DOI: 10.1111/j.1468-1293.2008.00646.x
HIV Medicine (2009), **10**, 12–18

ORIGINAL RESEARCH

Liver enzyme elevation after lamivudine withdrawal in HIV–hepatitis B virus co-infected patients: the Swiss HIV Cohort Study

C Bellini,[1] O Keiser,[2] J-P Chave,[3] JM Evison,[4] J Fehr,[5] L Kaiser,[6] R Weber,[7] P Vernazza,[8] E Bernasconi,[9] A Telenti,[10] M Cavassini[1] and the Swiss HIV Cohort Study

[1]Infectious Diseases Service, University Hospital Centre and University of Lausanne, Switzerland, [2]Institute of Social and Preventive Medicine, University of Bern, Switzerland, [3]Infectious Diseases Service, La Source Hospital, Lausanne, Switzerland, [4]Infectious Diseases Service, University Hospital, Bern, Switzerland, [5]Infectious Diseases Service, University Hospital, Basel, Switzerland, [6]Infectious Diseases Service, University Hospital, Geneva, Switzerland, [7]Infectious Diseases Service, University Hospital, Zurich, Switzerland, [8]Infectious Diseases Service, Cantonal Hospital, St Gall, Switzerland, [9]Infectious Diseases Service, Regional Hospital, Lugano, Switzerland and [10]Institute of Microbiology, University Hospital Centre and University of Lausanne, Switzerland

Background

The principal causes of liver enzyme elevation among HIV–hepatitis B virus (HBV) co-infected patients are the hepatotoxic effects of antiretroviral therapy (ART), alcohol abuse, ART-induced immune reconstitution and the exacerbation of chronic HBV infection.

Objectives

To investigate the incidence and severity of liver enzyme elevation, liver failure and death following lamivudine (3TC) withdrawal in HIV–HBV co-infected patients.

Methods

Retrospective analysis of the Swiss HIV Cohort Study database to assess the clinical and biological consequences of the discontinuation of 3TC. Variables considered for analysis included liver enzyme, HIV virological and immunological parameters, and medication prescribed during a 6-month period following 3TC withdrawal.

Results

3TC was discontinued in 255 patients on 363 occasions. On 147 occasions (109 patients), a follow-up visit within 6 months following 3TC withdrawal was recorded. Among these patients, liver enzyme elevation occurred on 42 occasions (29%), three of them (2%) with severity grade III and five of them (3.4%) with severity grade IV elevations (as defined by the AIDS Clinical Trials Group). Three patients presented with fulminant hepatitis. One death (0.7%) was recorded.

Conclusions

HBV reactivation leading to liver dysfunction may be an under-reported consequence of 3TC withdrawal in HIV–HBV co-infected patients. Regular monitoring of HBV markers is warranted if active therapy against HBV is discontinued.

Keywords: 3TC, flare, HBV, hepatitis, HIV, lamivudine

Accepted 1 July 2008

Introduction

Chronic hepatitis B virus (HBV) infection, defined as hepatitis B surface antigen (HBsAg) seropositivity for at least 6 months, affects an estimated 5% of the world's population [1]. HBsAg seroprevalence is increased by 1.5-fold among HIV-infected individuals. It affects 7% of the patients enrolled in the Swiss HIV Cohort Study (SHCS) and about 9% of the EuroSIDA Cohort [2–4].

Lamivudine (3TC), emtricitabine and tenofovir are nucleos(t)ide analogues that are effective for the control

Correspondence: Cristina Bellini, Service of Preventive Medicine and Infectious Diseases, University Hospital, 1011 Lausanne, Switzerland. Tel: + 41 21 314 02 72; fax: + 41 21 314 02 62; e-mail: cristina.bellini@chuv.ch

of HIV and HBV replication, by inhibiting the reverse transcriptase and DNA polymerase [1].

Among HIV-negative patients undergoing treatment for chronic hepatitis B, withdrawal of 3TC can result in the rebounding of serum HBV DNA levels, with an accompanying liver enzyme elevation in 10–50% of patients and associated hepatic failure in a small number of patients [5,6]. Uncontrolled replication of HBV with acute hepatitis has also been observed in patients whose virus developed 3TC resistance [7].

