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Early Viral Suppression Predicting Long-term Treatment Success Among HIV Patients Commencing NNRTI-based Antiretroviral Therapy

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Abstract

Non-nucleoside reverse transcriptase inhibitor (NNRTI) -based antiretroviral therapy (ART) regimens have been recommended and widely used in resource-limited settings because of their reliable efficacy, low pill burden, and low cost. This study sought to determine outcomes and toxicities of NNRTI-based ART over a period of 208 weeks. A total of 244 HIV/AIDS Thai patients with a mean (±SD) age of 36 (±8.1) years initiated NNRTI-based ART in 2004. The median (inter-quartile range) baseline CD4 cell counts and HIV RNA levels were 34 (13-101) cells/mm^3 and 5.4 (4.96-5.79) log copies/ml, respectively. At week 208, 84.6% of patients achieved HIV RNA loads <50 copies/ml, 88.5% continued NNRTI based regimens, 6.1% developed virologic resistance to NNRTIs, and 3.3% lost to follow up. Baseline CD4<50 cell/mm^3 (p=0.019), and viral load ≥50 copies/ml at 6 months post-ARV (p<0.001) were associated with treatment failure. At the end of the study, 39.8% lipoatrophy and 35.7% hyperlipidemia were identified. In conclusion, NNRTI-based regimens result in high virologic success; early undetectable viral load is key to predicting long-term virologic success.

Keywords: ART; HIV; NNRTI; Treatment outcomes; Toxicity

Introduction

The substantial success of antiretroviral drugs in reducing death rates by 50-80% over one decade makes HIV a manageable chronic illness (Herbst et al., 2009; Blacker, 2004; Palella et al., 1998; Brinkhof et al., 2009). The distribution of antiretroviral drugs has coincided with a dramatic drop in the number of officially reported AIDS deaths in Thailand, from 5,020 in 2004, to 1,640 in 2005. Use of combinations from among over 20 drugs currently licensed for antiretroviral therapy (ART) has achieved good levels of effectiveness in sustaining undetectable HIV viral loads and immunologic improvement. These include the preferred combination regimens using 2 nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) with either a non-nucleoside reverse transcriptase (NNRTI-based regimens) or ritonavir-boosted protease inhibitors (PI based regimens) (Hammer et al., 2008; http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf). Since 2002, the Thai government has released a low-priced fixed combination drug comprising nevirapine (NVP), and has made an official commitment to ensuring access to treatment for all Thai people living with HIV. As a result, NNRTI-based regimens have become the most common and widely used first-line therapy in Thailand (Chasombat et al., 2009).

The increasing coverage of ART, composed of a selection of initial regimens from among the various current possible antiretrovirals, is usually dictated by issues other than antiviral activity, such as tolerability, drug-drug interaction, and patient-specific morbidities. Quite frequently, patients change from one regimen to another because of treatment failure, pill burden, drug toxicity, drug interactions, and financial problems. This cohort study evaluated the long-term outcomes of NNRTI-based ART among HIV-infected treatment-naïve patients, to ascertain retention rates and short- and long-term toxicity of NNRTI-based ART in HIV-infected patients, especially metabolic complications after 208 weeks' treatment.

Materials and Methods

This cohort study was conducted at Bamrasnaradura Infectious Diseases Institute, Nonthaburi, Thailand. It was approved by the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University and the Institutional Review Board of Bamrasnaradura Infectious Diseases Institute. All ART-naïve patients commencing NNRTI-based ART during the period January-December 2004 were enrolled. The inclusion criteria were: HIV-infected patients proven by positive serology for anti-HIV antibody by two ELISA tests; age 15 years and older. Excluded were pregnant patients commencing antiretroviral drug regimens to prevent mother-to-child transmission (PMTCT) who discontinued postpartum, and those with < 3 months follow-up.

