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ORIGINAL ARTICLE

Treatment response to unboosted atazanavir in combination with tenofovir disoproxil fumarate and lamivudine in human immunodeficiency virus-1-infected patients who have achieved virological suppression: A therapeutic drug monitoring and pharmacogenetic study☆

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protease inhibitor

Abstract *Background/Purpose:* Treatment response to switch regimens containing unboosted atazanavir and tenofovir disoproxil fumarate (TDF)/lamivudine guided by therapeutic drug monitoring in human immunodeficiency virus-infected patients is rarely investigated.
Methods: Consecutive patients with plasma human immunodeficiency virus RNA load $<$ 200 copies/mL switching to unboosted atazanavir plus zidovudine—lamivudine (coformulated), abacavir—lamivudine (coformulated), or TDF/lamivudine $>$ 3 months were included for determinations of treatment response, plasma atazanavir concentrations, and single-nucleotide polymorphisms of *MDR1*, *PXR*, and *UGT1A1* genes from 2010 to 2014. Treatment failure was defined as either discontinuation of atazanavir for any reason or plasma viral load $\geq$ 200 copies/mL within 96 weeks.
Results: During the study period, 128 patients switched to unboosted atazanavir with TDF/lamivudine (TDF group) and 186 patients switched to unboosted atazanavir with two other nucleoside reverse-transcriptase inhibitors (non-TDF group). There were no statistically significant differences in the distributions of single-nucleotide polymorphisms of *MDR1* (2677 and 3435), *PXR* genotypes (63396), and *UGT1A1*28* between the two groups. Recommended plasma atazanavir concentrations were achieved in 83.5% and 64.9% of the TDF group and non-TDF group, respectively ($p < 0.01$). After a median follow-up duration of 96.0 weeks, treatment failure occurred in 19 (14.9%) and 34 (18.3%) patients in the TDF group and non-TDF group, respectively ($p = 0.60$). Low-level viremia (40—200 copies/mL) before switch (adjusted hazard ratio, 2.12; 95% confidence interval, 1.12—4.01) and without therapeutic drug monitoring (adjusted hazard ratio, 2.08; 95% confidence interval, 1.16—3.73) were risk factors for treatment failure.
Conclusion: Switch to unboosted atazanavir with TDF/lamivudine achieves a similar treatment response to that with two other nucleoside reverse-transcriptase inhibitors in patients achieving virological suppression with the guidance of therapeutic drug monitoring.

Introduction

Protease inhibitors (PIs) boosted with ritonavir in combination with two nucleos(*t*)ide reverse-transcriptase inhibitors (NRTIs) are recommended antiretroviral regimens with good virological efficacy and a high genetic barrier to resistance.[1—3] Boosted atazanavir and darunavir are preferred for the initial treatment of human immunodeficiency virus (HIV) infection because each has demonstrated better lipid effects and tolerability than ritonavir-boosted lopinavir.[4—6] Despite being administered at a low dose (100 mg), ritonavir can lead to lipid disturbances, glucose intolerance, insulin resistance, liver enzyme elevations, gastrointestinal symptoms, and body fat abnormalities[7,8]; furthermore, the potential drug—drug interactions between ritonavir and nonantiretroviral medications may potentially lead to clinically significant adverse events.[9—11]

Randomized clinical trials have demonstrated similar virological efficacy between the switch regimens consisting of unboosted atazanavir and those consisting of boosted atazanavir in patients who had achieved suppression of HIV-1 replication after initial therapy with boosted atazanavir-containing regimens.[12—15] Regimens containing unboosted atazanavir may provide better efficacy in virological suppression and improvement of lipid parameters, compared with those containing other PIs such as boosted lopinavir, boosted or unboosted indinavir, boosted or unboosted saquinavir, and nelfinavir.[16] These issues were especially relevant to aging HIV-positive patients who are likely to have polypharmacy.[17]

Unlike other NRTIs, tenofovir disoproxil fumarate (TDF) is not recommended in combination with unboosted atazanavir because TDF may decrease atazanavir concentrations by 23—40%, although the mechanisms for this interaction remain unclear.[18—20] Lower plasma concentrations and higher interindividual variability due to the diverse distribution of genetic polymorphisms that are responsible for variations of atazanavir pharmacokinetics in different ethnic populations are the major concerns.[21] In the clinical setting, studies have revealed that coadministration with TDF was not associated with lower plasma exposure to unboosted atazanavir.[22,23] In terms of virological response, others studies have suggested that a combination of TDF with unboosted atazanavir may be safe in selected populations.[23—25]

In this study, we aimed to compare the treatment response to a switch regimen of unboosted atazanavir in combination with TDF and lamivudine versus regimens of unboosted atazanavir with two other NRTIs with the information provided with therapeutic drug monitoring (TDM) and pharmacogenetic investigations.

