

Evaluation of the Efficacy and Safety of Changes in Antiretroviral Regimens for HIV-infected Patients

Hiroyuki Tanaka^{1,4}, Tatsuhiko Wada², Yoko Takayama³, Keisuke Matsumoto¹, Koichiro Atsuda¹, Mitsutoshi Satoh^{*4}

¹ Department of Pharmacy, Kitasato University Hospital, 1-15-1 Kitasato, Minamiku, Sagamihara, Kanagawa, 252-0375, JAPAN; ² Department of Rheumatology and Infectious Diseases, Kitasato University School of Medicine, 1-15-1 Kitasato, Minamiku, Sagamihara, Kanagawa, 252-0374, JAPAN; ³ Research and Development Center for New Medical Frontiers Kitasato University School of Medicine, 1-15-1 Kitasato, Minamiku, Sagamihara, Kanagawa, 252-0374, JAPAN; ⁴ Department of Toxicology and Pharmacology, Faculty of Pharmaceutical Sciences, Toho University, 2-2-1 Miyama, Funabashi, Chiba, 274-8510, JAPAN.

Received, February 28, 2014; revised, June 4, 2014; accepted, July 12, 2014; published, July 30, 2014

ABSTRACT - Purpose. Antiretroviral therapy is now available for HIV-infected patients, and so-called highly active antiretroviral therapy (HAART) now makes it possible to strongly suppress viral proliferation and restore immunity. However, the development of new drugs and regimens for HAART is still in progress, with the aim of overcoming a number of associated problems. For this purpose, changes in the prescribed anti-HIV drugs are often made. In the present study, we attempted to clarify the actual effects of such treatment modifications in patients who had been started on HAART. **Methods.** We retrospectively investigated HIV-infected patients who had been started on HAART at Kitasato University Hospital between April 1997 and March 2013. The patients' backgrounds, characteristics and laboratory data were established from the hospital medical records. **Results.** The total follow-up time was 447.3 person-years. The patients remained on their initial regimen for a median period of 2040 days, and 39 patients took a second regimen for a median of 2714 days. There was no treatment failure due to regimen change. The reason for the regimen change was adverse effects in 49 cases, poor adherence/virological failure in 4, immunological failure in 3, patient request in 2, and proposals made by health care workers, or for simplification, in 11. The number of patients who required regimen change due to renal dysfunction showed a gradual increase. The number of times anti-HIV drugs were taken per day was not altered when the regimen changed, being mainly once or twice a day. **Conclusion.** In the present study, there were no instances of treatment failure due to regimen change. Through appropriate regimen change, it is possible to avoid serious adverse effects, and to improve patient adherence. Further adverse effects associated with long-term antiretroviral therapy, and reduction of adherence through medication fatigue should be considered. Drug selection and regimen change should be considered in relation to long-term prognosis.

This article is open to **POST-PUBLICATION REVIEW**. Registered readers (see "For Readers") may **comment** by clicking on ABSTRACT on the issue's contents page.

INTRODUCTION

HIV is a retrovirus that infects mainly CD4 cells and macrophages. In Japan, zidovudine (AZT), a nucleoside reverse transcriptase inhibitor (NRTI) and the first anti-HIV drug, was approved in 1987 and adopted for treatment of HIV. However, because HIV easily becomes drug-resistant, the therapeutic effect of a single agent was found to be temporary. In 1992, didanosine (ddI), another NRTI, was approved, and combination 2NRTI therapy was introduced. In 1997, indinavir (IDV), a protease inhibitor (PI), was approved. Since then,

highly active antiretroviral therapy (HAART) that combines three or more anti-HIV drugs has been available, making it possible to strongly suppress viral proliferation and restore immunity. Consequently, the outcome of treatment for HIV infection has improved dramatically, and both mortality from, and onset of AIDS have decreased significantly (1).

