d4Tを含んだ治療の副作用としての顔面のやせに対する治療法開発

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研究要旨

FLに対する治療法開発は、当初2種類の充填物注入法と自己脂肪幹細胞の注入法をRCTにて2段階で比較する研究を予定していた。しかし、今年度の予備調査により、形成外科的手法を用いた修復術の安全性と有効性に関する研究をパイロット研究として東大形成外科と共同で実施することになり、現在研究プロトコールの倫理審査中である。

A. 研究目的

HIV感染症の予後は劇的に改善したが、d4Tを含んだ治療の副作用より顔面の脂肪が萎縮するFacial Lipoatrophy（FL）が後遺症として残り、著しく生活の質を低下させている感染者が少なくない。本研究は、FLに対する新規治療法の開発を目的として、形成外科的手法を用いた修復術の安全性と有効性を検討することになった。

B. 研究方法

当初は、顔面への2種類の充填物の無作為割り付け試験（RCT）の後、脂肪幹細胞注入とのRCTという2段階での研究を計画していた。しかし、研究方法をパイロット試験に変更し、以下の通りとした。本研究は、HIV関連顔面脂肪萎縮に対する形成外科的手法を用いた修復術の安全性と有効性を検索するための、非対照、探索的研究である。対象者から同意を取得したのち、腹部、腰背部、大腿部などの自家脂肪が利用できる症例（一般的にはBMI＝20以上）においては、全身麻酔下に自家脂肪移植術を行う（A群）。それ以外の症例においては、局所麻酔下に架橋ヒアルロン酸注射剤（Restylane SubQ®）注入術を行う（B群）。いずれの群においても、処置は日本形成外科学会専門医の資格を有する医師が行う。血友病症例が対象となる場合には、周術期に適切な凝固因子製剤投与を行う。予定登録数は10例で、治療後約48週間を観察期間とし、安全性と有効性を検討する。

（倫理面への配慮）

現在、国立国際医療研究センター倫理委員会にて審査中である。倫理委員会の承認を得た後、「臨床研究に関する倫理指針」を遵守し実施する。データは、漏洩がないよう厳重に管理し、データ解析は連結可能匿名化された後に実施する。研究成果の公表に際しては、個人が特定されることのないように配慮する。研究に参加しない場合においても以後の治療を含むあらゆる事に関して不利益を被らないことを保証するとともに、一旦得られた同意に関しても、どの段階においても撤回できる事を保証する。

C. 研究結果

本研究を開始するにあたり、形成外科の専門家2名と綿密な検討を行った。その結果、第一段階のPLLAとヒアルロン酸の比較は、物質の差よりも術者のテクニックの差の方が大きく、RCTにはなじまないという結論になった。また、当初予定していた自己脂肪注入両方も、脂肪幹細胞を使う必要は無く、採取した脂肪をそのまま戻すことでも十分な効果が期待できることがわかった。このため、研究の論点

を、脂肪幹細胞注入の効果ではなく、HIV でミトコンドリア障害がある場合と HIV 非感染者の場合の脂肪注入の比較を行うこととした。また、予備的な検討から、対象患者には、極度に脂肪組織が退行し脂肪吸引の手技自体が危険を伴う可能性が高い方の含まれるため、この様な場合には、ヒアルロン酸を注入する方法も選択できるようにした。本研究のフローチャートを以下に示す。

D. 考察

この分野の技術の進歩は著しく、脂肪注入も幹細胞を使用する必要がないことがわかった。このため、当初予定していた 2 段階の RCT ではなく、自己脂肪注入療法になったが、HIV の場合と非 HIV の場合の比較を行うことは病態の理解という観点からも意義深い。次年度は、スムーズに研究を開始し、症例数を積み重ねたい。

E. 結論

当初予定と、大きく研究方法が変更してしまったが、研究プロトコールもほぼ固まり次年度は早急に研究を実施したい。

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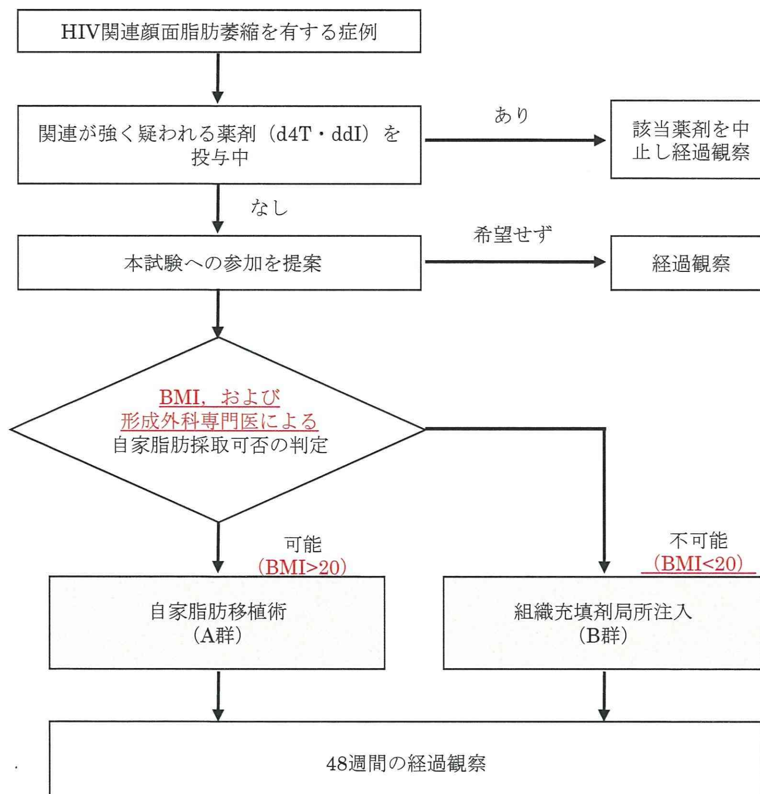

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G. 知的財産権の出願・登録状況（予定を含む）

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

なし

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INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Abacavir/Lamivudine versus Tenofovir/Emtricitabine with Atazanavir/Ritonavir for Treatment-naive Japanese Patients with HIV-1 Infection: A Randomized Multicenter Trial

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Abstract

Objective To compare the efficacy and safety of fixed-dose abacavir/lamivudine (ABC/3TC) and tenofovir/emtricitabine (TDF/FTC) with ritonavir-boosted atazanavir (ATV/r) in treatment-naïve Japanese patients with HIV-1 infection.

Methods A 96-week multicenter, randomized, open-label, parallel group pilot study was conducted. The endpoints were times to virologic failure, safety event and regimen modification.

