Diponegoro University, and Dr. Kariadi General Referral Hospital in Semarang.

Measurements

Pill counts were calculated as the number of pills taken (the number of pills dispensed – the number of pills counted). Pill Counts Adherence Rate (PCAR) was done by counting the number of pills or drugs that have been consumed divided by the number of medications prescribed for a certain period and then multiplied by 100% (Wu et al., 2015). The number of pills expected to have been taken was calculated by multiplying the daily dose (1/2, 1 or 2 tablets) by the number of days since the date dispensed (Achieng et al., 2013). Previous studies have found that pill count adherence assessment was able to show different adherence in treatment and indicated the rate of adherence so that it can detect non-adherence (Achieng et al., 2013). Adherence can be categorized into optimal adherence in which PCAR is $\geq 95\%$ and suboptimal adherence in which PCAR is $< 95\%$ (Joshi et al., 2014).

Data analysis

The univariate and bivariate analyses were applied. The univariate data were presented in frequency and percentage for categorical data, mean and SD for numerical data. Fisher's exact test was used as the bivariate analysis.

RESULTS

Participants characteristics

In the first table, the average age of the participants was 37.63 years with an average antiretroviral treatment duration of 4.13 years. Participants in this study were dominated by men as many as 51 (65%) people, and 51 (65%) participants had jobs. The side effects of antiretroviral experienced by participants were mostly dizziness (52.9%) and nausea (47.1%).

Table 1. Participants' characteristics (n=78)

Variable	Frequency (%)	Mean \pm SD
Age	78 (100)	37.63 \pm 10.075
Durations of antiretroviral used	78 (100)	4.13 \pm 3.188
Level of adherence		88.77 \pm 3.35
Gender	51 (65)	
Male	22 (28)	
Experienced side effects	29 (37)	
Not experienced side effects	27 (35)	

Variable	Frequency (%)	Mean±SD
Female	12 (15)	
Experienced side effects	15 (20)	
Not experienced side effects		
Employment Status		
Working	51 (65)	
Not Working	27 (35)	
Kind of side effects (SE)		
Gastrointestinal SE		
Nausea	16 (47.1)	
Vomiting	10 (29.4)	
Diarrhea	3 (8.8)	
Abdominal bloating	3 (8.8)	
Central nervous SE		
Dizziness	18 (52.9)	
Insomnia	6 (17.6)	
Difficult to concentrate	7 (20.6)	
Others SE		
Limp	6 (17.6)	
Rash	8 (23.5)	
Drowsiness	7 (20.6)	

Side effects on antiretroviral adherence

Table 2 explains the number of participants who experienced antiretroviral side effects as many as 34 (44%). Two participants had optimal compliance (2.5%) and 32 participants (42%) had suboptimal compliance. Participants who did not experience antiretroviral side effects but had optimal adherence were 35 (45%) and suboptimal were 9 (11.5%). The correlation between drug side effects and adherence to antiretroviral medication showed a p-value <0.001; with a *coefficient correlation* 0.590 (59%).

Table 2. Side effects on antiretroviral adherence (n=78)

Side Effect	Adherence			r	p
	Optimal (%)	Suboptimal (%)	Total (%)		
Experienced (%)	2 (2.5)	32 (41.0)	34 (44)	0.590	<0.001
Not experienced (%)	35 (45.0)	9 (11.5)	44 (56)		
Total	37 (47.5)	41 (52.5)	78 (100)		

DISCUSSION

The results of this study indicate there were 34 participants who experienced side effects after taking antiretroviral, 12 females and 22 males. A consistent finding explains that female sex has been shown to be at a higher risk factor for clinically relevant adverse drug reactions (Anderson, 2008). To assess the side effect of antiretroviral drugs, the patients' own report on adverse effects was used. After initialization of antiretroviral treatment subjects reported experiencing side effects such as dizziness and nausea. The mean level of adherence is reported to be in value 88.77% (Table 1). High adherence (>95%) is needed to prevent treatment failure (Ministry of Health Republic of Indonesia, 2012); UNAIDS, 2016).

