Do HIV Care Providers Appropriately Manage Hepatitis B in Coinfected Patients Treated with Antiretroviral Therapy?

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Background. The common occurrence of hepatitis B virus (HBV) infection in patients who carry the human immunodeficiency virus (HIV) demands that both viruses be recognized, evaluated, and treated when appropriate.

Methods. We identified 357 HIV- and hepatitis B surface antigen–positive patients who underwent testing from 1999 to 2003; 155 patients who were new to our clinic and who initiated therapy for HIV and HBV coinfection were considered for inclusion in the study. The frequency of HIV testing (to determine HIV load and $CD4^+$ cell count) performed during the first year of therapy was compared with the frequency of HBV measurements (to determine hepatitis B e antigen, antibody to hepatitis B e antigen, and HBV load), abdominal ultrasound examination, and measurement of levels of α-fetoprotein in serum.

Results. HBV load data were obtained for only 16% of patients before initiation of antiretroviral therapy (ART), whereas HIV load was determined for 99% of patients before initiation of ART. The total number of HIV load measurements obtained during the first year after ART initiation was 497 (median number of HIV load measurements per patient, 3.0), compared with 85 measurements of HBV load (median number of HBV load measurements per patient, <1; $P < .001$). The percentage of patients who received any level of HBV monitoring (i.e., tests to determine hepatitis B e antigen, antibody to hepatitis B e antigen, and HBV load) after ART initiation increased from 7% in 1999 to 52% in 2001 ($P < .001$), whereas the percentage of patients who underwent HIV load testing remained at 80%–90% during the same period.

Conclusions. Health care providers treating patients with HIV infection during the period 1999–2003 infrequently monitored HBV response in coinfected patients, but they systematically monitored HIV response after ART initiation. Improved physician adherence to guidelines that better delineate HBV treatment and monitoring for patients with HIV-HBV coinfection is needed.

In the United States, up to 10% of all HIV-infected persons are coinfected with hepatitis B virus (HBV) [1–3]. As HIV-infected patients live longer as a result of antiretroviral therapy (ART), HBV infection has increasingly gained importance as a cause of death in such patients [2–5]. When patients receive drugs with dual activity (e.g., lamivudine, tenofovir disoproxil fumarate, and emtricitabine), they may experience acute flares of hepatitis resulting from immune reconstitution, drug withdrawal, the development of HBV drug-resistance mutations, or all 3 causes [6–12]. The increased risk of hepatocellular carcinoma (HCC) [13] and the emergence of HBV drug-resistant mutations necessitates careful monitoring of coinfected patients after antiviral therapy is begun.

Over the last 10 years, HBV therapy has improved considerably. Suppression of HBV replication using nucleoside and nucleotide analogues results in histologic improvement, slower disease progression, and increased long-term survival [14]. Effective case management for patients receiving drugs active against HBV requires monitoring HBV disease markers, aminotransferase levels, hepatitis B e antigen (HBeAg) status, and, in particular, HBV load to determine if therapy is needed and to assess response to treatment [15–17]. The goal of HBV therapy continues to be suppression of HBV replication and, if possible, HBeAg clearance [16, 18]. In addition, HBV management guidelines recommend

Received 1 September 2006; accepted 22 December 2006; electronically published 21 February 2007.

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Clinical Infectious Diseases 2007; 44:996–1000

1058-4838/2007/4407-0020$15.00
DOI: 10.1086/512367

screening for cirrhosis with imaging, α-fetoprotein (AFP) testing, and liver biopsy, if appropriate [16]. Previous HIV treatment guidelines [19] have outlined both when HIV therapy should be initiated and when HIV loads should be measured, and current guidelines [20] recommend agents for treating patient with HIV-HBV coinfection but do not suggest how to monitor HBV response. To date, no studies have focused on how HIV care providers evaluate and monitor HIV-HBV–coinfected patients. Thus, the goal of our study was to determine the level of care for HBV infection that was being provided to patients with HIV infection by their health care providers.