Methods

Study population

In this retrospective observational study, we included HIV-infected adults aged 20—65 years who switched to unboosted atazanavir plus two NRTIs after achieving

plasma HIV RNA load (PVL) $<$ 200 copies/mL with combination antiretroviral therapy (cART) for .$>$ 3 months at the National Taiwan University Hospital in Taipei, Taiwan between 2010 and 2014. NRTIs were chosen with consideration of full treatment history, comorbidity, and available resources. Patients with a history of virological failure while receiving PI-based cART or with HIV-1 strains harboring resistance-associated mutations to PIs were excluded. Patients who were taking any H2 blockers or proton-pump inhibitors were also excluded. Patients were evaluated every 12 weeks after the treatment switch for $>$ 3 months to assess their tolerance and adherence and to undergo laboratory monitoring, including PVL, CD4 count, renal and liver function, fasting glucose, total cholesterol, and triglycerides. The study was approved by the Research Ethics Committee of National Taiwan University Hospital (registration no. 201103077RC) and the patients gave written informed consent for TDM of plasma atazanavir concentrations and pharmacogenetic investigations.

Measurement of plasma atazanavir concentration

TDM to measure plasma atazanavir concentrations was performed in patients switching to unboosted atazanavir-containing regimens after November 2011. After patients had taken atazanavir for 2 weeks or longer, measurements of plasma atazanavir concentrations, C12 (12 $\pm$ 1 hour after intake) or C24 (24 $\pm$ 1 hour after intake) based on feasibility, were performed during their routine clinic visits using high-performance liquid chromatography (HPLC) with a modified method reported by Müller et al.[26] Blood samples were collected into potassium and ethylenediaminetetraacetic acid-containing 10-mL tubes. Plasma was stored at -20°C prior to analysis. In brief, 400 μL of plasma was added to 400 μL of 2M sodium carbonate containing diazepam (internal standard). The resulting solution was extracted with 800 μL of ethyl acetate-n-hexane, 1:1 (vol/vol), and the organic layer was dried under nitrogen. The extract was then dissolved with 200 μL of methanol for HPLC analysis. The HPLC system consisted of a L-2130 HTA solvent delivery pump, a L-2200 autosampler, a L-2420 UV-Vis detector, and the HPLC D-2000 Elite on Windows (version 1.2, Hitachi High Technologies Corporation, Tokyo, Japan) chromatographic data system. Chromatography was performed on a Mightysil RP-18 GP column (250 $\times$ 4.6 mm, 5 μm; Kanto Corporation, Portland, OR, USA). The mobile phase was composed of 10mM phosphate buffer (pH 2.5) mixed with acetonitrile at a ratio of 58:42 (vol/vol), and the flow rate was 1 mL/min. The detection wavelength was at 245 nm. The injection volume was 20 μL. The retention time of atazanavir and internal standard was 11.95 minutes and 16.4 minutes, respectively. The calibration curve of atazanavir was linear over the range of 100–10000 ng/mL. The extraction recovery was 104%. The accuracy ranged from 94.0% to 104.0%. The peak area of the intra- and interassay coefficients of variation at 5000 ng/mL ranged from 1.22–3.5% and 0–1.19%, respectively.

Pharmacogenetic study

Single nucleotide polymorphisms [SNPs; multidrug resistance 1 (MDR1) 2677G->T/A, MDR1 3435C->T, and pregnane X receptor (PXR) 63396C->T] were reported to be associated with atazanavir concentrations, and differences in the frequencies of common alleles encoding these proteins among different ethnic groups can be related to the variability in drug response.[21,27,28] For example, the MDR1 G2677$\rightarrow$T/A polymorphism was more common in Asians (83–88%) than in Caucasians (67–69%).[21,29,30] In this study, DNA samples extracted from peripheral blood specimens were obtained from participants. MassARRAYiPLEX GoldSNP Genotyping was then performed to determine the SNPs of transcription factor binding sites of PXR regulatory regions and *MDR1* (*ABCB1*), while uridine diphosphate-glucuronosyltransferase 1A1 *(UGT1A1)* UGT1A1*28 were determined by methods described previously by Beutler et al.[31]

