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Ⅳ. 研究成果の刊行物・別冊

肝炎をめぐる医療政策

正木尚彦／まさきなおひこ
国立国際医療研究センター 肝炎・免疫研究センター 肝炎情報センター

わが国には肝炎ウイルスキャリアが約350万人存在すると推定されており，その内訳はB型肝炎110～140万人，C型肝炎190～230万人である．さらに“ウイルス肝炎は国民病である”との認識が妥当であり，国の医療政策の原点となっている．とくに2010年1月に“肝炎対策基本法”が施行されたことにより，現行の肝炎総合対策に対しこれまで以上の俊敏さ，具体的実効性が求められている．

■肝炎対策基本法

さて，この法律の前文には「B型肝炎及びC型肝炎に係るウイルスへの感染については，国の責めに帰すべき事由によりもたらされ，又はその原因が解明されていなかったことによりもたらされたものがある．特定の血液凝固因子製剤にC型肝炎ウイルスが混入することによって不特定多数の者に感染被害を出した薬害肝炎事件では，感染被害者の方々に甚大な被害が生じ，その被害の拡大を防止し得なかったことについて国が責任を認め，集団予防接種の際の注射器の連続使用によってB型肝炎ウイルスの感染被害を出した予防接種禍事件では，最終の司法判断において国の責任が確定している（下線は著者による追加）」と明記されていることからわかるように，ウイルス肝炎蔓延の原因の一部にわが国固有の事案が存在する．誌幅の都合上，詳細は割愛するが，薬害肝炎事件は凝固因子製剤（フィブリノゲン，第Ⅸ因子）へのC型肝炎ウイルスの混入に起因し（推定患者数1万人以上），一方，予防接種禍事件は，集団予防接種など（予防接種およびツベルクリン反応検査）の際の注射器の連続使用によってB型肝炎ウイルスの水平感染を招いたとされる事案（推定患者数40万人以上）である．前者では患者・国・製薬会社の3者間，後者では患者・国の2者間での和解が成立し，補償が進められているところである．

■都道府県肝疾患診療ネットワークの構築

国がこれまで行ってきたさまざまな肝炎対策のなかで，もっとも画期的な施策の一つが2002～2006年度の5年間全国で展開された節目検診，節目外検診である．B型肝炎ウイルス検診受診者はのべ8,704,587人で，うち100,983人（1.16%）が“陽性”と判定された．一方，C型肝炎ウイルス検診

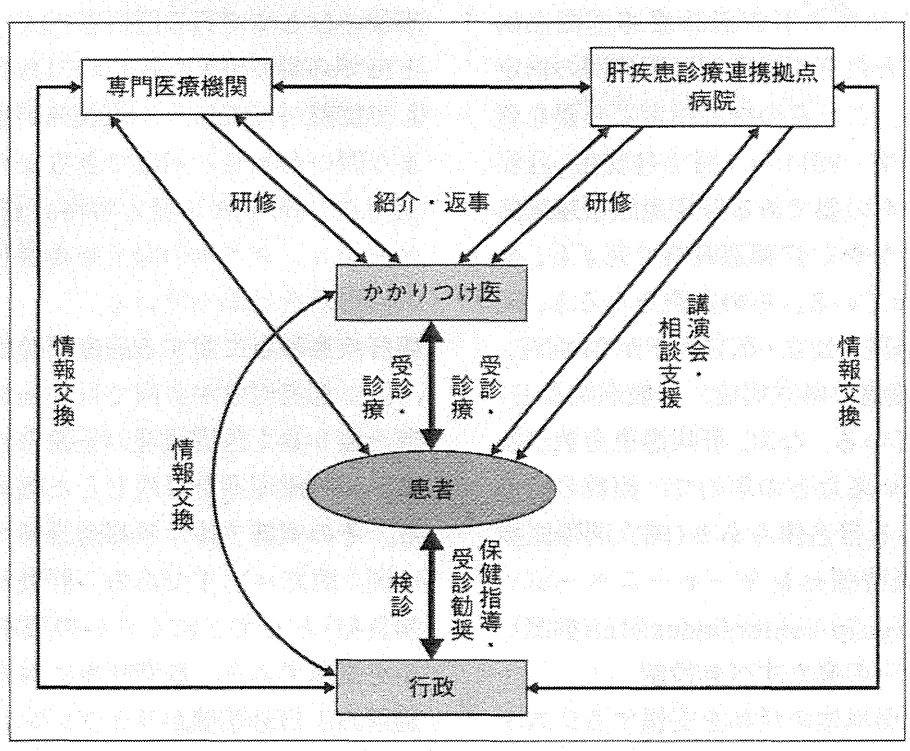

図1 都道府県における肝疾患診療ネットワーク構築（2007年1月厚生労働省）

表 1　肝疾患診療連携拠点病院，専門医療機関に必要とされる資格要件

肝疾患診療連携拠点病院
①肝疾患診療にかかわる一般的な医療情報の提供
②都道府県内の専門医療機関等に関する情報の収集や紹介
③医療従事者や地域住民を対象とした研修会や講演会の開催や肝疾患に関する相談支援
④肝疾患に関する相談医療機関と協議の場の設定
専門医療機関
①専門的な知識をもつ医師による診断と治療方針の決定が可能
②インターフェロンなどの抗ウイルス療法が可能
③肝癌の高危険群の同定と早期診断が可能