PATIENTS AND METHODS

Of 357 hepatitis B surface antigen (HBsAg)–positive patients seen from 1999 to 2003 at Parkland Health and Hospital System outpatient HIV clinic (Dallas, TX), we identified 155 who were new to the HIV clinic and who had initiated ART after 1999; these patients formed the basis of our study. Of the 357 patients seen from 1999 to 2003, 124 (35%) were excluded from the study because they initiated ART before 1999, 45 (13%) were excluded because they had test results positive for HBsAg after ART initiation, 32 (9%) were excluded because they had no HIV or HBV therapy documented, and 1 was excluded because HBsAg seroconversion had occurred prior to ART initiation. In the group of patients who did not have a record of ART initiation, most had high $CD4^+$ cell counts and/or did not return for follow-up visits and were never assessed fully for severity of liver disease. For the 155 patients in the cohort, baseline data collected included patient demographic data, serum aminotransferase levels, $CD4^+$ cell counts, HIV load, HCV antibody (anti-HCV) levels, hepatitis delta antibody (anti-HDV) levels, risk factors for HIV acquisition, and HIV and/or HBV therapy (including the date of therapy initiation). We determined the frequency of HBV testing (i.e., testing to determine HBeAg, antibody to HBeAg [anti-HBe], and HBV load) from 90 days prior to baseline to 1 year after initiation of therapy. In addition, the frequency of HIV load and $CD4^+$ cell count measurements was determined during the first year after initiation of therapy. Patients were grouped by frequency of HIV load measurements into those with 0–1, 2–3, and ⩾4 virus load measurements during the first year of therapy. This served as a surrogate for the number of follow-up visits. To examine overall monitoring for HBV infection, we determined the frequency of HBV testing (i.e., testing to determine HBeAg, anti-HBe, and HBV load) and screening for HCC (i.e., ultrasound or AFP measurements). In addition, we examined pharmacy data for patients with $CD4^+$ cell counts <200 cells/μL to determine whether this group was administered pneumocystis pneumonia prophylaxis, as recommended by HIV practice guidelines [21], in a timely fashion (i.e., within 2 months) after ART initiation. We determined the time intervals from initiation of ART to first HBV DNA quantification assay or HBeAg and anti-HBe test and from initiation of treatment to first measurement of HIV RNA level and $CD4^+$ cell count for every year of the study. The University of Texas Southwestern Medical Center's institutional review board approved the study.

Jonckheere-Terpstra analysis was used to test ordered differences among start year and HBV testing and HIV load testing, as well as to test HIV load groups and HBV and HCC testing during the first year of therapy. The χ^2 test or Fisher's exact test were used to compare the occurrence of HBV and HCC testing for patients compared with baseline characteristics. Comparisons of time to and frequency of determination of HBV load and HIV load were analyzed by the sign test for paired data. A P value of <.05 was considered to be statistically significant.

RESULTS

Use of drugs active against HBV. The patients' baseline demographic and clinical data are shown in table 1; the majority of patients were male, and 52% were black. No patients were identified as Asian. Twenty-one (14%) of 154 patients had test results positive for anti-HCV, whereas only 1 (2.5%) of 41 patients had test results positive for anti-HDV. Ninety-two percent of patients received nucleosides and/or nucleotides that were active against HBV; 88% of patients received lamivudine.

Initial HIV and HBV testing. All but 1 of the 155 patients had at least 1 HIV load measurement, and all 155 patients had at least 1 $CD4^+$ cell count assessment before initiation of ART. However, only 25 (16%) received testing to determine HBV load and HBeAg and anti-HBe levels before initiation of ART; 27 (17%) of 155 had an ultrasound examination of the liver, and 51 (26%) of 155 had an AFP test performed prior to or within 6 months after ART initiation.

Monitoring HIV and HBV infection during the first year of ART. The total number of tests to determine HIV load performed during the first year of therapy was 497 (median number of tests per patient, 3 per year), whereas only 85 tests were performed to determine HBV load during the same time period in the same patient group (median number of tests per patient, <1 per year; $P < .001$, by the sign test). Failure to measure HIV loads at any time during the first year after ART initiation was observed in 20 (13%) of the patients, whereas HBV load was not measured for 104 (67%) during the same time period. Because lack of follow-up may have influenced whether HBV tests were performed, we grouped patients into those who had 0–1 (35 patients), 2–3 (49 patients), and ⩾4 (71 patients) HIV load tests performed during their first year of treatment, as an approximation of the number of follow-up visits. No relationship was found between frequency of HIV load or $CD4^+$ cell count measurements and any HBV testing (data not shown). More frequent follow-up visits were not

Table 1. Demographic data, risk factors for HIV infection, baseline liver and HIV parameters, and hepatitis B virus (HBV) therapy in patients with HIV and HBV coinfection who initiated antiretroviral therapy during the period 1999–2003.