This study showed correlations between side effects and nonadherence to antiretroviral. The correlations between side effects on adherence of antiretroviral was shown in Fisher's exact test with p-value <0.001. The level of correlation shown by a *coefficient correlation* 0.590. This suggests that drug side effects may explain its effect on non-adherence consuming ARV as much as 59%. Severity of medication adverse effects was related to an increased nonadherence. This is consistent with other studies that identified adverse effects as a predictor of nonadherence (Okoronkwo, Okeke, Chinweuba, & Iheanacho, 2013; Rudy, Murphy, Harris, Muenz, & Ellen, 2009; Wakibi, Ng, & Mbugua, 2011). The result of this study is consistent with the conceptualization of adherence as a multifaceted construct and influenced by a wide range of dynamic factors. This current study contributes to the understanding of the correlations between side effects and adherence to antiretroviral by identifying specific adverse effects related to nonadherence.

Drug-induced side effects are more common in PLWHA than in the general population. Side effects can be caused by immune hyperactivation factors, changes in metabolism in the body, cytokine profile, oxidative stress, and genetic predisposition (Latif, Maria, & Syafar, 2014). Antiretroviral side-effects generally occur within the first three months of treatment, but not all PLWHA will experience adverse effects after taking antiretroviral drugs (Latif et al., 2014). This is in line with a study conducted in Nigeria suggesting that drug side effects are more likely to occur in the first six months of treatment than with long-standing antiretroviral therapy (Eluwa, Badru, & Akpoigbe, 2012). Another study which is not in line with the results of this study explains that the period of time needed to undergo therapy and the time to suffer from the disease can increase the high risk of decreasing the level of adherence (Kammerer, Garry, Hartigan, Carter, & Erlich, 2007). It can be caused by the patient's perception about the medication side effects.

Thus, developing clinical interventions that address the self-management of side effects is needed. Interventions focus on psychosocial factors and reduce risk behaviors. Studies have shown that symptom management interventions have been effective at increasing self-care ability in managing medication side effects with HIV+ individuals (Chen et al., 2013). This study had certain limitation. It was performed in a small sample size, which might influence the significant differences in the level of adherence based on patient characteristics.

CONCLUSION

The results of this study showed that antiretroviral side effects have an impact on patient's antiretroviral therapy poor adherence. Antiretroviral adverse reactions were the single most common reason for poor adherence. Therefore, healthcare providers especially nurses should be able to recognize and give concern on antiretroviral side effect management. Identifying risk factors for the occurrence of non-adherence is of crucial importance to optimize the initial choice of antiretroviral regimen before initiating the therapy.