Results 109 patients were enrolled and randomly allocated (54 patients received ABC/3TC and 55 patients received TDF/FTC). All randomized subjects were analyzed. The time to virologic failure was not significantly different between the two arms by 96 weeks (HR, 2.09; 95% CI, 0.72-6.13; p=0.178). Both regimens showed favorable viral efficacy, as in the intention-to-treat population, 72.2% (ABC/3TC) and 78.2% (TDF/FTC) of the patients had an HIV-1 viral load <50 copies/mL at 96 weeks. The time to the first grade 3 or 4 adverse event and the time to the first regimen modification were not significantly different between the two arms (adverse event: HR 0.66; 95% CI, 0.25-1.75, p=0.407) (regimen modification: HR 1.03; 95% CI, 0.33-3.19, p=0.964). Both regimens were also well-tolerated, as only 11.1% (ABC/3TC) and 10.9% (TDF/FTC) of the patients discontinued the allocated regimen by 96 weeks. Clinically suspected abacavir-associated hypersensitivity reactions occurred in only one (1.9%) patient in the ABC/3TC arm.

Conclusion Although insufficiently powered to show non-inferiority of viral efficacy of ABC/3TC relative to TDF/FTC, this pilot trial suggested that ABC/3TC with ATV/r is a safe and efficacious initial regimen for HLA-B*5701-negative patients, such as the Japanese population.

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Introduction

The fixed-dose combinations of tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg and abacavir sulfate 600 mg/lamivudine 300 mg are components of antiretroviral therapy for treatment-naïve patients with HIV-1 infection in developed countries (1, 2). The efficacy and safety of tenofovir/emtricitabine (TDF/FTC) and abacavir/lamivudine (ABC/3TC) remain the focus of ongoing debate. The ACTG 5202 trial demonstrated that the viral efficacy of ABC/3TC is inferior to that of TDF/FTC among treatment-naïve patients with a baseline HIV viral load of >100,000 copies/mL receiving efavirenz or ritonavir-boosted atazanavir as a key drug (3). On the other hand, the HEAT study showed that the viral efficacy of ABC/3TC is not inferior to that of TDF/FTC, regardless of the baseline viral load when used in combination with lopinavir/ritonavir (4).

With regard to safety, the occurrence of ABC-associated serious hypersensitivity reactions, the most important adverse effect of ABC affecting 5-8% of patients, has limited its use (5). However, screening for HLA-B*5701 or prescribing ABC in HLA-B*5701-negative populations, such as the Japanese, can reduce the incidence of immunologically-confirmed hypersensitivity to 0% (6, 7). Another negative aspect of ABC use is its association with myocardial infarction, as reported by the D:A:D study (8). However, the possible association of myocardial infarction with ABC was not confirmed by a recent meta-analysis report of the US Food and Drug Administration (9). On the other hand, renal proximal tubular damage leading to renal dysfunction and a loss of phosphate, which can result in decreased bone mineral density, is a well-known adverse effect of TDF (10-14).

Taking this background into account, the American Department of Health and Human Services (DHHS) Guidelines place TDF/FTC as the preferred drug and ABC/3TC as an alternative choice, whereas other international guidelines, including the European AIDS Clinical Society (EACS) Guidelines and the Japanese Guidelines, recommend both TDF/FTC and ABC/3TC as preferred choices (1, 2, 15).

Randomized control trials comparing TDF/FTC and ABC/3TC have been conducted in the US and Europe, but not in other parts of the world (4, 16, 17). The efficacy and safety of these two fixed-dose regimens in patients with different genetic backgrounds and body statures might not be similar to the results of previous trials, especially considering that the prevalence of HLA-B*5701 is zero in the Japanese population (7). Moreover, the degree of decrement in the renal function with TDF is larger in patients with a low body weight, such as the Japanese, which might limit the use of TDF in patients with a high risk for renal dysfunction (18-20).

Based on the above described background, the present randomized trial was originally designed in 2007 to elucidate whether the viral efficacy of ABC/3TC is not inferior to that of TDF/FTC with ritonavir-(100 mg) boosted atazanavir (300 mg) in treatment-naïve Japanese patients, whose body weight is much lower than Whites or Blacks (21). However, the independent data and safety monitoring board (DSMB) recommended that the protocol be modified to examine the efficacy, safety and tolerability among Japanese patients with HIV-1 infection for 96 weeks as a pilot trial because only 109 patients were enrolled and randomized at the end of the enrollment period despite a planned sample size of 240 patients, primarily due to the above mentioned negative reports of ABC use in the D:A:D study and ACTG 5202 (3, 8).

Materials and Methods

This clinical trial was designed and reported according to the recommendations of the Consolidated Standard of Reporting Trials (CONSORT) statement (22). The protocol and supporting CONSORT checklist are available as supplementary files (see Supplementary files 1 and 2).

Ethics statement

The Research Ethics Committee of each participating center approved the study protocol. All patients enrolled in this study provided a written informed consent. This study was conducted according to the principles expressed in the Declaration of Helsinki.

Study design

The Epzicom-Truvada study is a phase 4, multicenter, randomized, open-label, parallel group pilot study conducted in Japan that compared the efficacy and safety of a fixed dose of ABC/3TC and TDF/FTC, both combined with ritonavir-boosted atazanavir (ATV/r) for the initial treatment of HIV-1 infection for 96 weeks. Enrollment of patients began in November 2007 and ended in March 2010, and the follow-up period ended in February 2012. With a one to one ratio, the patients were randomly assigned to receive either a fixed dose of ABC/3TC or TDF/FTC, both administered with ATV/r. The randomization was stratified according to each participating site and conducted at the data center with

independent clinical research coordinators using a computer-generated randomization list prepared by a statistician with no clinical involvement in the trial.

