Factors Affecting Virological Outcome When First-Line Antiretroviral Therapy Is Reintroduced After Unplanned Interruption

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Abstract
There is no guideline concerning choice of antiretroviral therapy (ART) for HIV-infected patients after unplanned interruption. We conducted a retrospective cohort study of HIV-infected patients reintroduced to first-line ART after having unplanned interruption for at least 1 month. Viral load was evaluated at 6 to 18 months after the reintroduction. There were 100 patients included in our study, and 55 of them achieved virological success. History of single interruption (adjusted odds ratio [aOR] 5.51%, 95% confidence interval [CI] 1.82-16.68, \( P = 0.003 \)) and CD4 count ≥200 cell/mm³ at the time of reintroduction (aOR 4.33, 95% CI 1.14-16.39, \( P = 0.031 \)) increased likelihood to achieve virological success.

Keywords
unplanned interruption, ART reintroduction, virological success

Introduction
Antiretroviral therapy (ART) decreases morbidity and mortality arising from HIV infection.1 Nevertheless, unplanned ART interruption may occur in nonmedical conditions such as patients being lost to follow-up due to poor adherence or unavailability of ART and in medical conditions such as severe drug intoxication, interfering intercurrent illnesses, or cessation of oral therapy due to surgery.2 However, many of these patients return to health centers to resume ART and no recommendations to guide the choice of ART regimen for patients with history of unplanned interruptions. Reintroduction of first-line ART has a risk of failing because the virus could easily develop resistance to several drugs in first-line ART regimen such as non-nucleoside reverse transcriptase inhibitors (NNRTIs) and lamivudine (3TC).3 Ideally, patients should have a drug resistance test before reintroduction as commonly practiced in the United States and Europe,2,4,5 but resistance test is not yet an operating standard in Indonesia, for both first-line and second-line failure. On the other hand, a hasty decision to switch to second-line ART may lead to more serious concerns regarding the higher cost and the fact that if the virus had developed a resistance to second-line ART then it would had been resistant to every class of available antiretroviral drugs.6 Consequently, there would be no more options available, since third-line ART is not yet available in Indonesia.7

There were several studies on the probability of virological success of ART reintroduction and its associated factors. History of previous antiretroviral exposure reduces the probability of achieving virological success.8-10 Several studies used protease inhibitors (PIs) antiretroviral class, which is only used as second-line ART in Indonesia, or the studies involved patients with history of planned interruptions.8,11-13 Other

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studies did not address tenofovir (TDF) as base nucleoside reverse transcriptase inhibitors (NRTIs), while TDF is also the drug of choice for first-line ART in Indonesia. The outline of this study is to analyze factors that contribute to virological success in first-line ART reintroduction based on Indonesia ART regimen.

**Methods**

**Study Patients**

Retrospective cohort study was conducted on patients who received ART reintroduction in Dr Cipto Mangunkusumo Hospital (RSCM) in Jakarta. Inclusion criteria were 18 years of age or older and having an unplanned ART interruption for 1 month or longer before reintroduction. Patient was excluded from the analysis if he or she had history of confirmed virological failure in previous ART, had received anything other than standard first-line ART regimen, had an unknown previous ART regimen, had severe liver and/or kidney dysfunctions comorbidity, and did not have 6 to 18 months of viral load (VL) data after reintroduction. Study patients were drawn with total sampling by reviewing medical records of patients that fulfilled the inclusion criteria and did not fulfill the exclusion criteria.

First-line ART regimen in this study was a combination of 2 NRTIs and 1 NNRTI as defined by the recommendation of the Indonesian Ministry of Health. The choice of NRTI was a combination of zidovudine (ZDV) or stavudine (d4T) or TDF plus 3TC or emtricitabine. The choice of NNRTI was nevirapine (NVP) or efavirenz (EFV). First-line ART reintroduction covered readministering of the same ART or a combination other than the ones regulated by switch strategy. Combination of ZDV or d4T-based NRTI was called a switch if replaced with TDF, and vice versa if TDF-based NRTI was replaced with ZDV or d4T.

**Results**

**Recruitment and Characteristics of Study Patients**

A search of medical records identified 100 patients restarted first-line ART and tested for VL after 6 to 18 months. Sixty-seven percent were male. Median age at the time of reintroduction was 31.4 (23.0-58.7) years. Most patients had interrupted once (79%), followed by twice (17%), 3 times (3%), and 4 times (1%). There were 61% of patients with CD4 count <200 cell/mm³. Median previous ART duration was 12.3 (0.7-94.0) months. Most patients had interruption interval ≥6 months (64%), BMI ≥ 18.5 kg/m² (60%), and Hb ≥ 11.0 g/dL (49%). Only 24% of patients presented with TB coinfection, while stages III and IV seemed comparable to stages I and II (57% and 53%, respectively). Nine percent used TDF as NRTI basis. Only 69% patients reported ≥95% adherence.

