Table 4 Overall response in the per-protocol set (PPS) excluding patients deemed to be "unable to be judged"[a] from the PPS population

	Caspofungin		Micafungin	
Number of patients in PPS	44		41	
Number of patients determined as "unable to be judged" for overall response	5		1	
Number of patients analyzed for overall response	39		40	
Overall response	Favorable response rate, % (n/m)[b]	(95 % CI)	Favorable response rate, % (n/m)[b]	(95 % CI)
Esophageal candidiasis	100.0 (6/6)	(54.1, 100.0)	83.3 (5/6)	(35.9, 99.6)
Invasive candidiasis	100.0 (3/3)	(29.2, 100.0)	100.0 (1/1)	(2.5, 100.0)
Chronic pulmonary aspergillosis including aspergilloma	46.7 (14/30)	(28.3, 65.7)	42.4 (14/33)	(25.5, 60.8)

CI confidence interval

[a]Patients who were determined as "unable to be judged" were excluded from the PPS analysis for overall response

[b]*n/m* number of patients with favorable overall response/number of patients analyzed

45.0 % (9/20) and 46.7 % (14/30), respectively. The overall response of caspofungin in aspergilloma patients was 50.0 % (5/10), and there were no aspergilloma patients in the micafungin group. In general, the favorable overall responses were similar across the two treatment groups for each disease. Since the efficacy evaluation was independently assessed from an event of death, a listing of patients in the PPS population who died during the study period is shown in Table 5. Three of the four patients in the caspofungin group and one of four patients in the micafungin group died due to the worsening of primary infection (chronic pulmonary aspergillosis in all cases). Three patients deemed to be "unable to be judged" were not included in the calculation of the favorable overall response rate (two patients in the caspofungin group and one patient in the micafungin group).

Additionally, in the FAS population, the favorable overall response rates in the caspofungin group and the micafungin group were 77.8 % (7/9) and 85.7 % (6/7) for patients with esophageal candidiasis, 33.3 % (3/9) and 11.1 % (1/9) for patients with invasive candidiasis, 45.5 % (15/33) and 37.8 % (14/37) for patients with chronic pulmonary aspergillosis including aspergilloma, respectively. The results were generally comparable between the treatment groups, such as those seen in the PPS population.

Duration of therapy and relationships with overall response in aspergillosis patients

Among patients with aspergillosis in the PPS population, an exploratory assessment was performed to compare the number of days on study therapy between the treatment groups

Table 5 Listing of patients who died in the PPS population

Treatment group	Disease	Study therapy duration	Overall response (by the IEAC)	Date of death (relative day after study therapy completion)	Cause of death (by primary investigators)
Caspofungin	Chronic pulmonary aspergillosis	11 days	Unable to judge (due to severe co-infection of bacteria)	Day 1	(Worsening of) chronic pulmonary aspergillosis
	Chronic pulmonary aspergillosis	84 days	Unfavorable	Day 11	(Worsening of) chronic pulmonary aspergillosis
	Chronic pulmonary aspergillosis	84 days	Unable to judge (due to repeated co-infection of bacteria)	Day 12	(Worsening of) chronic pulmonary aspergillosis
	Candidemia	15 days	Favorable	Day 11	(Worsening of) peritoneal mesothelioma
Micafungin	Chronic pulmonary aspergillosis	8 days	Unable to judge (due to inconsistent imaging data)	Day 2	(Worsening of) lung cancer
	Chronic pulmonary aspergillosis	20 days	Unfavorable	Day 7	(Worsening of) chronic pulmonary aspergillosis
	Chronic pulmonary aspergillosis	8 days	Unfavorable	Day 19	(Worsening of) COPD
	Chronic pulmonary aspergillosis	13 days	Unfavorable	Day 8	Death (unknown cause of death)

and by treatment outcome. The mean number (range) of days on study therapy among patients with a favorable response was 36.1 (8 to 84) days for the caspofungin 70/50 mg group (n=14) and 61.5 (22 to 84) days for the micafungin group (n=14). The mean treatment duration was shorter among patients with a favorable response in the caspofungin 70/50 mg group than in the micafungin group. On the other hand, the mean number (range) of days on study therapy among patients with an unfavorable response with aspergillosis was 39.3 (14 to 84) days for the caspofungin 70/50 mg group (n=16) and 35.6 (7 to 84) days for the micafungin group (n=19). The treatment duration was generally comparable between the groups in patients with unfavorable responses.

Susceptibility of fungal isolates to caspofungin

The geometric mean (range) of the caspofungin minimum inhibitory concentration (MIC) of clinical isolates of *Candida* spp. detected at screening (baseline isolates) was 0.25 (0.06–0.5) μg/mL and 0.5 μg/mL for *C. albicans* (19 strains) and *C. glabrata* (one strain), respectively. The geometric mean (range) of the caspofungin minimum effective concentration (MEC) of clinical isolates of *Aspergillus* spp. detected at screening was 0.25 (0.12–0.5) μg/mL, 0.25 (0.25) μg/mL, 0.25 (0.12–0.5) μg/mL, and 0.12 μg/mL for *A. fumigatus* (nine strains), *A. niger* (three strains), *A. flavus* (two strains), and *Aspergillus* spp. (one strain), respectively.

Discussion

This study is a prospective, randomized, double-blind study to evaluate the efficacy and safety of caspofungin versus micafungin in Japanese patients with *Aspergillus* or *Candida* infections. The caspofungin doses investigated in this study were the same as the approved clinical doses outside of Japan. Although the approved standard dose of micafungin for aspergillosis and candidiasis is 50–150 mg once daily and 50 mg once daily, respectively, and the dose can be increased up to 300 mg once daily in Japan, the average daily micafungin dose which has been actually used in a clinical setting is reported to be 110 mg [14]. In addition, in the Japanese "Diagnosis and Treatment Guideline for Deep-Seated Fungal Infections", micafungin doses of 100 to 150 mg daily and 150 to 300 mg daily are recommended for the treatment of candidiasis and aspergillosis, respectively [15]. Based on these data, a micafungin dose of 150 mg daily was determined to be an appropriate comparison to caspofungin (50 mg or 70/50 mg once daily).

Several efficacy findings deserve further attention. The efficacy results from the patients who were in the PPS excluding "unable to be judged" patients (n=79) suggest that the efficacy of caspofungin 50 mg or 70/50 mg once daily was almost comparable to that of micafungin 150 mg once daily. However, it should be noted that two patients in the PPS population receiving caspofungin died due to worsening of the primary disease of chronic pulmonary aspergillosis after 1 and 12 days following the completion of study therapy, respectively, and were assessed as "unable to be judged" by the IEAC because both patients also had bacterial infection and the efficacy of caspofungin could not be evaluated based on their clinical symptoms. Since the ultimate cause of death was the worsening of primary disease, these two patients were highly likely not to respond to caspofungin, and, consequently, the efficacy of caspofungin might be slightly lower in this study. All *Candida* spp. isolates detected at screening in this study showed caspofungin MIC below the current CLSI clinical breakpoint (2 μg/mL) and were deemed to be susceptible. No CLSI clinical breakpoint for *Aspergillus* spp. has been established; however, the MEC values were similar to the data reported to date [16]. Therefore, *Candida* spp. and *Aspergillus* spp. in Japan appear to be susceptible to caspofungin.

Both caspofungin and micafungin demonstrated favorable treatment efficacy against *Candida* infections. This result is similar to that in the fluconazole-controlled comparative studies of caspofungin and micafungin in patients with esophageal candidiasis [3, 17] and to that in the direct comparative study between caspofungin and micafungin in patients with invasive candidiasis [7].

On the other hand, the favorable response rate was slightly below 50 % in aspergillosis. In this study, no patients in the primary efficacy analysis group were confirmed by the IEAC to have invasive aspergillosis, and, thus, all patients who were categorized into the aspergillosis population had subacute to chronic stage of aspergillosis. As for the study evaluating the efficacy against chronic pulmonary aspergillosis, a study has been conducted comparing micafungin with voriconazole. In this study, the favorable overall response rates at the completion of study therapy with micafungin (average dose 167.4 mg/day) or voriconazole (6 mg/kg twice daily on Day 1, followed by 4 mg/kg twice daily on Day 2 onwards) were 60.0 % and 53.2 %, respectively [18]. Although a direct comparative assessment is difficult due to the different enrollment and efficacy evaluation criteria, based on this previous report and the results from the current study (favorable overall response rate of 46.7 % in the caspofungin group and 42.4 % in the micafungin group), it can be considered that both agents are effective to some extent against chronic pulmonary aspergillosis. Additionally, among the chronic pulmonary aspergillosis patients who showed favorable efficacy response, we found that the duration of therapy in the caspofungin group was numerically shorter than that in the micafungin group. Since the number of patients was very limited (n=14 in each group) and any adjustment based on the

medical history or concomitant diseases including risk factors for fungal infection was not considered, it is difficult to conclude that the difference in periods show antifungal responses. However, it might be interesting to investigate the difference of echinocandins, and, thus, further investigation in the patients with more controlled status is needed.