Study patients

This study population included treatment-naïve Japanese patients aged 20 or over with HIV-1 infection who met the eligibility criteria for the commencement of antiretroviral therapy according to the DHHS Guidelines in place in the U.S. at the time of the writing of the study protocol (a CD4 count <350/μL or a history of AIDS-defining illness regardless of the CD4 count) (23). Patients were screened and excluded if they had previously taken lamivudine, tested positive for hepatitis B surface antigens, had comorbidities such as hemophilia or diabetes mellitus that required medical treatment, congestive heart failure or cardiac myopathy or if they were considered not suitable for enrollment by the attending physicians. Candidates were also excluded if their alanine aminotransferase level was 2.5 times greater than the upper limit of normal, they had an estimated glomerular filtration rate (eGFR) calculated using the Cockcroft-Gault equation of <60 mL/min, {creatinine clearance = [(140- age) × weight (kg)]/(serum creatinine ×72)(×0.85 for females)} or a serum phosphate level <2 mg/dL or had active opportunistic diseases that required treatment (24). Each patient's actual body weight was used for the calculation of eGFR. At screening, a genotypic drug resistant test and screening for the HLA-B*5701 allele were permitted but not required because the prevalence of both the drug resistant virus and the HLA-B*5701 allele are low in Japanese patients (7, 25). Medical history, including a history of AIDS-defining illnesses and other comorbidities, was also collected. Enrollment stopped on March 3, 2008 due to the recommendation from the DSMB of the trial based on the interim analysis of the ACTG5202 that ABC/3TC is less effective than TDF/FTC in patients with a baseline viral load >100,000 copies/mL (3). Accordingly, the DSMB recommended that the trial should be restarted with modified inclusion criteria: to enroll patients with an HIV-1 viral load of <100,000 copies/mL at screening, and the enrollment restarted from April 1, 2008.

Study procedures

Required visits for participants for clinical and laboratory assessments were at screening, enrollment and every 4 weeks until the viral load diminished to <50 copies/mL. For patients with a viral load <50 copies/mL, the required visit interval was every 12 weeks for the duration of the study. The evaluation performed at each visit included a physical examination, CD4 cell count, HIV-1 RNA viral load, a complete blood cell count and blood chemistries (total bilirubin, alanine aminotransferase, lactate dehydrogenase, serum creatinine, potassium, phosphate, triglycerides and low-density lipoprotein (LDL) cholesterol) and a urine examination of the levels of phosphate, creatinine and β2 microglobulin. The values of urinary β2 microglobulin were expressed relative to a urinary creatinine level of 1 g/L (/g Cr). The percent tubular resorption of phosphate was calculated using the following formula: {1-[(urine phosphate × serum creatinine)/(urine creatinine × serum phosphate)]} ×100 (26). All data, including the HIV-1 RNA viral load, were collected at each participating site and sent to the data center. Grade 3 or 4 serious adverse events were reported to the DSMB, which made a judgment whether they were caused by the study drugs. Independent research coordinators at the data center visited at least 10 facilities every year to monitor the accuracy of the submitted data and compliance to the study protocol. All authors vouch for the completeness and accuracy of the reported data.

Statistical analysis

The sample size calculation was originally conducted as follows: Assuming a 90% success rate in the TDF/FTC arm at week 48, a sample size of 224 patients (112 patients per arm) provided 80% power (one sided, α=0.05) to establish non-inferiority of ABC/3TC to TDF/FTC each in combination with ATV/r. Non-inferiority was defined as the lower bound of the two-sided 95% confidence interval (CI) with the treatment difference being above -10%. Based on this assumption, the targeted sample size was set to 240 patients (120 in each arm). However, as previously described, due to the shortage of accrued subjects, this study was underpowered and conducted as a pilot trial.

The primary efficacy endpoint was the time from randomization to virologic failure (defined as a confirmed HIV-1 RNA >1,000 copies/mL at or after 16 weeks and before 24 weeks or >200 copies/mL at or after 24 weeks) (3). The secondary efficacy endpoints included the time from randomization to either virologic failure or ART modification and a comparison of the proportions of patients with HIV-1 RNA <50 copies/mL at weeks 48 and 96 regardless of previous virologic failure. The intent-to-treat (ITT) population comprising all randomized subjects was used to assess the efficacy data; however, a comparison of the proportion of virologically-suppressed patients was conducted with both the ITT and a per protocol population while on the initial randomized regimen.

The safety endpoint was the time from randomization to the first occurrence of grade 3 or 4 laboratory data or abnormal symptoms that were at least one grade higher than the baseline. Isolated hyperbilirubinemia was excluded from the safety endpoints. The grade of adverse events was classified according to the Division of AIDS Table for grading the severity of adult and pediatric events, version 2004 (27). The tolerability endpoint was the time from randomization to any regimen modification. The safety and tolerability endpoints were calculated in the ITT population. Changes per protocol in the CD4 cell count, lipid markers and renal tubular markers at weeks 48 and 96 were compared using the Mann-Whitney test. A repeated measures mixed model was used to estimate and compare changes in the renal function between the two arms (17). The renal function was calculated using the Modification of Diet in Renal Disease study

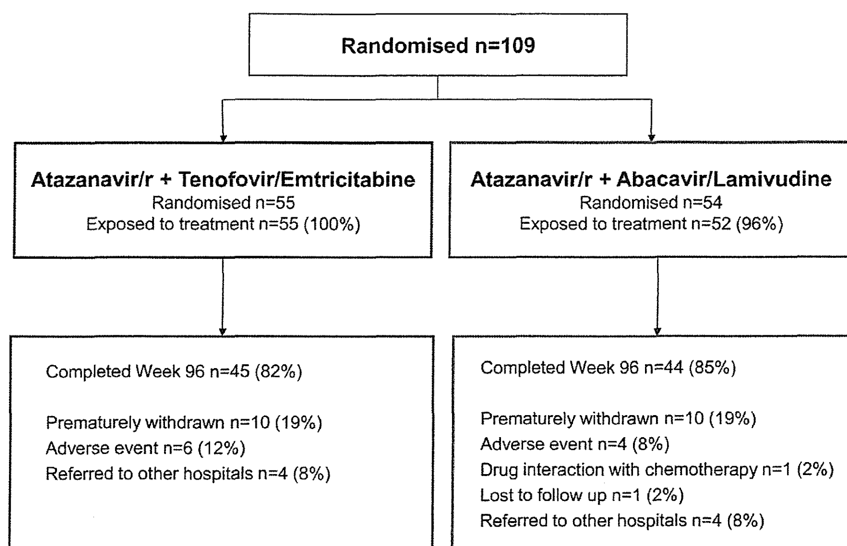

Figure 1. Enrollment, randomization and disposition of patients.