Virological success was achieved in 55 patients (95% confidence interval [95% CI]: 45.25-64.75). Patients who had low...
CD4 count and multiple frequencies of interruptions were at higher risk of not achieving virological success (adjusted odds ratio = 4.33 and 5.51, 95% CI: 1.14-16.39 and 1.82-16.68, P = .031 and .003) (Table 1).

Table 1. CD4 Count and Interruption Frequency Were Associated With Virological Success.

| Variables                             | Successful, n (%) | Unsuccessful, n (%) | Crude Odds Ratio (95% CI) | P  | Adjusted Odds Ratio (95% CI) | P   |
|---------------------------------------|-------------------|--------------------|---------------------------|----|-----------------------------|-----|
| Interruption frequency (n = 100)      |                   |                    |                           |    |                             |     |
| 1 time                                | 50 (63.3)         | 29 (36.7)          | 5.52 (1.83-16.63)         | .002| 5.51 (1.82-16.68)           | .003|
| ≥2 times                              | 5 (23.8)          | 16 (76.2)          |                           |    |                             |     |
| Previous ART duration (month), median (Q1-Q3), (n = 100) | 17.9 (4.1-33.9)   | 11.5 (2.0-22.4)    | 1.01 (0.99-1.03)          | .162| 1.02 (0.99-1.04)            | .139|
| Last interruption interval (n = 100)  |                   |                    |                           |    |                             |     |
| ≥6 months                             | 36 (53.7)         | 31 (46.3)          | 0.86 (0.37-1.98)          | .716| 0.85 (0.37-1.98)            | .710|
| <6 months                             | 19 (57.6)         | 14 (42.4)          |                           |    |                             |     |
| BMI, kg/m² (n = 80)                   |                   |                    |                           |    |                             |     |
| ≥18.5                                 | 35 (58.3)         | 25 (41.7)          | 1.40 (0.51-3.87)          | .516| 1.14 (0.35-3.78)            | .826|
| <18.5                                 | 10 (50.0)         | 10 (50.0)          |                           |    |                             |     |
| Hb, g/dL (n = 68)                     |                   |                    |                           |    |                             |     |
| ≥11                                   | 26 (53.1)         | 23 (46.9)          | 1.02 (0.35-2.94)          | .975| 1.38 (0.38-5.10)            | .627|
| <11                                   | 10 (52.6)         | 9 (47.4)           |                           |    |                             |     |
| CD4, cell/mm³ (n = 82)                |                   |                    |                           |    |                             |     |
| ≥200                                  | 17 (81.0)         | 4 (19.0)           | 4.11 (1.24-13.65)         | .021| 4.33 (1.14-16.19)           | .031|
| <200                                  | 31 (50.8)         | 30 (49.2)          |                           |    |                             |     |
| TB coinfection (n = 100)              |                   |                    |                           |    |                             |     |
| Without                               | 45 (59.2)         | 31 (40.8)          | 2.03 (0.80-5.16)          | .136| 1.78 (0.45-7.06)            | .416|
| With                                  | 10 (41.7)         | 14 (58.3)          |                           |    |                             |     |
| HIV stage (n = 100)                   |                   |                    |                           |    |                             |     |
| Stage I and II                        | 31 (58.5)         | 22 (41.5)          | 1.35 (0.61-2.98)          | .457| 0.92 (0.34-2.53)            | .876|
| Stage III and IV                      | 24 (51.1)         | 23 (48.9)          |                           |    |                             |     |
| NRTI base (n = 100)                   |                   |                    |                           |    |                             |     |
| ZDV or d4T                            | 53 (58.2)         | 38 (41.8)          | 4.88 (0.96-24.81)         | .056| 5.03 (0.53-47.84)           | .160|
| TDF                                   | 2 (22.2)          | 7 (77.8)           |                           |    |                             |     |
| Adherence (n = 100)                   |                   |                    |                           |    |                             |     |
| ≥95%                                  | 37 (53.6)         | 32 (46.4)          | 0.84 (0.36-1.97)          | .680| 0.89 (0.37-2.14)            | .799|
| <95%                                  | 18 (58.1)         | 13 (41.9)          |                           |    |                             |     |

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; CI, confidence interval; Hb, hemoglobin; NRTI, nucleoside reverse transcriptase inhibitors; TB, tuberculosis; TDF, tenofovir; ZDV, zidovudine.

