



Co-infection: HIV & Viral Hepatitis

A Guide for Clinical Management

4th Edition 2010



Australian Government
Department of Health and Ageing

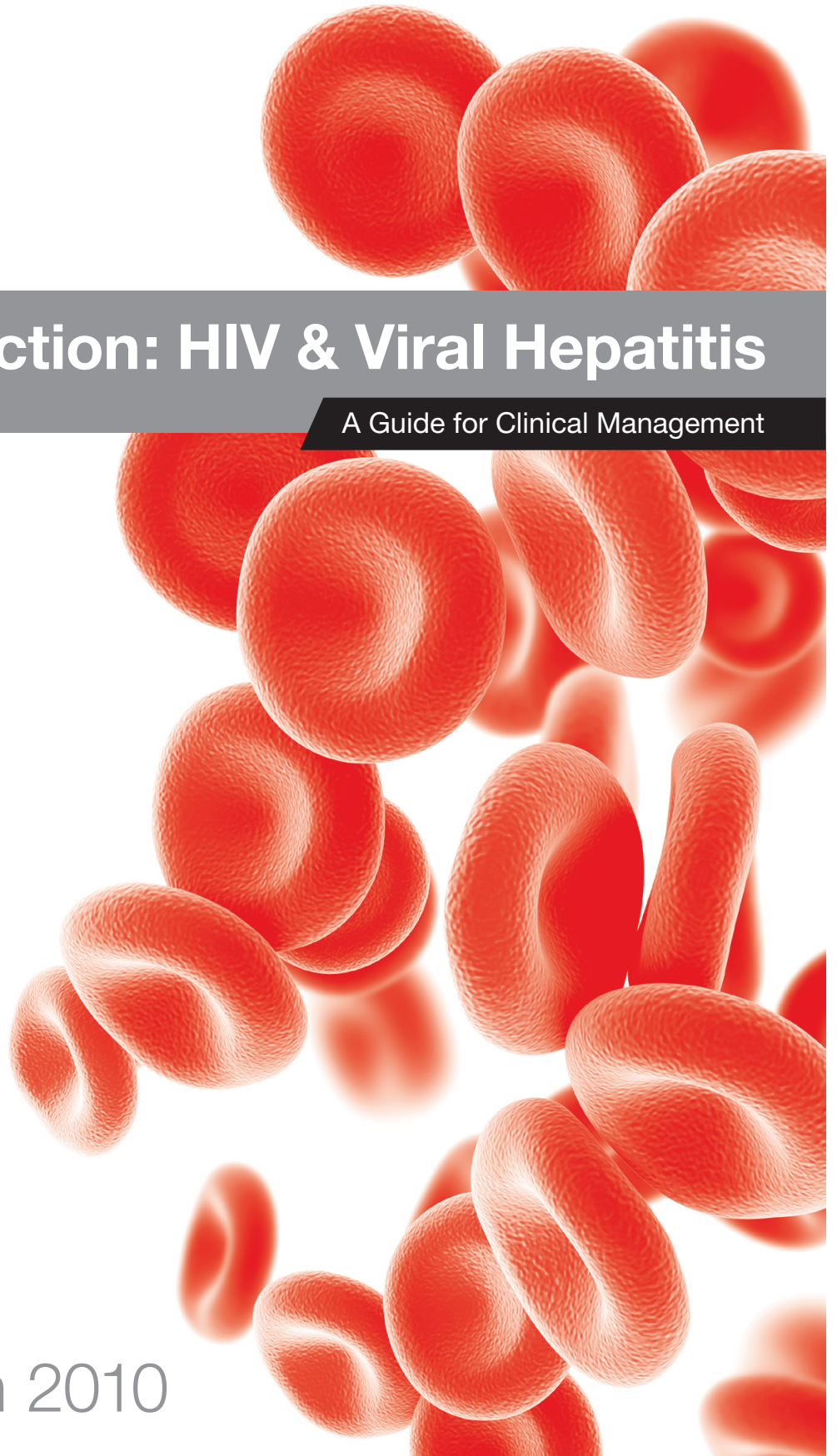
Co-infection: HIV & Viral Hepatitis

A Guide for Clinical Management

Editors

Benjamin Cowie
Gregory Dore
Joe Sasadeusz

4th Edition 2010



Co-infection: HIV & Viral Hepatitis a guide for clinical management

is published by the:

Australasian Society for HIV Medicine (ASHM)

Locked Bag 5057, Darlinghurst, NSW 1300

Phone: (61) (02) 8204 0700

Fax: (61) (02) 9212 2382

Email: ashm@ashm.org.au

Website: www.ashm.org.au

ABN: 48 264 545 457

First published in 2003

Reprinted with minor revisions 2005

Reprinted with minor revisions 2006

Reprinted and revised 2010

Editors: Benjamin Cowie, Gregory Dore, Joe Sasadeusz

ASHM Professional Education Division Manager: Liza Doyle

ASHM Program Manager, BBV/STI Program, Professional Education Division: Thanos Lygdas

ASHM Project Officer: Natalie Candarakis

Designer: Shehana Mohammed

Copy-editing: Paul McQueen

Indexing: Master Indexing

Printed by: TTR Print Management

Cover photo: 'Red Blood Cells'. Copyright 2010 Bioraven. Sourced from www.shutterstock.com (id:53920912)

Funded by the Australian Government Department of Health and Ageing.

Publishing logistics - Previous editions: Levinia Crooks, Marina Carman; Vicky Fisher (2005, 2006 eds)

National Library of Australia cataloguing-in-publication data:

Co-infection. HIV and Viral hepatitis: a guide for clinical management

Includes index.

ISBN: 978-1-920773-81-6

1. HIV infections – Chemotherapy.
2. Hepatitis, Viral – Chemotherapy
3. HIV infections – Chemotherapy – Complications.
4. Hepatitis, Viral – Chemotherapy – Complications.
5. Hepatotoxicology. I. Cowie, Benjamin, 1972 - . II. Dore, Gregory, 1962- . III. Sasadeusz, Joe, 1956- . IV. Australasian Society for HIV Medicine. V. Co-infection: HIV and Viral Hepatitis: a guide for clinical management 616.9792061

© Australasian Society for HIV Medicine 2010

Apart from any fair dealing for the purpose of research or study, criticism or review, as permitted under the Copyright Act 1968, no part of this book may be reproduced by any process without written permission. Direct enquiries to the Australasian Society for HIV Medicine.

Effort has been made to get permission from copyright owners for use of copyright material. We apologise for any omissions or oversight and invite copyright owners to draw our attention to them so that we may give appropriate acknowledgment in subsequent reprints or editions.

The statements or opinions that are expressed in this book reflect the views of the contributing authors and do not necessarily represent the views of the editors or publisher. Every care has been taken to reproduce articles as accurately as possible but the publisher accepts no responsibility for errors, omissions or inaccuracies contained therein or for the consequences of any action taken by any person as a result of anything contained in this publication.

All terms mentioned in the book that are known to be trademarks have been appropriately capitalised. ASHM cannot attest to the accuracy of this information. Use of a term in this book should not be regarded as affecting the validity of any trademark.

Although every effort has been made to ensure that drug doses and other information are presented accurately in this publication, the ultimate responsibility rests with the prescribing clinician. For detailed prescribing information or instructions on the use of any product described herein, please consult the prescribing information issued by the manufacturer.

Contents

Foreword.....	4
Chapter 1 The epidemiology of HIV and viral hepatitis co-infection.....	5
Gail Matthews, Gregory Dore	
Chapter 2 The management of HIV and hepatitis C virus co-infection.....	13
Gregory Dore, Joe Sasadeusz	
Chapter 3 The management of HIV and hepatitis B virus co-infection.....	20
Joe Sasadeusz, Benjamin Cowie	
Chapter 4 Antiretroviral therapy-related hepatotoxicity predictors and clinical management.....	28
Gregory Dore, Benjamin Cowie	
Glossary of terms.....	35
List of drugs.....	37
Index.....	38

Foreword

Since the first edition of *Co-infection: HIV & Viral Hepatitis a guide for clinical management* was published in 2003, our understanding of co-infection with HIV and chronic viral hepatitis has improved significantly. Evidence regarding the epidemiological and clinical importance of co-infection has increased, new agents and new approaches to clinical management have been developed, and there has been an increasing recognition of strategies to avoid potentially serious adverse effects of therapy for both HIV and viral hepatitis in people living with co-infection.

Infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) contribute significantly to morbidity and mortality in people living with HIV. The similarities in modes of transmission of these infections lead to a high prevalence of co-infection, with significant overlap in the populations most affected. The presence of HIV infection, particularly when associated with significant immunosuppression, has a negative impact on many aspects of the natural history of both HBV and HCV infection, including higher rates of progression to chronic infection, and more rapid development of cirrhosis and associated complications. The extent to which this more severe course of illness can be avoided is dependent both on the optimal management of HIV infection, and early identification and appropriate treatment of viral hepatitis. For these reasons, an understanding of the epidemiology of HIV and viral hepatitis co-infection is fundamental and is contained in Chapter 1 of this monograph.

Chapter 2 outlines the important diagnostic and therapeutic approaches to co-infection with HIV and HCV. There is increasing evidence that immune restoration through combined antiretroviral therapy (cART) can slow liver disease progression in people living with HIV-HCV co-infection. In addition, clinical trials published since the first edition of this monograph have clearly demonstrated that combination therapy with pegylated (as opposed to conventional) interferon plus ribavirin is associated with superior rates of attaining sustained virologic response (SVR) as is the case in HCV mono-infection. However, treatment responses remain suboptimal, particularly in the setting of genotype 1 HCV. The issue of therapeutic prioritisation for HIV or HCV is complex, and the current move towards earlier initiation of cART for HIV will impact on this question. This topic is discussed in detail in Chapter 2.

The management of chronic HBV infection has been evolving rapidly in recent years, with many new agents available. One unique therapeutic aspect for patients co-infected with HIV and HBV is that many antiretroviral agents are also effective against HBV. However there are a number of complexities to clinical decision making. For example, since the last edition of this monograph it has been demonstrated that entecavir, a potent anti-HBV agent, also can select for HIV resistance mutations and therefore should not be used as monotherapy in co-infected patients. Avoidance and management of cART-induced immune reconstitution hepatitis flares is another important issue as this syndrome can be associated with significant morbidity and mortality. These and other aspects of clinical management of co-infection with HIV and HBV are discussed in Chapter 3.

Severe hepatotoxicity associated with cART remains a significant problem facing patients with co-infection, with underlying chronic viral hepatitis being a major risk factor. The availability of new antiretroviral agents (and new therapeutic classes) has the potential to mitigate this problem to a certain extent, but in resource poor settings access to these newer, more expensive agents is limited. Although the majority of episodes of cART-associated hepatotoxicity are not associated with adverse hepatic outcomes, careful monitoring and investigation of alternative and contributing factors is essential. These and other practical issues relating to cART-associated liver injury are covered in Chapter 4.

The new edition of this monograph is a comprehensive and a practical reference for clinicians caring for people living with HIV and viral hepatitis co-infection. It will assist them in keeping abreast of the relatively rapid pace of research and related changes to clinical practice in the field.

Benjamin Cowie
May 2010

The epidemiology of HIV and viral hepatitis co-infection

1

Gail Matthews
Gregory Dore

National Centre in HIV Epidemiology and Clinical Research, The University of New South Wales, Sydney, NSW
National Centre in HIV Epidemiology and Clinical Research, The University of New South Wales, Sydney, NSW

KEY POINTS

- ▶ Both hepatitis B virus (HBV) and hepatitis C virus (HCV) are more common in people with human immunodeficiency virus (HIV) infection than in the general population because of shared risk factors for viral acquisition.
- ▶ Populations of injecting drug users are at particularly high risk for HIV-HCV co-infection.
- ▶ In the setting of both HBV and HCV infections, co-infection with HIV results in a greater likelihood of chronicity and enhanced viral replication.
- ▶ HIV infection hastens HBV- and HCV-related liver disease, with faster progression to cirrhosis, decompensated liver disease and earlier occurrence of hepatocellular carcinoma.
- ▶ There is little evidence that HBV has any negative effect on HIV-related disease progression or the response to combination antiretroviral therapy (cART). The evidence for the effect of HCV on HIV progression is uncertain, with conflicting results in studies to date. Long-term follow up of people on cART is therefore required.
- ▶ Several antiretrovirals used in the treatment of HIV also have significant anti-HBV activity. Although HIV antiretrovirals have little long-term effect on HCV viraemia, cART may be associated with reduced necroinflammatory activity in people with HIV-HCV co-infection and have a beneficial effect on fibrosis progression.
- ▶ Morbidity and mortality from end-stage liver disease in people with HIV infection remains high; every effort should be made to identify, educate and appropriately treat those people with HBV and/or HCV co-infection.