Table 1. Demographic and Baseline Characteristics

	ABC/3TC (n=54)	TDF/FTC (n=55)	Total (n=109)
Sex (male), n (%)	53 (98.1)	54 (98.2)	107 (98.2)
Age (years)†	39 (28.8-44)	35 (29-42)	36 (29-42.5)
CD4 count (/μL)†	236.5 (194-301.3)	269 (177-306)	257 (194-305)
HIV RNA viral load (log_{10}/mL)†	4.29 (3.92-4.67)	4.28 (3.86-4.60)	4.28 (3.89-4.67)
HIV RNA viral load >100,000 log_{10}/mL, n (%)	1 (1.9)	0 (0)	1 (0.9%)
Route of transmission (homosexual contact), n (%)	47 (87)	49 (89.1)	96 (88.1)
History of AIDS n (%)	1 (1.9)	5 (9.1)	6 (5.5)
Body weight (kg)†	64 (59-72.1)	63.1 (58-69)	64 (58.3-70.7)
Body mass index (kg/m^2)†	22.6 (20.4-24.2)	21.9 (20.3-23.6)	22.4 (20.3-23.7)
eGFR (mL/min/1.73 m^2)†	96.9 (82.7-107.3)	94.4 (83.6-105.7)	96.7 (83.0-106.7)
Creatinine clearance (mL/min)†	119.3 (105.4-136.6)	124.6 (103-139.3)	120.3 (104.7-138.3)
Serum creatinine (mg/dL)†	0.76 (0.67-0.83)	0.75 (0.68-0.84)	0.76 (0.68-0.83)
Urinary β2 microglobulin (μg/g Cre)†	195.8 (98.3-505.3)	138.4 (86.8-426.4)	172.9 (88.3-458.7)
Tubular resorption of phosphate (%)†	92.9 (90-95.1)	92.3 (87.7-95.2)	92.7 (89.3-95.1)
LDL-cholesterol (mg/dL)†	91.5 (75-125.5)	94 (72.5-111.5)	94 (74.5-114)
Triglycerides (mg/dL)†	132 (98-170.5)	114 (73-184)	127 (85.5-175)
Hypertension, n (%)	3 (5.6)	1 (1.8)	4 (3.7)
Diabetes mellitus, n (%)	0 (0)	0 (0)	0 (0)
Concurrent use of nephrotoxic drugs, n (%)	10 (18.5)	10 (18.2)	20 (18.3)
Hepatitis C, n (%)	0 (0)	0 (0)	0 (0)

†median (interquartile range)

IQR: interquartile range, AIDS: acquired immunodeficiency syndrome, eGFR: estimated glomerular filtration rate, LDL: low-density lipoprotein

equation adjusted for the Japanese population (28), and a sensitivity analysis was conducted using the above mentioned Cockcroft-Gault equation.

Time-to-event distributions were estimated using the Kaplan-Meier method and compared using the two-sided log-rank test. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) were estimated using the Cox proportional hazards model. For grade 3 or 4 serious adverse events caused by the study drugs, the description and severities were recorded. Statistical significance was defined at two-sided p values <0.05. All statistical analyses were performed with The Statistical Package for Social Sciences ver. 17.0 (SPSS, Chicago, IL).

Results

Patient disposition and baseline characteristics

109 patients from 18 centers were enrolled and randomized between November 2007 and March 2010. Of these patients, 54 and 55 were allocated to the ABC/3TC and TDF/FTC arms, respectively (Fig. 1). The baseline demographics and characteristics are shown in Table 1. Most patients were men, with a median body weight of 64 kg. The median CD4 cell count was 257/μL (IQR: 194-305). One patient in the ABC/3TC arm had a baseline HIV-1 RNA level of >100,000

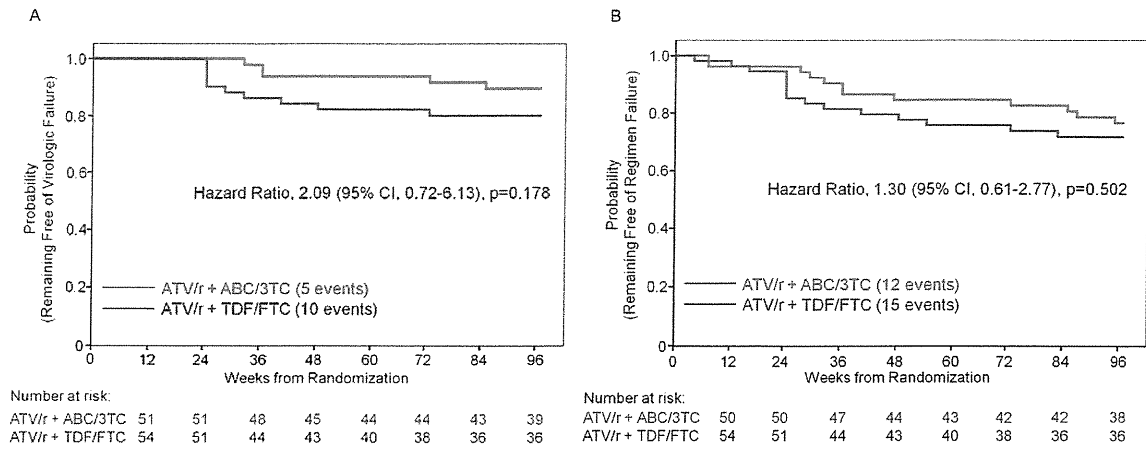

Figure 2. Efficacy results over 96 weeks. (A) Time to protocol-defined virologic failure. (B) Time to the first occurrence of either virologic failure or discontinuation of the initially randomized regimen. ATV/r: ritonavir-boosted atazanavir, ABC/3TC: abacavir/lamivudine, TDF/FTC: tenofovir/emtricitabine

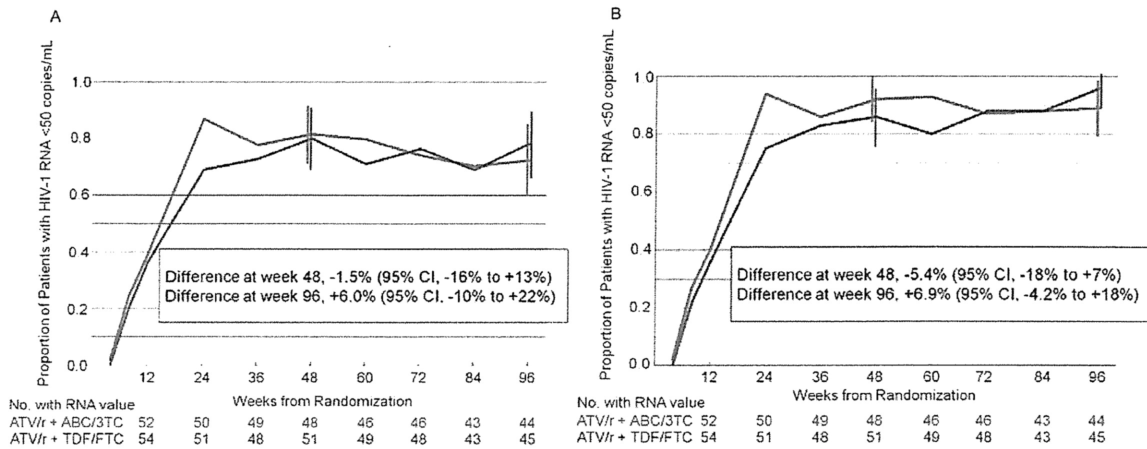

Figure 3. Efficacy results at 48 and 96 weeks. Proportion of patients with an HIV RNA level <50 copies/mL regardless of previous virologic failure with 95% binomial confidence intervals at 48 and 96 weeks. (A) Intention-to-treat analysis. (B) Per protocol analysis. ATV/r: ritonavir-boosted atazanavir, ABC/3TC: abacavir/lamivudine, TDF/FTC: tenofovir/emtricitabine