While acute exacerbation of chronic hepatitis B after discontinuation of 3TC is well described among HIV-negative patients, only a few case reports have documented such events among HIV-positive patients [5,6,8–14]. Hepatitis flares among HIV–HBV co-infected patients are also reported upon the discontinuation of tenofovir and emtricitabine, with the emergence of 3TC (and emtricitabine) resistance, or (less frequently) because of hepatitis B envelope antigen (HBeAg) or HBsAg seroconversion or superinfection with another hepatitis virus (e.g. hepatitis A or D virus) [15,16].

The aim of this retrospective analysis was to investigate the incidence and severity of liver enzyme elevation, liver failure and death following 3TC withdrawal in a large longitudinal cohort of individuals undergoing treatment for HIV.

Patients and methods

Patients

The study population included all HIV–HBV co-infected adults (HBsAg positive) participating in the prospective SHCS (www.shcs.ch) who received 3TC-containing antiretroviral therapy (ART) for a minimum of 4 weeks prior to its discontinuation, between January 1988 and April 2004. Patients were followed at hospital centres participating in the SHCS.

Clinical, medical and laboratory data

We extracted the following patient characteristics from the SHCS database: age, gender, HIV transmission group [intravenous (IV) drug use, men who have sex with men (MSM), heterosexual and other], prior and current IV drug use, hepatitis C virus (HCV) status and ART history.

Laboratory data included alanine aminotransferase (ALT) levels during the 12 months preceding 3TC withdrawal and the 6 months following this timepoint, HIV viral load and CD4 T-cell counts.

We compared variables pre- and post-3TC withdrawal in each individual over the 12 months preceding the event and up to 6 months thereafter. The 'baseline' laboratory value was defined as the earliest recorded value obtained during the 12 months prior to 3TC withdrawal, the 'pre-3TC stop' was the most recent recorded value before 3TC withdrawal and the 'post-3TC stop' was the highest value registered within 6 months after 3TC withdrawal. Where available, we performed additional tests on stored samples (within the same window period) concerning HBV-related variables such as serum HBeAg (Roche Elecsys®; Roche Diagnostics, GmbH, Manheim, Germany), Anti-hepatitis B envelope (HBe) (Roche Elecsys®; Roche Diagnostics) and HBV DNA levels (Roche cobas ampliPrep® and Roche cobas TaqMan HBV®; Roche Diagnostics).

For each patient, the medical record was reviewed to identify potential causes of liver enzyme elevation [such as ART or other drug toxicity, acute alcohol consumption, hepatitis C co-infection, active IV drug use or hepatitis caused by immune reconstitution inflammatory syndrome (IRIS)] and to record additional liver function tests performed outside scheduled SHCS visits.

Hepatotoxicity grades

Hepatotoxicity (liver enzyme elevation) grades were based on ALT levels and were defined in accordance with AIDS Clinical Trials Group (ACTG) criteria [22]: grade I, 1.25–2.5 times the upper limit of normal (ULN); grade II, 2.5–5.0 $\times$ ULN; grade III, 5–10 $\times$ ULN; grade IV, $>10 \times$ ULN. Mild hepatotoxicity was defined as ACTG grades I and II, and severe toxicity as grades III and IV. Hepatic flare was defined as an abrupt elevation of ALT levels over 200 IU/L or five times the ULN. Fulminant hepatitis was defined as a severe and rapidly progressive form of hepatitis with signs and symptoms of hepatic failure. In order to avoid misclassification of patients with elevated pre-3TC stop ALT levels, worsening hepatotoxicity was defined as the difference between transaminase values before and after 3TC withdrawal. The degree of this difference is also expressed in grades using the same ACTG criteria (i.e. if a patient had an ALT pre-3TC stop value of 150 and an increase to 400 after 3TC withdrawal, this worsening hepatotoxicity was considered a grade III).