受診者はのべ8,634,509人に達し，うち99,950人(1.16%)が“現在，C型肝炎ウイルスに感染している可能性がきわめて高い”と判定された．しかし，その結果が検診受診者に通知されたにもかかわらず，二次精検を目的とした医療機関への受診率は3〜4割程度にとどまり，インターフェロン療法などの抗ウイルス療法を受けた患者数も当初の期待に遠く及ばなかったと推定された．さらに，全国津々浦々における肝疾患診療体制がかならずしも整備されていないという状況も指摘されていた．これを改善するために，国は2007年1月に“都道府県における肝炎検査後肝疾患診療体制に関するガイドライン”を発出し，各都道府県において“かかりつけ医と患者の最小単位”を支援する診療ネットワークを行政側，医療側含めて構築することとした(図1)．この施策に基づいて，自治体ごとに原則1カ所の肝疾患診療連携拠点病院，二次医療圏ごとに肝疾患専門医療機関の指定が進められてきた．これらの施設指定に必要な資格要件を表1に示す．2011年4月1日現在，肝疾患診療ネットワークの要である肝疾患診療連携拠点病院の指定がようやく47都道府県で完了し，全国で70病院となっている．その内訳をみると，国立大学法人が34病院，公立・私立大学が24病院，その他(国立病院機構，県立病院，一般病院など)が12病院となっている．なお，肝疾患患者数が多く広域に分布しているなどの理由で，複数の拠点病院を指定している自治体もある(国立国際医療研究センター肝炎情報センターホームページ：http://www.ncgm.go.jp/center/index.html参照)．

■肝炎情報センターの果たすべき役割

さらに，都道府県単位の活動を支援するシステムとして，国立国際医療センター(現国立国際医療研究センター)に2008年11月，肝炎情報センターが設置された(千葉県市川市)．その果たすべき役割として3つのミッションがある[1]．

第1に“インターネットなどによる最新情報提供”であり，2008年12月には肝疾患医療に関する診療ガイドライン，肝炎診療をめぐる国内外の情報などを“一般向け，医療従事者向け，および肝臓専門医向け”に発信するためのホームページを立ち上げた．第2に“拠点病院間での情報共有を支援する”ことで，肝疾患診療連携拠点病院で構成する連絡協議会を年に2回開催し，拠点病院事業における問題点の解決をめざした話し合いを行っている．第3に，肝疾患診療連携拠点病院などに勤務する医療従事者(医師，看護師，相談員，臨床検査技師ほか)を対象とした“研修会”の企画・立案・推進を行っている．とくに，拠点病院事業のひとつである肝疾患相談センターの運営にとって必要不可欠な相談員の育成は最重要課題として位置づけており，相談員が患者からのさまざまな問い合わせに対応できるように，医療資源の活用法に関する知識の習得，患者とのコミュニケーションスキルの向上をめざした研修プログラムの提供をはかっている．

■肝疾患患者に対する医療費助成事業

国と都道府県が共同で行う施策には，肝疾患患者を取り巻く医療環境の整備のほかに，肝疾患患者への治療促進を目的とした医療費助成事業がある．その実施主体は各都道府県であり，財源負担は国：地方＝1：1である．肝炎治療に1カ月分(3割負担)としてどれくらいの薬剤費が必要であるかを概算すると，B型肝炎に対する核酸アナログ製剤の1日分薬価がラミブジン，アデホビル，エンテカビルそれぞれ，622.00円，1,252.10円，