copies/mL. This patient was enrolled before the announcement of the interim analysis of ACTG5202 in March 2008 and achieved an HIV-1 RNA level of <50 copies/mL by the end of that month. One patient in the TDF/FTC arm had a history of lamivudine use. That patient was included in the analysis because this aspect of the medical history was identified after randomization and initiation of the allocated treatment.

Efficacy results

In the primary efficacy analysis, the time to virologic failure was not significantly different in the ABC/3TC arm from that observed in the TDF/FTC arm by 96 weeks (HR, 2.09; 95% CI, 0.72-6.13; p=0.178). Virologic failure occurred in 5 and 10 patients in the ABC/3TC and TDF/FTC arms, respectively (Fig. 2A). In the secondary efficacy analysis, the times to the first occurrence of confirmed virologic failure or discontinuation of the initially allocated regimen were not different between the two arms (HR, 1.30; 95% CI, 0.61-2.77; p=0.502) (Fig. 2B). Among the ITT population, the proportion of patients with an HIV RNA level <50 copies/mL at week 48 regardless of previous virologic failure was 81.5% in the ABC/3TC group and 80% in the TDF/FTC group, for a difference of -1.5% (95% CI, -16% to 13%), and at week 96, 72.2% and 78.2% for the ABC/3TC and TDF/FTC groups, respectively, for a difference of 6% (95% CI, -10% to 22%) (Fig. 3A). The per protocol analysis showed that the proportions at week 48 were 91.7% and 86.3% for the ABC/3TC and TDF/FTC groups, respectively, for a difference of -5.4% (95% CI, -18% to 7%). At week 96, the proportions were 88.6% and 95.6% for the ABC/3TC and TDF/FTC groups, respectively, for a

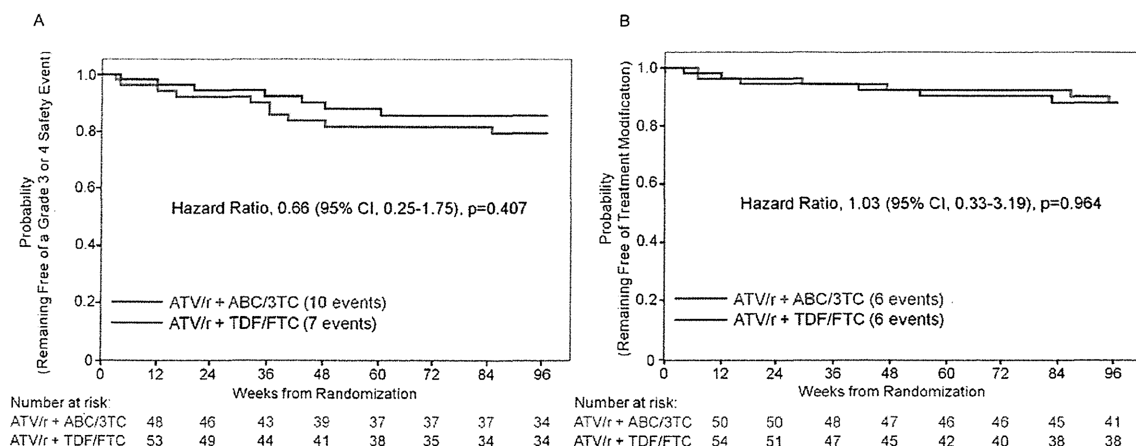

Figure 4. Safety and tolerability results over 96 weeks. (A) Time to first primary safety endpoint, defined as the first grade 3 or 4 event on the initial randomized regimen, which was at least one grade higher than baseline. (B) Time to tolerability endpoint, defined as the first change in regimen. ATV/r: ritonavir-boosted atazanavir, ABC/3TC: abacavir/lamivudine, TDF/FTC: tenofovir/emtricitabine

Table 2. Selected Grade 3 or 4 Events While Receiving Randomized Antiretroviral Drugs

	ABC/3TC (n=54)	TDF/FTC (n=55)	Total (n=109)
Overall, n (%)	13 (24)	10 (18)	23 (21)
Laboratory, n (%)	12 (22)	7 (13)	19 (17)
Alanine aminotransferase, n	0	1	1
LDL-cholesterol, n	6	2	8
Triglycerides, n	0	3	3
Uric acid, n	1	0	1
Serum phosphate, n	2	0	2
Serum calcium, n	1	0	1
Serum creatinine, n	1	0	1
Platelets count, n	1	1	2
Symptoms, n (%)	1 (2)	3 (5)	4 (4)
Depression, n	0	2	2
Fever, n	1	1	2

More than one event occurred in 2 patients.
LDL: low-density lipoprotein

difference of 6.9% (95% CI, -4.2% to 18%) (Fig. 3B). The primary and secondary efficacy analyses did not show a significant difference in viral efficacy between the two arms.

Safety and tolerability results

10 (18.5%) and 7 (12.7%) patients in the ABC/3TC and TDF/FTC groups, respectively, experienced 23 grade 3 or 4 adverse events related to the study drugs while on the initial regimen. The time to the first adverse event was not significantly different between the two arms (HR 0.66; 95% CI, 0.25-1.75, p=0.407) (Fig. 4A). Table 2 shows a list of selected grade 3 or 4 safety events. Among the adverse events, 48% included elevation of lipid markers. The tolerability endpoint, the time to first ART modification, was not significantly different between the two arms (HR 1.03; 95% CI, 0.33-3.19, p=0.964), and only 6 (11.1%) and 6 (10.9%) patients in the ABC/3TC and TDF/FTC arms, respectively, discontinued the initially allocated regimen by 96 weeks (Fig. 4B). The most common reason for regimen modification was drug toxicity (n=10; 4 in ABC/3TC and 6 in TDF/FTC arm; suspected ABC hypersensitivity reactions based on the appearance of rash and fever in HLA-B*5701-negative patient; n=1, depression; n=3, jaundice; n=3, nausea; n=2, and lipodystrophy; n=1). One patient in the ABC/3TC group developed a cerebral infarction during week 39 but was able to continue the study drugs. No deaths were registered during the study period.