Statistical analysis

Differences between hepatotoxicity groups were compared using one-way analysis of variance for normally distributed continuous data and Wilcoxon test for data that were not normally distributed. χ^2 tests were used for categorical data. Associations between hepatotoxicity groups and the following variables were assessed in univariate and multi-

variate logistic regression analysis: age; gender; hepatitis C status; HIV risk group; baseline, pre-3TC stop and post-3TC stop CD4 T-cell counts; duration of ART; duration of 3TC therapy; and discontinuation of 3TC alone or along with the rest of ART.

Differences between groups were considered to be significant at a *P*-value <0.05. STATA version 9.2 for Windows (StataCorp LLP, College Station, TX, USA) was used for all statistical analyses.

Results

From January 1988 to April 2004, a total of 12 969 HIV-infected persons were followed in the SHCS. HBsAg determination was available for 58% (7664) of those individuals. Among them, we identified 255 patients with a positive HBsAg who had discontinued 3TC on 363 occasions. For 216 occasions, no liver enzyme measurements within 6 months of 3TC discontinuation were available ($n = 65$) or they occurred in private practice ($n = 151$) and were therefore not included in the analysis (exclusion criteria because of the difficulty in accessing medical records). Results are based on 147 occasions of 3TC withdrawal in 109 patients.

After 3TC withdrawal, a median ALT increase of 90 IU/L (IQR 45–152) was observed on 42 occasions (29%), eight (5.5%) of them with a severe (grades III and IV) hepatotoxicity.

Among 88 3TC withdrawals in patients with normal baseline transaminase levels, liver enzyme elevation was observed on 22 occasions (25%); five of them (6%) resulted in grade III and IV hepatotoxicity. One patient (0.7%) died of fulminant liver failure attributed to hepatitis B reactivation. This patient was HBeAg-negative, HCV-negative and had documented liver fibrosis on liver biopsy (no score available). Table 1 shows the demographic, clinical and laboratory data of the included patients.

Among 59 3TC withdrawals in patients with pre-existing baseline transaminase elevation, worsening liver enzyme elevation was observed on 20 occasions (34%); three of them (5%) resulted in severe hepatotoxicity (one grade III and two grade IV) (Table 1).

Univariate analysis showed no significant difference in hepatotoxicity groups with regard to age, gender, HIV

Table 1 Demographic, clinical and laboratory characteristics of 109 HIV-1-positive/hepatitis B surface antigen-positive patients who discontinued a minimum of 4 weeks of 3TC treatment between 1994 and 2004

		Worsening hepatotoxicity after lamivudine withdrawal			
	No worsening hepatotoxicity	Grade I	Grade II	Grade III	Grade IV
	Number (%) Median (IQR)	Number (%) Median (IQR)	Number (%) Median (IQR)	Number (%) Median (IQR)	Number (%) Median (IQR)
Number of events ($n = 147$)	105 (71%)	25 (17%)	9 (6%)	3 (2%)	5 (4%)
Median ALT at baseline	44 (28–73)	45 (32–78)	71 (44–86)	41 (27–56)	40 (37–109)
Median ALT before 3TC stop	44 (23–89)	49 (37–63)	47 (37–53)	32 (22–39)	34 (22–37)
Median ALT peak after 3TC stop	NA	98 (87–127)	169 (160–236)	510 (339–525)	629 (623–927)
Median days from 3TC stop to ALT peak	NA	88 (64–121)	52 (44–108)	25 (15–107)	41 (13–42)
Sex					
Male, $n = 122$ (83%)	89	22	6	2	3
Female, $n = 25$ (17%)	16	3	3	1	2
Median age at 3TC stop, years	37 (33–40)	41 (38–45)	39 (37–42)	40 (35–46)	42 (31–51)
Risk group					
HET, $n = 28$ (19%)	18	6	1	1	2
MSM, $n = 43$ (29%)	29	8	2	2	2
IDU, $n = 58$ (39%)	44	7	6	0	1
Other, $n = 18$ (13%)	14	4	0	0	0
Median 3TC treatment duration (days)	292 (85–769)	625 (243–1287)	398 (218–910)	335 (238–1006)	214 (194–441)
Median ART duration (days)	914 (555–1316)	1201 (700–1458)	1029 (615–1499)	1256 (1021–1491)	214 (194–1006)
ART discontinuation*, $n = 71$	58	6	1	1	5
New ART* without 3TC, emtricitabine or tenofovir, $n = 76$	47	19	8	2	0
Median CD4 nadir (cells/μL)	140 (49–257)	68 (26–138)	200 (70–314)	138 (113–179)	104 (70–240)
Median CD4 before 3TC stop (cells/μL)	266 (103–538)	281 (191–395)	330 (269–556)	222 (182–363)	172 (80–304)
HCV					
Positive, $n = 63$ (43%)	47	8	5	1	2
Negative, $n = 79$ (54%)	55	15	4	2	3