All necessary medical information, demographic data, laboratory investigations, occurrence of opportunistic infections, medications, toxicities, CD4 cell counts, plasma HIV RNA loads, and genotypic resistance assay (if indicated), were studied. Adherence to ART was assessed by a physician-in-charge. At every visit, patients were considered adherent if they had taken at least 95% of their prescribed drugs. The physician-in-charge decided which laboratory investigations were to be conducted *vav* routine screening and follow-up. CD4-counts were measured twice per year by flow cytometry with TriTEST CD3 FITC= CD4 PE=CD45 PerCP and TriTEST CD3 FITC=CD8 PE=CD45 PerCP (BD Bioscience, San Jose, CA), and HIV RNA levels at least once a year by reverse transcriptase polymerase chain reaction (RT-PCR) with COBAS Amplicor HIV-1 Monitor Test version 1.5 (Roche Diagnostics, Branchburg, New Jersey), for assessment and to ensure a favorable treatment outcome. The study outcomes were periodically

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evaluated in terms of CD4 count (every 6 months) and virologic success (months 6, 12, 24, 36 and 48). Treatment outcome measures comprised 1) virologic success, defined as viral load <50 copies/μL at 24 weeks and after of ART and virologic failure, defined as viral load ≥50 at 24 weeks of ART and after, including virologic rebound after virologic suppression; 2) Immunologic success, defined as CD4 count ≥ 200 cells/μl and sustaining from baseline at 24 weeks of ART and after; 3) retention, defined as a NNRTI remaining in the current combined antiretroviral regimen at 208 weeks, and; 4) lost to follow-up, defined as >3 months late for a follow-up visit.

HIV-1 genotypic resistance assays were performed using RT gene sequencing with the ABI PRISM dideoxy Dye Terminator Cycle Sequencing Kit (BigDye, Applied Biosystems, Foster City, California, USA), and analyzed on an ABI PRISM 310 automatic sequencing system and Sequence Navigator Software (Applied Biosystems) by the Vaccine and Cellular Immunology Laboratory, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand (Sirivichayakul et al., 2003). The assays were interpreted based on the definitions of the IAS-USA Drug Resistance Mutations Group and the Stanford University HIV drug resistance database. Adverse ART-related reactions were classified into grade I, II, III, and IV toxicity, according to the descriptive scale used in all clinical trials developed and/or sponsored by the AIDS Clinical Trial Group (ACTG). Study data were entered in a computer data-file and analyzed using Statistical Package for the Social Sciences(SPSS) software version 11.5 (SPSS Inc, Chicago, Illinois). Mean (± SD), median (interquartile range, IQR) and frequency (%) were used to describe the patients' characteristics. For association analysis for categorical data, Chi square test or Fisher exact test was used to determine the associated factors as appropriate. For continuous data, Mann Whitney U test was used to determine the association of the outcomes. Logistic regression was used for multivariate analysis to determine the independent association of factors related to treatment success after 208 weeks' treatment. Survival analysis was used to determine the onset of toxicity. A 2-sided P value < 0.05 was considered statistically significant.

Results

Background charateristics

A total of 244 patients started antiretroviral therapy (ART) during the period January-December 2004; their baseline characteristics demonstrated that 58.2% were male, mean age (± SD) was 36 (±8.1) years and 12.3% had a history of injecting drug use. Tuberculosis (TB) was the most common (39.3%) pre-ART opportunistic infection. *Pneumocystis jiroveci* pneumonia (PCP) and cryptococcosis were noted as 13.5% and 4.9%, respectively. Oral candidiasis (38.1%) and pruritic papular eruption (PPE) (37.7%) were the most common pre-ART findings. Hepatitis B (HBV) and hepatitis C (HCV) coinfection were 3.7 and 4.9%, respectively. Regarding WHO staging, baseline status was classified as Stage I 18.9%; Stage II 12.2%; Stage III 24.2%; and Stage IV 44.7%. Almost all (95%) of the patients commenced NVP-containing regimens, with the remainder commencing efavirenz (EFV)-containing regimens (see Figure 1). The 2 NRTI background regimens were stavudine (d4T) plus lamivudine (3TC) (96.6%), zidovudine (ZDV) plus 3TC (2.6%), and abacavir (ABC) plus 3TC (0.8%). Regarding NNRTI-based ART used as the first-line regimen, the baseline characteristics of each group are shown in Table 1.

Study outcomes

At 208 weeks' follow-up, 88.5% of patients were still using NNRTI-based ART regimens. Among the patients using NVP-based regimens, 9% (21 of 232 patients) changed to EFV-containing regimens due to NVP skin toxicity (76.2%) and NVP hepatotoxicity (23.8%) with a median duration of 1.6 months after start of ART. Among those using EFV-based regimens, 2 patients changed to NVP due to their physicians' advice. Immunologic outcomes, assessed by monitoring CD4-cell-count responses at each study time-point, are shown with the median CD4 cell counts of 162, 222, 266, 319.5, 338.5, 365.5, 381, and 419.5 cells/mm^3 at 6, 12, 18, 24, 30, 36, 42, and 48 months, respectively. The increase in median CD4 counts was demonstrated for 4 years' treatment (see Figure 2). The virologic and immunologic success rates are shown in Table 2. At the end of treatment, the virologic and immunologic success was 84.6% and 92%, respectively.