Introduction

There is now wide recognition that infections with hepatitis B virus (HBV) and hepatitis C virus (HCV) contribute significantly to continuing morbidity and mortality among people with human immunodeficiency virus (HIV). Natural history studies examining the effect of HIV on outcomes in people with HBV and HCV and vice versa have enabled a greater understanding of the reciprocal interactions between these viruses. This knowledge is particularly important as the treatment of each of these chronic viral infections continues to evolve. This chapter reviews the available epidemiology of HIV and viral hepatitis co-infection and the consequences of co-infection on disease progression.

Global prevalence

The global burden of HIV, HBV and HCV infections is substantial, with significant overlap of these infections in the geographical areas and populations most affected. Patterns of risk behaviour and similarities in modes of transmission result in extremely high co-infection rates within certain groups, particularly for HIV-HCV co-infection.

In Europe, rates of HIV-HCV co-infection show distinct geographical variation. In the EuroSIDA cohort of over 3000 patients, the prevalence of HIV-HCV co-infection was 33%.¹ In areas of southern Europe, such as Spain and Portugal, rates may be over 50%,² whereas in northern Europe, rates are much lower (10–37%).^{3,4,5} These differences are primarily related to a higher proportion of injecting drug use (IDU)-related HIV infection in southern Europe.

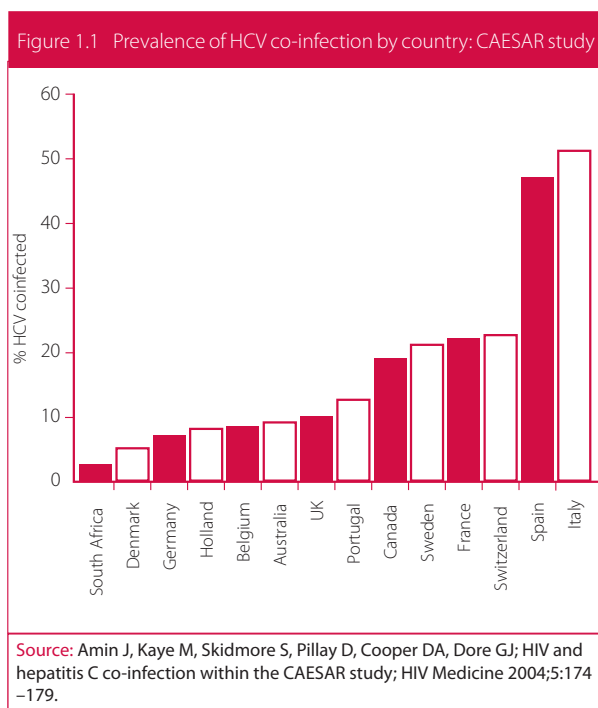
Geographical variation also exists within countries. The USA has a significant burden of co-infection with around 240 000 people with HIV-HCV co-infection (a prevalence of 30%)⁶ but this rate varies considerably in studies from different states.⁷

A study from New York estimated seroprevalence of HCV as 40% in people with HIV infection,⁸ whereas a study from San Francisco estimated prevalence at only 14%.⁷ Within a large AIDS Clinical Trials Group (ACTG) study, HCV prevalence was 16%.⁹ As in European studies, variability in HCV prevalence relates to different proportions of high-risk groups such as injecting drug users and people with haemophilia within study populations.

Elsewhere, similar patterns have been observed with prevalence rates being determined primarily by risk factors. In Manipur, India, 92% of injecting drug users with HIV were estimated to be co-infected with HCV.¹⁰ In Malawi, where the predominant mode of HIV transmission is through heterosexual spread, the HCV prevalence (approximately 16.5%) was similar in women with and without HIV.¹¹

A retrospective analysis of HCV infection in the multinational Canada, Australia, Europe, South Africa (CAESAR) study demonstrated an overall prevalence of 15.6%, ranging from 1.9% in South Africa to 48.6% in Italy (Figure 1.1).¹²

The prevalence of active HBV infection in people with HIV is also significantly higher than in the general population, particularly in low HBV prevalence populations where transmission most commonly occurs in adulthood. In areas where HBV



is predominantly vertically acquired and highly endemic, prevalence rates in the co-infected population are more similar to those in the general population. The prevalence of hepatitis B surface antigen (HBsAg) is in the range of 4–17%,¹³ with less geographical and HIV risk category variation than is the case for HCV prevalence.