*Simultaneously to the time of 3TC withdrawal.
3TC, lamivudine; ALT, alanine aminotransferase (IU/L); ALT peak, highest ALT value measured up to 180 days following 3TC stop; ART, antiretroviral therapy; HCV, hepatitis C virus; HET, heterosexual; IDU, intravenous drug users; IQR, interquartile range; MSM, men having sex with men; NA, not applicable.

transmission group, CD4 T-cell counts, ART and 3TC treatment duration, ART discontinuation simultaneous to 3TC withdrawal or the start of a new ART regime. Therefore, multivariate analysis was not performed. The risk of worsening liver enzyme elevation was not different for patients with a pre-existing liver enzyme elevation compared to those with normal baseline liver enzyme [odds ratio (OR) 1.58, 95% confidence interval (CI) 0.75–3.35, $P = 0.22$].

Figure 1 shows the change in liver enzyme for patients before and after 3TC withdrawal. Peak ALT occurred 81 ± 52 days after 3TC withdrawal. Grade IV hepatotoxicity occurred 40 ± 36 days after 3TC withdrawal.

HCV co-infection was present in 40 patients (63 occasions of 3TC withdrawal). A pre-existing baseline liver enzyme elevation was identified on 32 occasions (51%, 32/63). Of those, we observed a worsening liver enzyme elevation after 3TC withdrawal on 10 occasions (31%, 10/32), of which two (6%, 2/32) had severe (grades III and IV) hepatotoxicity.

Normal baseline liver enzyme values were present on 31 occasions (49%, 31/63). We observed a worsening liver enzyme elevation after 3TC withdrawal on six occasions (19%, 6/31), of which one (3%, 1/31) had severe (grades III and IV) hepatotoxicity (OR 1.7, 95% CI 0.59–5.0, $P = 0.32$).

Seventy-nine 3TC withdrawals (53.7%, 79/147) occurred among HCV-negative patients. Of those, 22 (28%, 22/79) presented elevated transaminase at baseline. Worsening liver enzyme elevation was observed more frequently within HCV-negative patients who presented elevated transaminases at baseline (36%, 8/22) than among those with normal baseline transaminases (28%, 16/57) (OR 1.90, 95% CI 0.59–6.1, $P = 0.27$).

The analysis of complete HBV serology (HBeAg, anti-HBe and HBV DNA before and after 3TC withdrawal) was available for 32 episodes (22%, 32/147). HBV-DNA rebound (more than 1 log copies/mL elevation) could be ascertained in two out of five patients with grade III and IV hepatotoxicity (Table 2). For the remaining three patients, HBV DNA could not be performed concurrently to liver enzyme peak (no frozen serum samples available). HBeAg seroconversion associated with HBV DNA rebound was observed in only one patient, who presented a mild, grade II hepatotoxicity 56 days after 3TC withdrawal. No significant difference in CD4 T-cell counts was observed before and after 3TC withdrawal in patients with or without liver enzyme elevation.

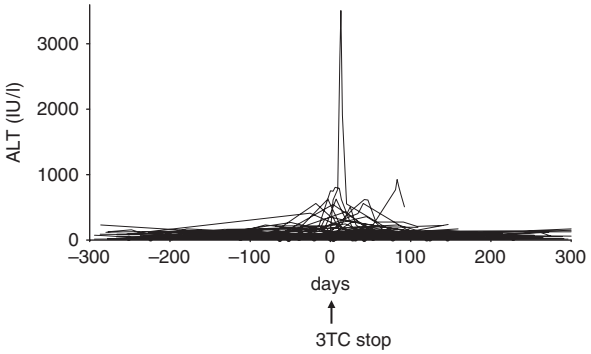

Fig. 1 Alanine aminotransferase (ALT) evolution of 109 HIV-1-positive/hepatitis B surface antigen-positive patients who discontinued a minimum of 4 weeks of lamivudine (3TC) treatment between 1994 and 2004.