REFERENCES

- Achieng, L., Musangi, H., Billingsley, K., Onguit, S., Ombegoh, E., Bryant, L., ... Keiser, P. (2013). The use of pill counts as a facilitator of adherence with antiretroviral therapy in resource limited settings. *PLoS ONE*, 8(12), 1-6.
- Al-Dakkak, I., Patel, S., McCann, E., Gadkari, A., Prajapati, G., & Maiese, E. M. (2013). The impact of specific HIV treatment-related adverse events on adherence to antiretroviral therapy: A systematic review and meta-analysis. *AIDS Care - Psychological and Socio-Medical Aspects of AIDS/HIV*, 25(4), 400-414.
- Anderson, G. D. (2008). Gender differences in pharmacological response. *International Review of Neurobiology*, 83(8), 1-10.
- Chen, W. T., Shiu, C. S., Yang, J. P., Simoni, J. M., Fredriksen-Goldsen, Karen I., Lee, T. S. H., & Zhao, H. (2013). Antiretroviral therapy (ART) side effect impacted on quality of life, and depressive symptomatology: A mixed-method study. *Journal of AIDS and Clinical Research*, 4(3), 218-234.
- Directorate General of Disease Control and Environmental Health. (2011). *National guidelines for clinical management of HIV infection and antiretroviral therapy in adults* (2011th ed.). Jakarta: Ministry of Health Republic of Indonesia.
- Directorate General of Disease Control and Environmental Health. (2016). *Statistics of HIV / AIDs case in Indonesia first quarter of 2016* (2016th ed.). Jakarta: Ministry of Health Republic of Indonesia.
- Eluwa, G. I., Badru, T., & Akpoigbe, K. J. (2012). Adverse drug reactions to antiretroviral therapy (ARVs): incidence, type and risk factors in Nigeria. *BMC Clinical Pharmacology*, 12(7), 1-9.
- Joshi, B., Chauhan, S., Pasi, A., Kulkarni, R., Sunil, N., Bachani, D., & Mankeshwar, R. (2014). Level of suboptimal adherence to first line antiretroviral treatment & its determinants among HIV positive people in India. *Indian Journal of Medical Research*, 140(JUL), 84-95.
- Kammerer, J., Garry, G., Hartigan, M., Carter, B., & Erlich, L. (2007). Adherence in patients on dialysis: Strategies for success. *Nephrology Nursing Journal: Journal of the American Nephrology Nurses' Association*, 34(5), 479-486.
- Latif, F., Maria, I. L., & Syafar, M. (2014). Efek samping obat terhadap kepatuhan pengobatan antiretroviral orang dengan HIV / AIDS [Drug Side Effects on Adherence to Antiretroviral Treatment among People Living with HIV/AIDS]. *Jurnal Kesehatan Masyarakat Nasional*, 9(2), 101-106.
- Masenyetse, L. J., Manda, S., & Mwambi, H. G. (2015). An assessment of adverse drug reactions among HIV positive patients receiving antiretroviral treatment in South Africa. *AIDS Research and Therapy*, 12(1), 6.
- Ministry of Health Republic of Indonesia. (2012). *Guidelines for sustainable implementation of HIV-IMS services* (2012th ed.). Jakarta: Ministry of Health Republic of Indonesia.
- Okoronkwo, I., Okeke, U., Chinweuba, A., & Iheanacho, P. (2013). Nonadherence factors and sociodemographic characteristics of hiv-infected adults receiving antiretroviral therapy in Nnamdi Azikiwe University Teaching Hospital, Nnewi, Nigeria. *International Scholarly Research Notices AIDS*, 2013, 1-8.

- Rudy, B. J., Murphy, D. A., Harris, D. R., Muenz, L., & Ellen, J. (2009). Patient-related risks for nonadherence to antiretroviral therapy among HIV-infected youth in the United States: A study of prevalence and interactions. *AIDS Patient Care and STDs*, 23(3), 185-194.
- Semarang City Health Office. (2015). *Health profile of Semarang City 2015* (2015th ed.). Semarang: Semarang City Health Office.
- Teklay, G. (2013). Adverse effects and regimen switch among patients on antiretroviral treatment in a resource limited setting in Ethiopia. *Journal of Pharmacovigilance*, 1(4), 1-5.
- UNAIDS. (2016). *Prevention Gap Report 2016*. Geneva. Retrieved from http://www.unaids.org/sites/default/files/media_asset/2016-prevention-gap-report_en.pdf
- Wakibi, S. N., Ng, Z. W., & Mbugua, G. G. (2011). Factors associated with non-adherence to highly active antiretroviral therapy in Nairobi, Kenya. *AIDS Research and Therapy*, 8(43), 1-8.
- Wu, P., Johnson, B. A., Nachega, J. B., Wu, B., Ordóñez, C. E., Hare, A. Q., ... Marconi, V. C. (2015). The combination of pill count and self-reported adherence is a strong predictor of first-line ART failure for adults in South Africa. *Current HIV Research*, 27(4), 1251-1265.