NNRTI was discontinued or missing among 29 patients in this study due to virologic failure (6.1%), loss to follow-up (3.3%), and referral to another hospital (2.5%) (see Figure 1). Regarding the 15 patients with virologic failure, all had been treated with NVP with a median (range) of virologic resistance-detection time of 28 months (7.7-46.6). Genotypic resistance assays confirmed that all had NNRTI resistance mutations Y181C (60%), G190A (33.3%) and K103N (20%).

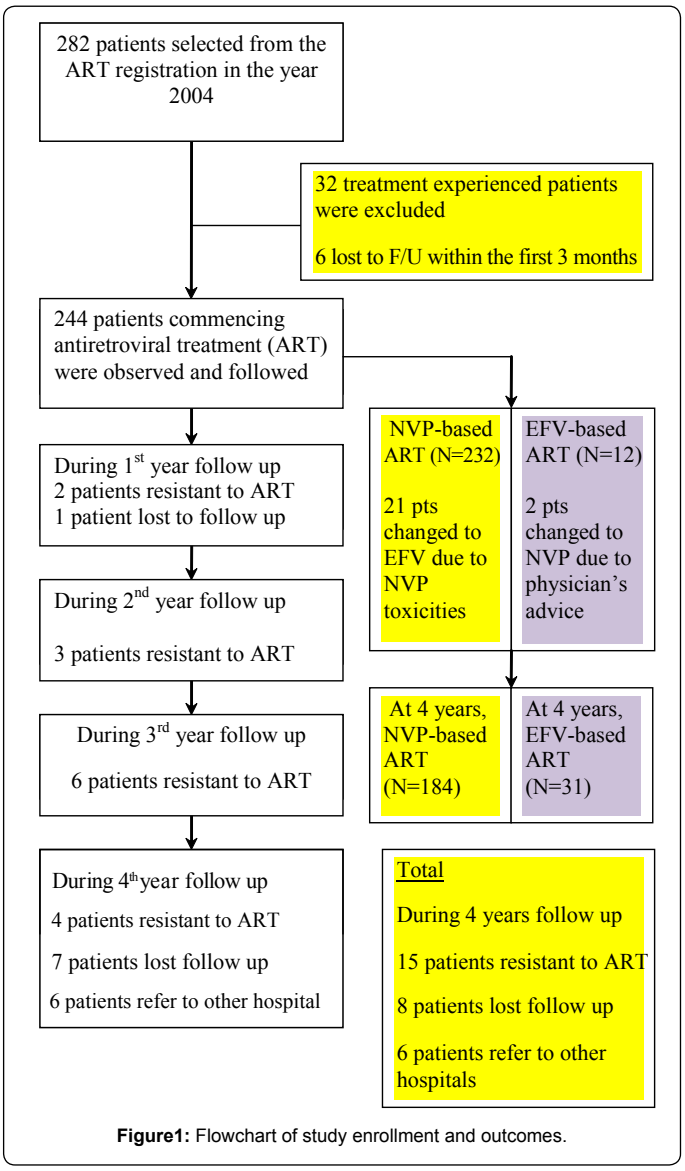

Figure1: Flowchart of study enrollment and outcomes.

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Characteristic	Nevirapine-based Regimens N=232	Efavirenz-based Regimens N=12	P-value
Male (%)	134 (57.8)	8 (66.7)	0.766*
Mean age (± SD)	36.04±7.9	35±11.I	0.389**
Single including widowed/divorced (%)	119 (44.8)	7 (58.3)	0.69
No career (dependent) (%)	47 (20.3)	3 (25)	0.715*
WHO Stage 4 (%)	103 (44.4)	6 (50)	0.933
Body weight (Kg), mean ± SD	54.44 ±9.9	62.38±13.6	0.04**
Baseline CD4 cell count (cells/mm^3), median (IQR)	34 (14-100)	64 (8-108)	0.633**
Baseline log HIV RNA, median (IQR) (n=104)	5.4 (4.96-5.77)	5.68 (4.93-5.86)	0.545**
Treatment outcomes			
Virologic success (%), overall	86.5	100	0.30*
Resistance to antiretroviral treatment (%)	6.5	0	1.00*
Tolerability (%), overall	79.3	93.9	0.076
Lost to follow up (%)	3.4	0	1.00*

Chi-Square test, *Fisher exact test, **Mann-Whitney U test

Table 1: Baseline characteristics and treatment outcomes of the 244 HIV-infected patients.

