gradient mode of CH_3CN solution containing 0.1% (v/v) TFA at a flow rate of 7 cm^3 min^{-1}. Microwave reactions were performed in Biotage Microwave Reaction Kit (sealed vials) in an Initiator™ (Biotage). The wattage was automatically adjusted to maintain the desired temperature for the desired period of time.

4.1. Chemistry

4.1.1. N^1-(4-Chlorophenyl)-N^2-(piperidin-4-yl)oxalamide (3)

To a stirred solution of *p*-choroaniline (**1**) (14.0 g, 110 mmol) in THF (146 mL) were added ethyl chloroglyoxylate (8.13 mL, 73.2 mmol) and triethylamine (Et_3N) (15.2 mL, 110 mmol) at 0 °C. The mixture was stirred for 6 h at room temperature. After the precipitate was filtrated off, the filtrate solution was concentrated under reduced pressure. The residue was dissolve in EtOAc, and washed with 1 M HCl, saturated $NaHCO_3$ and brine, then dried over $MgSO_4$. Concentration under reduced pressure gave the crude ethyl oxalamate, which was used without further purification. To a solution of the above ethyl oxalamate (1.27 g, 5.25 mmol) in EtOH (13.0 mL) were added Et_3N (1.46 mL, 10.5 mmol) and 4-amino-1-benzylpiperidine (2.97 mL, 15.8 mmol). The reaction mixture was stirred for 3 h at 150 °C under microwave irradiation. After being cooled to room temperature, the crystal was collected and washed with cold EtOH and *n*-hexane, and dried under reduced pressure to provide the corresponding amide (1.58 g, 81% yield) as colorless crystals. To a stirred solution of **S1** (1.46 g, 3.90 mmol) in CH_2Cl_2 (39.0 mL) was added dropwise 1-chloroethyl chloroformate (0.860 mL, 7.80 mmol) at 0 °C. After being stirred at room temperature for 30 min, the mixture was refluxed for 1 h. After concentration under reduced pressure, the residue was dissolved in MeOH and then refluxed for 1 h. After concentration under reduced pressure, the residue was diluted with EtOAc and washed with saturated $NaHCO_3$ and brine, then dried over $MgSO_4$. After concentration under reduced pressure, the residue was washed with cold EtOAc, and dried under reduced pressure to provide the title compound **3** (778 mg, 71% yield) as white powder.

^1H NMR (400 MHz, $CDCl_3$) δ 1.39–1.52 (m, 2H), 1.92–2.01 (m, 2H), 2.67–2.79 (m, 2H), 3.06–3.19 (m, 2H), 3.83–3.95 (m, 1H), 7.34 (d, J = 8.80 Hz, 2H), 7.44 (d, J = 7.64 Hz, 1H), 7.59 (d, J = 8.80 Hz, 2H), 9.28 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.0 (2C), 45.2 (2C), 47.9, 21.0 (2C), 129.3 (2C), 130.5, 135.0, 157.6, 158.8; HRMS (ESI), *m/z* calcd for $C_{13}H_{17}ClN_3O_2$ (MH^+) 282.1004, found 282.1002.

4.1.2. N^1-(1-Carbamimidoylpiperidin-4-yl)-N^2-(4-chlorophenyl) oxalamide (4)

To a stirred solution of **3** (50.0 mg, 0.178 mmol) in DMF (20.0 mL) was added 1-aminopyrazole hydrochlride (312 mg, 2.13 mmol) and Et_3N (0.390 mL, 28.1 mmol). The reaction mixture was stirred at room temperature for 24 h. After concentration under reduced pressure, purification by preparative HPLC gave the trifluoroacetate of the title compound **4** as white powder (36.0 mg, 61% yield).

^1H NMR (500 MHz, DMSO) δ 1.41–1.55 (m, 2H), 1.59–1.71 (m, 2H), 2.70–2.74 (m, 2H), 3.74–3.87 (m, 1H), 3.88–4.03 (m, 2H), 5.93 (s, 2H), 7.42 (d, J = 9.00 Hz, 2H), 7.85 (d, J = 9.00 Hz, 2H), 8.95 (d, J = 9.00 Hz, 1H), 10.80 (s, 1H); ^{13}C NMR (125 MHz, DMSO) δ 31.3 (2C), 43.0 (2C), 47.6, 122.4 (2C), 128.6, 129.1 (2C), 137.1, 158.2, 159.3, 159.5; HRMS (ESI), *m/z* calcd for $C_{14}H_{19}ClN_5O_2$ (MH^+) 324.1222, found 324.1213.

4.1.3. N^1-(1-Carbamothioylpiperidin-4-yl)-N^2-(4-chlorophenyl) oxalamide (5)

To a stirred solution of **3** (140 mg, 0.498 mmol) in $CHCl_3$ (5.00 mL) was added trimethylsilyl isothiocyanate (141 mL, 1.00 mmol) and stirred at room temperature for 1 h. The precipitate was collected and washed with cold $CHCl_3$, and dried under reduced pressure to provide the title compound **5** as white powder. (62.0 mg, 36% yield).