Discussion

In this HIV cohort study, we found liver enzyme elevations in 29% of episodes of 3TC withdrawal among HIV–HBV co-infected patients.

Hepatitis flare was observed in 4% of the study population 5–6 weeks after 3TC withdrawal, leading to fatal liver failure and death in one patient (0.7%). This is in contrast to a previous study in HIV-negative patients who reported hepatitis flare with median ALT peak 16 weeks after 3TC withdrawal [5].

HCV co-infection was present in 42% of our HIV- and HBV-infected patients. Generally, replication of one virus predominates over the other because of a reciprocal inhibitory effect [17]. At this point, the molecular mechanism(s) of reciprocal replicative suppression in HBV–HCV co-infection are unknown. In our study, patients who were HIV–HBV co-infected and had elevated baseline liver enzymes tended to develop liver enzyme elevations more frequently compared to patients who were HBV–HCV–HIV co-infected, although this was not statistically significant.

In previous studies, increased hepatic inflammation and cirrhosis have been seen to occur more frequently in patients who were HBeAg-negative but with HBV DNA replication [6,15,18]. This profile may result from infection with HBV mutants that do not produce HBeAg [15]. In the present study, we report a case of fulminant hepatitis, HBeAg-negative with documented liver cirrhosis. HBV DNA rebound in the presence of liver cirrhosis may have caused severe hepatic damage and death.

Other mechanisms for worsening liver enzyme elevations in HIV-positive patients with chronic hepatitis B include the direct toxic effect of ART or IRIS. This last entity usually occurs within the first 3 months of beginning the therapy, and corresponds to an immune response to HBV antigens, usually followed by a normalization of liver enzymes and clearance of HBV DNA [15,19]. The CD4 T-cell counts in the patients in the present study were not

Table 2 Hepatitis B virus (HBV) serology and viraemia for 14 patients who developed hepatic toxicity after lamivudine withdrawal

Patient	Toxicity grade at ALT peak	CD4 count (cells/μL)		HCV status	HBeAg		Anti-HBe		HBV DNA (10^3 copies/mL)		Number of days for		
		At baseline	Before 3TC stop		Before 3TC stop	After 3TC stop	Before 3TC stop	After 3TC stop	Before 3TC stop	After 3TC stop	HBV DNA sample		ALT peak
											Before 3TC stop	After 3TC stop	After 3TC stop
1	I	10	185	−	−	−	+	+	> 200	> 200	− 105	36	106
2	I	5	202	−	+	+	−	+	7300	1.8	− 132	51	46
3	I	2	6	+	−	−	+	+	0.5	< 0.3	− 136	10	10
4	I	30	350	NA	−	−	+	+	< 0.3	< 0.3	− 93	72	72
5	II	0	332	−	+	+	−	−	> 200	> 200	− 56	90	84
6	II	314	330	+	+	+	−	−	> 200	> 200	− 190	48	48
7	II	355	556	+	−	−	+	+	< 0.3	< 0.3	− 183	52	52
8	II	70	380	+	−	−	+	+	< 0.3	< 0.3	− 105	90	147
9	II	138	365	+	−	+	+	+	< 0.3	> 200	− 141	56	104
10	III	220	504	−	+	−	−	+	14.9	< 0.3	− 167	63	4
11	III	87	141	+	−	−	+	+	< 0.3	< 0.3	− 77	0	25
12	IV	5	7	−	−	−	NA	+	7250	1090	− 29	12	13
13	IV	240	240	−	+	+	+	−	4.7	> 200	− 90	81	98
14	IV	495	495	+	−	−	NA	+	0	210	− 34	34	41

3TC, lamivudine; ALT, alanine aminotransferase (IU/L); HBe, hepatitis B envelope; HBeAg, hepatitis B envelope antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; NA, not applicable.

significantly different before and after discontinuing 3TC, which makes IRIS unlikely in this population. However, we cannot exclude completely the occurrence of a concomitant IRIS in patients who may have discontinued a failing regimen containing 3TC in favour of a newer, more potent suppressive regimen.