Correspondence Author: Dr. Mitsutoshi Satoh, Department of Toxicology and Pharmacology, Faculty of Pharmaceutical Sciences, Toho University, 2-2-1 Miyama, Funabashi, Chiba, 274-8510, JAPAN.
Tel: +81-47-472-1491; E-mail: satoh@phar.toho-u.ac.jp

The early HAART regimen had many associated problems such as adverse effects, and the need to take many tablets several times a day to avoid interaction with concomitant medication and food. Thereafter, newer drugs with relatively few adverse effects, less interaction with concomitant medication and a longer half-life were developed, leading to the introduction of more effective drug combinations, and so far more than 20 types of anti-HIV drugs have become available in Japan.

More than 15 years after the introduction of HAART, new drugs and treatment regimes are still being investigated. This is because HAART cannot completely eliminate HIV from the body, and patients must continue taking the medication for life. Against this background, there are still various problems with the current HAART regimen, such as difficulties with patient adherence, adverse effects due to long-term medication, interactions with other drugs, and emergence of virus drug resistance.

For these reasons, the current situation is being revised once a year, even though the treatment guidelines of the United States Department of Health and Human Services (DHHS) are widely used.

Under these circumstances, in order to overcome the various problems associated with HAART, the prescribed anti-HIV drugs are often changed in clinical practice.

The purpose of the present study was to investigate the actual situation for patients who had been started on HAART at Kitasato University Hospital, and to evaluate the efficacy and safety of changes in the antiretroviral therapy regimen since April 1997, along with the associated issues.

METHODS

We retrospectively investigated HIV-infected patients who had been started on HAART at Kitasato University Hospital between April 1997 and March 2013. The patients' backgrounds and characteristics were established from the hospital medical records, and data included the CD4 cell count, the plasma HIV-RNA concentration, anti-HIV drug history, HAART regimen change, follow-up time, duration of each HAART regimen, reason for regimen change and relevant laboratory data, and HIV exposure category. The follow-up time and duration of each HAART regimen were measured up to March, 2013. CD4 cell count and

plasma HIV-RNA concentration were compared by using the values obtained before and three months after the regimen change. Other laboratory data were compared by using the values obtained before and six months after the regimen change. In the present study, we surveyed the following changes in regimen: from single abacavir (ABC) tablet plus lamivudine (3TC) tablet to a combination ABC/3TC tablet, from single AZT tablet plus 3TC tablet to a combination AZT/3TC tablet, from a combination ABC/3TC tablet to single ABC tablet plus 3TC tablet, and from a combination AZT/3TC tablet to single AZT tablet plus 3TC tablet. Changes in dose alone or dosage form were not considered to constitute a change in the regimen.

Statistical Analysis

The continuation rates and continuation durations of the first and second regimens were calculated by the Kaplan-Meier method. CD4 cell count and plasma HIV-RNA concentration, serum creatinine (Cr) concentration, and urinary N-acetyl- β -D-glucosaminidase (NAG) concentration before and after the regimen change were compared using paired *t* test. Differences at $P < 0.05$ were considered to be statistically significant.

Ethics

All the patients were surveyed after obtaining approval from the Institutional Review Board of Kitasato University Hospital (approval number; B13-85).

RESULTS

1. Patient Characteristics

The characteristics of the patients are shown in Table 1. Ninety-six patients (81 males, 15 females; mean age 41.7 (21-73) years) had been started on HAART at Kitasato University Hospital. Among them, 63 patients received NRTI+PI, 16 received NRTI+NNRTI, 15 received NRTI+INSTI, 1 received NRTI+CCR5A and 1 received NRTI+PI+CCR5A. The usage of each anti-HIV drug is shown in Table 2.