^1H NMR (400 MHz, DMSO) δ 1.45–1.69 (m, 2H), 1.69–1.81 (m, 2H), 2.67–2.81 (m, 2H), 3.02–3.16 (m, 2H), 3.75–3.89 (m, 1H), 7.41 (d, J = 9.00 Hz, 2H), 7.85 (d, J = 9.00 Hz, 2H), 9.00 (d, J = 8.50 Hz, 1H), 10.80 (s, 1H); ^{13}C NMR (125 MHz, DMSO) δ 27.8 (2C), 42.3 (2C), 44.4, 122.0 (2C), 128.2, 128.6 (2C), 129.5, 136.6, 158.6, 159.4; Anal. calcd for $C_{14}H_{18}ClN_4O_2S$: C, 49.34; H, 5.03; N, 16.44. Found: C, 49.32; H, 4.76; N, 16.11.

4.1.4. N^1-(1-Carbamoylpiperidin-4-yl)-N^2-(4-chlorophenyl) oxalamide (6)

To a stirred solution of **3** (60.0 mg, 0.213 mmol) in $CHCl_3$ (1.10 mL) was added trimethylsilyl isocyanate (56.0 µL, 0.421 mmol), and the mixture was stirred at room temperature for 1 h. The precipitate was collected and washed with cold $CHCl_3$, and dried under reduced pressure to provide the title compound **6** (20.1 mg, 30% yield) as white powder.

^1H NMR (500 MHz, DMSO) δ 1.44–1.55 (m, 2H), 1.58–1.71 (m, 2H), 2.65–2.78 (m, 2H), 3.76–3.87 (m, 1H), 3.87–4.01 (m, 2H), 5.94 (s, 1H), 7.42 (d, J = 9.00 Hz, 2H), 7.86 (d, J = 9.00 Hz, 2H), 8.95 (d, J = 9.00 Hz, 1H), 10.80 (s, 1H); ^{13}C NMR (125 MHz, DMSO) δ 30.8 (2C), 42.6 (2C), 47.1, 122.0 (2C), 128.1, 128.6 (2C), 136.7, 157.8, 158.8, 159.0; HRMS (ESI), *m/z* calcd for $C_{14}H_{18}ClN_4O_3$ (MH^+) 325.1062, found 325.1060.

4.1.5. N^1-(4-Chlorophenyl)-N^2-(1-(phenylcarbamoyl)piperidin-4-yl)oxalamide (7)

To a stirred solution of **3** (140 mg, 0.498 mmol) in $CHCl_3$ (5.00 mL) was added phenyl isocyanate (54.0 µL, 0.500 mmol) and stirred at room temperature for 1 h. The precipitate was collected and washed with cold $CHCl_3$, and dried under reduced pressure to provide the title compound **7** as white powder. (64.1 mg, 32% yield).

^1H NMR (500 MHz, DMSO) δ 1.52–1.66 (m, 2H), 1.68–1.80 (m, 2H), 2.81–2.95 (m, 2H), 3.84–3.96 (m, 1H), 4.08–4.20 (m, 2H), 6.91–6.94 (m, 2H), 7.21–7.24 (m, 2H), 7.36–7.52 (m, 4H), 7.86 (d, J = 9.00 Hz, 2H), 8.53 (s, 1H), 8.99 (d, J = 8.50 Hz, 2H), 10.81 (s, 1H); ^{13}C NMR (125 MHz, DMSO) δ 31.3 (2C), 43.4 (2C), 47.5, 120.0 (2C), 122.0, 122.4 (2C), 128.6, 128.7 (2C), 129.1 (2C), 137.1, 141.1, 155.2, 159.2, 159.5; HRMS (ESI), *m/z* calcd for $C_{20}H_{22}ClN_4O_3$ (MH^+) 401.1375, found 401.1372.

4.1.6. N^1-(1-Benzoylpiperidin-4-yl)-N^2-(4-chlorophenyl) oxalamide (8)

To a stirred solution of **3** (500 mg, 1.78 mmol) in $CHCl_3$ (17.8 mL) was added benzoyl chloride (307 µL, 2.67 mmol) and the mixture was stirred at room temperature for 1 h. The precipitate was collected and washed with cold EtOAc, and dried under reduced pressure to provide the title compound **8** (232 mg, 34% yield).

^1H NMR (500 MHz, $CDCl_3$) δ 1.21–1.68 (br, 4H), 1.96–2.08 (br, 2H), 3.02–3.16 (br, 2H), 4.04–4.07 (m, 1H), 7.35 (d, J = 9.00 Hz, 2H), 7.41–7.43 (m, 5H), 7.52 (d, J = 8.00 Hz, 1H), 7.59 (d, J = 9.00 Hz, 2H), 9.25 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.4 (2C), 41.0 (2C), 47.6, 121.0 (2C), 126.9 (2C), 128.6 (2C), 129.3 (2C), 129.9, 130.6, 134.8, 135.6, 157.2, 159.0, 170.5; HRMS (ESI), *m/z* calcd for $C_{20}H_{21}ClN_3O_3$ (MH^+) 386.1266, found 386.1276.