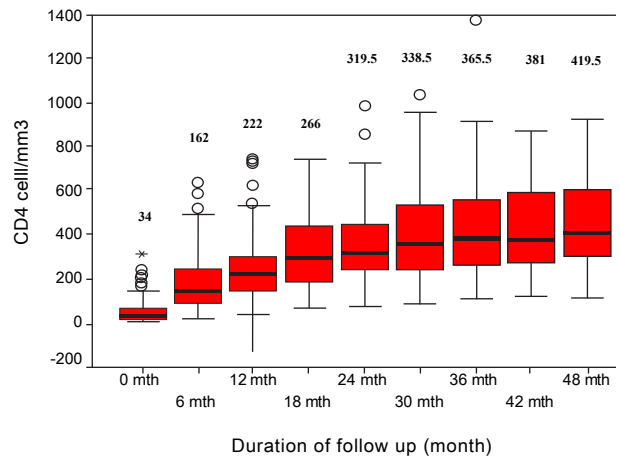

Figure2: Numbers, median (IQR) of CD4 cell count increase during 4 years' follow-up.

Time of treatment evaluation (months)	Virologic Success (VL<50copies/ml)	Immunologic Success (CD4 counts > 200 cells/mm^3)
6 months	157/174 (90.2%)	73/162 (45.1%)
12 months	187/202 (92.6%)	114/191 (59.7%)
24 months	193/205 (94.1%)	145/176 (82.4%)
36 months	201/212 (94.8%)	169/184 (91.8%)
48 months	170/201 (84.6%)	162/176 (92.0%)

Table 2: Treatment success and immunologic success during the study (n=244).

Of 15 cases, 40% were detected 2 NNRTI resistance mutations; Y181C and K103N, 13.33%; Y181C and G190A, 13.33%; Y181C and V108I, 13.33%. The common NRTI resistance mutations detected were M184V (71.4%), K65R (21.4%), and D67N (21.4%). Recurrent HSV (11%) and TB (10.2%) were commonly noted after ART. Other infections occurring after ART included CMV retinitis (4.9%), cryptococcosis (1.6%), and PCP (1.2%). There was a significant association between the occurrence of opportunistic infections after ART and baseline WHO classification (p=0.009). There was a trend of increase in opportunistic infections after ART, when more advanced baseline WHO stages were found. The proportions of opportunistic infections post-ART, among high and low baseline CD4 (≥ 50 and <50 cell/mm^3), showed significant associations between opportunistic infections post-ART and low baseline CD4 levels (p=0.001) with a relative risk (95% CI) of 1.89 (1.29<RR<2.78).

Factors associated with virologic failure

HIV-infected treatment-naïve patients with <50 cells/mm^3 CD4 at baseline (59.6%) were associated with virologic failure during 4 years of ART (p=0.019). No other baseline characteristic was associated with virologic failure. After commencement of ART, patients with ≥50 copies/ml HIV RNA at 6 months (10.9%) were significantly associated with virologic failure (p<0.001). The relative risk (RR) of developing virologic failure in the group with baseline CD4 count < 50 cells/mm^3 and no virological suppression at 6 months of ART were 8.95(95% CI, 1.2<RR<66.96) and 29.05(95% CI, 11.79<RR<79.60), respectively.

The information about missing or delayed doses of ART showed that 22.6% of the patients were considered poorly adherent with at least once detected having taken less than 95% of their prescribed drugs for 208 weeks. Among documented poor adherence to ART, 24.4% showed virologic failure. Virologic failure was significantly associated with poor adherence to ART (p<0.0001). In multivariable regression models, no virological suppression at 6 months of ART (p<0.0001) and poor adherence to ART (p=0.002) continued to predict long-term virologic success at 4 years' treatment, whereas the effect of baseline CD4 counts < 50 cells/mm^3 virtually disappeared (p=0.454).

Tolerability of antiretroviral treatment

At the end of the study, 43% of patients were maintaining their initial regimens--D4T+3TC+NVP (42.2%), and D4T+3TC+EFV (33.3%). Out of all patients, 138 patients changed their first-line regimen to others: NVP to EFV, d4T to ZDV or tenofovir, etc. The most common reasons were lipoatrophy, 57 (41.3%); NVP-associated toxicities, 21 (15.2%); symptomatic lactic acidosis, 10 (7.2%); hyperlipidaemia, 10 (7.2%); and peripheral neuropathy, 7 (5%); of the patients. Median time to change from D4T to AZT was 2.2 years after start of ART. Median time to change from D4T to TDF was 3.5 years after start of ART.