1,032.30円であることから，ラミブジン耐性患者でラミブジン・ヘプセラを併用すると1,874.1×28×0.3＝15,742円，エンテカビル単独で1,032.3×28×0.3＝8,671円となる．一方，C型慢性肝炎の標準的治療であるペグインターフェロン・リバビリン併用療法については，ペグイントロン100 μg注29,550.0円，レベトール200 mgカプセル764.60円であることから，体重65 kgとして1カ月分(3割負担)で(29,550×4＋764.6×4×28)×0.3＝61,151円となる．ペガシス・コペガス併用療法の場合も，ほぼ同額である．さらに，2011年9月に保険承認されたテラプレビル(テラビック®)も1錠1,422.1円と非常に高額で，1日分(9錠)が1,422.1×9×0.3＝3,840円のため，12週間3剤併用＋12週間2剤の24週間治療で3割負担の場合，約68.9万円(1カ月分11.5万円)に達する．したがって，抗ウイルス療法を広く普及させるためには，医療費助成がきわめて有効と考えられる．このような観点から，国と都道府県は肝炎治療特別促進事業として，2008年度からはB型・C型ウイルス性肝炎に対するインターフェロン治療，2010年度からはB型肝炎に対する核酸アナログ製剤治療への医療費助成を開始している．自己負担限度額は所得に応じて当初は1万円・3万円・5万円であったが，その後，1万円・2万円とさらなる負担軽減がはかられている．テラプレビルについても，医療費助成の対象となることが2011年11月28日付でいち早く決定された．これとは別に，身体障害者認定による重度肝硬変患者への医療費助成が2010年度から開始されている．対象者は，肝硬変の重症度分類として繁用されているChild-Pugh分類の合計点数10点以上(グレードCに該当)が3カ月以上持続していることが前提で，加えて日常生活活動の制限などに関する項目数などに応じて，もっとも障害程度の重い1級から，もっとも軽症な4級までの4等級に分類されている．肝硬変の原因として肝炎ウイルスに起因するもの以外も含まれているが，とくにアルコールに起因するものについては，6カ月以上の禁酒の確認が厳しく求められている．さらに，肝移植とこれに伴う医療も自立支援医療の対象とされており，医療費の自己負担額軽減がはかられている．とくに，移植後に抗免疫療法を必要とする期間は，これを実施しないと肝機能が廃絶する危険性があるため，障害程度1級と認定される．

■おわりに

冒頭で述べたように，現行の肝炎総合対策は“肝炎対策基本法”という法律に基づいて進められている．第一章第一条において「国，地方公共団体，医療保険者，国民及び医師等の責務を明らかにし，……」と述べられているように，国民すべてに担うべき役割があることを認識すべきである．

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ORIGINAL ARTICLE

Chronic hepatitis B in patients coinfected with human immunodeficiency virus in Japan: a retrospective multicenter analysis

Shintaro Yanagimoto · Hiroshi Yotsuyanagi · Yoshimi Kikuchi · Kunihisa Tsukada · Michio Kato · Junki Takamatsu · Shuhei Hige · Kazuaki Chayama · Kyoji Moriya · Kazuhiko Koike

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Abstract A nationwide survey in Japan revealed that about 6 % of human immunodeficiency virus (HIV)-positive patients are coinfected with hepatitis B virus (HBV). To further analyze the features of liver disease in HIV/HBV-coinfected patients, we analyzed 252 patients from six hospitals in the HIV/AIDS (acquired immunodeficiency syndrome) Network of Japan. The mean age was 39.5 years, and the proportion of male patients was very high (243 of 252; 96 %). The main transmission route was male homosexual contact (186 of 252; 74 %), followed by heterosexual contact. The HBV genotype was determined in 77 patients. Among them, genotype A HBV was the most frequent (58 of 77; 75 %) and was detected almost exclusively in homosexual patients. Acute hepatitis B was documented in 21 patients (8 %). Three of the 252 HIV/HBV-coinfected patients developed advanced liver disease with the complication of ascites, hepatic encephalopathy, or hepatocellular carcinoma. A comparison between patients not treated and those treated with antiretroviral drugs including anti-HBV drugs revealed that the baseline liver function was worse in treated patients. However, the serum albumin levels and platelet counts in both groups increased after treatment and were similar. Liver disease-associated death was not observed. Here, we characterize the clinical features of liver disease in HIV/HBV-coinfected patients in Japan for the first time. The findings suggest that antiretroviral therapy with anti-HBV drugs may retard the progression of a liver disease and prevent liver disease-associated death in such patients.

Keywords Acquired immunodeficiency syndrome · Chronic liver disease · HBV DNA · Genotype

S. Yanagimoto · H. Yotsuyanagi (✉) · K. Moriya · K. Koike
Department of Internal Medicine, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
e-mail: hyotsu-tky@umin.ac.jp