Variable	Patients (n = 155)
Demographic characteristic	
Male sex	136 (88)
Age, median years (range)	38 (19–59)
Race	
White	59 (38)
Black	80 (52)
Hispanic	11 (7)
Other	5 (3)
Risk factors for HIV infection[a]	
MSM	100 (65)
Heterosexual sex	46 (30)
IDU	24 (15)
Other	10 (16)
Liver and HIV parameters	
HCV antibody positive	21 (14)[b]
HDV antibody or antigen positive	1 (3)[b]
ALT level, median IU (range)	34 (6–481)
AST level, median IU (range)	37 (13–387)
$CD4^+$ cell count, median cells/μL (range)	137 (1–1089)
$CD4^+$ cell count <200 cell/μL	90 (58)
HIV load, median $\log_{10}$ copies/mL (range)	4.81 (1.69–6.11)
Active HBV therapy[a]	
Lamivudine	137 (88)
Tenofovir	18 (12)
Emtricitabine	2 (1)
Adefovir	1 (<1)

NOTE. Data are no. (%) of patients, unless otherwise indicated. ALT, alanine aminotransferase; ART, antiretroviral therapy; AST, aspartate aminotransferase; HCV, hepatitis C virus; HDV, hepatitis D virus; IDU, injection drug use; MSM, men who have sex with men.

[a] Total does not equal 100%.

[b] Missing data.

associated with more frequent HBV assessments: only one-third of patients had HBV tests performed at any time in the group that had ⩾4 HIV load measurements obtained. However, a higher proportion of AFP measurements and a trend towards more ultrasound examinations was observed in the group who had more HIV load measurements.

Improvement in monitoring of HBV infection during the study. The proportion of patients receiving any HIV load testing during the first year of ART remained constant from 1999 to 2003. However, although only 7%–13% of patients who started receiving HIV medications in 1999 or 2000 had some form of HBV testing during the year after ART initiation (figure 1), a significantly higher proportion of those initiating ART from 2001 to 2003 received HBV testing (43%–52%; $P \leqslant .001$, by Jonckheere-Terpstra analysis). Despite this improvement, by 2003, nearly 50% of the patients still did not receive any monitoring for HBV response, whereas 80%–90% of these patients received HIV monitoring during the same time period.

Time to initial HBV load measurement. After ART initiation, the time to first HBV load measurement, compared with the time to first HIV load measurement, was greatly delayed, both in 1999 (median time to first measurement, 1067 days vs. 46 days; $P < .001$, by the sign test) and in 2000 (median time to first measurement, 664 days vs. 59 days; $P = .002$, by the sign test). However, this delay decreased considerably by 2001, and by 2003, at least those who received HBV load measurements obtained them near the time of ART initiation.

HBV evaluations in patients with and patients without AIDS. No difference in overall HBV evaluation rates was observed between patients with $CD4^+$ cell counts <200 cells/μL and patients without AIDS. We found that 90 (97%) of the patients with $CD4^+$ cell counts <200 cells/μL were given pneumocystis pneumonia prophylaxis at the time of ART initiation.

Outcomes and monitoring for complications. Monitoring for complications of HBV infection (e.g., for development of HCC) was done infrequently. Among the entire cohort of HIV-HBV–coinfected patients, 130 (36%) of 357 received ⩾1 abdominal ultrasound examinations. Despite this, the number of positive findings was remarkably high: 50% of the abdominal ultrasounds that were performed had an abnormal finding, with liver cirrhosis being the most common abnormality. One hun-