The NRTI drug toxicities found in our study were lipoatrophy 97 (39.8%), hyperlipidemia 87 (35.7%), peripheral neuropathy 49 (20.1%), dyspepsia 11 (4.5%), and anemia 8 (3.3%). The NNRTI-associated toxicities were skin toxicity, 22 (9.0%); insomnia, 16 (6.5%); dizziness, 8 (3.3%); and hepatotoxicity, 7 (2.9%). Time to development of lipoatrophy among 25% of the affected patients was 2.14 years of ART (see Figure 3); 65% of lipoatrophic patients decided to change their regimens in a median (IQR) time of 28 (13.9-48.1) months; 3 (3.1%) of the patients developed lipoatrophy in the 1st year, 49 (50.5%) in the 2nd year, 28 (28.9%) in the 3rd year, and 17 (17.5%) in the 4th year of treatment. Figure 4 shows the time to detection of hyperlipidaemia; 25% were found at 3.12 years of treatment. Most hyperlipidaemia patients (39 cases) were ACTG Grade II, with Grade I, 32; Grade III, 10;

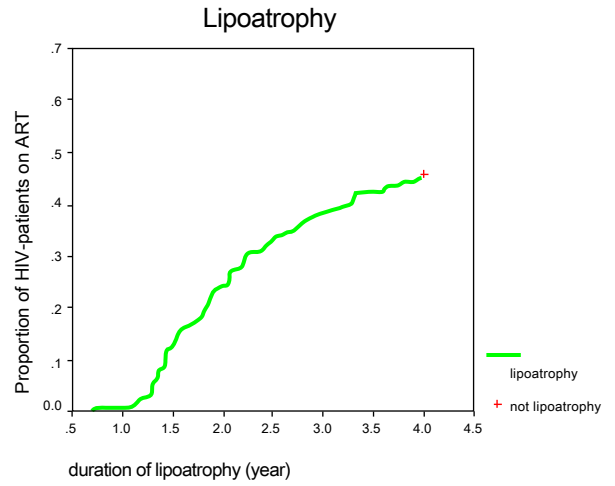

Figure 3: Kaplan-Meier estimate of time to develop lipoatrophy among 244 adult HIV-positive treatment-naïve patients.

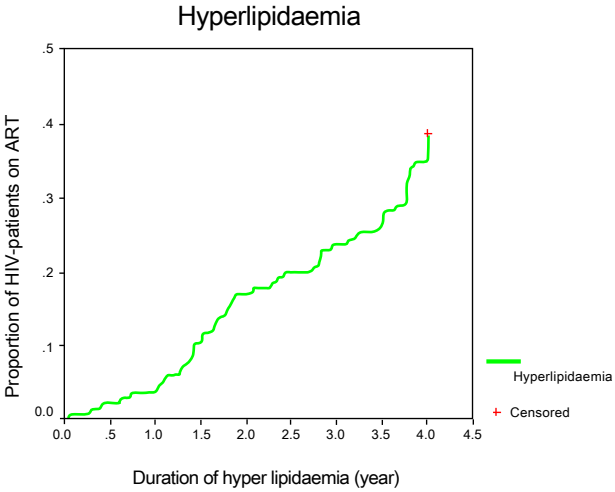

Figure 4: Kaplan-Meier estimate of time to develop hyperlipidaemia among 244 adult HIV-positive treatment-naïve patients.

and Grade IV, 6. Only 15% of the affected patients decided to change their regimens at the median (IQR) time of 37.6 (15.4-49.5) months. Of the total 87 hyperlipidaemia patients, 37 (42.5%) were prescribed lipid-lowering agents. Lactic acidosis was related to stavudine (93.8%) and zidovudine (6.2%), with a median time (IQR) of 1.3 years (0.7-3.7 years).