4.1.7. Amine (10)

To a stirred solution of 2,2,6,6-tetramethylpiperidin-4-one (7.75 g, 50.0 mmol) and cyclohexanone (15.5 mL, 150 mmol) in DMSO (71.0 mL) was added NH_4Cl (16.1 g, 300 mmol) and stirred at 60 °C for 5 h. The reaction mixture was diluted with H_2O

(150 mL), acidified with 7% aq HCl, and extracted with Et_2O (200 mL × 3). The water layer was adjusted to pH 9 using 10% aq K_2CO_3 and then back-extracted with EtOAc. The extract was washed with brine and dried over Na_2SO_4. After concentration under reduced pressure, the residue was dissolve in MeOH (60.0 mL) and benzylamine (10.9 mL, 100 mmol) was added. After being stirred at room temperature for 1 h, sodium cyanoborohydride was added and stirred at room temperature for 6 h. The reaction mixture was poured into saturated $NaHCO_3$ and extracted with EtOAc, then dried over $MgSO_4$. After concentration under reduced pressure, the residue was dissolve in MeOH (150 mL) and 10% Pd/C (5.32 g, 5.00 mmol) was added and stirred at room temperature for 24 h under hydrogen atmosphere. After the reaction mixture was filtered through celite, the filtrate solution was concentrated under reduced pressure followed by flash chromatography over silica gel with EtOAc–EtOH (4:1) to gave the title compound **10** (820 mg, 7 % yield) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.730 (t, J = 12.0 Hz, 2H), 1.15–1.85 (m, 23H), 2.01–3.7 (m, 2H), 2.95–3.05 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.2 (2C), 22.8 (2C), 26.2 (2C), 37.3 (2C), 42.3 (2C), 43.6 (2C), 47.0, 53.2 (2C); HRMS (ESI), m/z calcd for $C_{15}H_{29}N_2$ (MH^+) 237.2325, found 237.2321.

4.1.8. N^1-(4-Chlorophenyl)-N^2-(2,6-dicyclohexylpiperidin-4-yl) oxalamide (11)

To a solution of **10** (722 mg, 3.05 mmol) in EtOH (15.0 mL) was added ethyl 2-((4-chlorophenyl)amino)-2-oxoacetate (363 mg, 1.50 mmol) and triethylamine (0.415 mL, 3.00 mmol) and stirred for 3 h at 150 °C under microwave irradiation. The mixture was filtered and the precipitate was collected and washed with cold EtOH, and dried under reduced pressure to provide the compound **11** (108 mg, 17% yield) as white powder.

^{1}H NMR (500 MHz, DMSO) δ 1.12–1.91 (br, 24H), 4.02–4.07 (m, 1H), 7.42 (d, J = 9.00 Hz, 2H), 7.84 (d, J = 9.00 Hz, 2H), 8.76 (br, 1H), 9.25 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.1 (2C), 22.7 (2C), 26.0 (2C), 37.2 (2C), 42.5 (2C), 42.9 (2C), 43.6, 52.7 (2C), 120.9 (2C), 129.3 (2C), 130.4, 135.0, 157.6, 158.8; HRMS (ESI), m/z calcd for $C_{23}H_{33}ClN_3O_2$ (MH^+) 418.2256, found 418.2261.

4.1.9. N^1-(4-Chlorophenyl)-N^2-(4-fluorophenyl)oxalamide (14)

To a solution of the ethyl 2-((4-chlorophenyl)amino)-2-oxoacetate (1.21 g, 5.00 mmol) in EtOH (25.0 mL) were added Et_3N (1.38 mL, 10.0 mmol) and 4-fluoroaniline **12** (1.44 mL, 15.0 mmol). The reaction mixture was stirred for 3 h at 150 °C under microwave irradiation. After being cooled to room temperature, the crystal was collected and washed with cold EtOH and n-hexane, and dried under reduced pressure to provide the compound **14** (601 mg, 41% yield) as colorless crystals. Compounds **15** and **16** were similarly synthesized.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07–7.14 (m, 2H), 7.35–7.40 (m, 2H), 7.59–7.63 (m, 4H), 9.29 (s, 1H), 9.33 (s, 1H); ^{13}C NMR (125 MHz, DMSO) δ 115.8 (d, J = 22.5 Hz, 2C), 122.5 (2C), 122.8 (d, J = 7.5 Hz, 2C), 128.8, 129.1 (2C), 134.4, 137.1, 158.3, 158.9 (d, J = 42.5 Hz), 160.2; HRMS (ESI), m/z calcd for $C_{14}H_{11}ClFN_2O_2$ (MH^+) 293.0488, found 293.0485.

4.1.10. N^1-(4-Chlorophenyl)-N^2-(2-(pyridin-2-yl)ethyl) oxalamide (17)

To a solution of the ethyl 2-((4-chlorophenyl)amino)-2-oxoacetate (726.3 mg, 3.00 mmol) in EtOH (10.0 mL) were added Et_3N (0.831 mL, 6.00 mmol) and 2-(pyridin-2-yl)ethanamine 14 (1.07 mL, 9.00 mmol). The reaction mixture was stirred for 3 h at 150 °C under microwave irradiation. After being cooled to room temperature, the crystal was collected and washed with cold EtOH and n-hexane, and dried under reduced pressure to provide the title compound **17** (336 mg, 37% yield) as colorless crystals.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.08 (t, J = 6.50 Hz, 2H), 3.82 (q, J = 6.50 Hz, 2H), 7.12–7.21 (m, 2H), 7.30–7.37 (m, 2H),7.54–7.66 (m 3H), 8.40 (s, 1H), 8.60 (d, J = 5.00 Hz, 1H), 9.26 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.5, 39.0, 121.0 (2C), 121.8, 123.4, 129.2 (2C), 130.3, 135.1, 136.7, 149.5, 157.5, 158.6, 159.6; HRMS (ESI), m/z calcd for $C_{15}H_{15}ClN_3O_2$ (MH^+) 304.0847, found 304.0850.

4.2. Molecular modeling

The structures of compounds **11** and **12** were built in Sybyl and minimized with the MMFF94 force field and partial charges.[17] Dockings were then performed using FlexSIS through its SYBYL module, into the crystal structure of gp120 (PDB: 1RZJ).