Taken together, the overall efficacy results seem consistent to those of other previous reports, although there is a limitation to comparing the efficacy to each candidiasis and aspergillosis between caspofungin and micafungin due to the small number of patients in each subset of infection.

Amongst the proportion of patients with significant drug-related adverse events, the primary endpoint of this study was 5.0 % in the caspofungin group and 10.0 % in the micafungin group. The 95 % CI for the treatment difference in the incidence was −15.9 % to 5.2 %, thereby, showing no significant difference. Furthermore, no apparent difference between the treatment groups was observed in the incidence of specific adverse events or drug-related adverse events. In addition, relatively common drug-related adverse event categories were similar to those previously reported in association with caspofungin [3–5]. Drug-related adverse events relating to liver function enzymes have been commonly reported in association with echinocandins. Since these events were also frequently reported compared to other drug-related adverse events in this study, these events were further assessed. When maximal levels of AST, ALT, and ALP were graded in accordance with CTCAE Version 3 criteria, all abnormal changes observed in the caspofungin group were Grade 2 (>2.5–5 × ULN), but some patients in the micafungin group had Grade 3 levels (>5.0–20.0 × ULN). Since multiple types of drugs were concomitantly used with the study therapy in this trial, a discussion of the drug association with elevation of these enzymes is difficult to make. However, the monitoring of liver function enzymes is generally recommended for patients receiving echinocandins.

Conclusion

In Japanese patients with *Aspergillus* or *Candida* infections, the safety of the treatment with caspofungin 50 mg or 70/50 mg once daily was similar to that of micafungin 150 mg daily. Consistent to other data on these two agents, caspofungin treatment showed similar efficacy to micafungin.

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Conflict of interest Shigeru Kohno received honorarium, consultation fee, and research grant from both Astellas Pharma, Inc. and MSD K.K. Koichi Izumikawa received honorarium from both Astellas Pharma, Inc. and MSD K.K. Yoshihito Niki received honorarium, consultation fee, and research grant from both Astellas Pharma, Inc. and MSD K.K. Shinichi Oka received a research grant from MSD K.K. Minoru Yoshida, Yoshio Takesue, Katsuhiko Kamei, and Yoshitsugu Miyazaki received per diem stipends from MSD K.K. for attending the committee meeting. Tomoko Yoshinari is an employee of MSD K.K., a group of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ, USA, and Nicholas Kartsonis is an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ, USA.

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INTERNAL MEDICINE

□ CASE REPORT □

Infectious Endocarditis Caused by *Lactobacillus acidophilus* in a Patient with Mistreated Dental Caries

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Abstract

We present a rare case of infectious endocarditis caused by *Lactobacillus acidophilus* in a patient on long-term steroid use for autoimmune hepatitis. *In vitro* susceptibility-guided antibiotics with benzylpenicillin plus clindamycin and successive mitral annuloplasty resulted in a favorable outcome. Infectious endocarditis was suspected to be a complication of mistreated periodontal infection. Maintenance of oral hygiene is important in immunocompromised patients.

Key words: infectious endocarditis, lactobacillus species, immunocompromised, dental infection

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Introduction

Lactobacilli are commensal bacteria in the human oral cavity, gastrointestinal tract, and female genital tract. Lactobacilli are widely used in food and as probiotics, and are effective in the treatment of infantile and adult diarrhea and antibiotic-associated diarrhea (1, 2). However, rare cases of lactobacilli-induced bacteremia, meningitis, or endocarditis have been reported particularly in immunocompromised patients (3, 4). Here we report a case of infectious endocarditis caused by *Lactobacillus acidophilus* in a patient with autoimmune hepatitis.

Case Report

A 28-year-old female of East Asian origin was hospitalized in our clinic with a 3-month history of fever and pain in the right foot. She had a history of autoimmune hepatitis and had been taking prednisolone (2.5 mg/day) for more than one year. She had also been treated for dental caries, but she stopped seeing the dentist six months before admission. There was no history of cardiac disease, intravenous drug use or intake of probiotics. Since the appearance of fever, the patient was treated with levofloxacin (500 mg/day).

On admission, the patient was alert and oriented. The body temperature was 38.3℃. Physical examination showed a painful nodule in the 5th toe of the right foot. Oral examination showed multiple caries. Cardiac auscultation revealed grade 3/6 systolic murmur loudest over the apex, which was not evident during hospitalization 3 years earlier. Blood test showed leukocytosis (8,910/μL, neutrophil 87.4 %), microcytic anemia with hemoglobin of 9.9 g/dL, thrombocytopenia (platelet count: 102,000/μL), and elevated C reactive protein of 3.91 mg/dL. Liver function was relatively maintained with serum albumin 3.9 g/dL, total bilirubin 1.1 mg/dL, and prothrombin activity 75.1%. Liver transaminase and lactate dehydrogenase were within the normal ranges. Rheumatoid factor was positive, and anti-phospholipid antibody, anti-nucleus antibody, and anti-neutrophil cytoplasmic antibody were negative. Erythrocyte segmentation rate was 51 mm/hr.

Computed tomography of the abdomen showed a hypodense, wedge-shaped splenic lesion, suggestive of splenic infarction. There were heterogeneous hypoattenuating areas in the liver, but no ascites. Whole-body fluorodeoxyglucose positron emission tomography revealed high uptake in the 5th toe of the right foot, but no uptake in the splenic infarct

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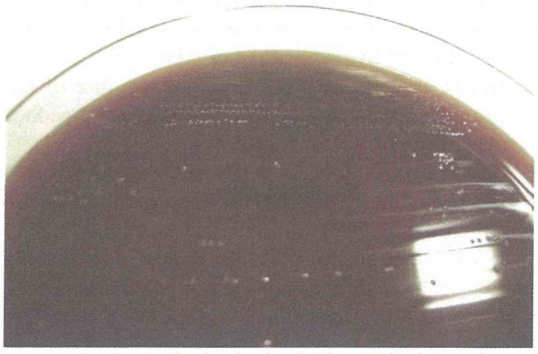

Figure 1. ***Lactobacillus acidophilus*** **cultured on ABHK agar.**

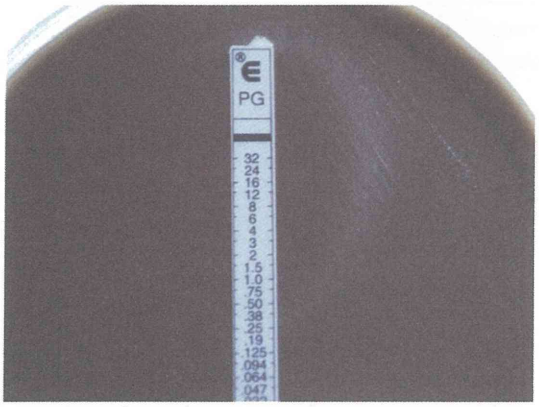

Figure 2. **Susceptibility testing of benzylpenicillin with Etest for** ***Lactobacillus acidophilus*****.**

area. Transesophageal echocardiography showed mitral prolapse with third-degree mitral regurgitation but no valvular vegetation was found. Dental consultation indicated multiple apical periodontitis and dental treatment was commenced.

All four culture bottles of two sets of blood samples drawn the day before admission showed Gram positive rods (GPR) on day 3. The patient was treated with intravenous antibiotics (meropenem 2 g plus clindamycin 2,400 mg). Another set of four culture bottles of two blood samples taken on day 3 also revealed GPR. *L. acidophilus* was identified on day 8, and the isolate was susceptible to benzylpenicillin (minimum inhibitory concentration [MIC] 0.12 μg/mL), ampicillin (MIC 0.25 μg/mL), imipenem (MIC ≤ 0.25 μg/mL) and clindamycin (MIC ≤0.12 μg/mL) (Fig. 1). MIC was measured with Etest® for penicillin according to the Clinical and Laboratory Standards Institute guidelines, and others with the microbroth dilution method [(5); Fig. 2]. On day 9, the antibiotics were replaced with benzylpenicillin (24 million units) plus clindamycin (2,400 mg). The final diagnosis was infectious endocarditis caused by *L. acidophilus* with Osler's node in the right foot and splenic infarction.

One anaerobic culture bottle of two sets of blood samples taken on day 6 revealed *L. acidophilus*, but no growth was observed in blood cultures prepared on day 14 and thereafter. Computed tomography on day 32 confirmed the disappearance of the nodule in 5th toe of the right foot. She was discharged on day 42 after 6 weeks of intravenous antibiotics treatment, and continued to take clindamycin 1,800 mg orally for 6 more weeks. Mitral annuloplasty was performed one year later, and no relapse has been observed for 2 years.