Assessment of treatment outcomes

Patients were divided into two groups according to NRTIs prescribed: TDF-based group in which patients received TDF, lamivudine, and unboosted atazanavir; and non-TDF-based group in which patients received coformulated zidovudine/lamivudine or abacavir/lamivudine and unboosted atazanavir. The primary outcome of interest was time-to-treatment failure, which was defined as virological failure (PVL $\geq$ 200 copies/mL) confirmed by a second test within 3 months; or regimen modification or discontinuation for any reason (intention-to-treat analysis), with the first date of PVL $\geq$ 200 copies/mL or the date of regimen modification as the failure date. The secondary primary outcome was treatment failure by 24 weeks and 48 weeks. Participants who did not experience the endpoint event were censored at the time of 96 weeks.

Absolute changes in lipid levels from baseline were summarized by treatment regimens through the last on-study visit or the visit when a lipid-lowering agent was added for the two groups of patients. Lipid data were excluded from analyses after the initiation of lipid-lowering agents.

Baseline characteristics and pharmacogenetic factors were assessed for the association with the occurrence of Grades 3–4 hyperbilirubinemia that was defined as a total bilirubin $>$ 2.5 times the upper limit of normal after a switch to unboosted atazanavir.

Statistical analysis

Categorical data were analyzed using Chi-square test or Fisher's exact tests as appropriate, and continuous variables, expressed as median and interquartile range, were compared using the Mann–Whitney *U* test. Paired *t*-test was used to analyze within-subject means over the two test conditions. The regression models were built using a forward stepwise procedure using demographic characteristics, clinical characteristics that included hepatitis B virus

(HBV) or hepatitis C virus coinfection, and HIV status that included virological response to the prior cART, and CD4 counts. Logistic regression analysis was used to test predictive factors associated with Grades 3–4 hyperbilirubinemia. The confidence interval (CI) was set at 95%. All statistical tests were 2-tailed, and p values < 0.05 were considered to be statistically significant. The analysis was conducted using the statistical package SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

During the study period, 314 patients who switched to unboosted atazanavir in combination with two NRTIs were included: 128 (40.8%) switched to TDF, lamivudine plus unboosted atazanavir; and 186 (59.2%) to abacavir/lamivudine ($n = 161$) or zidovudine/lamivudine ($n = 25$) plus unboosted atazanavir. Baseline characteristics of both groups of patients are shown in Table 1. Compared with patients in the non-TDF group, patients in the TDF group were younger (38.7 years vs. 43.0 years, $p < 0.01$), had a higher proportion of chronic HBV infection (28.9% vs. 14.0%, $p < 0.01$), and lower fasting triglycerides (139.5 mg/dL vs. 222.0 mg/dL, $p < 0.01$) and total cholesterol levels (168.5 mg/dL vs. 213.5 mg/dL, $p < 0.01$) before the switch. The proportion of patients having achieved PVL < 40 copies/mL before the switch was 83.6% and 87.6% in the TDF group and non-TDF group, respectively ($p = 0.32$). Within-class substitution, from boosted PIs to unboosted atazanavir, was the most common switch strategy, especially in the TDF group. Deintensification from a ritonavir-boosted atazanavir-containing regimen to unboosted atazanavir-containing regimen was more common in the TDF group (67.2% vs. 20.4%, $p < 0.01$; Table 1).

Treatment response

After a median follow-up for 96 weeks (25th quartile, 74.0 weeks; 62.4% censored at Week 96), 53 (16.9%) experienced treatment failure. By Week 24, four patients (3.1%) in the TDF group and 12 (6.5%) in the non-TDF group experienced treatment failure (Chi-square test, $p = 0.19$); and by Week 48, 10 (7.8%) in the TDF group and 19 (10.2%) in the non-TDF group experienced treatment failure (Chi-square test, $p = 0.48$). There was no statistically significant difference between the two groups in time-to-treatment failure at Week 96 (14.9% vs. 18.3%, log-rank $p = 0.60$; Figure 1). Results of Cox proportional hazards model including all listed covariables are shown in Table 2. Independent risk factors for treatment failure included low-level viremia (40–200 copies/mL) before the switch