Changes in the CD4 cell count and other parameters of interest

The increase in the median CD4 count from baseline to 48 weeks was marginally larger in the ABC/3TC arm than in the TDF/FTC arm (median: ABC/3TC: 216, TDF/FTC: 192, p=0.107). This difference was significantly larger at 96

FTC, this pilot study is the first randomized study conducted in Asia to elucidate the efficacy and safety of fixed doses of these two regimens each administered in combination with ATV/r for initial HIV-1 therapy. Viral efficacy, safety, and tolerability were not significantly different in the two arms of Japanese patients with a baseline HIV viral load <100,000 copies/mL over 96 weeks. Both regimens showed favorable viral efficacy, as in the ITT population, 72.2% and 78.2% of the patients in the ABC/3TC and TDF/FTC arms, respectively, had HIV-1 viral loads of <50 copies/mL at 96 weeks. Both regimens were also well-tolerated, as only 11.1% and 10.9% of the patients in the ABC/3TC and TDF/FTC arms, respectively, discontinued the allocated regimen by 96 weeks. Clinically suspected (not immunologically-confirmed) ABC-associated hypersensitivity reaction occurred in only one (1.9%) patient in the ABC/3TC arm, confirming that ABC hypersensitivity is rare in populations in which HLA-B*5701-positive patients are uncommon. Thus, this trial suggests that ABC/3TC may be an efficacious and safe regimen for use in HLA-B*5701-negative populations, such as the Japanese, with a baseline HIV viral load <100,000 copies/mL.

The usefulness of ABC/3TC has recently received higher recognition for two reasons. One, a meta-analysis by the FDA did not confirm the association between ABC use and myocardial infarction (9). Two, it became clear that TDF-induced renal tubulopathy results in decreased bone mineral density due to phosphate wasting and a decreased renal function, both of which might develop into serious complications with long-term TDF use (12-14, 29, 30). On the other hand, greater deteriorations in the levels of lipid markers were noted in ABC/3TC than in TDF/FTC in clinical trials comparing these two agents (16, 17). The present study also demonstrated that the increases in the LDL-cholesterol and triglyceride levels were higher in the ABC/3TC arm than in the TDF/FTC arm.

TDF-induced nephrotoxicity is of particular interest in this study because a low body weight is an important risk factor, and body stature was much smaller in this study population (median baseline body weight 64 kg), than in the ASSERT study (72 kg), which compared the renal function between patients receiving ABC/3TC and TDF/FTC with efavirenz in Europe (17, 18, 20). This study showed that changes in the renal function from baseline were not significantly different between the two arms, similar to the findings of the ASSERT study. None of the patients in the TDF/FTC arm exhibited progression of CKD stage. On the other hand, the levels of urinary β2 microglobulin deteriorated significantly from baseline in the TDF/FTC arm, whereas improvements were observed in the ABC/3TC arm. This is also similar to the findings reported by the ASSERT trial. This suggests that urinary β2 microglobulin is a more sensitive marker for evaluating TDF nephrotoxicity than the renal function calculated by serum creatinine, as also demonstrated in our previous work (31). Tubular resorption of phosphate, another marker examined to evaluate the renal tubular function, did not exhibit any changes from baseline or between the two arms, suggesting that urinary β2 microglobulin may be a better marker for evaluating TDF nephrotoxicity than tubular resorption of phosphate. Of note, in both arms, the renal function did significantly decrease from baseline. To our knowledge, this is the first randomized trial comparing ABC/3TC and TDF/FTC that observed deterioration of the renal function after the initiation of ART. This result highlights the importance of regular monitoring of renal function after initiation of ART, although it is difficult to draw a firm conclusion on the prognosis of the renal function from this study, due to the limited length of the observation period and the small number of enrolled patients.

Only one patient (1.9%) in the ABC/3TC arm developed a clinically suspected ABC-associated hypersensitivity reaction, which was diagnosed based on the appearance of a skin rash and fever six weeks after commencement of the study drug. The patient fully recovered after discontinuation of the drugs. The ASSERT trial of HLA-B*5701-negative patients reported a similar incidence (3%) of clinically suspected ABC hypersensitivity reactions (17). The one case observed in our trial could be a false positive, because ABC hypersensitivity reactions commonly occur 9-11 days after the initiation of therapy (32), and ABC hypersensitivity was not confirmed immunologically. Nonetheless, immediate discontinuation of ABC is highly recommended even in HLA-B*5701-negative patients suspected of ABC hypersensitivity, since ABC hypersensitivity can occur in such patients (33) and errors in genotyping for HLA or reporting a genotype might occur in practice (34).

Several limitations of this trial should be acknowledged. First, due to the shortage of enrolled patients, the trial was insufficiently powered to test non-inferiority of the viral efficacy of ABC/3TC against TDF/FTC, as initially planned. However, the safety and tolerability data of these regimens in Asia are a valuable asset for patients from this region, and efficacy data could be utilized as part of a meta-analysis in the future. Second, the enrolled subjects were mostly men (primarily men who had sex with men and very few injection drug users). Further studies are needed to examine the efficacy and safety of these regimens in women and patients with different routes of transmissions in Asia.

In summary, this randomized trial demonstrated high efficacy and safety of fixed-dose ABC/3TC and TDF/FTC in combination with ATV/r over 96 weeks for treatment-naïve Japanese patients with a baseline HIV-1 viral load <100,000 copies/mL, although it was insufficiently powered to show non-inferiority of the viral efficacy of ABC/3TC compared with TDF/FTC. ABC/3TC with ATV/r is a safe and efficacious initial regimen for treating HLA-B*5701-negative patients with a baseline HIV-1 viral load <100,000 copies/mL.