Discussion

We reported a rare case of infectious endocarditis caused by *L. acidophilus* in a patient on long-term steroid use for autoimmune hepatitis. To our knowledge, only 28 cases (3 cases in Japan), including this case, of infectious endocarditis caused by lactobacilli have been reported since 1992 after the publication of Duke's criteria (4, 6-9).

Endocarditis was diagnosed based on modified Duke's criteria (9). This patient fulfilled one major criterion: new valvular regurgitation, and four minor criteria: fever, major arterial embolus (splenic infarction), immunologic phenomenon (Osler's node in one toe), and microbiological evidence (positive blood culture).

Since the data for treatment and susceptibility of lactobacillus is scarce, there is no recommended empiric therapy (4). Salminen et al. indicated that the choice of antibiotics should depend on the susceptibility testing of lactobacilli, and that therapy guided by *in vitro* susceptibility tests significantly reduced mortality (10). Accordingly, we chose the combination therapy of intravenous benzylpenicillin plus clindamycin for 6 weeks and thereafter, clindamycin orally for 6 weeks. Mitral annuloplasty was conducted for severe mitral regurgitation, and no relapse was observed during the 2-year post-discharge period.

Maintenance of oral hygiene is important in immunocompromised patients in order to prevent systemic infection (11). Cannon et al. reported that dental procedures or oral diseases are the predisposing condition in almost half of the patients with lactobacillus-induced endocarditis (3). The present patient developed endocarditis caused by *L. acidophilus* after she discontinued dental treatment. Thus, dental infection was highly likely the predisposing factor for endocarditis.

In summary, we presented a case of infectious endocarditis caused by *L. acidophilus* in a patient with autoimmune hepatitis. Long-term use of *in vitro* susceptibility-guided antibiotics and mitral annuloplasty led to a favorable outcome. Maintenance of oral hygiene is important in immunocompromised patients.

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

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CASE REPORT

Chemotherapy for thymic carcinoma in an adult patient with HIV infection

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Abstract A 69-year-old man was referred to our hospital in June 2010 after the diagnosis of an anterior mediastinal tumor and HIV infection. Histopathological examination of a CT-guided needle biopsy specimen showed undifferentiated thymic carcinoma. Chest CT revealed pleural dissemination, bone invasion, and left lung metastases. The final diagnosis was Masaoka stage IVb. Surgery was considered inappropriate. Instead, the patient first underwent highly active antiretroviral therapy for HIV infection, followed by four courses of cisplatin, doxorubicin, vincristine, and cyclophosphamide chemotherapy for thymic carcinoma. A partial response was achieved. To our knowledge, this is the first report of thymic carcinoma in an adult patient with HIV infection.

Keywords Thymic carcinoma · ADOC chemotherapy · HIV infection · HAART · Cytochrome

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Introduction

Although the number of HIV-infected patients is increasing, the development of highly active antiretroviral therapy (HAART) has made it possible to control the disease. HIV infection has thus become a chronic disease, and the incidence of malignant tumors other than AIDS-defining malignancies has been increasing [1, 2].

Thymic epithelial tumors are reported to comprise approximately 25–46.1 % of all mediastinal tumors in adults and are classified as thymomas or thymic carcinomas [3, 4]. The incidence of thymic carcinoma is low, but this malignancy is associated with poor prognosis, with a 5-year survival rate of 35–50.5 % [3–5].

We report here a case of HIV infection complicated with thymic carcinoma. The patient was successfully treated with raltegravir (RAL)-containing HAART and cisplatin, doxorubicin, vincristine, and cyclophosphamide (ADOC) chemotherapy.

Case report

A 69-year-old man visited his local physician for cough and exertional dyspnea since April 2010, and was found to have an anterior mediastinal tumor on a chest radiograph. Subsequent follow-up and laboratory tests identified HIV infection in June 2010, and he was referred to our hospital for further management. In mid-July 2010, a CT-guided needle biopsy of the mediastinal tumor was performed due to pleural dissemination and infiltration of the left seventh rib. Histopathological examination of the biopsy material showed undifferentiated carcinoma of the thymus. In addition, diagnostic imaging showed pleural dissemination, bone invasion, and metastases in the left lung. The final

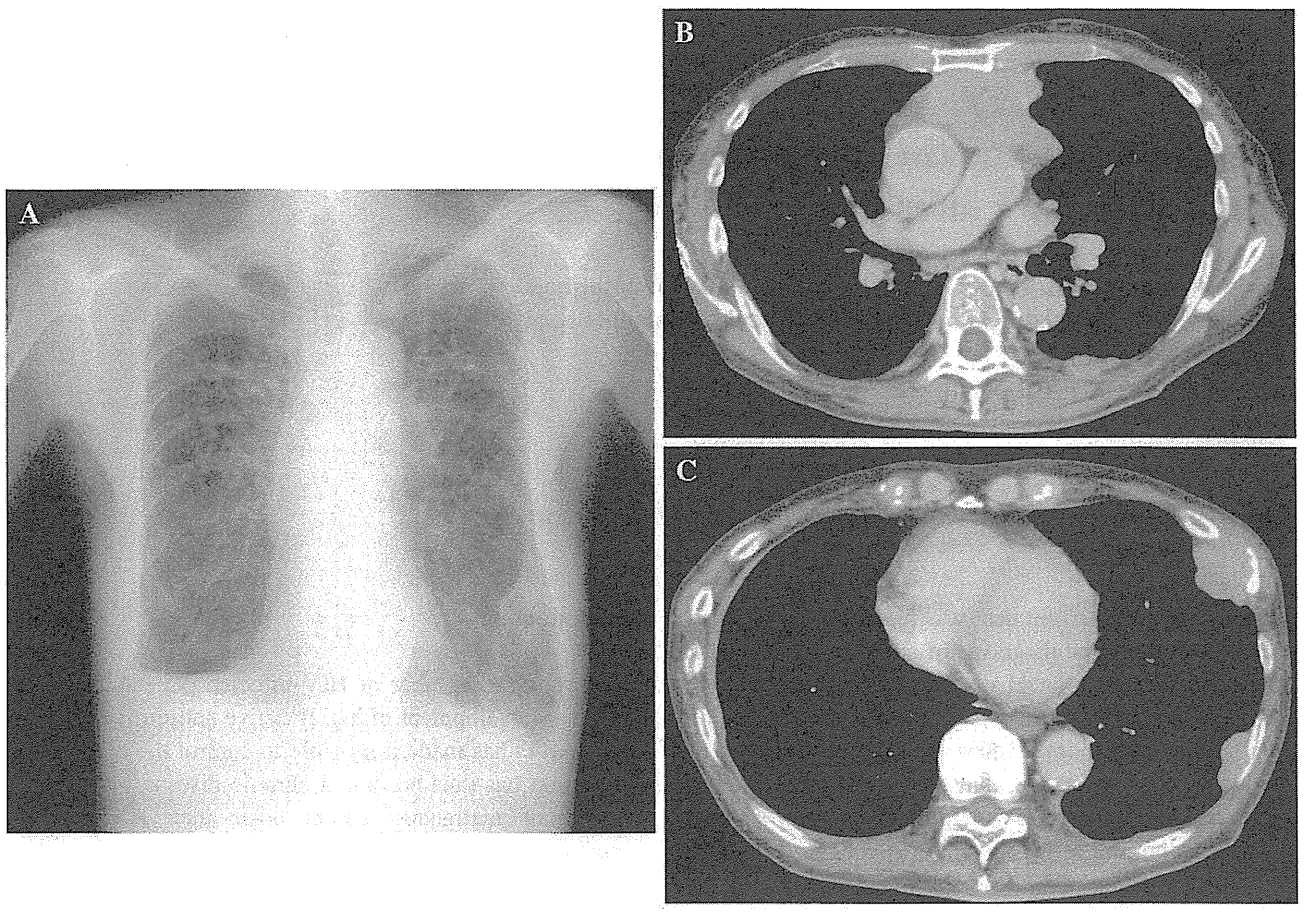

Fig. 1 **a** Chest radiograph on admission shows a mass protruding from the mediastinum into the left hilar region. **b**, **c** Enhanced chest CT scans on admission show the mediastinal mass and pleural dissemination