Table 1 Baseline characteristics of 314 patients who switched to unboosted atazanavir in combination with two nucleos(*t*)ide reverse-transcriptase inhibitors.[a]

Characteristics	Total ($n = 314$)	Tenofovir group ($n = 128$)	Nontenofovir group ($n = 186$)	p
Male sex	297 (94.6)	121 (94.5)	176 (94.6)	0.97
Age (y)	40.7 (33.9–46.9)	38.7 (32.1–43.5)	43.0 (34.9–48.9)	<0.01
Weight (kg)	65.0 (59.0–73.0)	65.1 (58.0–72.6)	64.0 (60.0–73.0)	0.44
BMI (kg/m^2)	22.4 (20.8–24.9)	22.5 (20.5–24.8)	22.3 (20.9–24.9)	0.56
Mode of transmission				0.18
MSM	234 (74.5)	102 (79.7)	132 (71.0)	
Heterosexual	57 (18.2)	16 (12.5)	41 (22.0)	
IDU	14 (4.5)	6 (4.7)	8 (4.3)	
Unknown	9 (2.8)	4 (3.1)	5 (2.7)	
HBsAg-positive	63 (20.1)	37 (28.9)	26 (14.0)	<0.01
Anti-HCV-positive	22 (7.0)	10 (7.8)	12 (6.5)	0.64
CD4 cell count at switch (cells/mm^3)	526 (370–682)	516 (355–665)	530 (393–696)	0.37
HIV-1 RNA < 40 copies/mL at switch	270 (86.0)	107 (83.6)	163 (87.6)	0.32
Triglycerides (mg/dL)	188.0 (109.0–329.0)	139.5 (96.0–221.0)	222.0 (128.5–393.5)	<0.01
Total cholesterol (mg/dL)	188.5 (157.0–232.0)	168.5 (145.0–202.0)	213.5 (167.5–250.0)	<0.01
Antiretroviral regimens before switching				<0.001
Boosted atazanavir + 2 NRTIs	124 (39.5)	86 (67.2)	38 (20.4)	
Boosted PI (nonatazanavir) + 2 NRTIs	79 (25.2)	17 (13.3)	62 (33.3)	
Raltegravir + 2 NRTIs	2 (0.64)	0 (0)	2 (1.1)	
NNRTI + 2 NRTIs	95 (30.3)	23 (18.0)	72 (38.7)	
3 NRTIs	14 (4.5)	2 (1.6)	12 (6.5)	

[a] Comparisons of continuous data are made using the Mann–Whitney *U* test and categorical variables using either Fisher's exact test or χ^2 test.
Data are presented as n (%) or median (interquartile range).
BMI = body-mass index; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; IDU = injecting drug user; MSM = men who have sex with men; NRTI = nucleos(*t*)ide reverse-transcriptase inhibitor; NNRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor.

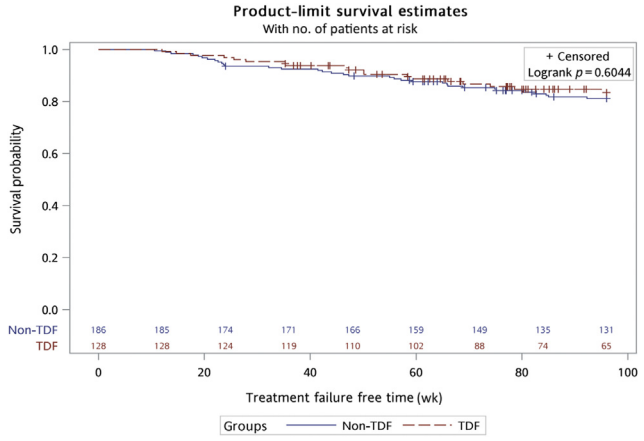

Figure 1. Time-to-virological failure in patients who switched to unboosted atazanavir plus two nucleos(*t*)ide reverse-transcriptase inhibitors (tenofovir-based vs. non-tenofovir-based regimens). TDF = tenofovir disoproxil fumarate.

[adjusted hazard ratio (AHR), 2.12; 95% CI, 1.12—4.01] and without TDM (AHR, 2.08; 95% CI, 1.16—3.73).