4.3. FACS analysis

JR-FL (R5, Sub B) chronically infected PM1 cells were pre-incubated with 100 μM of a CD4 mimic for 15 min, and then incubated with an anti-HIV-1 mAb, 4C11, at 4 °C for 15 min. The cells were washed with PBS, and fluorescein isothiocyanate (FITC)-conjugated goat anti-human IgG antibody was used for antibody-staining. Flow cytometry data for the binding of 4C11 (green lines, Fig. 4) to the Env-expressing cell surface in the presence of a CD4 mimic are shown among gated PM1 cells along with a control antibody (anti-human CD19: black lines, Fig. 4). Data are representative of the results from a minimum of two independent experiments. The number at the bottom of each graph in Figure 4 shows the mean fluorescence intensity (MFI) of the antibody 4C11.

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Supplementary data

Supplementary data (NMR charts of compounds) associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2011.09.045.

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INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Open-Label Randomized Multicenter Selection Study of Once Daily Antiretroviral Treatment Regimen Comparing Ritonavir-Boosted Atazanavir to Efavirenz with Fixed-Dose Abacavir and Lamivudine

Miwako Honda[1], Michiyo Ishisaka[1], Naoki Ishizuka[2], Satoshi Kimura[3], Shinichi Oka[1] and behalf of Japanese Anti-HIV-1 QD Therapy Study Group

Abstract

Background The side-effects of anti-retroviral drugs are different between Japanese and Caucasian patients. Severe central nerve system (CNS) side-effects to efavirenz and low rate of hypersensitivity against abacavir characterize the Japanese.

Objective The objective of this study was to select a once daily regimen for further non-inferior study comparing the virological efficacy and safety of the first line once daily antiretroviral treatment regimens in the current HIV/AIDS guideline.

Methods The study design was a randomized, open label, multicenter, selection study. One arm was treated with efavirenz and the other with ritonavir-boosted atazanavir. A fixed-dose lamivudine plus abacavir were used in both arms. The primary endpoint was virologic success (viral load less than 50 copies/mL) rate at 48 weeks. Patients were followed-up to 96 weeks with safety as the secondary endpoint. Clinicaltrials.Gov (NCT 00280969) and the University hospital Medical Information Network (UMIN000000243).

Results A total of 71 participants were enrolled. Virologic success rates in both arms were similar at week 48 [efavirenz arm 28/36 (77.8%); atazanavir arm 27/35 (77.1%)], but were decreased at week 96 to 55.6% in the efavirenz arm and 68.8% in the atazanavir arm (p=0.33). At the 96-week follow-up, 52.8% of the EFV arm and 34.3% of the ATV/r arm reached total cholesterol more than 220 mg/dL and required treatment. None of the patients developed cardiovascular complications in this study by week 96.

Conclusion There was no significant difference in the efficacy of efavirenz and ritonavir-boosted atazanavir combined with lamivudine plus abacavir at 48 weeks. The evaluation of safety was extended to 96 weeks, which also showed no significant difference in both arms.

Key words: HIV, antiretroviral treatment, efavirenz, atazanavir, abacavir, lamivudine

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Introduction

The use of a non-nucleoside transcriptase inhibitor (NNRTI) or ritonavir-boosted protease inhibitor as the key drug, combined with two nucleoside reverse-transcriptase inhibitors (NRTI), as the backbone drugs, is recommended as an initial therapy in human immunodeficiency virus type 1 (HIV-1) infection. For the key drug, when efavirenz (EFV) or ritonavir-boosted atazanavir (ATV/r) is selected, once daily therapy is possible. EFV is a widely used NNRTI, however, in some clinical studies conducted in Asia, a higher rate of adverse events, especially central nervous system-related symptoms, has been noted (1-3).

In terms of backbone drugs, didanosine (ddI), stavudine (d4T) and zidovudine (ZDV) were widely used NRTIs.

[1]AIDS Clinical Center, National Center for Global Health and Medicine, Japan, [2]Division of Preventive Medicine, Research Institute, National Center for Global Health and Medicine, Japan and [3]Tokyo Teishin Hospital, Japan
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Correspondence to Dr. Miwako Honda, honda-1@umin.ac.jp

However, their mitochondrial toxicity made long-term use difficult (4-7). Due to HLA-B*5701-related hypersensitivity, abacavir (ABC) is listed as the second line drug under the United States Department of Health and Human Services (DHHS) guidelines. However, HLA-B*5701 is quite rare among Japanese, and thus the incidence of hypersensitivity to ABC in Japanese patients is lower than that of Caucasians (8-10). Although tenofovir (TDF) is widely used as the first line drug, the dose-dependent nephrotoxicity is a major concern in Japanese because Japanese body weight is lighter than that of Caucasians (11, 12).

The present study was designed in 2006, when the combination of TDF, lamivudine (3TC) or entiricitabine (FTC), and EFV was the first line regimen of antiretroviral treatment (13). To explore the optimal antiretroviral combination for the best clinical outcome among Japanese HIV-1 patients (14), a selection study was designed to compare the efficacy and safety of once daily treatment with EFV or ATV/r combined with a fixed-dose ABC and 3TC (ABC/3 TC).

Objective

The objective of this study was to select a once daily regimen for further non-inferior study comparing the virological efficacy and safety of the first line once daily antiretroviral treatment regimens in the current HIV/AIDS guideline.

