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단백분해효소 억제제를 포함한 항레트로바이러스 병용 치료중인 HIV 감염 한국인에서 Atazanavir로 변경 후 지질 수치의 변화

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Lipid Profile Changes after Switch to Atazanavir from other Protease Inhibitor-based Combined Antiretroviral Treatment in HIV-infected Korean

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Dyslipidemia, one of the major disadvantages of use of protease inhibitor (PI), is a risk factor for cardiovascular disease in HIV-infected patients receiving antiretroviral treatment. Little is known about the effect of a switch from another PI to unboosted atazanavir (ATV) on the lipid profile. The aim of this study was to evaluate changes in the lipid profile after switching from another PI to either unboosted or boosted ATV in HIV-infected Koreans. We retrospectively collected data on the serum lipid profile at the time of the switch (week 0), and weeks 12 and 24 after the switch, as well as clinical characteristics at week 0 in a total of 27 patients. Triglyceride (TG) showed a significant decrease at weeks 12 and 24 in all patients (196 vs. 174 mg/dL, *P*=0.048 and 196 vs. 150 mg/dL, *P*=0.021, respectively). However, these effects were only observed in the unboosted ATV group (N=14; 239 vs. 125 mg/dL, *P*=0.017 and 239 vs. 87 mg/dL, *P*=0.021, respectively). For total cholesterol, only the unboosted ATV group at 24 weeks showed a significant decrease (184 vs. 158 mg/dL, *P*=0.031). No significant changes were observed in LDL- and HDL-cholesterol at weeks 12 and 24 in both the unboosted and boosted ATV groups. These results suggest that changing to unboosted ATV from another PI may ameliorate high TG and total cholesterol in HIV-infected Koreans.

Key Words: HIV, Highly active antiretroviral therapy, Protease inhibitors, Atazanavir, Lipids

The introduction of ritonavir (RTV)-boosted protease inhibitor (PI) has contributed significantly to successful implementation of combined antiretroviral treatment (cART), resulting in a significant reduction in morbidity and mortality associated with AIDS-defining illnesses [1]. As the lifespan of HIV-infected individuals grows longer, the metabolic complications in chronic asymptomatic HIV-infected individuals are becoming a more important problem [2, 3].

Metabolic abnormality, especially dyslipidemia, is one of the major

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disadvantages of boosted PI-containing cART; therefore, the risk for CVD must be closely monitored in patients receiving boosted PI [4].

Since approval of atazanavir (ATV) as the first PI for once-daily dosing by the U.S. FDA [5], large numbers of randomized controlled trials have demonstrated that ATV is comparable in efficacy to other established PIs [6, 7], and that ATV has fewer effects on metabolic abnormalities [8], suggesting a strategy for avoidance of the primary side effect of PI. As a result, boosted ATV (ATV/r) is recommended as one of the preferred PI drugs [9, 10]

Unboosted ATV has shown similar efficacy and safety, compared with ATV/r, both when used as a component of the initial regimen and when used for maintenance after initial suppression with another boosted PI [11]. Significantly favorable results for lipid profile were observed for the unboosted ATV, confirming its lower metabolic side effects [12]. However, because these studies were conducted mainly in Western countries [12], the effect of ATV on lipid profile in HIV-infected East Asians has not been clarified. Therefore, we conducted this study in order to investigate the impact of ATV according to RTV co-administration on changes in lipid profile after switching from other PI in HIV-infected Koreans. Identification of HIV-infected Koreans who received switching therapy from another PI to unboosted or boosted ATV with maintenance of the same nucleoside-analogue reverse transcriptase inhibitors between December 2005 and December 2009 was based on a retrospective review of the electronic database at Severance Hospital. Subjects with good adherence assessed through clinic visits and lipid testing with regular three-month intervals during a period of more than a six months after the switch were included. We excluded patients who had previously taken lipid-lowering agents or other drugs that can cause a change in lipid level. In addition, patients with opportunistic infection or malignancy while undergoing current treatment or underlying condition of chronic renal or liver disease according to the International Classification of Disease, 10th Revision [13] were excluded from the study. The switching therapy was determined by each HIV-special physician. As it presented no risk to prejudice subject rights and welfare, the Institutional Review Board approved the design of the study.