Reasons for treatment failure of the 53 patients are summarized in Table 3. Twenty patients, including five (3.9%) in the TDF group and 15 (8.1%) in the non-TDF group, experienced virological failure (PVL $\geq$ 200 copies/mL) during follow-up. Using Kaplan—Meier analysis, no statistically significant difference was found in time to virological failure between the two groups ($p = 0.18$). The adjusted Cox proportional hazards model revealed that low-level viremia before switch was a predictive factor of virological failure (AHR, 3.46; 95% CI, 1.34—8.92). No emergence of resistance-associated mutations to atazanavir or NRTIs was detected in the HIV-1 strains from the patients who experienced virological failure.

Lipid profile and hyperbilirubinemia

After the switch to unboosted atazanavir plus two NRTIs, both groups showed similarly significant decrease of the total cholesterol levels from baseline: −16.6 mg/dL (95% CI, −11.8—−21.4) in the TDF group and −23.2 mg/dL (95% CI, −15.7—−30.7) in the non-TDF group ($p = 0.14$). A significant decrease in fasting triglycerides was also found after the switch in both groups: −58.1 mg/dL (95% CI, −25.9—−90.3) in the TDF group and −99.4 mg/dL (95% CI, −43.1—−155.6) in the non-TDF group ($p = 0.21$). During the study period, 23.2% of the patients experienced Grades 3—4 hyperbilirubinemia (32.8% and 16.7% for TDF and non-TDF group, respectively). In patients who switched from boosted atazanavir to unboosted atazanavir, the total bilirubin levels decreased from 2.48 mg/dL to 2.13 mg/dL [difference, −0.31 (95% CI, −0.43—0.17)] in the TDF group ($n = 86$) and from 2.17 mg/dL to 1.80 mg/dL [difference, −0.37 (95% CI, −0.74—−0.12)] in the non-TDF group ($n = 38$). In multivariate analysis, age (per 1-year increase, adjusted odds ratio 1.05; 95% CI, 1.01—1.09; $p < 0.01$) and HBV coinfection (adjusted odds ratio 2.73; 95%CI, 1.02—7.29; $p = 0.04$) were the two independent predictors of Grades 3—4 hyperbilirubinemia.

Table 3 Reasons for treatment failure in both groups of patients.

Reasons	Tenofovir-based ($n = 19$)	Nontenofovir-based ($n = 34$)
Plasma HIV RNA load > 200 copies/mL	5 (26)	15 (44)
Discontinuation of atazanavir	14 (74)	19 (56)
Loss to follow up	2 (11)	7 (21)
Irregular dosing interval	4 (21)	5 (15)
Jaundice	3 (16)	5 (15)
Alopecia	1 (5.2)	0
Elevated serum creatinine and proteinuria	2(10)	0
Unknown	2(10)	2 (6)

Data are presented as *n* (%).
HIV = human immunodeficiency virus.

Plasma atazanavir concentrations

TDM of atazanavir concentrations (C12 and C24) were conducted in 197 patients (62.7%; TDF group vs. non-TDF

Table 2 Univariate and multivariate analysis for factors associated with virological failure in 314 patients.[a]

Variables	Reference	HR	95% CI	*p*	HR	95% CI	*p*
Tenofovir-based	Non-tenofovir-based	0.87	0.49—1.52	0.61			
Age (y)	Per 1-y increase	1.01	0.98—1.03	0.65			
HBsAg-positive	HBsAg-negative	1.10	0.58—2.10	0.76			
Anti-HCV-positive	Anti-HCV-negative	0.75	0.24—2.42	0.64			
CD4 count (cells/μL) before switch	Per 100-cell/μL increase	0.97	0.87—1.08	0.56			
Baseline plasma HIV RNA load (HIV RNA, 40—200 copies/mL)	HIV RNA < 40 copies/mL	2.08	1.11—3.90	0.02	2.12	1.12—4.01	0.02
Without therapeutic drug monitoring	With therapeutic drug monitoring	2.00	1.16—3.43	0.01	2.08	1.16—3.73	0.01

[a] HRs and 95% CIs were calculated using Cox regression analysis.
CI = 95% confidence interval; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HR = hazard ratio.

group, 80.5% vs. 50.5%, $p < 0.01$) and the results are shown in Figure 2. No statistically significant differences in the clinical characteristics were observed between the patients who had undergone TDM and those who had not (data not shown). In the TDF group, 16.5% (17/103) patients had plasma atazanavir concentrations below the recommended therapeutic values (230 ng/mL for C12 and 150 ng/mL for C24),[32] whereas in the non-TDF-based group, 35.1% (33/94) had atazanavir concentrations below the recommended therapeutic values ($p < 0.01$).