Subjects and Methods

Study design

The study was designed as a randomized, open label, multicenter selection study, which means the superior regimen at the end point is to be selected as alternate arm to compare with the current first line regimen in the next step. Therefore, this study was not to compare superiority or non-inferiority of both arms. As the selection study, the main objective is to select a treatment regimen for further pivotal study and the secondary objective is safety. The primary endpoint was the proportion of patients in each arm who achieved virologic success (HIV-1 RNA less than 50 copies/mL in plasma) at week 48. The secondary endpoints were death, AIDS and serious non-AIDS events, non-AIDS defining cancer, treatment-related serious or grade 3 to 4 adverse events, and discontinuation of antiretroviral treatment before week 96.

The inclusion criteria of this study were those who were treatment-naïve, HIV-1 positive Japanese men with a CD4+ count ranging from 100 to 300 cell/mm^3. The exclusion criteria included current active AIDS, acute retroviral syndrome and persistent active hepatitis B infection (HBs-Ag positive). Patients with a history of 3TC treatment for hepatitis B infection were also excluded. After obtaining informed consent, eligible participants were randomized into once daily 600 mg EFV or 100 mg RTV and 300 mg ATV (EFV arm vs ATV/r arm). All participants received a fixed dose of 600 mg of ABC and 300 mg 3TC (ABC/3TC).

At baseline, the demographic characteristics and a complete medical history were recorded, physical examination was performed, and various laboratory tests were obtained (CD4+ count, HIV-1 RNA, complete blood count, biochemistry, liver and renal function tests, and total cholesterol). Participants were examined at baseline, then every 4 weeks until week 96. Careful clinical examination was provided at each visit, including history taking of any adverse event, adherence to treatment, and physical examination. Furthermore, blood tests were obtained including complete blood count, biochemistry, liver and renal function tests, CD4+ count and HIV-1 RNA. When HIV-1 RNA became less than 50 copies/mL, participants were rescheduled to be seen every 4 to 12 weeks. All participants underwent clinical examination at week 48 as the primary endpoint, then every 12 weeks until week 96 as the secondary follow-up period for evaluation of safety.

The study recruitment period was started on September 1st of 2005 for 2 years. The study protocol was originally designed to follow patients for 48 weeks, however, during the study period, cardiovascular adverse events of ABC-containing regimen were reported (15, 16). Considering the importance of adherence to safety, the follow-up period was extended to 96 weeks.

Independent data and safety monitoring board reviewed virology and safety data by treatment allocation were obtained when all participants had completed 24 weeks of the study. A total of 18 academic medical institutions in Japan participated in this study. The study protocol was approved by the ethics committee of each site and was registered at Clinicaltrials. Gov (NCT00280969) and the University Hospital Medical Information Network (UMIN000000243).

Statistical analyses

The estimated proportion of virologic failure, representing HIV-1 RNA of more than 50 copies/mL at 48 weeks of treatment, was 30% over one year. To choose one treatment group with a probability of 0.90, if it is superior to another treatment by >10%, if any, a sample size of 40 participants per group was necessary according to the selection design (17).

To assess differences in proportions, we used Fisher's exact test and calculated exact confidence intervals (CIs). We conducted intent-to-treat analysis and used the T test to compare the efavirenz arm and the ritonavir boosted atazanavir arm, unless the data showed skewed distribution, in which case the Wilcoxon's test was used. All analyses used a two-sided alfa of 0.05. No adjustment for each test was made for multiple comparisons due to the fact that we have several tests to compare the efficacies and safeties of two groups. All analyses, unless otherwise specified, were determined a priori and were hypothesis driven. Statistical analyses were performed using SAS version 9.1.

Table 1. **Baseline Characteristics of Participants**

Variable	efavirenz	atazanavir/r	p
Number of patients	36	35	NS
Age (yrs) median	35	36	NS
HIV-RNA (log_{10} copies/mL)			
median	4.6	4.4	NS
range	2.8–5.4	3.0–5.3	
CD4 count (cells/mm^3)			
median	220	226	NS
range	121–323	103–324	
Total Cholesterol (mg/dL)			
median	155.5	159.5	NS
range	122–208	112–215	
Total bilirubin (mg/dL)			
median	0.6	0.5	NS
range	0.3–1.7	0.3–1.5	
ALT (IU/L)			
median	24	20	NS
range	8–71	8–78	
Creatinine (mg/dL)			
median	0.80	0.75	NS
range	0.6–1.03	0.6–1.02	

Results

Participants

In the study recruitment period, 71 participants were randomly assigned to two groups (36 in EFV arm and 35 in ATV/r arm). The baseline characteristics of the subjects are listed in Table 1. Among the 71 participants, 62 (87.3%) for the primary endpoint and 58 (80.6%) for the secondary endpoint completed the study protocol. By week 96, 9 participants had withdrawn due to clinical events, 2 declined to continue the study for personal reasons, one died by accident and 3 were transferred to other non-participating institutions.

Primary endpoint

At week 48, by intent-to-treat, missing-equals-failure analysis, 28 of 36 participants (77.8%, 95% CI: 60.9-89.9) in the EFV arm and 27 of 35 (77.1%, 95% CI: 59.9-89.9) in the ATV/r arm achieved the goal of HIV-1 RNA less than 50 copies/mL. There was no significant difference between the two arms (p=0.95).