Data on demographic characteristics, PI used before the switch, and results of blood tests, including CD4+ cell counts, plasma HIV-RNA viral load (VL), and lipid level were retrospectively collected. The Friedewald formula was used for calculation of Low-density lipoprotein (LDL)-cholesterol [14], except in patients with triglyceride (TG) higher than 400 mg/dL.

Subjects were divided into two groups based on whether or not RTV was taken simultaneously with ATV. The baseline characteristics at the time of the switch (week 0) were compared between the groups. In addition, the lipid profile of total cholesterol, TG, high-density lipoprotein (HDL)-cholesterol, LDL-cholesterol, and total/HDL-cholesterol ratio at 0, 12, and 24 weeks after the switch were compared in each group.

Because all continuous variables showed skewed distribution, these data were expressed as median and interquartile range (IQR). The Mann-Whitney *U* and Fisher's exact test were used in comparisons between unboosted and boosted ATV groups. Wilcoxon signed-rank tests were used for identification of the change in lipid profile from week 0 in each group. SPSS software for Windows, version 18.0 (SPSS, Chicago, IL, USA) was used in performance of all statistical tests. *P*-value$\leq$0.05 was considered statistically significant.

Among a total of 27 participants, 14 were switched to unboosted ATV, while 13 were switched to ATV/r. The median age of total patients was 39 (25-46) years. The CD4+ T cell count and plasma HIV-RNA VL at week 0 were 430 (250-535) cells/mm^3 and 1.59 (1.27-4.17) log $_{10}$ copies/mL, respectively. The PI used before the switch was lopinavir/ritonavir (77.8%) or nelfinavir (22.2%). In comparison of the two groups according to RTV use at week 0, the age of subjects in the ATV/r group was higher than that of subjects in the unboosted ATV group (45 vs. 36 years, P=0.018). TG in the unboosted ATV group was higher than that of the ATV/r group (239 vs. 195 mg/dL, *P*=0.021) (Table 1). At 12 and 24 weeks after the switch, plasma HIV-RNA VL was similar between the unboosted and boosted ATV group (1.27 vs. 2.17 log 10 copies/mL, *P*=0.168 and 1.27 vs. 1.27 log $_{10}$ copies/mL, *P*=0.684, respectively). CD4+ T cell counts were significantly higher in the unboosted ATV group, compared with the boosted ATV group at 12 weeks only (480 vs. 233 cells/mm^3, *P*=0.031).

At week 12, TG of all patients had decreased, from 196 to 174 mg/dL (*P*=0.048). This decrease continued to week 24 (150 mg/dL, *P*=0.021). TG of the unboosted ATV group decreased from 239 to 125 mg/dL (*P*=0.017) at week 12 and the continued decrease was observed (87 mg/dL, *P*$\langle$0.001) at week 24. In the ATV/r group, no significant change in TG was observed until week 24 (Table 2). TG was significantly lower in the unboosted ATV group, compared with the ATV/r group at both week 12 (*P*=0.034) and at week 24 (*P* $\langle$0.001).

Total cholesterol in the unboosted ATV group showed a significant decrease, from 184 to 158 mg/dL at week 24 only (*P*=0.031). In the ATV/r group, no significant changes in total

Table 1. Baseline Characteristics and Demographics of All Study Participants at the Time of Switching to Unboosted or Boosted Atazanavir (0-week)