The mechanism behind the higher risk for HBV infection in people with HIV is related to shared routes of sexual and parenteral transmission. Progression to chronic infection following acute HBV infection is also much more common in people infected with HIV, with the likelihood of failing to clear HBV related to the degree of immunodeficiency.¹⁴ Furthermore, expansion of the HIV epidemic into regions with high HBV prevalence such as Asia are leading to a significant increase in the numbers of people with HIV-HBV co-infection.¹⁵

Australian prevalence

By the end of 2007 the total number of people living in Australia with HIV was estimated at 16 692, whilst approximately 207 600 individuals were living with chronic hepatitis C infection.¹⁶ A further 70 000 people were estimated to have been exposed to HCV with documented HCV antibodies but no evidence of active infection. The exact prevalence of chronic HBV infection is unknown, with most recent estimates suggesting that approximately 160 000 to 200 000 people in Australia are HBsAg positive.^{17,18} The Australian HIV Observational Database (AHOD) collects demographic information on people with HIV from 24 sites around Australia and has so far recruited over 2000 participants.¹⁹ Seventy-seven per cent of this cohort have been tested for HBsAg and 82% for anti-HCV antibody. The prevalence of HBsAg and HCV antibody were found to be 6.3% and 13.1%, respectively (overall cohort prevalence of 4.8% and 10.1%, respectively if missing data are treated as negative). Of the tested participants, 1.3% (1.0% in the cohort as a total) were documented as positive for HIV, HBV and HCV. These

prevalence data are considerably higher when compared to those in the general Australian population and reflect the cumulative effect of overlapping risks of exposure.

Among injecting drug users in Australia, the prevalence of HCV has been estimated to be approximately 60% whereas the prevalence of HBV infection is approximately 3%²⁰ and that of HIV infection around 1%.²¹ The proportion of injecting drug users with HIV–HCV co-infection is therefore also no more than 1%. This co-infection rate is in contrast to other countries such as the USA and Spain where the prevalence of co-infection in injecting drug users is much higher. The low Australian rate reflects the success of Australia's harm reduction programs in limiting the spread of HIV within this risk group.

Table 1.1 Prevalence of HCV antibody in people with HIV infection (%)

	CAESAR	AHOD13
No of patients	1604	2086
Overall prevalence	15.6	13.1
Prevalence by risk factor for HIV acquisition		
IDU	92.7	63.9
Blood products	52.8	57.1
MSM-IDU	44.4	50.0
MSM	3.4	8.7
Heterosexual	–	9.9

AHOD = Australian HIV Observational Database; IDU = injecting drug use; MSM = men who have sex with men; CAESAR = Canada, Australia, Europe, South Africa study; HCV = hepatitis C virus.

Source: Amin J, Kaye M, Skidmore S, Pillay D, Cooper DA, Dore GJ. HIV and hepatitis C co-infection within the CAESAR study. HIV Medicine 2004;5:174–9

Prevalence by risk factors for HIV and viral hepatitis transmission

HIV shares major routes of transmission with both HCV and HBV: HCV is predominantly spread parenterally through IDU and unscreened blood products, and HBV through vertical transmission at birth, horizontal transmission in childhood, and parenterally and through sexual transmission in adulthood. The likelihood of viral transmission is dependent not only on the route of exposure but also on the size of inoculum and the duration of exposure. People with haemophilia, transfused with untreated blood products prior to the introduction of blood screening techniques, were exposed on multiple occasions to large quantities of hepatitis C virus. Thus, rates of HCV infection in this group may reach 80–90% and virtually all people with haemophilia and HIV will also be HCV co-infected.²²

Globally, IDU remains one of two principal risk factors for HCV infection (the other being unsafe injections in health care settings), and a major risk factor for HIV infection. Duration of injecting, frequency of use and other injecting behaviour significantly influence the likelihood of co-infection. In studies of injecting drug users with HIV, rates of HCV infection vary from 40%⁷ to over 90%.^{1,13} Although prevalence of HIV is lower

among injecting drug users and other populations with HCV,²² it should always be suspected.