diagnosis was Masaoka stage IVb. The case was considered unsuitable for surgery. In late July 2010, the CD4 count was 379 cells/μL and viral load (VL) was 6.0×10^5 copies/mL. He received HAART, consisting of the combination of abacavir and lamivudine (ABC/3TC) and RAL for treatment of HIV infection. The patient was hospitalized for chemotherapy in late-August 2010. The medical history included hypertension, diabetes mellitus, and pulmonary tuberculosis (in 2006). He was a smoker of three packs of cigarettes per day for the preceding 45 years. On admission, physical examination showed no abnormal respiratory sounds and laboratory tests showed slightly reduced hemoglobin (11.7 g/dL), C-reactive protein 3.50 mg/dL, and elevated hemoglobin A1c (6.7 %). Analysis of various tumor markers showed high levels of CYFRA 21-1 (15.3 ng/mL) and 1-CTP (5.5 ng/mL). The CD4 count was 419 cells/μL and VL was 54 copies/mL. Chest radiography (Fig. 1a) showed a mass protruding from the mediastinum into the left hilar region, a nodular shadow and a granular shadow in the left upper and middle lung fields, respectively, and a nodular shadow in the lower left lung field. Enhanced chest CT scan (Fig. 1b, c) revealed a 7.3 × 5.2 × 8.5 cm tumor with an irregular border and heterogeneous internal contrast that was slightly to the left and superior to the anterior mediastinum. The mass had extensive contact with the aorta, pulmonary artery, epicardium, and left lung. Pleural dissemination and bone invasion of the left seventh rib were noted. Multiple shadows of small nodules were seen in the left lung field, and metastases in the left lung were suspected. A pathologic specimen revealed medullary proliferation of large atypical cells with fibrous stroma. Hassall corpuscle-like structure was observed, but no apparent keratinization was identified. Mucin production was not evident. Immunohistochemically, CD5 and c-kit were positive for tumor cells, and the MIB-1 index of tumor cells was 10–20 %. No TdT-positive T lymphocytes were observed. The lesion was diagnosed as thymic carcinoma (undifferentiated carcinoma) (Fig. 2).

The patient was started on ADOC chemotherapy consisting of drip infusion of doxorubicin 40 mg/m^2 and cisplatin 50 mg/m^2 on day 1, vincristine 0.6 mg/m^2 on day 3, and cyclophosphamide 700 mg/m^2 on day 4. Four courses of this ADOC chemotherapy were administered, at roughly

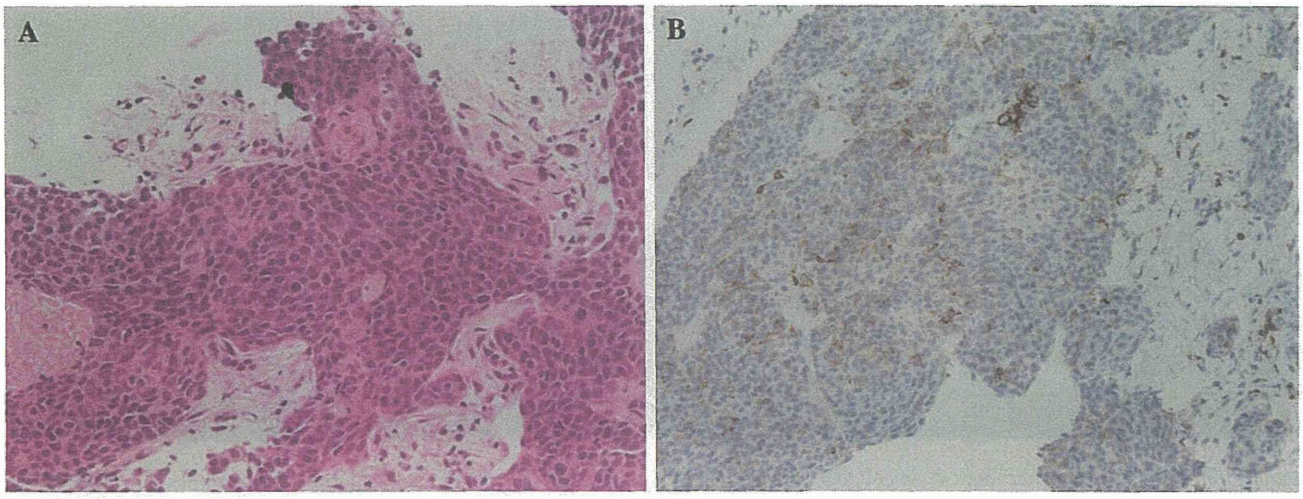

Fig. 2 **a** Microscopic findings of the CT-guided needle biopsy specimen diagnosed as undifferentiated thymic carcinoma (H&E stain). **b** Positive immunohistochemical staining for CD5 is seen in the cell membrane of tumor cells

4-week intervals, to allow for recovery of myelosuppression. Chest CT scan after chemotherapy showed a 5.1 × 3.7 × 6.0 cm tumor. The therapeutic efficacy was evaluated using Response Evaluation Criteria in Solid Tumors, and the evaluation was a partial response (Fig. 3). Hematological toxicity included grade 4 neutropenia and febrile neutropenia, while non-hematological toxicity included grade 1 anorexia, hiccups, and alopecia, but no hepatic or renal toxicity. The CD4 count was maintained at more than 300 cells/μL, and VL was suppressed to undetectable levels. Thus, disease control was achieved for both the thymic carcinoma and HIV infection. On the basis of the patient's history of pulmonary tuberculosis, acid-fast staining and sputum cultures were performed repeatedly, but results were negative. In the last outpatient visit, 9 months after diagnosis, the patient was in good general condition and no signs of recurrence or metastasis were noted.

Discussion

Thymic carcinomas, together with thymomas, are thymic epithelial tumors, and comprise approximately 14.1 % of thymic epithelial tumors [5]. Thymic carcinomas display clear cytological atypia and histological features and have the capacity to invade and metastasize both locally and to distant organs. At diagnosis, the thymic carcinoma is at an advanced stage in approximately 90 % of patients (at least Masaoka stage III, with invasion of surrounding organs) [5]. The indications for surgical treatment are limited compared with thymomas [3–5]. Our patient was diagnosed as Masaoka stage IVb [6] and was not considered a suitable candidate for surgery.

Thymic carcinomas do not show the high degree of sensitivity seen with thymomas, but some patients respond well to chemotherapeutic regimens that include cisplatin or carboplatin and anthracycline [7–12]. Koizumi et al. [9] described 8 patients with advanced thymic carcinoma who received ADOC chemotherapy, and reported a response rate of 75 % with a median survival time of 19 months. Yoh et al. [10] treated 12 patients with unresectable advanced thymic carcinoma by the cisplatin, vincristine, doxorubicin, and etoposide (CODE) regimen and reported a response rate of 41.7 % and median survival time of 46 months. Igawa et al. [11] administered carboplatin and paclitaxel to 11 treatment-naïve patients with unresectable thymic carcinoma, and reported a response rate of 36 % with a median survival time of 22.7 months. Lemma et al. [12] used the same combination of carboplatin plus paclitaxel for 23 treatment-naïve patients with advanced thymic carcinoma in a prospective phase II study, and reported a response rate of 21.7 % and median survival time of 20.0 months. On the other hand, a large percentage of thymic tumors are reported to express c-kit protein [13–15]. Strobel et al. [16] reported an objective response to imatinib, an inhibitor of c-kit protein, in a patient with thymic carcinoma, but results were negative in a later phase II study [17]. Thus, there are several reports on thymic tumors but the number of treated cases has always been small, and there is still no standard chemotherapy regimen for thymic carcinoma.

Following the development of HAART, which improved disease control, HIV infection began to be considered a chronic disease. Furthermore, an increased incidence of malignant tumors other than the AIDS-defining malignancies in HIV-infected individuals has been reported [1, 2]. However, although one case of both HIV

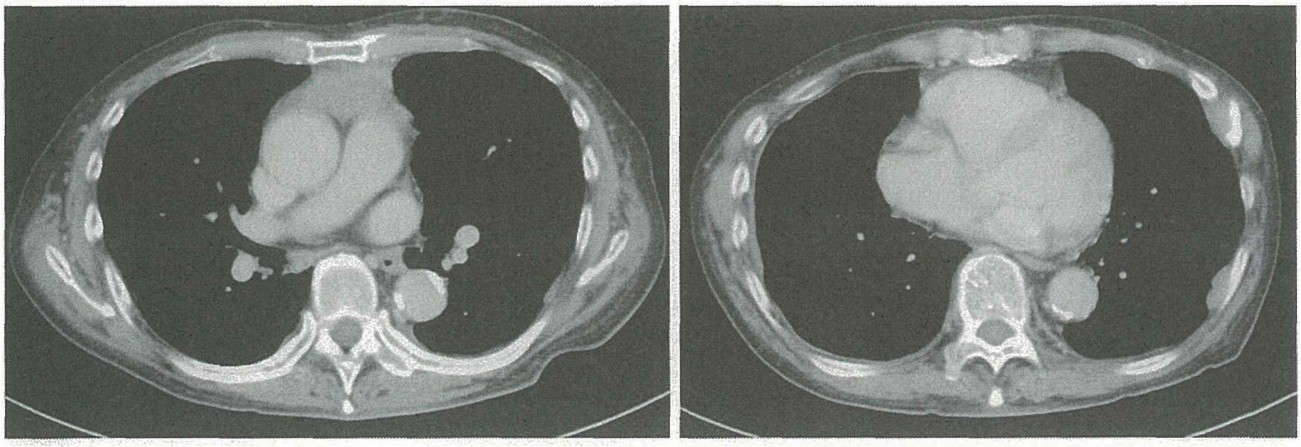

Fig. 3 **a**, **b** Chest CT scans after four cycles of ADOC chemotherapy show a decrease in both the mediastinal mass and pleural dissemination

infection and thymic carcinoma has been reported in a child [18], to our knowledge, there have been no such reports in adults, and the present case appears to be the first in the literature.