Y. Kikuchi · K. Tsukada
AIDS Clinical Center, International Medical Center of Japan, Tokyo, Japan

M. Kato
Department of Gastroenterology, Osaka National Hospital, Osaka, Japan

J. Takamatsu
Division of Transfusion Medicine, Nagoya University Hospital, Nagoya, Japan

S. Hige
Department of Gastroenterology and Hematology, Hokkaido University Graduate School of Medicine, Sapporo, Japan

K. Chayama
Department of Medicine and Molecular Science, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima, Japan

Introduction

The number of human immunodeficiency virus (HIV)-positive patients is growing in Japan [1]. Although combination therapy with antiretroviral agents has made HIV infection itself somewhat controllable in many cases since its introduction in 1996, and mortality from opportunistic infection has decreased, existing comorbidities are the focus of current patient care. In fact, more than 50 % of deaths in HIV-1-infected patients are not related to acquired immunodeficiency syndrome (AIDS); the mortality from liver disease is second only to AIDS-related mortality [2]. Risk factors related to significant liver

diseases among HIV-positive patients include a diagnosis of viral hepatitis [3], nonalcoholic fatty liver disease [4], and excessive alcohol consumption [5]. Among these factors, hepatitis B and hepatitis C are of particular importance because they can often lead to life-threatening diseases such as cirrhosis and hepatocellular carcinoma by themselves.

The estimated prevalence of chronic hepatitis B virus (HBV) infection in Japan is less than 1 %, or 0.9 million carriers [6]. However, about 6 % of HIV-positive patients are coinfected with HBV [7]; this coinfection rate is more than six times higher than that in the non-HIV population. In the United States, the HIV/HBV coinfection rate is reported to be in the range of 6–14 % [8–10].

Several issues make the management of HIV/HBV coinfection complicated. HBV infection tends to be persistent in HIV-positive patients [9, 11, 12]. Chronic HBV infection may lead to hepatitis, cirrhosis, or hepatocellular carcinoma. The progression of a liver disease associated with chronic HBV infection is more rapid in HIV/HBV-coinfected patients than in HBV-monoinfected patients [13].

Combination regimens of antiretroviral therapy (ART) for coinfected patients should be carefully determined. Initial combination regimens of ART for HIV/hepatitis C virus (HCV)-coinfected patients are basically the same as those for HIV patients without HCV infection. However, because some nucleoside reverse transcriptase inhibitors (NRTIs) used in HIV treatment have activity against HBV, and some NRTIs mainly used in HBV treatment have partial activity against HIV [14], careful choice of treatment agents is necessary in HIV/HBV coinfection. Abrupt discontinuation of NRTIs that are active against HBV may aggravate viral hepatitis. Administration of entecavir, which has a weak activity against HIV, to HIV/HBV-coinfected patients without simultaneous effective HIV treatment may cause the accumulation of drug-resistant HIV strains [15–17]. In such cases, drug resistance of HBV may occur as well [18].

Drug-induced liver injury following ART is another concern. HIV/HBV-coinfected patients show an increase in transaminase level at a higher rate [19, 20]. However, it is often unclear whether this increase is caused by drug hepatotoxicity because the treatment of HIV infection causes immune reconstruction in patients, which alone could contribute to the transaminase level increase in viral hepatitis.

The objective of this study is to clarify the clinical features of HIV/HBV coinfection in Japan and to clarify the impact of ART on liver function among HIV/HBV-coinfected patients. The estimated prevalence of chronic HBV infection among the general population in Japan is decreasing yearly, but it remains much higher than that in the United States [21], where universal hepatitis B vaccination is introduced. Thus, the detailed analysis of HIV/HBV coinfection in Japan is of particular importance.

Patients and methods

We have conducted a multicenter retrospective study based on the data from a nationwide survey in 2006 conducted by sending questionnaires to 372 member hospitals of the HIV/AIDS network of Japan as of January 2006, and part of the results was reported earlier [7]. Following the survey, 6 of the 207 hospitals that responded to the survey—Hokkaido University Hospital (Hokkaido, Japan), University of Tokyo Hospital (Tokyo, Japan), Nagoya University Hospital (Aichi, Japan), International Medical Center of Japan (currently, National Center for Global Health and Medicine, Tokyo, Japan), Osaka National Hospital (Osaka, Japan), and Hiroshima University Hospital (Hiroshima, Japan)—were chosen for further studies because more than two-thirds of the HIV/HBV-coinfected patients identified in the survey went to these hospitals, and because both HIV experts and hepatologists were following up those patients there.