Author's disclosure of potential Conflicts of Interest (COI).
Uchiumi H: Research funding, ViiV Healthcare. Koibuchi T: Research funding, Nihon Ultmarc Inc. Naito T: Research funding,

FTC, this pilot study is the first randomized study conducted in Asia to elucidate the efficacy and safety of fixed doses of these two regimens each administered in combination with ATV/r for initial HIV-1 therapy. Viral efficacy, safety, and tolerability were not significantly different in the two arms of Japanese patients with a baseline HIV viral load <100,000 copies/mL over 96 weeks. Both regimens showed favorable viral efficacy, as in the ITT population, 72.2% and 78.2% of the patients in the ABC/3TC and TDF/FTC arms, respectively, had HIV-1 viral loads of <50 copies/mL at 96 weeks. Both regimens were also well-tolerated, as only 11.1% and 10.9% of the patients in the ABC/3TC and TDF/FTC arms, respectively, discontinued the allocated regimen by 96 weeks. Clinically suspected (not immunologically-confirmed) ABC-associated hypersensitivity reaction occurred in only one (1.9%) patient in the ABC/3TC arm, confirming that ABC hypersensitivity is rare in populations in which HLA-B*5701-positive patients are uncommon. Thus, this trial suggests that ABC/3TC may be an efficacious and safe regimen for use in HLA-B*5701-negative populations, such as the Japanese, with a baseline HIV viral load <100,000 copies/mL.

The usefulness of ABC/3TC has recently received higher recognition for two reasons. One, a meta-analysis by the FDA did not confirm the association between ABC use and myocardial infarction (9). Two, it became clear that TDF-induced renal tubulopathy results in decreased bone mineral density due to phosphate wasting and a decreased renal function, both of which might develop into serious complications with long-term TDF use (12-14, 29, 30). On the other hand, greater deteriorations in the levels of lipid markers were noted in ABC/3TC than in TDF/FTC in clinical trials comparing these two agents (16, 17). The present study also demonstrated that the increases in the LDL-cholesterol and triglyceride levels were higher in the ABC/3TC arm than in the TDF/FTC arm.

TDF-induced nephrotoxicity is of particular interest in this study because a low body weight is an important risk factor, and body stature was much smaller in this study population (median baseline body weight 64 kg), than in the ASSERT study (72 kg), which compared the renal function between patients receiving ABC/3TC and TDF/FTC with efavirenz in Europe (17, 18, 20). This study showed that changes in the renal function from baseline were not significantly different between the two arms, similar to the findings of the ASSERT study. None of the patients in the TDF/FTC arm exhibited progression of CKD stage. On the other hand, the levels of urinary β2 microglobulin deteriorated significantly from baseline in the TDF/FTC arm, whereas improvements were observed in the ABC/3TC arm. This is also similar to the findings reported by the ASSERT trial. This suggests that urinary β2 microglobulin is a more sensitive marker for evaluating TDF nephrotoxicity than the renal function calculated by serum creatinine, as also demonstrated in our previous work (31). Tubular resorption of phosphate, another marker examined to evaluate the renal tubular function, did not exhibit any changes from baseline or between the two arms, suggesting that urinary β2 microglobulin may be a better marker for evaluating TDF nephrotoxicity than tubular resorption of phosphate. Of note, in both arms, the renal function did significantly decrease from baseline. To our knowledge, this is the first randomized trial comparing ABC/3TC and TDF/FTC that observed deterioration of the renal function after the initiation of ART. This result highlights the importance of regular monitoring of renal function after initiation of ART, although it is difficult to draw a firm conclusion on the prognosis of the renal function from this study, due to the limited length of the observation period and the small number of enrolled patients.

Only one patient (1.9%) in the ABC/3TC arm developed a clinically suspected ABC-associated hypersensitivity reaction, which was diagnosed based on the appearance of a skin rash and fever six weeks after commencement of the study drug. The patient fully recovered after discontinuation of the drugs. The ASSERT trial of HLA-B*5701-negative patients reported a similar incidence (3%) of clinically suspected ABC hypersensitivity reactions (17). The one case observed in our trial could be a false positive, because ABC hypersensitivity reactions commonly occur 9-11 days after the initiation of therapy (32), and ABC hypersensitivity was not confirmed immunologically. Nonetheless, immediate discontinuation of ABC is highly recommended even in HLA-B*5701-negative patients suspected of ABC hypersensitivity, since ABC hypersensitivity can occur in such patients (33) and errors in genotyping for HLA or reporting a genotype might occur in practice (34).

Several limitations of this trial should be acknowledged. First, due to the shortage of enrolled patients, the trial was insufficiently powered to test non-inferiority of the viral efficacy of ABC/3TC against TDF/FTC, as initially planned. However, the safety and tolerability data of these regimens in Asia are a valuable asset for patients from this region, and efficacy data could be utilized as part of a meta-analysis in the future. Second, the enrolled subjects were mostly men (primarily men who had sex with men and very few injection drug users). Further studies are needed to examine the efficacy and safety of these regimens in women and patients with different routes of transmissions in Asia.

In summary, this randomized trial demonstrated high efficacy and safety of fixed-dose ABC/3TC and TDF/FTC in combination with ATV/r over 96 weeks for treatment-naïve Japanese patients with a baseline HIV-1 viral load <100,000 copies/mL, although it was insufficiently powered to show non-inferiority of the viral efficacy of ABC/3TC compared with TDF/FTC. ABC/3TC with ATV/r is a safe and efficacious initial regimen for treating HLA-B*5701-negative patients with a baseline HIV-1 viral load <100,000 copies/mL.

Author's disclosure of potential Conflicts of Interest (COI).
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Authors' contributions

SO, MT (Takano), MI, HG, YK and YT designed the study. TE, MH, SK, HU, TK, TN (Naito), MY (Yoshida), NT, MU, YY, TF, SH, KT, MY (Yamamoto), SM, MT (Tateyama) and YT collected the data. HM supervised the study and reviewed and approved study report. TN (Nishijima), HK, HG and SO analyzed and interpreted the data. TN (Nishijima), HK, HG and SO drafted the manuscript and all other authors revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

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HIV/AIDS MAJOR ARTICLE

Prophylactic Effect of Antiretroviral Therapy on Hepatitis B Virus Infection

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Background. Hepatitis B virus (HBV) infection is common in individuals infected with human immunodeficiency virus, especially in men who have sex with men (MSM). Almost all currently used regimens of antiretroviral therapy (ART) contain lamivudine (LAM) or tenofovir disoproxil fumarate (TDF), both of which have significant anti-HBV activity. However, the prophylactic effect of ART on HBV infection has not been assessed previously.

Methods. Non-HBV-vaccinated HIV-infected MSM were serologically evaluated for HBV infection using stocked serum samples. Cases negative for HBV surface antigen (HBsAg), antibody to HBsAg (anti-HBs), and antibody to HBV core antigen (anti-HBc) in first serum samples were serologically followed until last available stocked samples. HBV genotype and LAM-resistant mutation (rtM204V/I) were analyzed in cases that became HBsAg-positive.