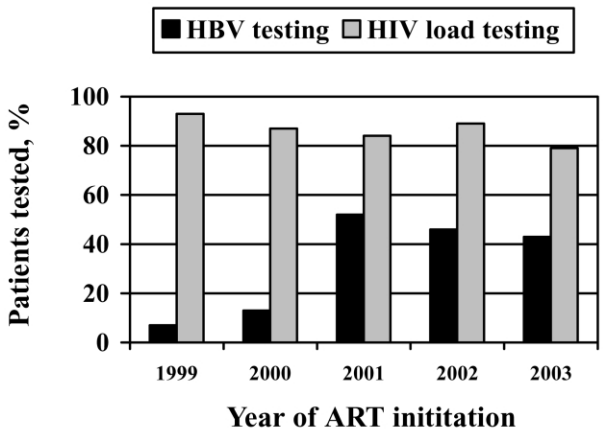

Figure 1. Proportion of patients who had hepatitis B virus (HBV) testing (either HBV load or hepatitis B e antigen and hepatitis B e antibody measurements) and ⩾1 HIV load measurement by year of antiretroviral therapy (ART) initiation. Improvements in the frequency of HBV testing were observed in the later years of the study, but the frequency of HBV monitoring did not approach that of HIV monitoring. The frequency of HBV testing improved over time ($P < .001$, by Jonckheere-Terpstra analysis), and the frequency of HIV testing remained constant over time ($P = .37$, by Jonckheere-Terpstra analysis).

dred and sixty-one patients (45% of the entire cohort) had an AFP measurement at any time point in the study.

DISCUSSION

Our data strongly indicate that, during the period from 1999 to 2003, HIV care providers frequently failed to initially evaluate or to subsequently monitor HBV infection status in coinfected patients despite careful follow-up for HIV infection. Although every patient is tested for HBsAg, anti-HCV, and antibodies for hepatitis A, only 16% had had an HBV load measured to assess the status of disease and the possible need for treatment of HBV infection prior to initiation of ART. However, 92% of this patient group received ART regimens that contained ⩾1 HBV-active nucleosides and/or nucleotides. Assessing baseline viral and serologic markers of HBV infection is essential to determining subsequent therapeutic response, including the development of drug-resistant infection. Because we only evaluated the initial regimen, it is unclear if follow-up adjustments were made to ART because of the development of drug-resistant HBV infection.

After the initiation of ART, adequate monitoring of HIV response was observed, with a median of 3 measurements of HIV load and $CD4^+$ cell count performed each year. HIV load measurements were consistently performed 6–8 weeks after ART initiation in all years of the study, and HIV loads were measured for 80%–90% of patients during each year. On the other hand, monitoring of HBV response by measurement of HBV load was done a median of <1 time during the first year of therapy, with no consistent timing of HBV load measurement. Lack of overall follow-up care was not the cause of fewer HBV load measurements. The percentage of patients who had an HBV load or HBeAg and anti-HBe measurements increased somewhat over the course of the study, from <10% of patients at study initiation to ~50% of patients in the later years of the study.

These data suggest that HIV care providers did not understand the need for and use of viral and serologic markers to monitor HBV treatment response. Because monitoring aminotransferase levels is part of HIV care, it is unclear if these tests were being used as surrogate markers of HBV response. The goal of therapy, which is suppression of HBV replication, may have been met in some patients, but it was not systematically determined.

Although HBV practice guidelines [16, 17] suggest regular monitoring of HBV loads, no similar recommendations for determining HBV response in HIV-HBV–coinfected patients are available in either current or former guidelines [19, 20, 22, 23]. Guidelines on monitoring HBV infection after ART initiation were limited during the period 1999–2003, which may explain the lack of monitoring for therapeutic response and clinical complications. Several guidelines [24–28], published after the time period of this study, do focus on the use of drugs and serologic and virologic markers of response; however, only 1 guideline [25] indicates how frequently this should occur. We have now implemented a detailed guideline in our clinic to standardize the management of HIV-HBV–coinfected patients (figure 2).

Our study was limited by its retrospective nature, its small sample size, and the fact that it was based on clinical practice in a single health care center. Data on the frequency of HBV load, HBeAg, and anti-HBe measurements, ultrasound examinations, and AFP tests were based on the tests that were completed. It was not possible to review medical records to determine how often providers ordered tests that were never performed. In addition, radiographic tests are less likely to be completed than serologic tests.