The questionnaire sent to the hospitals included items regarding the number of patients who visited the hospitals at least once between January and December in 2006 as follows: (1) the number of HIV-positive patients; (2) the number of hepatitis B surface antigen (HBsAg)-positive patients among (1); (3) the number of patients among (2) who were determined at least once to have a serum alanine aminotransferase (ALT) level higher than 100 IU/l; (4) the number of HIV-positive patients who contracted HIV from blood products; (5) the number of HBsAg-positive patients among (4); (6) the number of patients among (5) who were determined at least once to have a serum ALT level higher than 100 IU/l; (7) the number of HIV-positive patients whose presumed transmission route is through homosexual contact; (8) the number of HBsAg-positive patients among (7); (9) the number of patients among (8) who were determined at least once to have a serum ALT level higher than 100 IU/l; (10) the number of HIV-positive patients who presumably contracted HIV through injection drug use; (11) the number of HBsAg-positive patients among (10); (12) the number of patients among (11) who were determined at least once to have a serum ALT level higher than 100 IU/l; (13) the number of HIV-positive patients whose transmission routes were classified as "others"; (14) the number of HBsAg-positive patients among (13); and (15) the number of patients among (15) who were determined at least once to have a serum ALT level higher than 100 IU/l.

We defined confirmed HIV infection with positivity for serum HBsAg as the criterion for HIV/HBV coinfection.

After identifying HIV/HBV-coinfected patients, medical records including laboratory data of these patients were reviewed between the date of the oldest available record for these patients and the final date of the record acquired by the end of the study. The laboratory data at the diagnosis or first recognition of HBV infection and the latest data in the study period were compared for analysis unless otherwise noted. HBV genotypes (A through D) were determined serologically by enzyme immunoassay (EIA) using commercial kits (HBV GENOTYPE EIA; Institute of Immunology, Tokyo, Japan) on the basis of the pattern of detection using monoclonal antibodies of a combination of epitopes on preS2-region products, each of which was specific for each genotype [22, 23].

Ethical issues

The respective ethics committees of the six hospitals approved the study. Informed consent was obtained from each study participant.

Statistical analyses

For the comparison of means of collected data, Student's *t* test (paired *t* test) was performed unless otherwise specified. The chi-square test was performed to determine the independence of clinical parameters.

Results

Two hundred and fifty-two patients were identified to have HIV/HBV coinfection. The mean age was 39.5 years, and the proportion of male patients was very high (243 of 252; 96.4 %). The main presumed transmission route of HIV was male homosexual contact (186 of 252; 73.8 %), followed by heterosexual contact. Among those HIV/HBV-coinfected patients, 21 of the 252 (8.3 %) acquired acute hepatitis during the study period (Table 1).

Table 1 Clinical background of HIV/HBV-coinfected patients

Number (male:female)	243:9
Age (year)	39.5 ± 9.6[a]
Presumed Transmission Route	
Transfusion	14
Homosexual contact	186
Heterosexual contact	24
Injection drug use	2
Others	4
Onset as acute hepatitis	21

[a] Mean ± standard deviation

The HBV genotype was determined in 77 patients. Among them, genotype A HBV was the most frequent (58 of 77; 75.3 %), followed far behind by genotype C (7 of 77; 9.1 %), which is the predominant genotype in the entire chronic hepatitis B population in Japan. Genotype B, which is also common in Japan, was found only in three patients (3.9 %). Genotype A was detected almost exclusively in homosexual patients (57 of 58; 98.3 %) (Fig. 1).

At the end of the study period, 113 patients (44.8 %) received some type of anti-HBV drug such as interferon, lamivudine, adefovir, or entecavir, not as part of anti-HIV treatment. Ninety-seven (38.5 %) patients were still taking anti-HBV drugs by the end of the study period. The median ALT level was 30.0 IU/l (5th percentile, 11.1; 95th percentile, 128.9), suggesting the existence of some liver injury. Liver function was normal in most HIV/HBV-coinfected patients. The mean serum albumin level was 4.1 ± 0.6 g/dl, and the median serum total bilirubin level was 0.8 mg/dl (5th percentile, 0.3; 95th percentile, 3.8). The mean platelet count was 21.0 ± 6.1 × 10^4/ml. The hepatitis B e antigen (HBeAg) was detected in 84 patients, and the HBV DNA level was high (higher than 100,000 IU/l) in 55 patients (Table 2). Three of the 252 (1.1 %) HIV/HBV-coinfected patients developed advanced chronic liver diseases, such as cirrhosis with the complication of ascites and/or hepatic encephalopathy, or hepatocellular carcinoma. Although we tried to retrieve information on alcohol consumption of the patients, it was available for only a limited number of patients (26 of 252); among the 26, only 2 patients had a habit of taking more than 60 g alcohol per day. The remaining 24 patients took alcohol only on social occasions. The antiretroviral agents used for these study patients are listed in detail in Table 3. Among those who had a known history of ART, 158 of 252 (62.7 %) received regimens that include anti-HBV drugs at least once previously, whereas 42 (16.7 %) did not, and no information is available for the remaining 52. The most common drug combination for HIV/HBV-coinfected patients was ATV/r + FTC/TDF (22 of 172; 12.8 %) (Table 4). FTC/TDF, composed of two drugs active against HBV, is recommended for HIV/HBV-coinfected patients