Decreased hemopoietic function in HIV patients [19] results in susceptibility to chemotherapy-induced myelosuppression, and therapy often cannot be completed due to treatment-related toxicities [20]. In addition, exacerbation of HIV and opportunistic infections associated with such myelosuppression is a concern. The present case is significant because a treatment regimen comprising the coadministration of HAART and antineoplastic drugs was used. Although there are no previous studies regarding coadministration of HAART and antineoplastic drugs for cases of HIV complicated by thymic carcinoma, the utility of this treatment regimen has been reported for HIV patients with lung cancer, Kaposi's sarcoma, and malignant lymphoma [20–23]. HAART offers the following advantages during anticancer treatment: (1) improved immune function by decreasing CD4-positive lymphocyte counts; (2) reduced myelosuppression by inhibition of HIV; and (3) reduced incidence of HIV infection-related conditions (chronic inflammation, tumorigenicity, renal impairment, arteriosclerosis, etc.) [24].

Some anti-HIV drugs either interact with antineoplastic drugs or cause similar toxicities, making it necessary to exercise caution when these drugs are administered at the same time. In particular, ritonavir (RTV), a protease inhibitor, is a very potent inhibitor of the cytochrome P (CYP) 450 3A4 drug-metabolizing enzyme in the liver. RTV can cause the blood concentrations of coadministered antineoplastic drugs to increase and may cause serious toxicities [25]. Potential cumulative toxicities between HAART and antineoplastic drugs are primarily related to nucleoside reverse transcriptase inhibitors (NRTIs) [26, 27]. Zidovudine causes myelosuppression (especially anemia and neutropenia), tenofovir is nephrotoxic, and stavudine and didanosine cause peripheral neuropathy. If these anti-HIV drugs are coadministered with antineoplastic drugs that can cause the same types of toxicities, there is a strong possibility that the toxicities will become even more severe [26, 27]. Thus, such coadministration should be avoided whenever possible. In the patient reported here, ABC/3TC, a combination of abacavir and lamivudine, which are NRTIs, and RAL, which is an integrase strand transfer inhibitor, was used, and these drugs did not alter the blood concentrations of antineoplastic drugs because they are not metabolized by CYP [27].

Coadministration of platinum-containing and anthracycline antineoplastic drugs, which constitute key agents in systemic chemotherapy for thymic carcinoma, can be expected to deliver a marked antineoplastic effect, despite the risk of myelosuppression [7–12]. In the present case, we selected ADOC chemotherapy on the basis of treatment outcome in the previous study [9] and the low incidence of drug interactions with ABC/3TC and RAL [27]. During chemotherapy, white blood cells, neutrophils, CD4 counts, and HIV viral load were monitored as closely as possible, and neutropenia and febrile neutropenia were rapidly treated, enabling completion of four courses of ADOC therapy.

In conclusion, we reported an HIV-infected patient with thymic carcinoma, who responded well to ADOC chemotherapy and HAART. For HIV-positive patients with malignant tumors, care should be exercised in selecting anti-HIV drugs to optimize therapeutic efficacy and reduce potential antineoplastic drug toxicities.

Conflict of interest No author has any conflict of interest.

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Research Letter

AIDS 2012, **24**:000–000

Once-daily darunavir/ritonavir plus abacavir/lamivudine versus tenofovir/emtricitabine for treatment-naïve patients with baseline viral load >100,000 copies/mL

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The efficacy and safety of fixed-dose abacavir/lamivudine against tenofovir/emtricitabine, both with once-daily darunavir/ritonavir, was examined in 80 treatment-naïve patients with baseline HIV-1 viral load >100,000 copies/ml. The time to virologic failure by 48 weeks was not different between the two groups. The percentage of patients with viral suppression was not significantly different with per protocol population. Tenofovir/emtricitabine showed better tolerability; more patients on abacavir/lamivudine changed regimen than those on tenofovir/emtricitabine. A randomized trial to elucidate the efficacy and safety of these two regimens is warranted.

Little information is available on the efficacy and safety of antiretroviral therapy (ART) of ritonavir-boosted darunavir (DRV/r) plus fixed-dose abacavir/lamivudine (ABC/3TC) [1,2]. DRV/r is a protease inhibitor with proven efficacy and safety, and with high barrier to drug resistance [3,4]. ABC/3TC is an alternative choice of nucleoside reverse transcriptase inhibitors (NRTI) in the American Department of Health and Human Services Guidelines [5]. Here we conducted a single-center, observational pilot study to compare the efficacy and safety of DRV/r plus ABC/3TC versus TDF/FTC in patients with baseline HIV-1 viral load (VL) >100,000 copies/ml. Subjects with such VL were chosen because ACTG 5202 demonstrated that the time to virologic failure (VF) was significantly shorter with ABC/3TC than with TDF/FTC in patients with VL >100,000 copies/ml on efavirenz or ritonavir-boosted atazanavir [6]. All subjects were treatment-naïve who commenced once-daily DRV/r plus either fixed-dose ABC/3TC or TDF/FTC from November 2009 to August 2011 at the AIDS Clinical Center, Tokyo. Baseline data (basic demographics, CD4 count, and VL) were collected. VL was measured by Cobas TaqMan HIV-1 real-time PCR version 1.0 assay (Roche Diagnostics, NJ) to the end of November 2011, and later by Cobas TaqMan version 2.0 assay. It was the decision of the attending physician to start ART with either TDF/FTC or ABC/3TC, because the Japanese guidelines consider both TDF/FTC and ABC/3TC the preferred NRTIs [7].

The efficacy outcomes were the time from commencing ART to VF (defined as VL >1,000 copies/ml at or after 16 weeks and before 24 weeks, or >200 copies/ml at or after 24 weeks) [6], and the proportion of patients with VL < 50 copies/ml at 48 weeks regardless of previous VF. The tolerability outcome was the time to any regimen modification. Intent-to-treat (ITT) population, comprising all subjects, was used for all efficacy and tolerability analyses, while per protocol population was used in the efficacy analysis of the suppressed VL. Censored cases represented those who dropped out, referred to other facilities, or reached 48 weeks. Time-to-event distributions were estimated using the Kaplan-Meier method. Uni- and multivariate Cox hazards models estimated the impact of ABC/3TC use over TDF/FTC on the incidence of VF.

The study included 80 patients [ABC/3TC: 21, TDF/FTC: 59, median age: 37.9 years, males: 74 (92.5%), East Asian origin: 72 (90%)], of whom 66 (82.5%) were infected with HIV-1 through homosexual contact. Patients on ABC/3TC had lower baseline CD4 count (46/μl versus 100, $P=0.031$), higher VL (5.75 log10/ml versus 5.58, $P=0.044$), and more likely to have history of AIDS (71.4% versus 37.3, $P=0.010$), than patients with TDF/FTC. All subjects were HLA-B*5701-negative, and all underwent HIV-1 drug-resistance tests before commencement of ART and none had resistant mutations.

The time to VF with ABC/3TC [3 patients (14.3%)] was not significantly different from that with TDF/FTC [4 (6.8%)] by 48 weeks (Fig. 1a), by univariate and multivariate analyses adjusted by CD4 count and VL (HR, 2.651; 95% CI, 0.592–11.88; $P=0.203$, adjusted HR, 1.589; 95% CI, 0.341–7.401; $P=0.555$). At week 48, ITT analysis showed more patients with TDF/FTC had VL of <50 copies/ml (ABC/3TC: 38.1%, TDF/FTC: 64.4%, $P=0.043$) (Fig. 1c), whereas with per protocol analysis, no difference was noted (ABC/3TC: 57.1%, TDF/FTC: 73.1%, $P=0.328$) (Fig. 1d).