	Total (N=27)	Switch to ATV (N=14)	Switch to ATV/r (N=13)	*P*-value*
Age, years	39 (25-46)	36 (23-42)	45 (34-49)	0.018[a]
Gender, male	26 (96.3)	13 (92.9)	13 (100.0)	1.000[b]
PI used before switch				1.000[b]
Lopinavir/Ritonavir	21 (77.8)	11 (78.6)	10 (76.9)	
Nelfinavir	6 (22.2)	3 (21.4)	3 (23.1)	
Plasma HIV-RNA VL, log_{10} copies/mL	1.59 (1.27-4.17)	1.43 (1.27-2.28)	2.27 (1.27-4.51)	0.298[a]
CD4+ T cell counts, cells/mm^3	430 (250-535)	492 (299-567)	303 (162-477)	0.094[a]
Lipid profile				
Triglyceride, mg/dL	196 (150-288)	239 (154-298)	195 (113-294)	0.021
Total cholesterol, mg/dL	173 (165-203)	184 (172-222)	167 (149-176)	0.391[a]
LDL-cholesterol, mg/dL	94 (68-118)	116 (65-127)	90 (77-101)	0.112[a]
HDL-cholesterol, mg/dL	47 (40-52)	48 (42-52)	42 (38-60)	0.386[a]
Total/HDL-cholesterol ratio	4.5 (3.4-5.0)	4.8 (3.3-5.3)	4.2 (3.2-4.8)	0.211[a]

The data are presented as the median (interquartile ranges) or number (percent). *Comparisons between unboosted and boosted ATV groups.
[a]Mann-Whitney U test.
[b]Fisher's exact test.
ATV, atazanavir; ATV/r, ritonavir-boosted atazanavir; PI, protease inhibitor; VL, viral load; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Table 2. Changes of Lipid Profile and CD4+ T Cell Count, Plasma HIV-RNA Viral Load at 0, 12, and 24-week after the Switch to Unboosted or Boosted Atazanavir

	Week	Total (N=27)		Switch to ATV (N=14)		Switch to ATV/r (N=13)	
			P-value[a]		*P*-value[a]		*P*-value[a]
Triglyceride,mg/dL	0[b]	196 (150-288)		239 (154-298)		195 (113-294)	
	12	174 (100-280)	0.048	125 (76-277)	0.017	178 (152-327)	0.067
	24	150 (87-241)	0.021	87 (74-157)	<0.001	207 (136-280)	0.612
Total cholesterol,mg/dL	0[b]	173 (165-203)		184 (172-222)		167 (149-176)	
	12	171 (153-187)	0.357	172 (152-185)	0.198	170 (154-197)	0.236
	24	162 (139-204)	0.271	158 (135-203)	0.031	165 (155-205)	0.689
LDL-cholesterol,mg/dL	0[b]	94 (68-118)		116 (66-127)		90 (77-101)	
	12	84 (69-106)	0.382	88 (57-106)	0.091	84 (69-107)	0.753
	24	79 (71-120)	0.767	94 (62-130)	0.355	79 (73-100)	0.499
HDL-cholesterol,mg/dL	0[b]	47 (40-52)		48 (42-52)		42 (38-60)	
	12	42 (36-53)	0.575	48 (37-55)	0.865	39 (36-49)	0.463
	24	48 (39-57)	0.282	49 (39-61)	0.180	48 (38-58)	0.610
Total/HDL-cholesterol ratio	0[b]	4.5 (3.4-5.0)		4.8 (3.3-5.3)		4.2 (3.2-4.8)	
	12	3.9 (3.1-4.8)	0.422	3.4 (3.0-4.5)	0.063	4.5 (3.9-4.9)	0.345
	24	2.8 (2.6-4.8)	0.011	2.8 (2.6-5.3)	0.007	4.0 (2.6-4.4)	0.735
CD4+ T cell count, cells/mm^3	0[b]	430 (250-535)		492 (299-567)		303 (162-477)	
	12	403 (254-577)	0.653	480 (348-607)	1.000	233 (150-386)	0.463
	24	460 (270-545)	0.153	468 (341-518)	0.779	412 (245-556)	0.060
Plasma HIV-RNA VL, log_{10} copies/mL	0[b]	1.59 (1.27-4.17)		1.43 (1.27-2.28)		2.27 (1.27-4.51)	
	12	1.38 (1.27-1.74)	0.028	1.27 (1.27-1.69)	0.128	2.17 (1.27-4.45)	0.225
	24	1.27 (1.27-1.59)	0.050	1.27 (1.27-1.50)	0.465	1.27 (1.27-1.59)	0.063