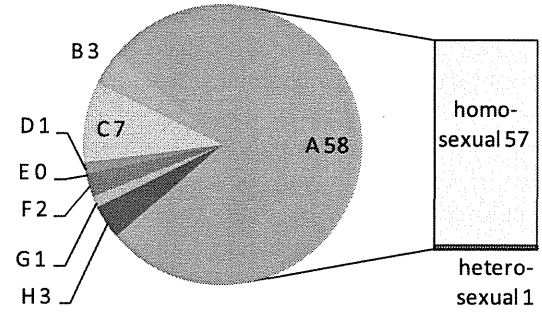

Fig. 1 Hepatitis B virus (HBV) genotype

Table 2 Liver function and related parameters of HIV/HBV-coinfected patients

Albumin (g/dl)	4.1 ± 0.6
Bilirubin[a] (mg/dl)	0.8 (5th percentile, 0.3; 95th percentile, 3.8)
ALT[a] (IU/l)	30.0 (5th percentile, 11.1; 95th percentile, 128.9)
WBC ($\times 10^3/\mu l$)	5.2 ± 1.6
Platelet ($\times 10^4/\mu l$)	21.0 ± 6.1
HBeAg (positive:negative)	84:68
HBV DNA (high:low)[b]	55:127

[a] Median and percentiles are provided instead of mean and standard deviation because of the nonnormality of the distribution

[b] HBV DNA level of 100,000 IU/l or higher is categorized as "high"

as one of the preferred NRTI backbones of the ART regimen [24].

We compared the clinical characteristics between patients who received the full ART and those who did not. Regarding the baseline statistical data, the observation period was longer for patients on ART, and there were more patients with AIDS in the ART group (10 of 64 vs. 52 of 162) (Table 5a). No significant difference was observed between the non-ART and ART groups in male/female ratio, age, transmission route, HBV markers, or advanced liver disease. Liver-related death was not observed, but hepatic failure with ascites and/or hepatic encephalopathy developed in 2 patients on ART and hepatocellular carcinoma developed in another patient.

Comparison between the ART group and the non-ART group revealed that the baseline liver function was worse in the ART group. At the beginning of the study period, the ART group showed a significantly lower CD4+ T-cell count than the non-ART group. The total white blood cell count and platelet count were also lower in the ART group. Although it is not statistically significant, the serum albumin level and prothrombin time (PT) index were lower in the ART group. However, at the end of the observation period, these parameters improved significantly in the ART group. The difference in CD4+ T-cell count between the ART and non-ART groups became marginal and became statistically insignificant (Table 5b).

Changes in the liver function of HIV/HBV-coinfected patients may not be fully explained by the changes in HBV activity because some parameters relevant to the estimation of liver function showed paradoxical changes. To clarify this observation, we compared the changes in liver function among HIV/HBV-coinfected patients on ART with respect to protease inhibitor (PI) use.

The mean serum total bilirubin level in patients on ART with PI use (PI group) at the beginning of the observation period was 1.1 mg/dl, whereas that in patients without PI use (non-PI group) was 0.8 mg/dl. The means at the end of the study period were 1.6 mg/dl in the PI group and 0.7 mg/dl in the non-PI group. Because the sample distribution of serum total bilirubin level did not follow the normal distribution by logarithmic transformation, we compared the means statistically. At the beginning, the difference in the mean between the PI group and the non-PI group was not significant ($p = 0.257$). At the end of the observation period, a statistically significant difference ($p = 0.001$) was observed. We then calculated the

Table 3 Antiretroviral treatment of HIV/HBV-coinfected patients

Antiretroviral drugs	Number of patients
NRTIs	
Zidovudine (AZT)	34
Didanosine (ddI)	9
Ddl / enteric coated	7
Zalcitabine (ddC)	1
Stavudine (d4T)	4
Lamivudine[a] (3TC)	84
Abacavir[3] (ABC)	38
Tenofovir[3] (TDF)	27
Emtricitabine (FTC) / TDF[a]	57
NNRTIs	
Nevirapine (NVP)	10
Efavirenz (EFV)	34
Delavirdine (DLV)	1
PIs	
Indinavir (IDV)	4
Ritonavir (RTV)	50
Nelfinavir (NFV)	8
Lopinavir (LPV)	3
Ritonavir-boosted LPV (LPV/r)	40
Atazanavir (ATV)	39
ATV/r	6
Fosamprenavir (FPV)	13

NRTI nucleoside reverse transcriptase inhibitor, *NNRTI* non-nucleoside reverse transcriptase inhibitor, *PI* protease inhibitor