Among the seven patients with VF, three (ABC/3TC: 1, TDF/FTC: 2) achieved sustained VL suppression after week 60 of the initial regimen. The other four underwent drug-resistance tests. One on ABC/3TC was switched to TDF/FTC at week 41; however, viral suppression was not achieved until raltegravir was added at week 74. The

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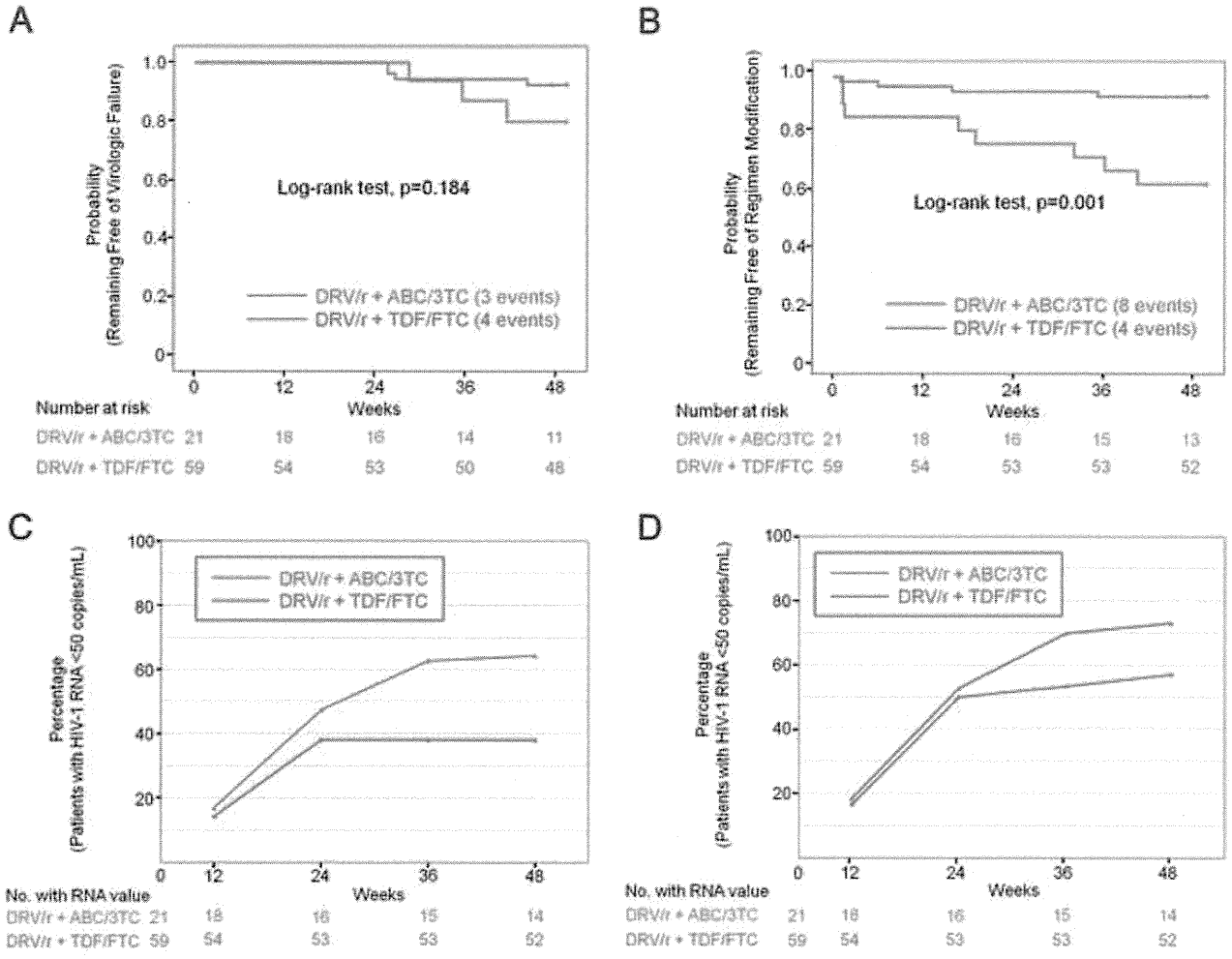

Fig. 1. Efficacy and tolerability results over 48 weeks. (a) Time to protocol-defined virologic failure. (b) Time to tolerability endpoint, defined as first change in treatment regimen. Percent of patients with HIV-1 RNA <50 copies/ml at week 12, 24, 36, and 48, regardless of previous virologic failure, with (c) intention-to-treat population, and with (d) per protocol population.

other with ABC/3TC was switched to TDF/FTC at week 49 and achieved viral suppression despite emergence of protease mutation M46I. Another patient on TDF/FTC had persistent viremia (100–200 copies/ml) without mutation. Another patient on TDF/FTC showed emergence of reverse transcriptase mutation V75L and viremia persisted with 200–500 copies/ml. Reverse transcriptase mutation M184I/T/V did not emerge in any patients.

More patients on ABC/3TC changed or discontinued the initial regimen during the research period [ABC/3TC: 8 (38.1%), TDF/FTC: 4 (6.8%), $P=0.001$] (Fig. 1b). Six [ABC/3TC: 4 (19%), TDF/FTC: 2 (3.4%)] changed ART due to adverse events or VF [ABC/3TC: VF ($n=1$), limb paresthesia ($n=1$), and nausea ($n=2$); TDF/FTC: tenofovir nephrotoxicity ($n=2$)]. None developed ABC-associated hypersensitivity.

This is the first comparison report of the efficacy and safety of ABC/3TC against TDF/FTC with DRV/r in treatment-naïve patients with VL >100,000 copies/ml. The time to VF by 48 weeks was not different between the two groups. Although a higher percentage of patients on TDF/FTC showed viral suppression than those on ABC/3TC at week 48 with ITT population, the difference was not significant with per protocol population. TDF/FTC showed better tolerability, as more patients on ABC/3TC changed regimen than those on TDF/FTC.

These results need to be interpreted with caution, because the baseline characteristics of patients of the two groups were not well-matched due to the nature of the observational study, and this study did not have sufficient power due to the small number of enrolled patients. Because our patients had small stature with median body weight of 58.1 kg, a risk factor for TDF nephrotoxicity, it

is sometimes our practice to avoid TDF in patients with multiple risks, such as advanced HIV-1 infection, to prevent possible acute kidney injury [8–10]. This is presumably the reason for prescribing ABC/3TC to patients with worse disease condition in this study. This allocation bias might have worked as a disadvantage for the efficacy and tolerability results of ABC/3TC.

The usefulness of ABC/3TC has recently received higher recognition than it did in the past; the FDA meta-analysis did not confirm the association between ABC use and myocardial infarction [11], and it became clear that TDF use is associated with decreased bone mineral density and renal dysfunction, both of which might develop into serious complications with long-term TDF use [12–17]. Thus, once-daily DRV/r, a protease inhibitor with high barrier to drug resistance, plus ABC/3TC could be good alternative, especially in patients who cannot tolerate TDF. A randomized trial to elucidate the efficacy and safety of ABC/3TC and TDF/FTC with once-daily DRV/r is warranted.

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Conflicts of interest

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Clinical Study

Differences in Lipid Measurements by Antiretroviral Regimen Exposure in Cohorts from Asia and Australia

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We explored the mean differences in routinely measured lipids (total cholesterol, triglycerides, and high-density lipoprotein cholesterol) according to exposure to different combination antiretroviral regimens in Asian (n = 2051) and Australian (predominantly Caucasian, n = 794) cohorts. The regimen was defined as at least 3 antiretroviral drugs with at least 2 nucleoside-reverse transcriptases (NRTIs) and either of at least one protease inhibitor (PI) or non-nucleoside-reverse transcriptases (NNRTIs). We categorised cART regimens as: NRTIs as tenofovir based or not; NNRTIs as nevirapine or efavirenz (but not both); and PI as atazanavir based or not. We found that the impact of various antiretroviral regimens on lipids in Asian and Australian cohorts was only different by cohort for total cholesterol (P for interaction between regimen and cohort: <0.001) but not in case of other lipids (P for interaction: >0.05). The differences in total cholesterol were however small and unlikely to be of clinical significance. Overall, tenofovir with nevirapine or atazanavir was associated with the most favorable lipids, while the PI regimens without tenofovir and atazanavir were associated with least favorable lipids. We conclude that the impact of various ART regimens on lipids is largely similar in Asian and Australian cohorts and that the newer drugs such as tenofovir and atazanavir are likely to provide similar benefit in terms of lipid profiles in both populations.

1. Introduction

Combination antiretroviral therapy (cART) for HIV infection is associated with adverse changes in lipid profiles and can include elevation in total cholesterol and triglycerides, which may increase the risk of coronary heart disease (CHD) [1–4]. Moreover, different classes of cART and drugs within each class have differential impacts on lipids [2]. Protease-inhibitors (PIs) are associated with more significant changes in lipid profile than nucleoside and nonnucleoside reverse transcriptase inhibitors (NRTIs and NNRTIs, resp.) [2, 3, 5]. And within NNRTI class, efavirenz (EFV) is associated with greater changes in the lipid profile than nevirapine (NVP) [2, 5, 6]. Also tenofovir (TDF) and atazanavir (ATV) are known to have a favorable impact on lipids [5, 7, 8].