Virologic success over time

Figure 1 shows the intent-to-treat analysis of participants who reached virologic success. At week 96, the rates of virologic success in the EFV arm were 55.6% (20 of 36) and 68.6% (24 of 35) in the ATV/r arm (p=0.33). The number of participants with a baseline HIV-1 RNA level of more than 100,000 copies/mL was 5 in the EFV arm and 2 in the ATV/r arm. One participant in each arm withdrew from the study at week 4 due to skin rash. The rest of the participants achieved virologic success in the EFV arm (4 out of 4) and in ATV/r arm (1 out of 1).

Secondary endpoints

In the EFV arm, 7 of 36 participants did not complete the study; 5 of the 7 developed psychiatric symptoms, including suicidal idealization, insomnia and irritation, 2 developed skin rashes and the remaining 2 were lost to follow-up because they were transferred to non-affiliated hospitals. In the ATV/r arm, 6 of 35 patients could not complete the study; one died by accident for unknown reason (the cause of death according to the coroner's report was not related to the cardiovascular system), 2 participants required treatment change (this was due to suicidal idealization in one and to skin rash in the other), one participant withdrew by own wish, one enrolled into another study, and one was transferred to another non-affiliated medical care facility.

Figure 2 shows the change of total cholesterol, liver function and total bilirubin from the baseline. At enrollment in the study, the median total cholesterol in the EFV arm was 155.5 mg/dL (range: 122-208) and in the ATV/r arm was 159.5 mg/dL (range: 112-215). The total cholesterol was not more than 220 mg/dL in any of the participants of both arms at baseline, and there was no significant difference between the two arms. During the study period, the total cholesterol increased to more than 220 mg/dL and required treatment with hypolipidemic agents in 52.8% of the EFV arm and 34.3% of the ATV/r arm. There was a significant increase in total cholesterol from the baseline in both arms ($p < 0.05$). There was no significant change in liver function tests during the study. New onset grade 3 hyperbilirubinemia was noted in 27 of 35 (77.1%) of the ATV/r arm but in none of the EFV arm. None of the hyperbilirubinemia in the ATV/r arm was associated with altered liver function, altered renal function, nephrolithiasis, or cholelithiasis.

Discussion

This study was designed as selection study, which means the superior regimen at the endpoint is to be selected as an alternate arm to compare with the current first line treatment in the next step. By definition of the selection study, the superior arm does not require statistical significance (17). At week 48, 77.8% of ATV/r arm and 77.1% of EFV arm reached HIV-VL of less than 50 copies/mL. Based on the definition of the selection study, the combination ABC/3TC/EFV was selected to compare the current first line treatment while the efficacy of each arm was almost even in this study.

In this clinical trial of 71 participants over a period of 96 weeks, no cardiovascular events or severe hypersensitivity reaction against ABC was observed. In this study, the efficacy of EFV combined with ABC/3TC and ATV/r combined with ABC/3TC was similar. Therefore, ABC based regimen can be selected as a safe combination to compare the efficacy of the first line combinations, such as EFV plus TDF/FTC or ATV/r plus TDF/FTC (18-20), in the next step for the best clinical benefits in Japanese patients.