In summary, HIV care providers often failed to monitor HBV response in their overall management of HIV-HBV–coinfected patients prior to and after initiation of ART. Adequate monitoring of HBV disease activity in coinfected patients helps identify viral seroconversion, the development of drug-resistant mutant strains, and hepatic decompensation. On the basis of our

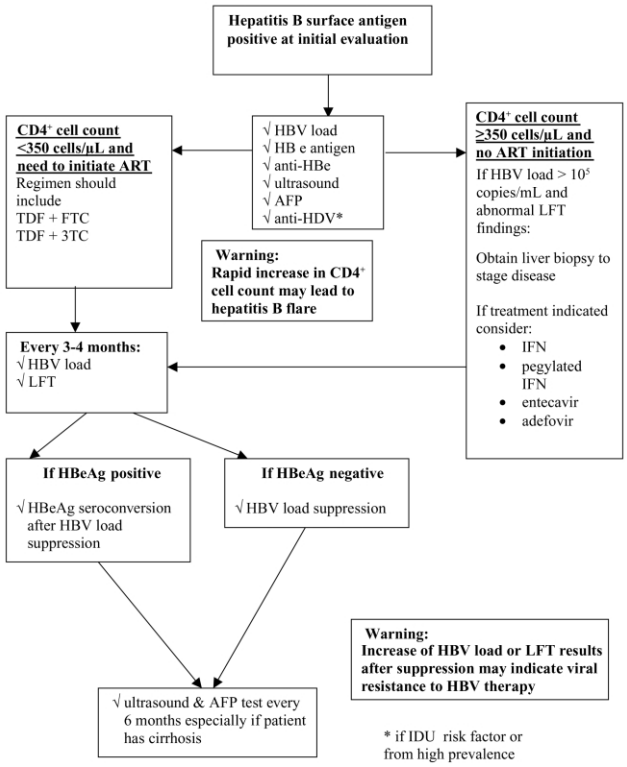

Figure 2. Guidelines introduced to the HIV clinic at Parkland Health and Hospital System (Dallas, TX). 3TC, lamivudine; AFP, α-fetoprotein; anti-HBe, hepatitis B e antibody; anti-HDV, hepatitis D antibody; ART, antiretroviral therapy; FTC, emtricitabine; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; LFT, liver function test; TDF, tenfovir disoproxil fumarate; HBV, hepatitis B; IDU, injection drug use.

findings, we propose modifying HIV treatment guidelines to focus not only on the selection of drugs but also on monitoring for therapeutic response in patients with HIV-HBV coinfection.

Acknowledgments

We thank April Gorman for her assistance in the statistical analysis.

Financial support. The Jeanne Roberts and Rollin and Mary Ella King Funds of the Southwestern Medical Foundation and K23 Career Development Award AI065630 (to M.K.J.).

Potential conflicts of interest. M.K.J. is on the Speaker's Bureau for Gilead Sciences. All other authors: no conflicts.