Table 1. Background and baseline characteristics of the study patients

		Number of patients (%) or mean [Range]
Gender	Male	81 (84.4)
	Female	15 (15.6)
Age (years)		41.7 [21-73]
CD4 cell count		151.0 [1-780]
Plasma HIV-RNA concentration		115825 [960-900000]
HIV exposure category	Homosexual	47
	Heterosexual	42
	Other	7
1st HAART regimen	NRTI+PI	63
	NRTI+NNRTI	16
	NRTI+INSTI	15
	NRTI+CCR5A	1
	NRTI+PI+CCR5A	1

HAART: highly active antiretroviral therapy, NRTI: nucleoside/nucleotide reverse transcriptase inhibitor, NNRTI: non-nucleoside reverse transcriptase inhibitor, PI: protease inhibitor, INSTI: integrase strand transfer inhibitor, CCR5A: CCR5 antagonist

2. Regimen Changes and Their Efficacy

Among the 96 patients, the HAART regimen was changed in 39. The total number of HAART regimen changes was 55; it was changed twice in 14 patients and three times in 2. The total follow-up time was 447.3 person-years. The median durations of the first and second regimens are shown in Figure 1. The patients remained on their first regimen for a median of 2040 days. The 39 patients

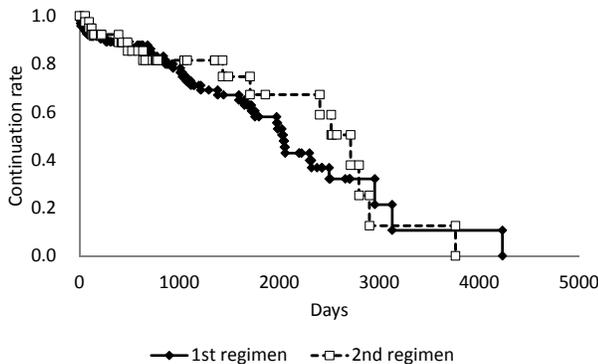


Figure 1. Duration of first and second HAART regimens

who were started on a second regimen remained on it for a median of 2714 days.

We compared the CD4 cell count and plasma HIV-RNA concentration before the HAART regimen change with those after the change. The CD4 cell count showed no significant change but the plasma HIV-RNA concentration was decreased significantly after the HAART regimen change (Figure 2). There was no instance of treatment failure due to the change in HAART regimen.

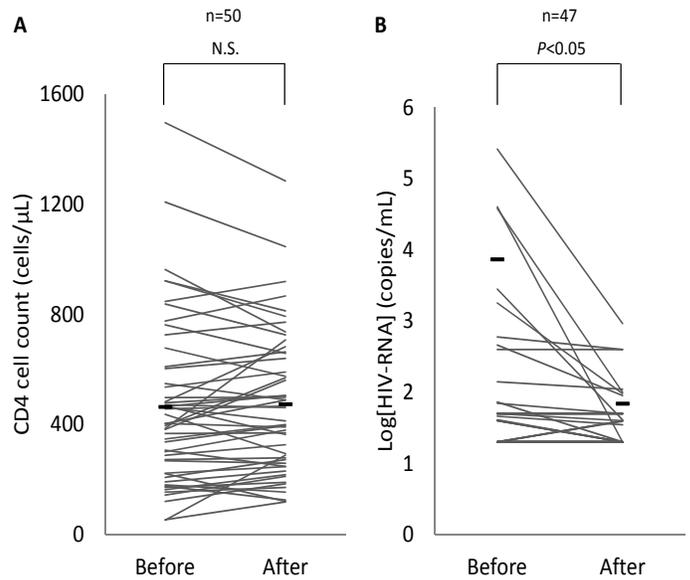


Figure 2. CD4 cell count (A) and plasma HIV-RNA concentration (B) before and after regimen change. — shows the mean. paired *t* test

3. Reasons for Regimen Changes and Adverse Effects

The reasons for the change in the HAART regimen were adverse effects in 49 cases, poor adherence/virological failure in 4, immunological failure in 3, the patient’s request in 2, proposals by health care workers, or for simplification, in 11, and other reasons in 2 (Table 3). Change in the HAART regimen became necessary for not only single reasons but also combinations of reasons. The adverse effect necessitating a change in the regimen was renal dysfunction in 11 cases, myelosuppression in 7, lipodystrophy in 6,