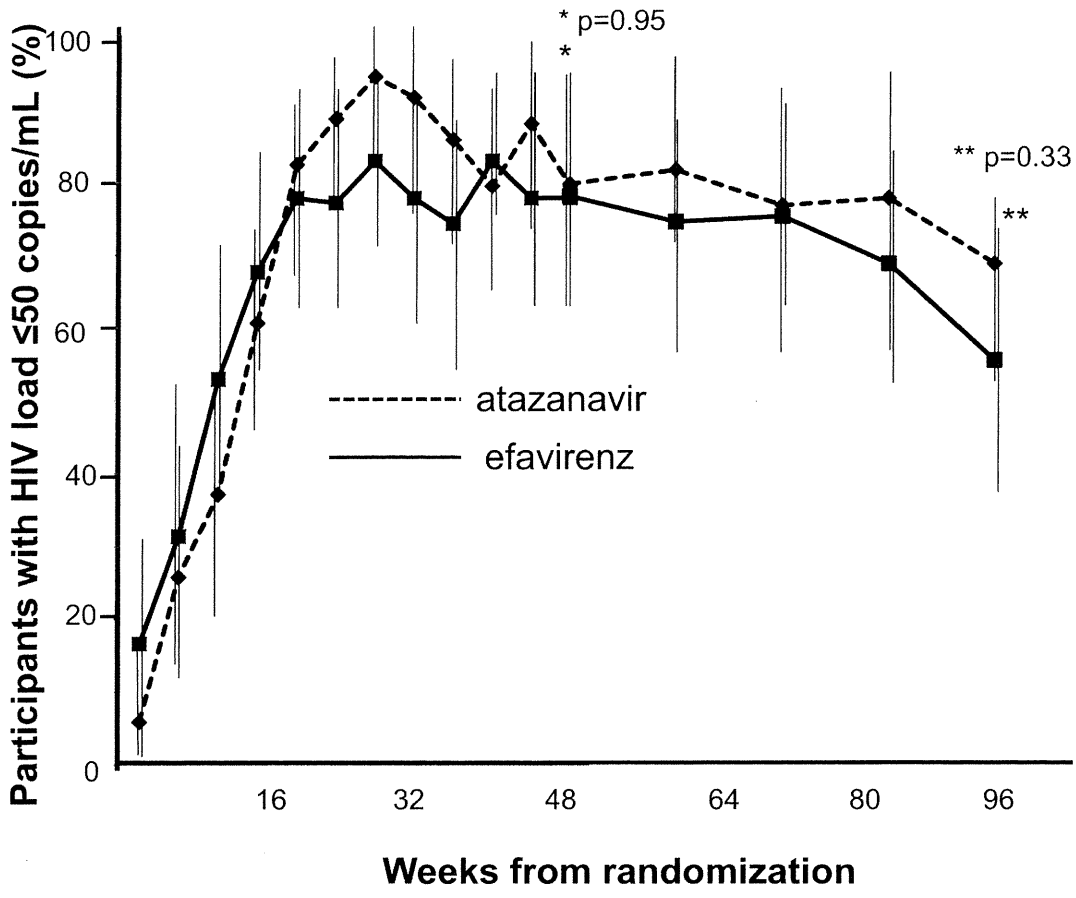

Figure 1. **Proportions of participants with HIV-RNA less than 50 copies/mL.**
The efficacies of the efavirenz arm and ritonavir-boosted atazanavir arm were compared with intent-to-treat analysis. There were no significant difference between arms at both week 48 (p=0.95) and week 96 (p=0.33).

In February 2008, the United States National Institution of Allergy and Infectious Disease announced that the data and safety monitoring board of ACTG 5202 recommended a modification of the study design because they found that among participants with high viral loads (100,000 or more copies/mL) at the time of screening, treatment combinations that included ABC/3TC were not as effective in controlling the virus as those of regimens containing TDF/FTC (19, 21). At that point, all of the present 71 participants were already enrolled in the study and the baseline HIV-1 RNA of 7 participants was more than 100,000 copies/mL. Of these 7 participants, 2 had already withdrawn from the study by week 4, and the rest of participants had reached HIV-1 RNA of less than 50 copies/mL. The safety monitor board made no recommendation to amend the protocol.

As a primary endpoint, 77.8% of the EFV arm and 77.1% of the ATV/r had reached virological success, however, total cholesterol in 58.1% of the EFV arm and 46.9% of the ATV/r arm increased to more than 220 mg/dL, which required treatment. Thus, the overall proportion of participants with good viral suppression and without severe adverse events or treatment modification was 39.6% for the EFV arm and 62.3% for the ATV/r arm. Considering the reasons for treatment modification, the neuro-psychiatric side effects required a regimen change in the EFV arm. Although several studies concluded that the neuro-psychiatric side effects are transient in nature, one study reported that treatment had to be changed in 16% of patients on EFV due to neuro-psychiatric side effects (22-24). Although there was no significant difference even with the small sample size, 5 out of 36 (13.9%) participants on EFV in our study required treatment change, compared with only 1 out of 35 (2.9%) of the ATV/r arm. This aspect of our study was similar to that reported in the Euro SIDA study (24). In the Swiss Cohort study, the treatment-limiting CNS adverse events was 3.8 (95% CI 2.7-5.2) per 100 person-years and it was clearly related to EFV (25). Considered together, these results emphasize the need for close observation of patients treated with EFV.

The incidence of hyperbilirubinemia in the present study was 77.1% in the ATV/r arm but none of these patients was above grade 4. Furthermore, none of the patients in this study developed liver function abnormality, altered renal function, renal stones, or cholelithiasis. As reported by Torti et al and Josephson et al, such clinical outcome can be used as a marker of adherence to ATV therapy (26, 27).

Limitations of this study include a small sample size.