References

1. Kellerman SE, Hanson DL, McNaghten AD, Fleming PL. Prevalence of chronic hepatitis B and incidence of acute hepatitis B infection in human immunodeficiency virus–infected subjects. J Infect Dis **2003**; 188:571–7.
2. Thio CL, Seaberg EC, Skolasky R Jr, et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). Lancet **2002**; 360:1921–6.
3. Konopnicki D, Mocroft A, de Wit S, et al. Hepatitis B and HIV: prevalence, AIDS progression, response to highly active antiretroviral therapy and increased mortality in the EuroSIDA cohort. AIDS **2005**; 19: 593–601.
4. Bonacini M, Louie S, Bzowej N, Wohl AR. Survival in patients with HIV infection and viral hepatitis B or C: a cohort study. AIDS **2004**; 18:2039–45.
5. Puoti M, Spinetti A, Ghezzi A, et al. Mortality for liver disease in patients with HIV infection: a cohort study. J Acquir Immune Defic Syndr **2000**; 24:211–7.
6. Drake A, Mijch A, Sasadeusz J. Immune reconstitution hepatitis in HIV and hepatitis B coinfection, despite lamivudine therapy as part of HAART. Clin Infect Dis **2004**; 39:129–32.
7. Thibault V, Benhamou Y, Seguret C, et al. Hepatitis B virus (HBV) mutations associated with resistance to lamivudine in patients coinfected with HBV and human immunodeficiency virus. J Clin Microbiol **1999**; 37:3013–6.
8. Bessesen M, Ives D, Condreay L, Lawrence S, Sherman KE. Chronic active hepatitis B exacerbations in human immunodeficiency virus–infected patients following development of resistance to or withdrawal of lamivudine. Clin Infect Dis **1999**; 28:1032–5.
9. Lascar RM, Gilson RJ, Lopes AR, Bertoletti A, Maini MK. Reconstitution of hepatitis B virus (HBV)–specific T cell responses with treatment of human immunodeficiency virus/HBV coinfection. J Infect Dis **2003**; 188:1815–9.
10. Neau D, Schvoerer E, Robert D, et al. Hepatitis B exacerbation with a precore mutant virus following withdrawal of lamivudine in a human immunodeficiency virus–infected patient. J Infect **2000**; 41:192–4.
11. Sellier P, Clevenbergh P, Mazeron MC, et al. Fatal interruption of a 3TC-containing regimen in a HIV-infected patient due to re-activation of chronic hepatitis B virus infection. Scand J Infect Dis **2004**; 36:533–5.
12. Jain M, Parekh N, Hester J, Lee W. Aminotransferase elevation in HIV/HBV co-infected patients treated with two active HBV drugs. AIDS Patient Care STDS **2006**; 20:1–6.
13. Chen CJ, Yang HI, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA **2006**; 295:65–73.
14. Mommeja-Marin H, Mondou E, Blum MR, Rousseau F. Serum HBV DNA as a marker of efficacy during therapy for chronic HBV infection: analysis and review of the literature. Hepatology **2003**; 37:1309–19.
15. Liaw YF. Treatment of chronic hepatitis B virus infection: who, when, what for and how. J Gastroenterol Hepatol **2000**; 15(Suppl):E31–3.
16. Lok AS, McMahon BJ. Chronic hepatitis B. Hepatology **2001**; 34: 1225–41.
17. Lau GK, Carman WF, Locarnini SA, et al. Treatment of chronic hepatitis B virus infection: an Asia-Pacific perspective. J Gastroenterol Hepatol **1999**; 14:3–12.
18. Lok AS, McMahon BJ. Chronic hepatitis B: update of recommendations. Hepatology **2004**; 39:857–61.
19. Fauci AS, Bartlett JG. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents (1999). Panel on clinical practices for treatment of HIV infection convened by the Department of Health and Human Services and the Henry J. Kaiser Family Foundation. Available at: http://AIDSinfo.nih.gov/Guidelines/. Accessed 28 November 2006.
20. Bartlett JG, Lane HC. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents (2006): Department of Health and Human Services panel on antiretroviral guidelines for adults and adolescents (a working group of the Office of AIDS Reserach Advisory Council. Available at: http://AIDSinfo.nih.gov/Guidelines/. Accessed 26 June 2006.
21. Masur H, Kaplan J, Holmes K. 1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. US Public Health Service (USPHS) and Infectious Diseases Society of America (IDSA). MMWR Recomm Rep **1999**; 48:1–59, 61–6.
22. Carpenter CC, Fischl MA, Hammer SM, et al. Antiretroviral therapy for HIV infection in 1998: updated recommendations of the International AIDS Society–USA Panel. JAMA **1998**; 280:78–86.
23. Masur H, Holmes KK, Kaplan JE. Introduction to the 1999 US Public Health Service/Infectious Diseases Society of America guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. Clin Infect Dis **2000**; 30(Suppl 1): S1–4.
24. Soriano V, Puoti M, Bonacini M, et al. Care of patients with chronic hepatitis B and HIV co-infection: recommendations from an HIV-HBV International Panel. AIDS **2005**; 19:221–40.
25. Lessells R, Leen C. Management of hepatitis B in patients coinfected with the human immunodeficiency virus. Eur J Clin Microbiol Infect Dis **2004**; 23:366–74.
26. Brook MG, Gilson R, Wilkins E. BHIVA guidelines on HIV and chronic hepatitis: coinfection with HIV and hepatitis B virus infection (2005). HIV Med **2005**; 6(Suppl 2):84–95.
27. Benhamou Y. Treatment algorithm for chronic hepatitis B in HIV-infected patients. J Hepatol **2006**; 44:S90–4.
28. Alberti A, Clumeck N, Collins S, et al. Short statement of the first European Consensus Conference on the treatment of chronic hepatitis B and C in HIV co-infected patients. J Hepatol **2005**; 42:615–24.