Table 2. The number of patients under antiretroviral drug usage of each HAART regimen

	1st regimen	2nd regimen	3rd regimen	4th regimen	Final regimen
NRTI					
AZT	12	4	—	—	—
d4T	11	4	—	—	—
ABC	3	2	—	—	—
3TC	27	12	1	—	1
TDF	3	2	1	—	1
TDF/FTC	61	10	7	1	59
ABC/3TC	6	15	5	—	20
AZT/3TC	1	—	—	—	—
NNRTI					
EFV	16	12	3	1	17
ETR	—	1	—	1	2
PI					
ATV	15	4	3	—	11
FPV	8	1	—	—	4
LPV/r	11	7	3	—	8
DRV	18	6	1	1	22
RTV	40	11	4	1	37
NFV	10	3	—	—	—
IDV	2	1	—	—	—
INSTI					
RAL	15	6	3	—	19
CCR5A					
MVC	2	2	—	1	4

NRTI: nucleoside/nucleotide reverse transcriptase inhibitor, AZT: zidovudine, d4T: sanilvudine, ABC: abacavir, 3TC: lamivudine, TDF: tenofovir, TDF/FTC: tenofovir/emtricitabine, ABC/3TC: abacavir/lamivudine, AZT/3TC: zidovudine/lamivudine, NNRTI: non-nucleoside reverse transcriptase inhibitor, EFV: efavirenz, ETR: etravirine, PI: protease inhibitor, ATV: atazanavir, FPV: fosamprenavir, LPV/r: lopinavir/ritonavir, DRV: darunavir, RTV: ritonavir, NFV: nelfinavir, IDV: indinavir, INSTI: integrase strand transfer inhibitor, RAL: raltegravir, CCR5A: CCR5 antagonist, MVC: maraviroc

Final regimen means the regimen that patients in our hospital at the time of this survey is using.

Table 3. Reasons for HAART regimen change in 39 patients

Reason for HAART regimen change	Number of cases
Adverse effect	49
Poor adherence/Virological failure	4
Immunological failure	3
Patient decision	2
Medical staff proposal/simplification	11
Other	2

HAART regimen change was for not only single but also multiple reasons. Therefore the total number did not equal 55.

hyperlipemia in 4, diarrhea in 4, and liver dysfunction in 3 (Figure 3). Among the patients for whom the HAART regimen had to be changed because of renal dysfunction, 10 had been receiving a tenofovir (TDF)-containing regimen. For these 11 patients with renal dysfunction, we compared the serum Cr concentration and urinary NAG concentration before and after the regimen change, and found that both parameters were reduced at 6 months after the change (Figure 4). Among the patients for whom a regimen change became necessary because of myelosuppression, all had been receiving AZT. Among those for whom the regimen had to be changed because of lipodystrophy, all had been receiving d4T.

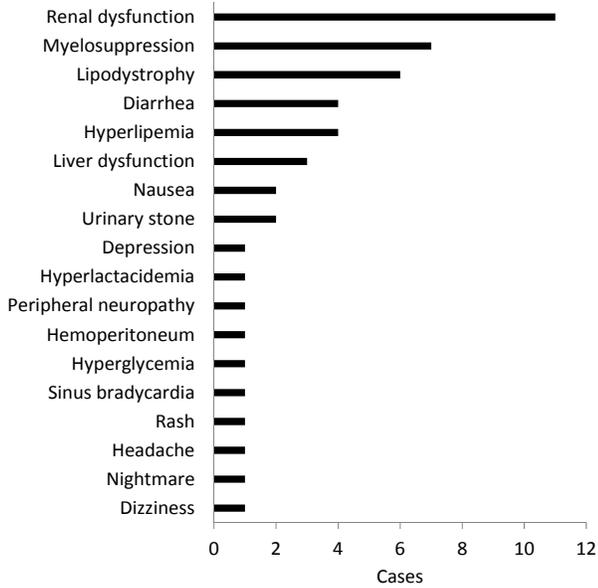


Figure 3. Adverse effects necessitating HAART regimen change.