The data are presented as the median (interquartile ranges).
[a]Wilcoxon signed-rank test.
[b]Reference values.
ATV, atazanavir; ATV/r, ritonavir-boosted atazanavir; LDL, low-density lipoprotein; HDL, high-density lipoprotein; VL, viral load

cholesterol were observed at both week 12 and week 24. Among subsets of serum cholesterol, only total/HDL-cholesterol ratio showed a significant decrease in the unboosted ATV group at week 24 (4.8 at week 0 vs. 2.8 at week 24, *P*=0.007) (Table 2).

Results of this study revealed a favorable effect on lipid profile in HIV-infected Koreans who received switch therapy from another PI to unboosted ATV. However, this result was observed in TG and total cholesterol, but not in LDL- or HDL-cholesterol. In the lipid profile of all patients, a significantly continuous decrease was observed in TG only at week 12 and week 24. The decreasing trend of TG and total cholesterol was prominent in the unboosted ATV group, whereas the ATV/r group showed no

specific changes in lipid profile after switch of PI.

Triglyceride was the parameter that distinctly confirmed the favorable effect in the ATV-based regimen [15]. Similar to several studies conducted in Western countries [4], in our study, the decrease of TG was more prominent in the unboosted ATV group. The baseline TG before the switch in the unboosted ATV group was higher than that in the ATV/r group. In patients with higher TG, physicians may decide to change to an unboosted ATV because boosting can affect a significant elevation in TG [16]. At week 12, significant difference of TG was observed between the unboosted and boosted ATV group. At week 24, decrease of TG in the unboosted ATV group became prominent, which was caused by a sustained decrease in TG of the unboosted ATV group. There may be two potential causes to account for this favorable change of TG in the unboosted ATV group. First, it could be due to removal of an unfavorable effect of RTV on TG [16]. Due to a high percentage of RTV use in both groups (unboosted ATV: 77.8%, ATV/r: 76.9%), the shift to unboosted ATV may possibly have brought about removal of the unfavorable effect of RTV on TG. Second, it is possible that superiority of ATV regarding metabolic abnormalities, compared with other PI, could aid in improvement of TG. Several studies have confirmed a favorable effect on TG of switching from boosted PI to ATV/r [17, 18].

Meanwhile, LDL- and HDL-cholesterol did not show improvement after the switch in both the unboosted ATV and ATV/r groups. This finding is in agreement with prior studies that compared ATV and ATV/r as a part of a maintenance regimen [11, 19]. ATV/r showed no superiority compared with other PI in LDL- and HDL-cholesterol [7, 17, 18]. One study reported improvement of HDL-cholesterol after the switch from another PI to unboosted ATV; however, the sample included in the previous study was made up of HIV-infected patients with hyperlipidemia, therefore, it is difficult to compare this with results of our study [20].

Considering that, in most established studies, shifting from another PI to ATV resulted mainly in improvement of total cholesterol and non-HDL-cholesterol [20], a switch to ATV is not believed to have a direct effect on HDL-cholesterol.

There are several limitations to this study. Because only 27 patients were included, subanalysis to evaluate the cause of the results could not be performed. In addition, the baseline characteristics of both groups had some differences. The age of subjects in the unboosted ATV group was lower than that of subjects in the ATV/r group. Considering that older age is associated with metabolic syndrome, this difference may be a limitation of this study. Another difference was that the baseline TG of the unboosted ATV group was higher than that of the ATV/r group. However, because the results showed a continuous decrease of TG until week 24 after baseline difference disappeared at week 12 in the unboosted ATV group, this difference was thought not to influence the outcome of our study.

In conclusion, results of our analysis may implicate that a switch to unboosted ATV from another PI is related to favorable changes in lipid profile, particularly TG, and that boosting removes the favorable effect of ATV on lipid profile in HIV-infected Koreans.

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