[a] Agents with anti-HBV activity

Table 4 Antiretroviral regimens used for HIV/HBV-coinfected patients

Antiretroviral regimen	Number of patients
ATV/r + FTC/TDF	22
LPV/r + 3TC + TDF	8
LPV/r + FTC/TDF	7
EFV + FTC/TDF	6
ATV/r + 3TC + TDF	5

Table 5 Comparison of changes in clinical parameters of HIV/HBV-coinfected patients with or without antiretroviral therapy (ART)

a. Baseline statistical data	Natural course[a] (without ART)	With ART	*p* value (with vs. without ART)
Number (male:female)	84:6	159:3	0.105†
Age (year)	37.0 ± 10.3	39.0 ± 9.1	0.362
Observation period (month)	34.5 ± 55.5	50.9 ± 43.9	0.022*
Presumed transmission route	Blood products:homosexual contact:heterosexual contact:injection drug use:other		
	5:60:12:2:3	9:126:12:0:1	0.052†
Recognized acute hepatitis	10	11	0.243†
HBeAg (positive:negative)	42:18	100:40	0.394†
HBV DNA (high:low)	29:18	83:37	0.356†
HBV genotype	A:B:C:D:F:G:H		
	17:0:1:1:1:0:1	31:3:6:0:1:1:2	0.372†
Ascites	1/56	2/144	1.000†
Hepatocellular carcinoma	0/62	1/159	1.000†
Acquired immunodeficiency syndrome (AIDS)	10/64	52/162	0.012*,†

b. Comparison of clinical parameters between pre- and post-ART among patients with and without ART	Natural course (without ART)	With ART	*p* value (with vs. without ART)
CD4 count (per μl)			
Start[b]	402.9 ± 180.1	242.5 ± 187.6	0.000*
End[c]	406.4 ± 212.4	398.1 ± 195.9	0.883
p value (start vs. end)	0.893	0.000*	
Albumin (g/dl)			
Start	4.1 ± 0.4	3.8 ± 0.8	0.292
End	3.9 ± 0.8	4.2 ± 0.4	0.025*
p value	0.473	0.001*	
Bilirubin[d] (mg/dl)			
Start	0.7 (0.30, 4.26)	0.5 (0.30, 2.62)	0.138
End	0.5 (0.25, 1.30)	0.9 (0.36, 4.32)	0.000*
p value	0.046*	0.000*	
ALT[d] (IU/l)			
Start	46.0 (15.0, 1418.2)	34.0 (12.8, 1,068.8)	0.120
End	27.0 (9.9, 229.9)	31.5 (12.73, 89.3)	0.713
p value	0.003*	0.000*	
Prothrombin time index (%)			
Start	89.4 ± 13.1	78.8 ± 23.0	0.650
End	78.8 ± 27.3	84.2 ± 16.3	0.531
p value	0.377	0.218	
WBC ($\times 10^3$/μl)			
Start	6.1 ± 2.4	4.8 ± 2.1	0.000*
End	5.4 ± 1.4	5.1 ± 1.6	0.404
p value	0.044*	0.247	
Platelet ($\times 10^4$ /μl)			
Start	22.2 ± 6.5	19.3 ± 6.3	0.010*
End	21.2 ± 6.5	20.8 ± 6.1	0.649
p value	0.204	0.001*	

* $p < 0.05$

† Chi-square test was performed

[a] Two patients with habitual alcohol intake were included in this group

[b] Start of observation period

[c] End of observation period

[d] Means were compared by log transformation because of the nonnormality of the distribution; median and percentiles (5th percentile, 95th percentile) are provided

difference in serum total bilirubin level between the beginning and the end of the observation period [Dbilirubin level = (bilirubin level at the end) − (bilirubin level at the beginning)] in individual patients and compared it between the PI group and the non-PI group. The mean Dbilirubin level in the PI group was 0.5 ± 3.4 mg/dl and that in the non-PI group was −0.2 ± 1.6 mg/dl ($p = 0.250$). The Dbilirubin level in a patient in the PI group who was coinfected with HCV besides HIV/HBV as well was −27.4 mg/dl. Excluding this single outlier, the mean Dbilirubin level was significantly different between the PI and non-PI groups (mean Dbilirubin level 0.8 vs. −0.2; $p = 0.01$).

Discussion

We have summarized here the data from our comprehensive survey of HIV/HBV coinfection in Japan, focusing particularly on the clinical features of the patients and the effect of ART on liver function. As we reported earlier, HIV/HBV coinfection was observed in 6.3 % of Japanese HIV-positive patients [7]. Certain considerations for HBV coinfection are important in HIV patient care.