Discussion

Treatment with combinations of antiretroviral drugs has led to dramatic and sustained decreases in mortality and morbidity due to HIV. This study demonstrates that the virologic success rate reached a peak (94.8%) at 3 years' ART, and began to decline at 4 years, even with continued treatment. This reflects ongoing viral replication and low-level resistance (Napravnik et al., 2005). Lacking excellent laboratory tools for early detection, the genetic determinants of drug resistance among circulating HIV genetic backgrounds (subtypes and recombinant forms), treatment adherence and therapeutic drug monitoring, were not explored adequately in this study (Smith and Schooley, 2008). All patients treated with efavirenz achieved virologic success. It seemed that overall, EFV had superior outcomes to NVP in better tolerability and maintaining EFV-based regimens for longer time. Other studies have detected no statistically significant difference in efficacy (measured by virologic failure) between NVP and EFV, when used in combination with 3TC and d4T (Siegfried et al., 2006; Van Leth et al., 2004), and our study showed similar findings (p=0.3). Although the baseline characteristics of the groups with NVP- and EFV-based regimens were comparable (see Table 1), baseline HIV loads were not ascertained for every patient. The limitation of viral load measurement may be a confounder in this study, due to the inferior virologic efficacy of nevirapine compared with EFV, with extensive resistance to other drug classes among patients with high baseline viral loads (Rey et al., 2009; Bannister et al., 2008). Therefore, nevirapine-based regimens should be used with close monitoring of virologic responses within early years of treatment. Over half the patients achieved CD4 cell counts > 200 cells/mm^3 after 1 year of ART, even when the majority had baseline CD4 cell counts < 100 cells/mm^3. Consistent with the findings from previous studies (Nash et al., 2008; Manosuthi et al., 2007), virologic suppression and immunologic improvement can be sustained, which proved the satisfactory long-term effectiveness of NNRTI-based ART among advanced AIDS cases in resource-limited settings.

The most common regimen, using a locally made, fixed combination of stavudine, lamivudine, and nevirapine, was simple, had a low pill burden (one tab), had fewer drug and food interactions, and it was easy to remember the dosing time (every 12 hours). Evidence that twice-daily regimens are preferential, based on their effectiveness and maintainability, which contribute to long-term success with ART, is substantial (Sherer et al., 2005). If potency and effectiveness are equivalent, patients prefer simple regimens with lower pill burdens (Nischal et al., 2005). HIV-infected treatment-naïve patients with baseline CD4 cell counts < 50 cells/mm^3 were 9 times more likely to develop virological failure during 4 years' ART treatment (p = 0.019). Similarly, one meta-analysis (Skowron et al., 2001; Miller et al., 1999) demonstrated a significant correlation between baseline CD4 cell counts and virologic suppression at 6 and 12 months, but not between baseline viral load and virologic suppression. Patients with > 50 copies/ml HIV RNA at 6 months have 29 times greater risk of developing drug resistance during 4 years' ART treatment (p <0.001). We suggest that assessment of HIV load is required at least during treatment year 1, to assure treatment success and indirectly assess treatment adherence in uncertain cases. No death or severe adverse events were reported in this study, which might be due to the exclusion of patients lost to follow-up in the first 3 months after initiation of ART. It is possible that treatment outcomes among the devastated or critically ill AIDS cases may be missing. The implications should be treated with caution, especially in this setting, although this exclusion criterion might infer poor adherence by the treatment group, which inversely influences treatment outcomes.

Concurrently, higher toxicity rates during ART, especially lipoatrophy (39.8 %) and hyperlipidemia (35.7%), were detected among one quarter of the patients after 2 years. The findings might be associated with the longer follow-up period, in which occurrences accumulated. These metabolic complications have been noted as related to the NRTIs used in this study (van Vonderen et al., 2009; Haubrich et al., 2009) and have resulted in discontinuation and/or changes in the regimens for the majority of patients. The gradual development of unsatisfactory lipoatrophic status greatly reduced the tolerability of the culprit antiretroviral drug after 3 years' treatment, when up to 60% of regimens were changed among the

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patients affected. A significant association was detected between rate of opportunistic infection post-ART and baseline advanced WHO classification. However, there was no significant association between low baseline CD4 count or pre-treatment opportunistic infection, and post-treatment opportunistic infection, in this study (data not shown). We assume that, given that most patients had very low CD4 cell counts, establishing a significant association between baseline CD4 cell count and post-treatment opportunistic infections was difficult.

Conclusion

The long-term outcomes from NNRTI-based ART in HIV-infected treatment-naïve patients were very encouraging during the 208-week follow-up evaluation, with favorable virologic and immunologic responses. The long-term toxicity that developed in our study was mostly related to NRTI, including lipoatrophy, hyperlipidemia, and peripheral neuropathy. The suspected occurrence of long-term NNRTI toxicity, especially metabolic complications, is warranted and deserves close monitoring.

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