*Adjusted for HIV-risk factor and age.
*Adjusted for HIV stage and Hb.
*Adjusted for NRTI base, HIV stage, BMI, and sex.
*Adjusted for HIV stage and interruption interval.
*Adjusted for BMI and Hb.
*Adjusted for Hb and HIV risk factor.
*Adjusted for Hb.
*Adjusted for NRTI base and HIV stage.

Discussion

Virological success was observed in 55% of patients. This finding is lower than similar study by Luebbert et al14 in Malawi which observed virological success of 61%. Other studies with the same objective but different settings (by including PI usage and unplanned interruption) observed a probability of around 80%.8,12 Virological success probability in our study is much lower compared to naive patients. A 2013 study in Bandung, Indonesia, observed virological success in 91% naive patients who had received ART for at least 6 months.19 A history of previous unplanned interruptions causes the patients to possibly carry virus that has developed ART resistance mutations, especially against first-line ART. Mutant virus is still persist in the reservoir and could redominate after reintroduction of the same ART.20-23

Our study shows that patients with interruption frequency of 1 time have a higher odds to achieve virological success in ART reintroduction. Repeated ART interruptions can increase the number of mutant virus resistant to antiretroviral drugs.3,24 Similar study by Luebbert et al14 did not find any significant association between interruption frequency and post reintroduction virological failure. Based on interruption frequency distribution, of 133 study patients in Luebbert et al,14 only 10% had 2 or more interruptions. This finding differs from our study where 21% of study patients had the interruption frequency of 2 or more. Other than that, the definition of
interruption in Luebbert et al. study not only covered the complete interruption of ART but it also included patients with treatment gaps (still taking ART once in a while). Both differences may be the cause of the different results with our study. A low CD4 count shows depleted immune system; thus, the capacity to recognize and suppress viral replication is also diminished. In addition, the effect of a higher baseline CD4 count on virological success may be the effect of a low baseline VL on the effectiveness of the treatment. The association between CD4 count at the time of reintroduction and virological response has been proven by Greig et al. Patients with higher CD4 count at the time of reintroduction have a lower odds to experience virological failure in ART reintroduction. Several other studies, notably by Vogler et al. and Touloumi et al., which did not succeed in proving this association, had patients with different CD4 count characteristics from our study, where their average CD4 counts before treatment resumption was higher, ranging at 265 to 332 cell/mm³. Patients in Vogler and Touloumi studies achieved virological response rate higher than our studies (81% and 86%). Vogler mentioned that baseline CD4 count was not associated with virological response but mentioned nonadherence as the main factor for failures.

The main limitation of this study is the retrospective study design that collected data from medical records. There were several variables with a large amount of missing data and possible information bias that we could not control. Viral load testing which was not done in series with equal interval on each patient might also cause this study to overlook post-ART reintroduction VL dynamics and time needed to achieve virological success. On both significant variables, there is a wide interval confidence. Hence, the application of our study on the population may not be precise.

Conclusion

Probability of virological success on first-line ART reintroduction after unplanned interruption was 55%. Patients who were interrupted once and patients with CD4 count ≥200 cell/mm³ at the time of reintroduction had a higher probability of success treatment.

Authors’ Note

This study does not directly involve human trial. Research methodology had been reviewed and approved by ethic committee of Faculty of Medicine Universitas Indonesia and ethical approval was obtained with ethical clearance number 196/UN2.F1/ETIK/2015. The ethic committee of Faculty of Medicine Universitas Indonesia waived the need for ethics approval and the need to obtain consent for the collection, analysis, and publication of the retrospectively obtained and anonymized data for this noninterventional study. This study abide by Helsinki Declaration and all patient’s medical record were confidential.