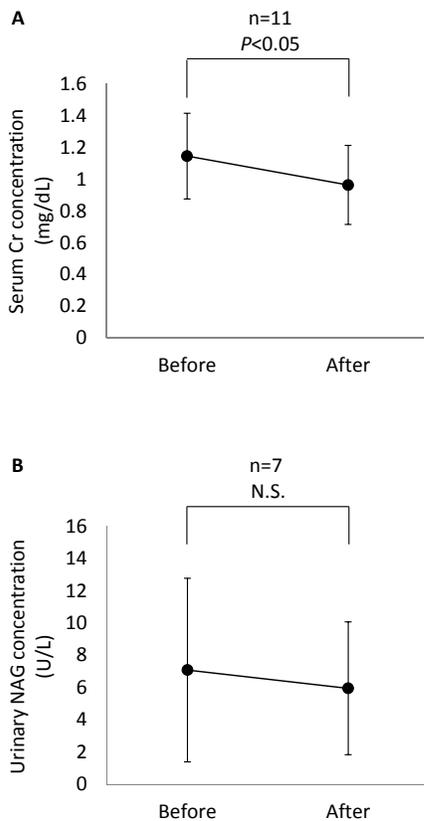


Figure 4. Comparison of serum Cr concentration (A) and urinary NAG concentration (B) before and after regimen change. mean±S.D. paired *t* test

4. Evaluation of Patient Adherence

With regard to patient adherence, we examined the number of taking times of anti-HIV drugs per day by individual patients. In the first regimen, 51% of patients took drugs once a day, 36% took them twice a day, and 13% took them three or more times a day. In the second regimen, 46% of patients took the drugs once a day, 44% took them twice a day, and 10% took them three or more times a day. In the third regimen, 57% of patients took the drugs once a day and 43% took them twice a day. In the fourth regimen, 50% took the drugs once a day and 50% did so twice a day. Among the 82 patients who visited our hospital at the time of this survey, 63% took their drugs once a day and 37% took them twice a day (data not shown). However, from the medical records, it was not possible to examine the degree to which patients complied with the therapy.

DISCUSSION

In the present study, among the 96 patients, the HAART regimen was changed in 39 (40.6%). And the total number of HAART regimen changes was 55 cases. As shown in Figure 1, the median duration of the first regimen was 2040 days, and that of the second regimen, used by 39 patients, was 2714 days. According to one Australian study, patients remained on the first regimen for a median period of 646 days, and on the second for 623 days (2). In one US study, patients remained on the first regimen for a median period of 581 days, and on the second for 324 days (3). In an Asian study, the corresponding mean periods were 3.2 years and 1.4 years, respectively (4). Here, we retrospectively investigated HIV-infected patients who had been started on HAART at our hospital between April 1997 and March 2013. The duration of our study was longer than any reported previously. And we found that the CD4 cell count was not reduced and that the plasma HIV-RNA concentration did not increase after the change in the HAART regimen. Therefore we considered that there was no virological or immunological failure due to the regimen change.

The HAART regimen had to be changed due to adverse effects in 49 cases, and sometimes there was more one adverse effect in the same patient. AZT is an anti-HIV drug that has been applied clinically for treatment of HIV for a long time, and

therefore its frequency of use was high in initial HAART regimens involving combinations of three or more anti-HIV drugs. Myelosuppression is a widely recognized adverse effect of AZT, and was responsible for changes in regimen in many cases at our hospital. d4T has been reported to have a relationship with lipodystrophy. All patients for whom the regimen had to be changed because of lipodystrophy had been taking d4T. In 2011, the European Agency recommended that: "prescribers are reminded of the severe side effects seen with d4T and should only use the medicine when other appropriate treatments are not available". Therefore, in view of the long-term toxicity of this agent, other agents should be considered if they are available.