Limitations of the present study are its retrospective and observational nature. In addition, there was no standard algorithm for the measurement of liver enzymes for all HIV–HBV co-infected patients. The incidence recorded may be lower if the patients who did not benefit from a specific follow-up were less likely to have abnormalities of liver function. Furthermore, asymptomatic liver enzyme elevations occurring earlier or later than the time at which laboratory tests were obtained may have been missed.

HBV DNA levels were not part of the routine laboratory tests performed during visits in our cohort and therefore were not available for all HIV–HBV co-infected patients. However, we measured serum HBeAg and HBV DNA on stored samples collected for the purposes of the cohort study. Nevertheless, the timing of the collection of these blood samples did not always coincide with the time of discontinuation of 3TC. Finally, we did not routinely have access to important information regarding potential confounders such as alcohol abuse and drug adherence, although we made attempts to reduce this bias by reviewing all the charts. To our knowledge, this study represents the largest HIV–HBV co-infected cohort that has analysed hepatitis induced by 3TC withdrawal. Hepatitis B reactivation upon nucleos(t)ide analogue discontinuation is well known in the hepatology community and careful monitoring of patients in this setting is the standard of care. We believe that physicians treating HIV–HBV co-infected patients may frequently overlook this potentially serious complication.

Conclusions

3TC discontinuation among chronic HIV–HBV co-infected patients can lead to severe liver dysfunction or even death caused by hepatitis B reactivation at a median peak of 5–6 weeks up to 7–8 weeks.

Careful monitoring of active HBV replication (HBV DNA) is warranted with the initiation of ART regimens containing an anti-HBV agent (3TC, emtricitabine, tenofovir). In addition, if such therapy has to be stopped, liver enzymes should be monitored closely for evidence of hepatitis reactivation. Monitoring of HBeAg only is inappropriate: some patients may still present an elevated HBV viraemia despite negative HBeAg.

This could also become an issue in the setting of HIV pre-exposure prophylaxis and post-exposure prophylaxis

using agents such as 3TC, tenofovir and emtricitabine in a population with high prevalence of hepatitis B.

Hepatitis flares that occurred after ART cessation should be treated by resumption of active anti-HBV treatment before significant liver failure occurs [14,20,21]. Because of emerging drug resistance, the use of regimens with at least two anti-HBV active agents is recommended [15,20,21].

Acknowledgements

We thank Dr P. Halfon and Dr R. Osih for helping in the statistical analysis, Prof. D. Moradpour for reviewing the manuscript, and Dr P. Burgisser and V. Musaro for the laboratory work.

This study has been financed in the framework of the Swiss HIV Cohort Study, supported by the Swiss National Science Foundation.

References

1 Benhamou Y. Antiretroviral therapy and HIV/hepatitis B virus coinfection. *Clin Infect Dis* 2004; **38** (Suppl. 2): 98–103.

2 Rockstroh J, Konopnicki D, Soriano V *et al*. Hepatitis B and hepatitis C in EuroSIDA cohort: prevalence and effect on mortality, AIDS progression and response to HAART. *11th Conference on Retrovirus and Opportunistic Infections*. San Francisco, CA, February 2004 [Abstract 799].

3 Rustgi VK, Hoofnagle JH, Gerin JL *et al*. Hepatitis B virus infection in the acquired immunodeficiency syndrome. *Ann Intern Med* 1984; **101**: 795–797.

4 Shire NJ, Rouster SD, Rajicic N, Sherman KE. Occult hepatitis B in HIV-infected patients. *J Acquir Immune Defic Syndr* 2004; **36**: 869–875.

5 Honkoop P, de Man RA, Niesters HG, Zondervan PE, Schalm SW. Acute exacerbation of chronic hepatitis B virus infection after withdrawal of lamivudine therapy. *Hepatology* 2000; **32**: 635–639.

6 Lim SG, Wai CT, Rajnakova A, Kajiji T, Guan R. Fatal hepatitis B reactivation following discontinuation of nucleoside analogues for chronic hepatitis B. *Gut* 2002; **51**: 597–599.