Drugs such as TDF, EFV, and ATV are becoming increasingly available in low-middle-income countries, including Asia [9, 10]. However, much of our knowledge about the relative impact of different cART regimens on lipids comes mainly from clinical trials and cohort studies from European or North-American settings [2, 4, 7, 8]. The impact of cART on lipids may vary in Asian settings due to differences in race/ethnicity, dietary, environmental, and lifestyle factors [11–13]. This has been demonstrated in other settings

where the magnitude of change in total cholesterol and triglycerides due to PIs differed between African Americans and Caucasians, highlighting the possible role of race [11, 12]. These findings illustrate the need for verifying our assumptions about the relative impact of different cART regimens on diverse populations, including Asian populations.

Observational cohort studies can complement information from clinical trials, and allow us to examine the effects of art medications in the context of combination regimens, as opposed to head-to-head comparisons of selected drugs in clinical trials. In the present study, we aim to compare the relative impact of various cart regimens on lipid profiles in Asian and Australian cohorts using data from the treat Asia and the Australian HIV observational databases (TAHOD and AHOD, resp.), which are formed on similar methodology and are known to be predominantly Asian and Caucasian, respectively [14].

2. Methods

2.1. The TAHOD and AHOD Cohorts. TAHOD and AHOD are clinical cohort studies of HIV-infected patients in Asia and Australia, respectively, and are part of the International Epidemiologic Databases to evaluate AIDS initiative. Both cohorts have similar methodologies, which have been previously published [15, 16]. Briefly, prospective data collection was commenced in 2003 for TAHOD and in 1999 for AHOD, with retrospective data being provided where available. In TAHOD, data are collected from 17 clinical sites in the Asian region, whereas for AHOD, data are collected from 27 clinical sites throughout Australia. Written informed consent was not a requirement of sites in TAHOD unless required by the site's local ethics committee because data are collected in an anonymous form, while in AHOD consent was obtained from all patients recruited at the time of enrolment. The TAHOD and AHOD cohorts are known to be predominantly of Asian and Caucasian ethnic composition, respectively [14].

Ethical approval for both the cohorts was obtained from the University of New South Wales, Sydney, Australia, and all other relevant institutional review boards. Data for both TAHOD and AHOD are transferred electronically to the Kirby Institute twice per year and include the same set of core variables. All data are subject to standardized quality control procedures.

2.2. Outcome. The outcomes of interest were mean (i) total cholesterol, (ii) triglycerides, (iii) high-density lipoprotein cholesterol (HDL-C) measured in mmol/L, and (iv) total cholesterol : HDL-C ratio. Lipid values are measured according to the local sites' standard of care in each cohort, and when measured, are captured during routine data transfer. TAHOD only records fasting lipids. In AHOD, both fasting and nonfasting lipids along with the fasting status are recorded. Further details of laboratory standards and methods at each site were not available.

Data collection on lipid profiles started later in AHOD (median date: January, 2007), compared to TAHOD (median date: March, 2006). The lipid values before starting cART (i.e., while patients were ART naive) were not available in most patients, and therefore changes from pre- to post-cART were not analysed. Mean lipid measurements were compared by different regimens and cohort.

2.3. Definition and Classification of Antiretroviral Regimens. The cART regimen variable was defined as a regimen containing at least 3 antiretroviral drugs, including at least two NRTIs and either of at least one PI or an NNRTI. In order to evaluate the net effect of a combination regimen, rather than that of a single drug or a class, we defined eight mutually exclusive regimens. We categorised cART regimens as: NRTIs as TDF based (NRTIs + TDF) or not (NRTIs); NNRTIs as NVP or EFV (but not both); and PI as ATV based (PI + ATV) or not (PI).

Based on these categories, the following mutually exclusive regimens were defined: (i) NRTIs (+TDF) + NVP; (ii) NRTIs (+TDF) + EFV; (iii) NRTIs + NVP; (iv) NRTIs + EFV; (v) NRTIs (+TDF) + PIs (+ATV); (vi) NRTIs (+TDF) + PI; (vii) NRTIs + PI (+ATV); (viii) NRTIs + PI. In all analyses, regimen (i) NRTIs (+TDF) + NVP was used as the reference group, as this regimen was thought to have the most favourable impact on lipids.

2.4. Inclusion Criteria and Time-Points Analysed. Patients from TAHOD and AHOD were eligible for inclusion in the analysis if they started cART and had at least one lipid measurement within the first 24 months of cART commencement. Time at risk was defined as time spent on any of the regimens described previously and risk time started from the commencement of that regimen. Follow-up was censored at first of 24-month exposure to regimen of interest, date of death, loss to follow-up, or 31 March, 2010. Lipids values measured at the 6-monthly intervals in the first 24 months of start of cART were used. Thus each patient on each regimen could have up to 4 measurements (1 in each interval). If more than one measurement was available in a given interval, one measured earliest in the given interval was used in the analysis. Intermittent changes in therapy including stopping part or all of a regimen for less than 14 days were not considered a stop in time at risk for that regimen. Each patient could contribute data to more than one regimen.

2.5. Variables and Statistical Analysis. The following *a priori* confounders were included in all models:

(1) fixed variables: cohort (TAHOD/AHOD), gender, HIV transmission group (homosexual contact ± intravenous drug user (IDU), IDU ± heterosexual, heterosexual, and other), and hepatitis B and C coinfection (defined as HBV surface antigen and HCV antibody positive, resp.);

(2) variables measured closest to the start of each cART regimen within past 6 months to 1 month after the

start of the regimen of interest: CD4+ T-cell count (categorised as <200, 200–350, and >350 cells/μL); HIV RNA viral load (categorised as <500, >500–<10,000, and >10,000 copies/mL); and body mass index (BMI) (categorised as <18.5, 18.5–25, 25–30, and >30 kg/m^2);

(3) variables recalculated at the start of each cART regimen: cumulative cART exposure and age.

We performed longitudinal data analysis using random effects models to take into account repeated lipid measures (defined previously). Since all lipid parameters were normally distributed with minimal skewness, data were not transformed. Separate models were fitted for each outcome. All models included time on regimen with lipid data, categorised as 6 monthly intervals. The interaction between the regimen and the cohort variables was assessed for each outcome. We also conducted the following sensitivity analyses: (i) restricting AHOD data to only lipid values which were documented to be taken as fasting in AHOD, (ii) excluding patients with missing BMI data, (iii) including only those with known Caucasian ethnicity in AHOD, and (iv) additional adjustment for stavudine (d4t) use in the multivariable model, as it was more common in TAHOD than AHOD.

Data were analysed using STATA version 10 (STATA Corporation, College Station, TX, USA).

3. Results

There were 2845 participants (2051 in TAHOD and 794 in AHOD) who met the inclusion criteria. In TAHOD, 736 (35.9%) were Chinese, 654 (31.9%) were Thai, 152 (7.4%) were Cambodian (Khmer), 100 (4.9%) were Japanese and 62 (3%) were Indian. Table 1 describes the patient characteristics at study entry for each cohort.

There were a total of 7897 total cholesterol values (5602 in TAHOD and 2295 in AHOD), 7293 triglyceride values (5002 in TAHOD and 2291 in AHOD), and 4669 HDL-C values (2949 in TAHOD and 1720 in AHOD). The frequency of total cholesterol measurements by regimen and cohort is shown in Table 2. The most common NRTI combinations for which total cholesterol measurements were available in TAHOD were zidovudine (AZT)/lamivudine (3TC) (39% of all measurements) and d4t/3TC (30% of all measurements) and in AHOD TDF/emtricitabine (FTC) (29% of all measurements) and abacavir (ABC)/3TC (18% of all measurements). The distribution was similar for triglycerides and HDL-C. In TAHOD and AHOD, 52% and 46% of measurements were taken while on NNRTI-based regimens, respectively. Of all the measurements on PI-based regimens, greater than 95% were on ritonavir-boosted regimens.

Patients contributed data to the median of 1 regimen (range: 1 to 4) with a median of 2 lipid measurements (IQR: 1–4) per patient. All measures of CD4 cell count, HIV viral load, and BMI were collected within 35 days of commencing the different ART regimens. Participants from TAHOD were more likely to be younger and female and have heterosexually acquired infection, hepatitis B coinfection, detectable HIV VL, lower median CD4+ count, shorter time spent on cART, lower BMI, lower mean total cholesterol, and higher HDL-C than those from AHOD (Table 1). Also a higher proportion of TAHOD participants had missing BMI and HIV viral load values compared with those in AHOD (Table 1).