In recent years, the proportion of cases requiring a change of regimen due to renal dysfunction has been increasing. In the present study, there were 11 such cases, and this was the most common reason for regimen change. Ten of these 11 cases had been receiving TDF, which is used widely and usually considered to be safe and well tolerated (5,6). On the other hand, TDF-induced Fanconi syndrome and tubule damage have been reported (7,8). In the latest DHHS guideline (2013.2.12), the NRTIs recommendation was a TDF/FTC combination tablet, and therefore TDF has been frequently used. In the present study, we compared the serum Cr concentration and urinary NAG concentration with before and after the HAART regimen change, and found that the two parameters were reduced at 6 months after the change. The renal impairment caused by TDF is thought to be reversible if TDF is discontinued (9,10), although some patients do not show (11,12). Yoshino et al. compared groups that should recover, mild recovery, and exacerbation, and concluded that the period of exposure to TDF was a factor affecting the recovery of renal function (13). Ten of the 11 cases in whom we evaluated the urinary NAG concentration and serum Cr concentration has been receiving TDF. In recent years, aging-related decline of physiological functions in HIV-infected patients has become an increasing problem. The high frequency of TDF use may prove to be a problem for continuous antiretroviral therapy, and further consideration of this issue may be necessary.

Adverse effects have been reported with the use of all anti-HIV drugs, and are among the most

common reasons for switching or discontinuing therapy, and also for non-adherence with medication (14). Adverse events revealed by laboratory tests are associated with higher rates of mortality, indicating the importance of overall management for patients receiving antiretroviral agents (15). With the use of newer HAART regimens, the rate of adverse effects in HAART-naïve patients appears to be declining. However, because many clinical trials have a relatively short follow-up duration, the longer-term complications of HAART may be underestimated.

In relation to patient adherence, we examined the number of taking time of anti-HIV drugs per day by individual patients. In the first regimen, 51% of patients took drugs once a day, 36% took them twice a day, and 13% took them three or more times a day. In the second regimen, 46% of patients took drugs once a day, 44% took them twice a day, and 10% took them three or more times a day. In the third regimen, 57% of patients took drugs once a day and 43% took them twice a day. In the fourth regimen, 50% took drugs once a day and 50% did so twice a day. Among the 82 patients who visited our hospital at the time of this survey, 63% took drugs once a day and 37% took them twice a day (data not shown). In this study, the number of times anti-HIV drugs were taken per day was not greatly altered as a result of regimen change. This was also a factor contributing to maintenance of adherence, and thus lack of treatment failure due to regimen changes. Krentz et al. reported that in the early period of the HAART regimen, the majority required dosing three times a day, but by 2010 nearly all HAART regimens were taken once or twice a day (16). In recent years, the combination tablet and new anti-HIV drugs, different mechanisms of action, capable of being taken once daily, few interactions with concomitant drugs and foods, have been introduced. As a result, both HAART-naïve and HAART-received patients have benefited from regimens that require fewer doses per day or fewer tablets per day. Systematic reviews in the non-HIV literature have shown that adherence is inversely related to the number of daily doses (17). Some prospective studies of HIV-infected patients have shown that those on regimens with a reduced dosing frequency have higher levels of adherence (5,18). Early HAART regimens imposed a considerable burden on patients, because they required many tablets to be taken several times

a day. It is considered that further improvements will ease this burden, and thus improve adherence. However, a lower number of doses per day means that the impact of any medication errors will be increased (19). Reduction of the medication rate may promote the development of drug-resistant viruses. Therefore, education of patients by health care workers will become increasingly important.

In the present study, there were no instances of treatment failure due to changes in HAART regimens. Through appropriate changes in HAART regimens, it should be possible to avoid serious adverse effects, and to improve patient adherence. Furthermore, it is necessary to consider the adverse effects associated with long-term antiretroviral therapy, and reduction of adherence due to medication fatigue. Drug selection and regimen change should be performed in accordance with the long-term prognosis.