Pharmacogenetic study

The distributions of *UGT1A1* genotypes, *MDR1* genotype at positions 2677 and 3435, and the *PXR* genotype at position 63396 are shown in Table 2. There were no statistically significant differences in the clinical characteristics between the patients who had undergone genotyping for each gene and those who had not (data not shown). The distributions of SNPs of these three genes were similar between the two groups. For example, *UGT1A1* genotypes were characterized in 196 patients, for which TA6/TA6 was noted in 78.6%, TA6/TA7 in 21.4%, and TA7/TA7 in 0% (Table 4).

Subgroup analysis

When we limited the analyses to those with TDM ($n = 197$), we found that 12.2% of the patients experienced treatment failure (10 of 103 in TDF group and 14 of 94 in non-TDF group, Chi-square test, $p = 0.30$). In Cox regression, concentration above the recommended target (AHR, 0.61; 95% CI, 0.25–1.44), low-level viremia (AHR, 2.02; 95% CI, 0.74–5.53), and TDF-containing regimen (AHR, 0.79; 95%

Table 4 Genotyping results of the patients who switched to unboosted atazanavir in combination with tenofovir and lamivudine (tenofovir-based group) or two other non-tenofovir nucleoside reverse-transcriptase inhibitors (non-tenofovir-based group).

Genotype	Total	Tenofovir group	Nontenofovir group	*p*
*UGT1A1**28 ($n = 196$)				0.71
TA6/TA6	154 (78.6)	82 (79.6)	72 (77.4)	
TA6/TA7	42 (21.4)	21 (20.4)	21 (22.6)	
TA7/TA7	0	0	0	
MDR1 2677 ($n = 169$)				0.54
G/G	46 (27.2)	18 (26.1)	28 (28.0)	
G/T	62 (36.7)	25 (36.2)	37 (37.0)	
G/A	22 (13.0)	10 (14.5)	12 (12.0)	
T/A	21 (12.4)	6 (8.7)	15 (15.0)	
T/T	17 (10.1)	9 (13.0)	8 (8.0)	
A/A	1 (0.6)	1 (1.5)	0 (0)	
MDR1 3435 ($n = 122$)				0.47
C/C	12 (9.8)	3 (7.5)	9 (11.0)	
C/T	89 (73.0)	32 (80.0)	57 (69.5)	
T/T	21 (17.2)	5 (12.5)	16 (19.5)	
PXR 63396 ($n = 122$)				0.79
C/C	22 (18.0)	6 (15.0)	16 (19.5)	
C/T	55 (45.1)	18 (45.0)	37 (45.1)	
T/T	45 (36.9)	16 (40.0)	29 (35.4)	

Data are presented as *n* (%).