3.1. Total Cholesterol. The relationship between mean total cholesterol and cART regimen differed by cohort (TAHOD/AHOD) ($P < 0.001$, test for interaction). Overall, the mean total cholesterol was slightly lower for TAHOD participants, compared to AHOD participants, after adjustment for demographic and HIV-related characteristics, in most of the regimens (Figure 1(a)). When compared to the NRTIs (+TDF) + NVP regimen (reference group), the NRTIs + PI regimen was associated with greater mean total cholesterol in both cohorts, with a slightly greater difference in AHOD participants (mean difference: +0.78 mmol/L, 95% CI: 0.57 to 1.00) compared to TAHOD participants (mean difference: +0.23 mmol/L, 95% CI: 0.02 to 0.44); NRTIs (+TDF) + PI (+ATV) regimen was associated with greater mean total cholesterol in AHOD (mean difference: −0.20 mmol/L, 95% CI: −0.43 to 0.02) as compared to TAHOD (mean difference: −0.62 mmol/L, 95% CI: −1.23 to −0.02).

3.2. Triglycerides, HDL-C, and Total Cholesterol: HDL-C Ratio. There was no significant interaction between cART regimen and the cohort type ($P > 0.05$, test for interaction) for triglycerides, HDL-C, and total cholesterol: HDL-C ratio. Table 3 provides adjusted analyses for each of these outcomes. As compared to the NRTIs (+TDF) + NVP regimen (reference group), the NRTIs + PI regimen was associated with the highest mean triglycerides (mean difference: 1.13 mmol/L, 95% CI: 0.83 to 1.43) and total cholesterol : HDL-C ratio (mean difference: 0.75, 95% CI: 0.47 to 1.03), followed by the NRTIs (+TDF) + PI regimen (mean difference in triglycerides: 1.06 mmol/L, 95% CI: 0.73 to 1.38, and mean difference in total cholesterol : HDl-C ratio: 0.66, 95% CI: 0.37 to 0.95), while NRTIs (+TDF) + PI (+ATV) regimen was not associated with a significant difference in triglycerides (mean difference: 0.15 mmol/L, 95% CI: −0.22 to 0.52) and total cholesterol : HDL-C ratio (mean difference: 0.29, 95% CI: −0.04 to 0.62). Also, the NRTIs + EFV regimen was associated with increase in triglycerides (mean difference: 0.64 mmol/L, 95% CI: 0.34 to 0.95) and total cholesterol : HDL-C ratio (mean difference: 0.29, 95% CI 0.01 to 0.56). The TAHOD cohort, as compared to AHOD, had higher mean triglycerides, but not total cholesterol : HDL-C ratio. Figures 1(b) and 1(c) provide the graphical representation of the adjusted mean triglycerides and total cholesterol : HDL-C ratio for each regimen and cohort, respectively.

When compared to the reference group, the NRTIs + NVP regimen and the NRTIs + EFV regimen were associated with higher mean HDL-C (mean difference of: 0.15 mmol/L, 95% CI: 0.08 to 0.21 and 0.09 mmol/L, 95% CI: 0.03 to 0.16,

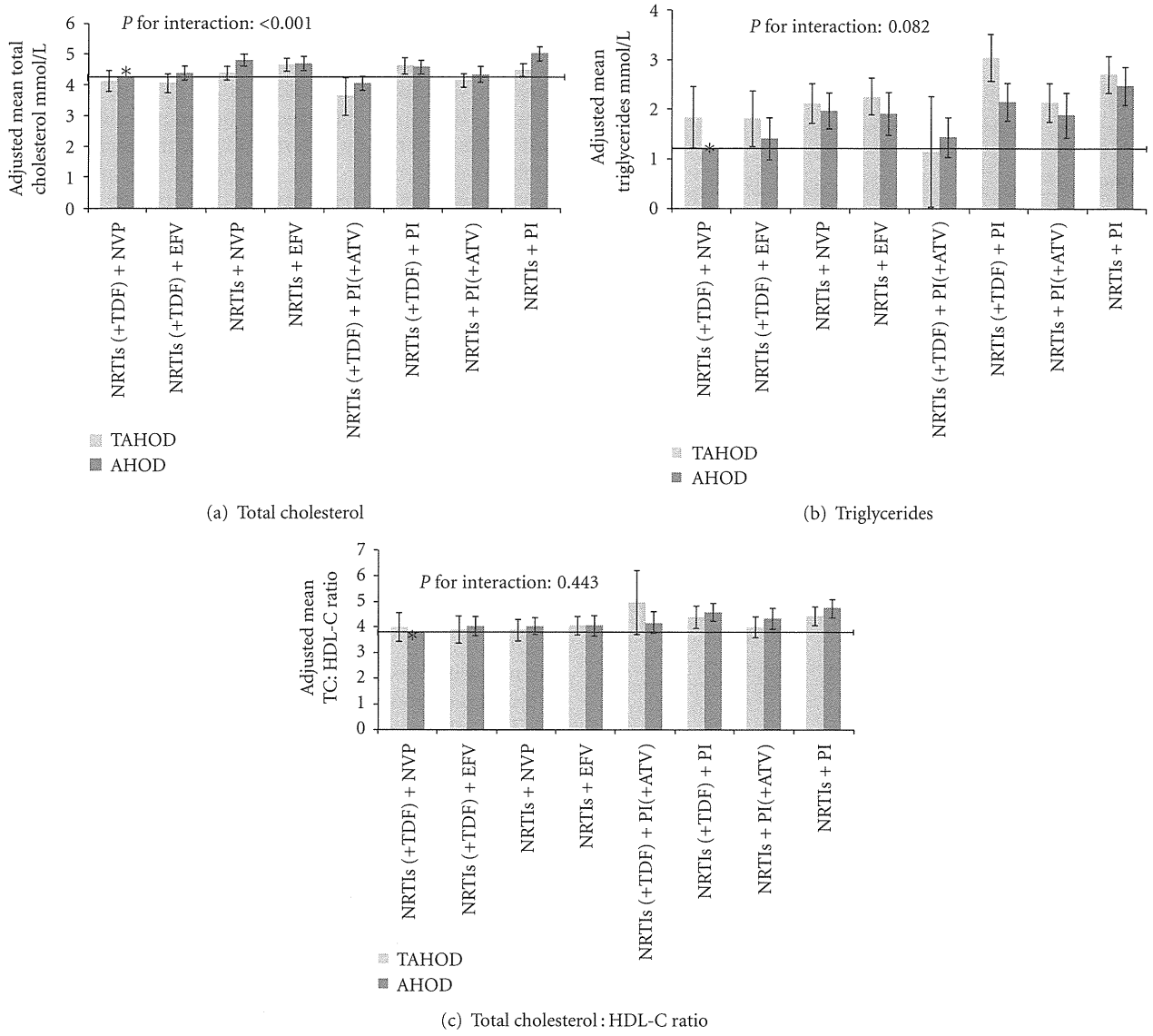

FIGURE 1: Adjusted Mean Lipids by regimen and cohort. Interaction between impact of regimen and cohort variables on lipids: (a) mean total cholesterol, (b) mean triglycerides, and (c) mean total cholesterol : HDL-C ratio. A statistically significant interaction suggests impact of regimen on lipids differed in magnitude by the cohort. Triglycerides were higher for TAHOD as compared to AHOD irrespective of the regimen, but the interaction between regimen and cohort was not significant. Means were *a priori* adjusted for time on given regimen, HBV and HCV confections, age, gender, HIV RNA viral load copies/mL, CD4+ T-cell count, BMI, cumulative exposure to cART at baseline, and HIV exposure category. *Reference category. Horizontal line shows the value of constant (mean lipid value in reference category). Error bars indicate 95% confidence interval. AHOD: Australian HIV Observational Database; ATV: Atazanavir; EFV: Efavirenz; NNRTIs: nonnucleoside reverse transcriptase inhibitors; NRTI: Nucleoside reverse transcriptase inhibitors; NVP: Nevirapine; PI: protease inhibitor; TAHOD: TREAT Asia HIV Observational Database; TDF: Tenofovir. *Key*. NRTIs are TDF based (NRTIs + TDF) or not (NRTIs) and PI as ATV based (PI + ATV) or not (PI).

resp.). Other regimens were not significantly different to the reference regimen.

3.3. Sensitivity Analyses. Forty-five percent of all of the AHOD measurements were taken fasting. Ethnicity was known in AHOD in 80% of participants, of whom greater than 80% were Caucasian. All of the sensitivity analyses, except for exclusion of missing BMI data, yielded very similar results, in terms of direction of effect, magnitude, and significance, as those from full analyses (data not presented). Since BMI was missing in a significant proportion of participants in both cohorts (Table 1), restriction of analysis to only patients with known BMI provided results that were of similar direction and magnitude of the effect, however in some cases less statistically significant, because of loss of power.