HAART is now an effective initial treatment for HIV-infected patients. From our study, we can be fairly certain that maintenance of patient adherence and avoidance of adverse effects for the treatment of HIV infection are key factors considering that the treatment must be continued throughout life, as it is important to keep the body's viral count low. For successful treatment of HIV infection, it is essential to monitor parameters related to treatment efficacy, including the resistance on regimen, and to maintain adherence. Some studies of the duration of HAART regimens and regimen change have been reported from other countries (2,3,4), but reports from Japan have been lacking. In the present study, the duration of the HAART regimen was longer than that reported in other countries. A number of studies have reported disparities in the relationships between race/ethnicity and adherence or adverse effects (20, 21, 22). In particular, the incidence of TDF-associated renal dysfunction in Japanese patients is high because of their comparatively small body weight (22). In the present study, among the patients for whom the HAART regimen had to be changed because of adverse effects, TDF-associated renal dysfunction was the main reason. Therefore, we thought that differences in race/ethnicity would impact on adverse effects or adherence. Furthermore, there is a possibility that such differences would affect the duration of HAART regimens. Accordingly, we considered it important to evaluate the impact of regimen duration as well

as outcomes after regimen change in our hospital. We found that TDF had been administered in many cases, and that TDF-associated renal dysfunction was the main reason for the HAART regimen change. Furthermore, we found that an appropriate regimen change normalized the laboratory data, and that the number of times anti-HIV drugs had to be taken per day was almost unaltered after the regimen change. No previously reported study has comprehensively evaluated the efficacy and safety of changes in HAART regimens, including the duration of the regimen as well as outcome after the regimen change. Therefore, we believe that our findings will make a significant contribution to medication planning for HIV-infected patients in the future.

REFERENCES

1. Crum NF, Riffenburgh RH, Wegner S, Agan BK, Tasker SA, Spooner KM, Armstrong AW, Fraser S, Wallace MR; Triservice AIDS Clinical Consortium. Comparison of causes of death and mortality rates among HIV-infected persons: analysis of the pre-, early, and late HAART (highly active antiretroviral therapy) eras. *J Acquir Immune Defic Syndr* 2006; 41: 194-200.
2. Australian HIV Observational Database. Rates of combination antiretroviral treatment change in Australia, 1997-2000. *HIV Med* 2002; 3(1): 28-36.
3. Chen RY, Westfall AO, Mugavero MJ, Cloud GA, Raper JL, Chatham AG, Acosta EP, Taylor KH, Carter J, Saag MS. Duration of Highly Active Antiretroviral Therapy Regimens. *Clin Infect Dis* 2003; 37: 714-722.
4. Srasuebku P, Calmy A, Zhou J, Kumarasamy N, Law M, Lim PL; for The TREAT Asia HIV Observational Database. Impact of drug class and treatment availability on the rate of antiretroviral treatment change in the TREAT Asia HIV Observational Database(TAHOD). *AIDS Res Ther* 2007; 4(18): 1-10.
5. Gallant JE, DeJesus E, Arribas JR, Pozniak AL, Gazzard B, Campo RE, Lu B, McColl D, Chuck S, Enejosa J, Toole JJ, Cheng AK; Study 934 Group. Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. *N Engl J Med* 2006; 354(3): 251-260.
6. Gallant JE, Staszewski S, Pozniak AL, DeJesus E, Suleiman JM, Miller MD, Coakley DF, Lu B, Toole JJ, Cheng AK; 903 Study Group. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naïve patients: a 3-year randomized trial. *JAMA* 2004; 292(2): 191-201.
7. Karras A, Lafaurie M, Furco A, Bourgarit A, Droz