Results. The first stocked samples were negative for all analyzed HBV serological markers in 354 of 1434 evaluated patients. The analysis of their last samples indicated HBV incident infection in 43 of them during the follow-up period. The rate of incident infections was lower during LAM- or TDF-containing ART (0.669 incident infections in 100 person-years) than during no ART period (6.726 incident infections in 100 person-years) and other ART (5.263 incident infections in 100 person-years) ($P < .001$). Genotype A was most prevalent (76.5%), and LAM-resistant HBV was more frequent in incident infections during LAM-containing ART (50.0%) than in those during no ART and other ART (7.1%) ($P = .029$).

Conclusions. LAM- and TDF-containing ART regimens seem to provide prophylaxis against HBV infection, although drug-resistant strains seem to evade these effects.

Keywords. lamivudine; tenofovir disoproxil fumarate; resistant; chronic infection.

Patients with human immunodeficiency virus (HIV) infection are at high risk for both hepatitis B virus (HBV) infection and development of chronic infection [1–4]. Based on information from Western countries, the rate of coinfection varies according to risk categories; the highest rate is in men who have sex with men (MSM), with a slightly lower rate among intravenous drug users, and much lower in individuals infected through heterosexual contacts [5–8]. In Japan, HIV/HBV coinfection is also significantly associated with MSM [9, 10]. The progression of chronic HBV infection to cirrhosis, end-stage liver diseases, and/or hepatocellular carcinoma is more rapid in HIV-infected persons than in those with chronic HBV infection alone [11, 12]. Vaccination of non-HBV-immunized HIV-infected individuals is recommended to prevent HBV infection [13]. However, all current recommended antiretroviral therapy (ART) regimens contain lamivudine (LAM) or tenofovir disoproxil fumarate (TDF), both of which have significant anti-HBV activity [14]. Do these ART regimens provide any prophylaxis against HBV infection? This is an important question, as a positive answer could influence the strategy applied to prevent HBV infection in HIV-infected individuals. To delineate the hepatitis B prophylactic effect of ART, we used stocked samples for serological evaluation of HBV infection in HIV-infected MSM. The present

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study included those patients who had tested negative for hepatitis B surface antigen (HBsAg), antibody to HBsAg (anti-HBs), and antibody to hepatitis B core antigen (anti-HBc) using their first stocked blood samples, who were followed up serologically to identify new HBV incident infections among them. The other part of the study covered analysis of the relation between the frequency of incident infection and ART regimens.

METHODS

Patients

Since April 1997, we have stocked serum samples taken at routine clinical practice from HIV type 1 (HIV-1)–infected patients who visited the Outpatient Clinic of the AIDS Clinical Center, National Center for Global Health and Medicine, Tokyo, Japan, under signed informed consent for use in virologic research. Every patient had been interviewed at the first visit by clinical nurse specialists at the HIV outpatient clinic using a structured questionnaire that includes items on sexuality and history of HBV vaccination. Most of the patients regularly visited our clinic every 1–3 months, and we had collected and stored their sera at almost all visits. The ethics committee of the National Center for Global Health and Medicine approved the collection and analysis of the samples. First, we selected HIV-1–infected MSM who met the following inclusion criteria: (1) the first visit to our clinic was between April 1997 and December 2009, (2) they had not received HBV vaccination before the first visit, and (3) at least 2 serum samples were available and collected at least 6 months apart. The first sample was defined as the baseline serum sample, and baseline clinical data were defined as those recorded on the date of sampling of the first stocked serum. Patients' baseline characteristics, including age, race, hepatitis C virus antibody, results of *Treponema pallidum* hemagglutination assay, and $CD4^+$ cell count were collected from the medical records.

HBV Analysis

In order to identify new HBV incident infection, we excluded patients with previously confirmed HBV infection. The baseline samples of the patients who met the inclusion criteria described above were serologically evaluated for HBsAg, anti-HBs, and anti-HBc using ARCHITECT HBsAg QT assay, anti-HBs assay, and anti-HBc assay, respectively (Abbott Laboratories, Chicago, Illinois) [15, 16]. Patients positive for any of HBsAg, anti-HBs, and anti-HBc at baseline were excluded from the serological follow-up. The remaining patients were considered to have never been infected with HBV before the baseline. Their last stocked sample taken before or in December 2010, or before HBV vaccination if performed during the follow-up period, was analyzed for HBsAg, anti-HBs, and anti-HBc. If the last sample was negative for all 3, the patient was considered to have never been infected with HBV up to the sampling date of the last stocked serum. If HBsAg, anti-HBs, or anti-HBc was positive in the last stocked serum, the patient was considered to have HBV incident infection during the follow-up period. In the latter case, the baseline samples were subjected to polymerase chain reaction (PCR) analysis for HBV DNA [17, 18], and all the stocked samples during the follow-up period were serologically analyzed to determine the date of HBV incident infection. The date of incident infection was defined as the sampling date of the first positive serum for any HBV serological marker. The time from the baseline to HBV incident infection was analyzed by the Kaplan-Meier method. The data were censored at the sampling date of the last stocked sample if it was negative for all analyzed HBV serological markers. Patients' age and $CD4^+$ cell count at the date of incident infection and alanine aminotransferase (ALT) values within 3 months of incident infection were collected. If an HBsAg-positive sample was available, HBV genotype and LAM-resistant mutation (rtM204V/I) were analyzed by PCR-invader assay [17–19]. The diagnosis of chronic HBV infection was considered when HBsAg was still positive in sera taken at 6 months or longer after the incident infection.

Antiretroviral Therapy

To determine the type of ART under which HBV incident infection occurred, the regimen information of ART was collected from medical records over the period spanning from the baseline to the incidence infection or to the end of follow-up. The treatment status was divided into 4 categories: (1) No ART, no treatment with any antiretroviral agent; (2) Other-ART, ART with regimens that did not contain LAM, TDF, or emtricitabine (FTC); (3) LAM-ART, ART with LAM-containing regimens that did not contain TDF or FTC; and (4) TDF-ART, ART with TDF-containing regimens with or without LAM or FTC. Data were censored on the sampling date of the last stocked sample if it was negative for all analyzed HBV serological markers. When the treatment category was modified, the data were censored on the date of category change for the previous treatment category and a new follow-up as a different case was initiated for the replacement treatment category.

Statistical Analysis

The time from the baseline to HBV incident infection was analyzed by the Kaplan-Meier method. The Cox proportional hazards regression analysis was used to assess the risk of HBV incident infections. The impact of patients' baseline characteristics, year of entry, the use of antiretroviral agents (any antiretroviral, and any of LAM, TDF, or FTC), and the frequency of changing ART regimen during the follow-up period was estimated with univariate analysis, and those with statistical significance were incorporated into multivariate analysis. The