The major transmission route of HIV was male homosexual contact, which accounted for the infection in about 80 % of the patients; thus, male patients were the majority in the present cohort. The most frequently found genotype of HBV was genotype A, which is infrequent in HIV-negative patients in Japan. Genotype A is often found in the United States, Europe, India, and the west coast of Sub-Saharan Africa [25]. Although the data on HBV subgenotypes were not available in our study, some reports showed that most genotype A strains detected in HIV/HBV-coinfected individuals are of genotype Ae [26]. These findings suggest that HBV infection among Japanese HIV carriers is not caused by the spread of indigenous HBV, such as transmission in the perinatal period, but rather specific strains are circulating among the homosexual population in Japan. Genotypes B and C accounted for more than 96 % of the entire Japanese chronic HBV infection [27, 28]. These findings are compatible with the report that the presumed transmission route of HBV in HIV/HBV-coinfected patients is not from Japanese female partners but from male partners, as shown by Koibuchi et al. [29].

Seventy-five percent of HIV/HBV-coinfected patients received ART with two agents against HBV, and its efficacy against HBV as well as HIV is considered to be high. As recommended by the United States Department of Health and Human Services (DHHS) and the Japanese guidelines on HIV treatment, the initiation of ART with NRTIs with anti-HBV activity as the backbone is indicated for HIV/HBV-coinfected patients regardless of HIV viral load or CD4+ T lymphocyte count [30]. Nucleoside analogues can improve liver function in HBV-monoinfected patients [31]. Our study shows that ART decreased the levels of ALT and albumin in HIV/HBV-coinfected patients. It is noteworthy that the regimen used in ART includes multiple drugs with anti-HBV activity such as lamivudine plus abacavir, which is unusual for HBV-monoinfected patients.

When we compared the characteristics of patients on ART with those not on ART, there were some notable differences in their immune status and liver function. At the beginning of the observation period, patients on ART showed a lower CD4+ T-cell count and poorer liver function. Our study is a retrospective observation, and patients were not grouped randomly. These observations are rather understandable because those who had a low CD4+ T cell count were more likely candidates for ART. Additionally, patients on ART had a longer observation period and were more likely to develop AIDS. These findings are also understandable because the longer the duration of HIV infection, the more likely is the immune system of the patient to deteriorate. Moreover, once ART is started, patients need to visit clinics or hospitals regularly for a long period; in reality, for the rest of their life. Following current recommendations for the initiation of ART for HIV infection, patients with worse immune status are more likely to receive the treatment. These findings can explain our observation.

Our data show that the serum albumin level and platelet count improved in the patients who were on ART. As the regimen of ART usually contains two drugs against HBV, ART suppresses HBV replication, which may lead to an improved liver function, as observed in HBV-monoinfected patients treated with nucleoside analogues [31]. Long-term treatment with lamivudine was shown to regress the fibrosis of the liver [32, 33] and decrease the proportion of patients with hepatocellular carcinoma complication [34]. In view of these findings, ART for HIV/HBV-coinfected patients may markedly improve the prognosis of patients. In our study, only a small number of patients with advanced liver diseases associated with HBV infection such as cirrhosis or hepatocellular carcinoma were observed, which could be attributable in part to the short observation period and the short duration of HBV infection. If we had a longer observational period, we would be able to clarify the difference in clinical course between the ART and non-ART groups, and the actual significance of ART for HIV/HBV-coinfected patients should become clearer.

We found that some parameters related to liver function changed paradoxically, particularly in the ART group. Although the mean serum albumin level, ALT level, and platelet count improved, the mean serum bilirubin level worsened, from 0.5 to 0.9 mg/dl. On the other hand, the serum bilirubin level in the non-ART group decreased. Both changes are statistically significant, which suggests

that the observed hyperbilirubinemia was not associated with HBV activity. The increase in serum bilirubin level is presumably caused by PIs. Hyperbilirubinemia following PI administration was previously reported [35]. Although it is unclear whether hyperbilirubinemia itself may lead to liver injury, PIs should be used carefully particularly for patients with advanced liver diseases.

Our present study has one major limitation; that is, the effect of alcohol on liver function was not analyzed because the history of alcohol consumption could not be obtained in the majority of the studied patients. Excessive alcohol consumption has been found to be an important risk factor for the development of severe hepatic injury in HIV-infected patients with [3] or without HCV coinfection [5]. Our present study showed that among the 26 patients whose history of alcohol consumption was available, only 2 patients were habitual drinkers. The results suggested that the effect of alcohol on liver function is small in HIV/HBV-coinfected patients in Japan.

In conclusion, ART with anti-HBV drugs may retard the progression of liver diseases and prevent liver-related death in HIV/HBV-coinfected patients. Multiple agents with anti-HBV activity seem essential for the efficacy. PIs should be carefully used particularly for patients with advanced liver diseases.

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