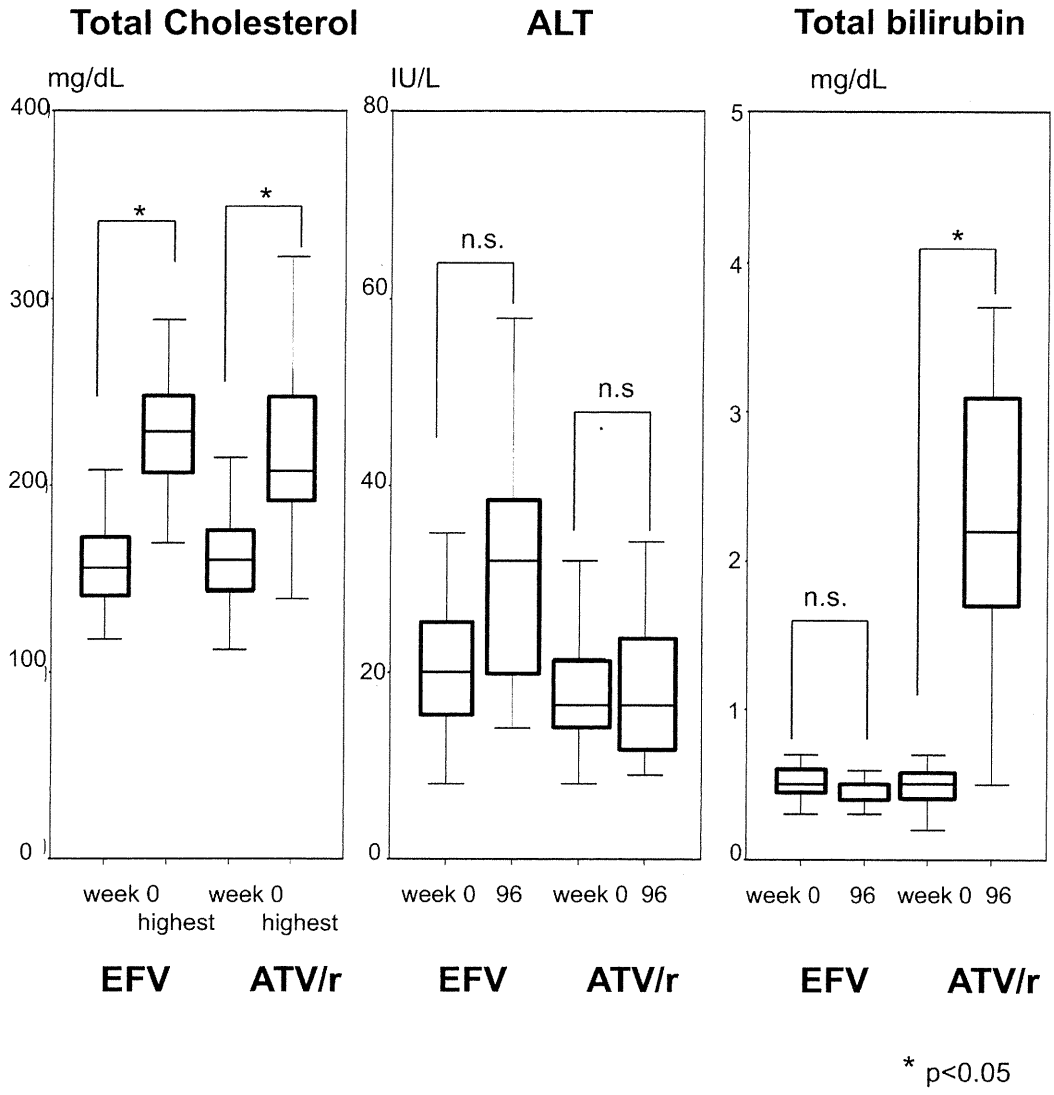

Figure 2. **Changes from baseline in total cholesterol, ALT and total bilirubin.**
ALT and total cholesterol at week 96 were compared with the baseline values. Since participants who developed hyperlipidemia were treated with lipid-lowering agents during the study period, the highest levels registered in each participant during the follow-up were collected for analysis. There were no significant differences in total cholesterol and ALT between the two arms, while hyperbilirubinemia was significantly higher in the ATV/r arm. Modification of treatment due to hyperbilirubinemia was not required in any of the patients of the ATV/r arm. In these box-and-whisker plots, the lines within the boxes represent median values; the upper and lower lines of the boxes represent the 25th and 75th percentiles, respectively; and the upper and lower bars outside the boxes represent the 90th and 10th percentiles, respectively.

Considering many studies on HIV treatment held in western countries that enrolled few Asian HIV-1 patients, it is important to collect data from Asian population. The current United States Department of Health and Human Services guidelines recommend TDF/FTC as the first line regimen, while the European AIDS Clinical Society recommends 3TC and ABC addition to TDF and FTC alone (28, 29). TDF/FTC is a known potent antiretroviral agent, however, its long-term efficacy and safety remain unclear (11, 12). Considering that the combinations of NRTI are limited, the efficacy and safety of ABC in the low HLA-B*5701 population need to be evaluated for wider treatment options for HIV-1 patients (9, 10).

Conclusion

This study was designed as a selection study to compare the virologic efficacy and treatment safety of EFV and ATV/r, both with ABC/3TC, in Japanese patients. The results showed no significant differences in efficacy between the two regimens at week 48. The evaluation of safety was extended to 96 weeks, which also showed no significant difference in both arms. The results of the present study have already been applied as the basis of a follow-up study that is

currently being conducted in Japan to compare NRTI combinations of ABC/3TC and TDF/FTC with ATV/r as key drugs.

The authors state that they have no Conflict of Interest (COI).

Members of the Japanese Anti-HIV-1 QD Therapy Study Group: Koji Watanabe[1], Tamayo Watanabe[1], Yasuhisa Abe[1], Ikumi Genka[1], Haruhito Honda[1], Hirohisa Yazaki[1], Junko Tanuma[1], Kunihisa Tsukada[1], Hiroyuki Gatanaga[1], Katsuji Teruya[1], Yoshimi Kikuchi[1], Misao Takano[1], Mikiko Ogata[1], Mizue Saida[2], Toshio Naito[2], Yoshiyuki Yokomaku[3], Motohiro Hamaguchi[3], Keiko Ido[4], Kiyonori Takada[4], Toshikazu Miyagawa[5], Shuzo Matsushita[5], Takeyuki Sato[6], Masaki Yoshida[7] Takafumi Tezuka[8], Yoshiya Tanabe[8], Isao Sato[9], Toshihiro Ito[9], Masahide Horiba[10], Mieko Yamada[11], Mikio Ueda[11], Kazufumi Matsumoto[12], Takeshi Fujii[12], Mariko Sano[13], Shin Kawai[13], Munehiro Yoshino[14], Takuma Shirasaka[14], Satoshi Higasa[15], Tomoyuki Endo[16], Norihiro Sato[16], Katsuya Fujimoto[16], Rumi Minami[17], Masahiro Yamamoto[17], Yukiko Nakajima[18]

[1]National Center for Global Health and Medicine, [2]Juntendo University, [3]National Hospital Organization, Nagoya Medical Center, [4]Ehime University, [5]Kumamoto University, [6]Chiba University, [7]The Jikei University, [8]Niigata University, [9]National Hospital Organization, Sendai Medical Center [10]East Saitama National Hospital, [11]Ishikawa Prefectural Hospital, [12]Institute of Medical Science, The University of Tokyo, [13]Kyorin University, [14]National Hospital Organization, Osaka Medical Center, [15]Hyogo College of Medicine, [16]Hokkaido University, [17]National Hospital Organization, Kyushu Medical Center, [18]Kawasaki City Hospital

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