7 Liaw YF, Chien RN, Yeh CT, Tsai SL, Chu CM. Acute exacerbation and hepatitis B virus clearance after emergence of YMDD motif mutation during lamivudine therapy. *Hepatology* 1999; **30**: 567–572.

8 Carr A. Toxicity of antiretroviral therapy and implications for drug development. *Nat Rev Drug Discovery* 2003; **2**: 624–634.

9 Altfeld M, Rockstroh JK, Addo M *et al*. Reactivation of hepatitis B in a long-term anti-HBs-positive patient with AIDS following lamivudine withdrawal. *J Hepatol* 1998; **29**: 306–309.

10 Waite J, Gilson RJ, Weller IV *et al*. Hepatitis B virus reactivation or reinfection associated with HIV-1 infection. *AIDS* 1988; **2**: 443–448.

11 Khanna N. Chronic hepatitis B exacerbations after antiretroviral therapy withdrawal in HIV-infected patients (in German). *Praxis* 2002; **91**: 2256–2258.

12 Manegold C, Hannoun C, Wywiol A *et al*. Reactivation of hepatitis B virus replication accompanied by acute hepatitis in patients receiving highly active antiretroviral therapy. *Clin Infect Dis* 2001; **32**: 144–148.

13 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**: 192–194.

14 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**: 1032–1035.

15 Levy V, Grant RM. Antiretroviral therapy for hepatitis B virus–HIV-coinfected patients: promises and pitfalls. *Clin Infect Dis* 2006; **43**: 904–910.

16 Nüesch R, Ananworanich J, Srasuebkul P *et al*. Interruptions of tenofovir/emtricitabine-based antiretroviral therapy in patients with HIV/hepatitis B virus co-infection. *AIDS* 2008; **22**: 152–154.

17 Soriano V, Barreiro P, Martin-Carbonero L *et al*. Treatment of chronic hepatitis B or C in HIV-infected patients with dual viral hepatitis. *J Infect Dis* 2007; **195**: 1181–1183.

18 Lok AS, McMahon BJ. AASLD practice guidelines. Chronic hepatitis B: update of therapeutic guidelines. *Rom J Gastroenterol* 2004; **13**: 150–154.

19 Carr A, Cooper DA. Restoration of immunity to chronic hepatitis B infection in HIV-infected patient on protease inhibitor. *Lancet* 1997; **349**: 995–996.

20 Benhamou Y. Hepatitis B in the HIV-coinfected patient. *J Acquir Immune Defic Syndr* 2007; **45** (Suppl. 2): 57–65.

21 Sulkowski M. The HIV-coinfected patient. *J Acquir Immune Defic Syndr* 2007; **45** (Suppl. 2): 66–67.

22 Adult AIDS Clinical Trial Group (AACTG). *Table for Grading Severity of Adult Adverse Experiences*. Division of AIDS, National Institute of Allergy and Infectious Diseases.

Appendix A: Swiss HIV Cohort Study members

M. Battegay, E. Bernasconi, J. Böni, H.C. Bucher, P. Bürgisser, A. Calmy, S. Cattacin, M. Cavassini, R. Dubs, M. Egger, L. Elzi, P. Erb, M. Fischer, M. Flepp, A. Fontana, P. Francioli (President of the SHCS, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland), H. Furrer (Chairman of the Clinical and Laboratory Committee), C. Fux, M Gorgievski, H. Günthard, H. Hirsch, B. Hirschel,

I. Hösli, C. Kahlert, L. Kaiser, U. Karrer, C. Kind, T. Klimkait, B. Ledergerber, G. Martinetti, B. Martinez, N. Müller, D. Nadal, M. Opravil, F. Paccaud, G. Pantaleo, A. Rauch, S. Regenass, M. Rickenbach (Head of Data Centre), C. Rudin (Chairman of the Mother and Child Sub-study), P. Schmid, D. Schultze, J. Schüpbach, R. Speck, P. Taffé, P. Tarr, A. Telenti, A. Trkola, P. Vernazza (Chairman of the Scientific Board), R. Weber, S. Yerly.