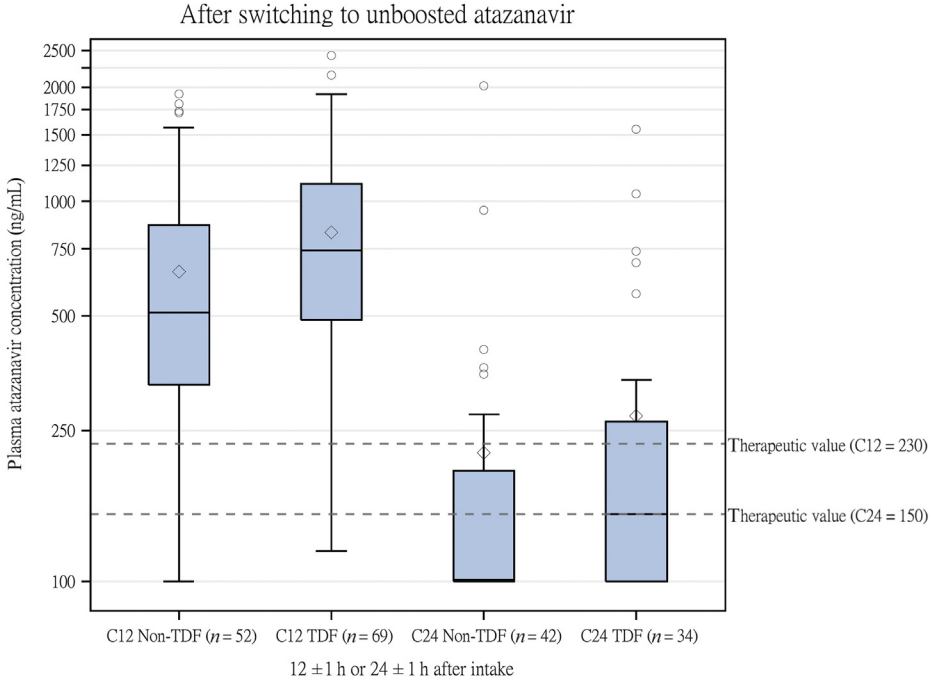

Figure 2. Plasma atazanavir concentrations, tenofovir/lamivudine + unboosted atazanavir, and abacavir-lamivudine (or zidovudine-lamivudine) + unboosted atazanavir.

CI, 0.33—1.89) were not statistically significantly associated with treatment failure at Week 96.

To explore whether there was evidence that the difference in treatment response depended on genetic characteristics, a planned subgroup analysis was conducted and the results were plotted (Figure 3). It did not suggest a statistically significant advantage in terms of time to treatment failure for either group.

Discussion

In this study, we found that in HIV-positive patients on suppressive antiretroviral therapy without documented resistance-associated mutations to PIs, a switch to unboosted atazanavir in combination with TDF and lamivudine provided comparable antiviral effectiveness to unboosted atazanavir with two other non-TDF NRTIs. A switch to unboosted atazanavir-containing regimens resulted in lower total cholesterol and triglycerides without addition of lipid-lowering drugs.

In randomized controlled trials, regimens consisting of unboosted atazanavir plus two NRTIs caused less hyperbilirubinemia and improvement of lipid profiles,[12,14] which are also observed in our study. While TDF is not recommended to be combined with unboosted atazanavir, an ongoing open-label randomized control trial (NCT01351740) will examine the clinical effect of the potential drug—drug interactions between TDF and unboosted atazanavir in HIV-positive patients achieving viral suppression. In the retrospective analysis of 886 patients who switched to unboosted atazanavir-containing regimens in an European multicenter cohort collaboration, Pavie et al[25] found that TDF used in combination with unboosted atazanavir in 36.9% of the patients did not increase the risk of virological failure.

In our study, we found that the risk of virological failure could be reduced by 50% with the information of TDM, and atazanavir concentrations below recommended target were not correlated with virological failure in patients with TDM, which is in line with the finding of other studies.[24,33] There was a higher proportion of our patients (75%) who had atazanavir concentrations above the recommended target, which suggests that pharmacogenetics or environmental influences may influence plasma atazanavir concentration to a greater extent than the potential drug—drug interaction. Our subgroup analyses consistently demonstrated insignificant differences between TDF and non-TDF groups regarding time-to-virological failure in patients with virological suppression subdivided by genetic polymorphisms. Although the small sample size of the subgroups is a concern, the results may help minimize the bias and draw a robust conclusion.

Plasma atazanavir concentrations are associated with atazanavir-related hyperbilirubinemia.[24,34] Recent studies also suggested that boosted atazanavir-containing regimens are associated with an increased risk of clinically significant renal stones or cholelithiasis.[35—38] Therefore, TDM to optimize drug levels and to minimize adverse effects can be clinically relevant in the long-term successful management of cART for HIV-positive patients. Our study is the first study