Declaration of Conflicting Interests

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References

1. Bartlett JG. A decade of HAART: historical perspective, successes, failures, and future considerations [Internet]; 2006. http://www.medscape.com/viewarticle/547646. Accessed June 2, 2014.
2. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents [monograph online]. Department of Health and Human Services; 2015. http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed July 27, 2015.
3. Schweighardt B, Ortiz GM, Grant RM, et al. Emergence of drug-resistant HIV-1 variants in patients undergoing structured treatment interruptions. AIDS. 2002;16(17):3242–3244.
4. Gunthard HF, Abeg JA, Eron JJ, et al. Antiretroviral treatment of adult HIV infection: 2014 recommendations of the international antiviral society-USA panel. JAMA 2014;312(4):410–425.
5. Williams I, Churchill D, Anderson J, et al. British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2012: updated November 2013. HIV Med. 2014;15(suppl 1):1–85.
6. Solem CT, Snedecor SJ, Khachatryan A. Burden of illness in a US commercially-insured HIV population: treatment patterns and costs. Paper presented at: 53rd ICAAC; September 10-13, 2013; Denver, CO.
7. Direktorat Jenderal Pengendalian Penyakit dan Penyehatan Lingkungan. Pedoman Nasional Tolakalaksana Klinis Infeksi HIV Dan Terapi Antiretroviral Pada Orang Dewasa Dan Remaja. Jakarta: Kementerian Kesehatan RI; 2011.
8. Greig JE, du Cros PA, Mills C, et al. Predictors of raised viral load during antiretroviral therapy in patients with and without prior antiretroviral use: a cross-sectional study. PLoS One. 2013;8(8):e71407.
9. Stringer JSA, McConnell MS, Kiarie J, et al. Effectiveness of non-nucleoside reverse-transcriptase inhibitor-based antiretroviral therapy in women previously exposed to a single intrapartum dose of Nevirapine: a multi-country, prospective cohort study. PLoS Med. 2010;7(2):e1000233.
10. Lockman S, Hughes MD, McIntyre J, et al. Antiretroviral therapies in women after single-dose nevirapine exposure. N Engl J Med. 2010;363(16):1499–1509.
11. Anaworaniich J, Siangphoe U, Hill A, et al. Highly active antiretroviral therapy (HAART) retreatment in patients on CD4-guided therapy achieved similar virologic suppression compared with patients on continuous HAART. J Acquir Immune Defic Syndr. 2005;39(5):523–529.
12. Vogler MA, Smeaton LM, Wright RL, et al. Combination antiretroviral treatment for women previously treated only in pregnancy: week 24 results of AIDS clinical trials group protocol a5227. J Acquir Immune Defic Syndr. 2014;65(5):542–550.
13. Touloumi G, Pantazis N, Stirnadel HA, et al. Rates and determinants of virologic and immunological response to HAART resumption after treatment interruption in HIV-1 clinical practice. *J Acquir Immune Defic Syndr.* 2008;49(5):492–498.

14. Luebbert J, Tweya H, Phiri S, et al. Virological failure and drug resistance in patients on antiretroviral therapy after treatment Interruption in Lilongwe, Malawi. *Clin Infect Dis.* 2012;55(3):441–448.

15. Direktorat Jenderal Pengendalian Penyakit dan Penyehatan Lingkungan. *Pedoman Nasional Terapi Antiretroviral.* Jakarta: Departemen Kesehatan Republik Indonesia; 2004.

16. Direktorat Jenderal Pengendalian Penyakit dan Penyehatan Lingkungan. *Pedoman Nasional Terapi Antiretroviral: Panduan Tatalaksana Klinis Infeksi HIV Pada Orang Dewasa Dan Remaja.* 2nd ed. Jakarta: Departemen Kesehatan Republik Indonesia; 2007.

17. World Health Organization. *Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach.* Geneva: WHO Press; 2013.

18. Guy R, Wand H, McManus H, et al. Antiretroviral treatment interruption and loss to follow-up in two HIV cohorts in Australia and Asia: implications for ‘test and treat’ prevention strategy. *AIDS Patient Care STDs.* http://www.ncbi.nlm.nih.gov/pubmed/24320013"TDS. 2013;27(12):681–691.

19. Fibriani A, Wisaksana R, Indrati A, et al. Virological failure and drug resistance during first line anti-retroviral treatment in Indonesia. *J Med Virol.* 2013;85(8):1394–1401.

20. Francois C. Mechanisms of HIV drug resistance: a primer. *PRN Notebook.* 2004;9(1):3–7.

21. Michaud V, Bar-Magen T, Turgeon J, Flockhart D, Desta Z, Wainberg MA. Role of pharmacogenetics in HIV treatment: mutations and polymorphisms regulating antiretroviral drug resistance and disposition. *Pharmacol Rev.* 2012;64(3):803–833.

22. Hance AJ, Lemiale V, Izopet J, et al. Changes in Human Immunodeficiency Virus type 1 populations after treatment interruption in patients failing antiretroviral therapy. *J Virol.* 2001;75(14):6410–6417.

23. Wang D, Hicks CB, Goswami ND, et al. Evolution of drug-resistant viral populations during interruption of antiretroviral therapy. *J Virol.* 2011;85(13):6403–6415.

24. Martinez-Picado J, Morales-Lopetegi K, Wrin T, et al. Selection of drug-resistant HIV-1 mutants in response to repeated structured treatment interruptions. *AIDS.* 2002;16(6):895–899.

25. Deeks SG, Wrin T, Liegler T, et al. Virologic and immunologic consequences of discontinuing combination antiretroviral-drug therapy in HIV-infected patients with detectable viremia. *N Engl J Med.* 2001;344(7):472–480.

26. Amoroso A, Etienne-Mesubi M, Edozien A, et al. Treatment outcomes of recommended first line antiretroviral regimens in resource limited clinics. *J Acquir Immune Defic Syndr.* 2012;60(3):314–320.