Sexual transmission is responsible for the majority of HIV–HBV co-infections in generally low HBV prevalence countries such as Australia, a majority of men who have sex with men (MSM) with HIV have evidence of past or chronic HBV infection.¹³ Sexual HCV transmission does occur, but is responsible for a small proportion of new infections overall.²³ HCV has been detected at low levels in semen,²⁴ much lower than is generally the case for people infected with HBV or HIV.²⁵ Factors that may be associated with sexual HCV transmission include multiple partners, traumatic sexual practices, HIV infection and other sexually transmitted infections.^{26,27} Several studies have confirmed that the risk of HCV transmission between sexual partners in heterosexual stable long-term relationships is low (< 2%),^{23,25,28,29} however the situation in the HIV positive population appears to be different. Multiple reports from Europe, Australia and the United States have confirmed a recent rise in the number of acute HCV cases occurring in HIV positive individuals linked to sexual (or permucosal) risk factors rather than IDU.^{30–33} The factors driving this epidemic and the relative contribution of behavioural or biological components to this higher risk are not fully understood, although a case-control study from the UK suggested an association with a number of sexual and drug use risk behaviours.³⁴ Screening of all HIV positive individuals for HCV on first assessment and on an annual basis thereafter is recommended.

All three viruses may be transmitted via the maternal-fetal route. Most countries have universal infant HBV vaccination but coverage is often suboptimal, especially in poor and rural areas, and inclusion of a birth dose (vital for prevention of vertical transmission) is often lacking. A limited number of countries provide universal antenatal HBV screening. Maternal-fetal transmission of HCV is infrequent, occurring in approximately 5% of infants born to women with HCV infection.^{35–38} Co-infection with HIV increases the rate of HCV transmission by up to three fold,^{35,38,39} presumably due to higher levels of maternal viraemia,³⁶ although cART appears to reduce this increased risk.³⁸ Caesarean section and avoidance of breast-feeding are advocated for mothers with co-infection to reduce the risk of perinatal HIV infection. It is important to recognise that in HIV negative women these measures do not affect the risk of transmission of HCV,³⁸ nor of HBV when timely vaccination and administration of hepatitis B immune globulin (HBIG) is provided.⁴⁰

The natural history of HIV and viral hepatitis co-infection

The effect of HIV on viral load, transmission and chronic infection

HIV–HBV

People infected with HBV in adulthood require the development of a vigorous immune response to resolve acute infection and prevent development of chronic infection: this is achievable in the majority of adults (> 90%) without HIV. In contrast, adults with HIV who acquire HBV have a reduced likelihood of resolution, which is directly proportional to the level of immunosuppression at the time of HBV acquisition.⁴¹

As routes of transmission for HBV and HIV are similar, a high prevalence of HIV–HBV co-infection exists, particularly in MSM, and markers of past or present HBV can be found in over 50% of MSM with HIV.^{19,42} It has long been recognised that reactivation of HBV in people who have previously lost detectable HBsAg may be associated with increasing immunosuppression in the context of HIV infection.⁴³ People with untreated HIV–HBV co-infection have increased rates of HBsAg/HBeAg positivity and higher HBV DNA levels; however they have lower transaminase values and reduced necro-inflammatory activity on histology compared with those people with HBV infection alone.^{44,45} Despite this state of apparent immune tolerance, progression to advanced liver disease including cirrhosis and hepatocellular carcinoma is enhanced.⁴⁶

HIV–HCV

After acute infection, the likelihood of chronic HCV infection is increased from 60–70% in people without HIV to 80–90% in HIV-positive people.^{47,48} As with HIV–HBV co-infection, people with HIV–HCV co-infection have been shown to have higher levels of viraemia than those with HCV alone^{49–51} and in some studies increased levels have been correlated with more advanced immunosuppression.⁵² High levels of HCV viraemia are likely to result in a greater risk of transmission and a reduction in success of therapy.⁵³ It is however unlikely that the increased HCV viraemia in people with HIV–HCV co-infection is responsible for greater rates of disease progression and fibrosis. There is no correlation between quantitative HCV and progression of fibrosis^{47,54} in people with HCV or HIV–HCV co-infection.