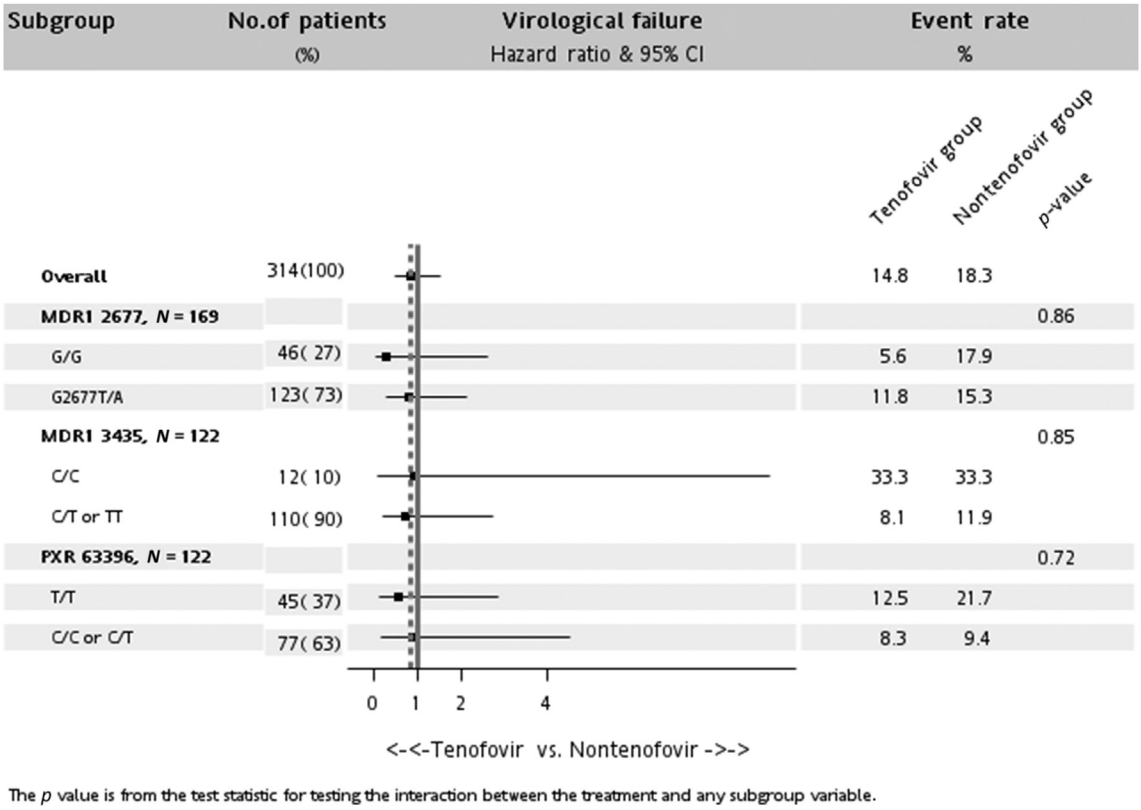

Figure 3. Forest plot showing the risk of virological failure according to subgroups. CI = confidence interval; MDR1 = multidrug resistance 1; PXR = pregnane X receptor.

to use TDM in a clinical care setting to minimize the adverse impact of drug—drug interactions between atazanavir and TDF on virological response and the long-term metabolic effects of ritonavir. While more clinical and pharmacogenetic studies are warranted to confirm our findings, our finding that use of TDM reduced risk of treatment failure gives support to the use of TDM in management of patients on regimens containing boosted atazanavir.

There are several limitations to our study. This is not a randomized clinical trial, and selection bias is likely to have occurred. Patients who were deemed highly adherent to cART might be more likely to be switched to unboosted atazanavir combined with lamivudine and TDF than to unboosted atazanavir combined with two other non-TDF NRTIs, which may lead to an underestimation of the risk of virological failure in the TDF group. However, the two groups of patients had similar baseline characteristics and distributions of genetic factors on the whole, which may help minimize the bias. Secondly, limited by the sample size, our study was not powered to demonstrate the non-inferiority of one regimen to another. Thirdly, most of the patients were middle-aged men who have sex with men and, therefore, the results may not be generalizable to all HIV-positive patients. Fourthly, not all patients in this study underwent TDM and genotyping. While our study was the first study to address the clinical responses to unboosted atazanavir in combination with TDF and lamivudine with the information of drug concentrations and pharmacogenetics, the missing data on the plasma atazanavir concentrations preclude us from establishing a prediction model to identify atazanavir levels that might optimize trade-offs between virological responses and adverse effects. Fifthly, the distributions of the SNPs that are related to metabolism of atazanavir are likely to differ among different ethnicities, and therefore, our data may not be generalizable to ethnicities other than Taiwanese. Lastly, the observation duration was not long enough and a longer duration of follow-up is warranted to assess the durability of the regimen in virological suppression.

Unboosted ataznavir in combination with TDF and lamivudine is as effective as unboosted atazanavir in combination with two other NRTIs in patients who have achieved virological suppression. This regimen may represent a viable option in the treatment simplification strategies in populations with access to TDM.

Conflicts of interest

C.C.H. has received research support from Janssen (Beerse, Belgium) and speaker honoraria from Abbvie (North Chicago, Illinois United States) Bristol-Myers Squibb (New York City, United States), Gilead Sciences (Foster City, California United States) and ViiV (Brentford, Greater London United Kingdom), and served on advisory boards for Gilead Sciences and Abbvie.

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