- D, Sereni D, Legendre C, Martinez F, Molina JM. Tenofovir-related nephrotoxicity in human immunodeficiency virus-infected patients: three cases of renal failure, Fanconi syndrome, and nephrogenic diabetes insipidus. *Clin Infect Dis* 2003; 36: 1070-1073.
8. Zimmermann AE, Pizzoferrato T, Bedford J, Morris A, Hoffman R, Braden G. Tenofovir-associated acute and chronic kidney disease: a case of multiple drug interactions. *Clin Infect Dis* 2006; 42: 283-290.
 9. Malik A, Abraham P, Malik N. Acute renal failure and Fanconi syndrome in an AIDS patient on tenofovir treatment-case report and review of literature. *J Infect* 2005; 51: E61-65.
 10. Kapitsinou PP, Ansari N. Acute renal failure in an AIDS patient on tenofovir: a case report. *J Med Case Rep* 2008; 2(94): 1-4.
 11. Kinai E, Hanabusa H. Progressive renal tubular dysfunction associated with long-term use of tenofovir DF. *AIDS Res Hum Retrovir* 2009; 25: 387-394.
 12. Wever K, van Agtmael MA, Carr A. Incomplete reversibility of tenofovir-related renal toxicity in HIV-infected men. *JAIDS* 2010; 55: 78-81.
 13. Yoshino M, Yagura H, Kushida H, Yonemoto H, Bando H, Ogawa Y, Yajima K, Kasai D, Taniguchi T, Watanabe D, Nishida Y, Kuwahara T, Uehira T, Shirasaka T. Assessing recovery of renal function after tenofovir disoproxil fumarate discontinuation. *J Infect Chemother* 2012; 18: 169-174.
 14. O'Brien ME, Clark RA, Besch CL, Myers L, Kissinger P. Patterns and correlates of discontinuation of the initial HAART regimen in an urban outpatient cohort. *J Acquir Immune Defic Syndr* 2003; 34(4): 407-414.
 15. Keiser O, Fellay J, Opravil M, Hirsch HH, Hirschel B, Bernasconi E, Vernazza PL, Rickenbach M, Telenti A, Furrer H; Swiss HIV Cohort Study. Adverse events to antiretrovirals in the Swiss HIV Cohort Study: Effect on mortality and treatment modification. *Antivir Ther* 2007; 12(8): 1157-1164.
 16. Krentz HB, Cosman I, Lee K, Ming JM, Gill MJ. Pill burden in HIV infection: 20 years of experience. *Antivir Ther* 2012; 17(5): 833-840.
 17. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther* 2001; 23(8): 1296-1310.
 18. Molina JM, Podsadecki TJ, Johnson MA, Johnson MA, Wilkin A, Domingo P, Hairrell JM, Rode RA, King MS, HannaGJ. A lopinavir/ritonavir-based once-daily regimen results in better compliance and is non-inferior to a twice-daily regimen through 96 weeks. *AIDS Res Hum Retroviruses* 2007; 23(2): 1505-1514.
 19. Vrijens B, Tousset E, Rode R, Bertz R, Mayer S, Urquhart J. Successful projection of the time course of drug concentration in plasma during a 1-year period from electronically compiled dosing-time data used as input to individually parameterized pharmacokinetic models. *J Clin Pharmacol* 2005; 45: 461-467.
 20. Gellad WF, Hass JS, Safran DG. Race/ethnicity and nonadherence to prescription medication among seniors: results of a national study. *J Gen Intern Med* 2007; 22(11): 1572-1578.
 21. Gunther M, Foisy M, Houston S, Guirguis L, Hughes C. Treatment beliefs, illness perceptions, and non-adherence to antiretroviral therapy in an ethnically diverse patient population. *Int J Clin Pharm* 2014; 36(1): 105-111.
 22. Nishijima T, Komatsu H, Gatanaga H, Aoki T, Watanabe K, Kinai E, Honda H, Tanuma J, Yazaki H, Tsukada K, Honda M, Teruya K, Kikuchi Y, Oka S. Impact of small body weight on tenofovir-associated renal dysfunction in HIV-infected patients: a retrospective cohort study of Japanese patients. *PLoS One* 2011; 6(7): e22661.