Effect of HIV on liver disease progression

HIV–HBV

Evidence for the adverse effect of HIV infection on the natural history of chronic HBV infection continues to develop,⁴⁶ an analysis of the Multicentre AIDS Cohort Study (MACS) cohort published in the *Lancet* in 2002 demonstrated an increased risk of liver-related mortality in people with HIV–HBV co-infection, particularly those with the greatest degree of immunosuppression.⁵⁵ In this study of 5293 MSM, 6% were HBsAg positive and 41% HIV-1 positive. Liver-related mortality was more than eight times as likely in those with HIV–HBV co-infection than those with HIV alone and almost 19 times as likely when compared to those with HBV alone. Individuals with a CD4 count nadir of < 100 cells/mm³ were at the highest risk of liver-related mortality and there was a trend for mortality to increase in the years after cART became available.

In 2005 the EUROSIDA study group further examined the effect of HBsAg positivity on progression to AIDS, death from all causes, liver disease related death and response to cART.⁵⁶ Amongst 5728 HIV-positive individuals tested for hepatitis B surface antigen (HBsAg), 498 (8.7%) were HBsAg positive. Liver disease related mortality was threefold higher in HBsAg positive patients than in the HBsAg negative group. No reduction in liver-related deaths was observed with the specific use of HBV-active cART in this study, although two other cohort studies have suggested that the use of cART (including agents active against HBV) may reduce liver-related mortality in HIV–HBV co-infected individuals.^{57,58}

HIV-HCV

There is convincing evidence that co-infection with HIV significantly worsens the prognosis of HCV-related liver disease. Chronic hepatitis C may result in cirrhosis, decompensated liver disease (DLD) and hepatocellular carcinoma, all of which are associated with high mortality. HIV not only increases the likelihood of chronic infection but also hastens the development of the above complications.⁵⁹⁻⁶¹ A recent meta-analysis of 17 studies involving 3567 HIV-HCV co-infected individuals confirmed the worse outcomes of chronic HCV in co-infected individuals, with an estimated cumulative probability of cirrhosis of 21% at 20 years and 49% at 30 years.⁶² Factors associated with increased risk of liver disease progression in people with HIV-HCV co-infection include heavy alcohol intake (> 50 grams/day), older age at HCV acquisition, low CD4 count,⁶³ increased quasispecies variability,⁶⁴ and occult HBV infection.⁶⁵

Hepatocellular carcinoma in HIV/viral hepatitis co-infection

At least four recent studies have confirmed the altered and often aggressive presentation of hepatocellular carcinoma (HCC) in the setting of HIV/viral hepatitis co-infection.⁶⁶⁻⁶⁹ HIV positive individuals are more likely to be younger at age of HCC presentation,^{66,69} to have multifocal and advanced disease, and have poorer survival rates.⁶⁹ Evidence from the Swiss HIV Cohort Study also suggested that lower CD4 cell counts were associated with a significantly increased risk of HCC in people with HIV co-infected with viral hepatitis, particularly HBV.⁶⁷ These findings highlight the need for awareness and appropriate screening policies for HCC in the HIV/viral hepatitis co-infected population.

Effect of cART on HBV-HCV progression

Hepatotoxicity with cART occurs in a significant number of people initiating therapy and the risk is two- to three-fold higher for those with HBV or HCV co-infection.^{4,70} The prevalence, mechanisms and management of cART-related hepatotoxicity are dealt with in Chapter 4.

The advent of cART has afforded both opportunities and potential difficulties for the management of HIV-HBV co-infection. With several antiretroviral agents also having anti-HBV activity, both infections can be treated with a single regimen of cART. However concerns such as development of resistance mutations in either virus, and reactivation of replication if HBV-active agents are ceased mean such regimens must be designed carefully and changed cautiously. A further consideration is that of immune reconstitution hepatitis flares with the initiation of cART. Where as such flares can lead to control of viral replication, they can also result in hepatic decompensation even if agents active against HBV are included in the regimen.⁷¹ These management complexities are discussed in Chapter 3.

Several studies have examined the effect of cART on HCV viraemia; results are conflicting. Most of these studies have found no evidence for an effect of cART on HCV viremia⁷²⁻⁷⁴ although two have reported significant transient increases after cART initiation, along with elevations in serum transaminases.^{75,76} Despite having little direct effect on HCV

viraemia, the commencement of cART has occasionally been reported to cause HCV clearance, presumably through immune-mediated mechanisms.⁷⁷ A recent histological study suggested that use of cART is also associated with a reduction in necroinflammatory activity in HCV co-infected patients.⁷⁸ In the meta-analysis by Thein et al (2008) cART was not shown to fully correct the adverse effect of HIV on HCV prognosis, although this may have been affected by the relatively short duration of follow-up.⁷⁹ Aspects of clinical management of HIV-HCV co-infection are covered in Chapter 2.

Effect of viral hepatitis on HIV disease progression

HIV-HBV

The interactions between HIV and HBV and the resultant effect on HIV disease progression have been debated. Before the availability of cART, some studies suggested that the presence of HBsAg could hasten progression to AIDS.⁸⁰ This was refuted in other studies that demonstrated no difference in time to AIDS development⁴⁴ or survival times after AIDS diagnosis⁸¹ in those who were HBsAg positive. Two large observational studies have recently examined this question further. In the MACS cohort from the USA, the presence of HBsAg in people with HIV infection had no effect on progression to AIDS, AIDS-related death, overall mortality or successful response to cART.⁸²

In the AHOD, individuals who commenced cART with HBV co-infection were no more likely to progress to AIDS or death than those without HBV co-infection.¹⁹ Similarly, both virological response to cART and CD4 cell count increases were unaffected by HBsAg. It therefore seems likely that HBV co-infection has little negative impact on the progression of HIV disease.

HIV-HCV

The magnitude of the effect of HCV infection on HIV disease progression is difficult to quantify due to a number of factors that may influence the findings of natural history studies.

Comparing people with HIV-HCV co-infection with those with HIV infection is complicated by the presence of significant differences between groups. Populations at higher risk of HCV acquisition such as those with haemophilia or injecting drug users have marked differences in behavioural characteristics and outcomes,⁸³ as well as in attitudes and adherence patterns to ART,⁸⁴ compared to populations with HIV alone. Failure to properly control for these differences has a marked impact on study findings.

Before the introduction of cART, many longitudinal and cross-sectional studies failed to show any significant effect of HCV on HIV progression⁸⁵⁻⁸⁷ while some studies were able to demonstrate a more rapid clinical progression to AIDS in people with HCV.⁸⁸⁻⁹⁰ More recently, two large cohort studies examining the effect of HCV in people receiving cART have reported different conclusions on HIV-related outcomes. In the Swiss Cohort Study risk of progression to AIDS or death was increased in those with HIV-HCV co-infection (hazard ratio 1.7; 95% CI: 1.26-2.30).³ Despite similar virological responses, people with HCV were also less likely to achieve increases in CD4 cell counts of at least 50 cells/mm³ by one year after start of therapy.

In contrast to the Swiss HIV Cohort Study data, a study from the USA demonstrated no differences between those with HIV alone and those with HIV–HCV co-infection with regard to incidence of AIDS, death or change in CD4 cell count over time.⁹¹ In particular, increases in CD4 cell count after cART were unimpaired in individuals with HIV–HCV co-infection. Findings from the AHOD support the lack of evidence for greater risk of HIV disease progression in people with HIV–HCV co-infection but, similar to the Swiss HIV Cohort Study results, were able to demonstrate marginally poorer CD4 cell count responses to cART in those with HCV.¹⁹ The most recent available evidence from the EuroSIDA cohort study demonstrated that infection with HCV did not influence CD4 cell count recovery in patients with maximal HIV virological suppression following initiation of cART.⁹²

Contribution of liver disease to HIV-related morbidity and mortality

The widespread availability of cART in resource-rich countries since the late 1990s has led to a dramatic shift in the spectrum of HIV-related morbidity and mortality. Life expectancy of people with HIV has been significantly extended; consequently, other chronic conditions, in particular liver-related pathologies, have become increasingly important. A study from the USA found that HCV is the leading cause of death in people with HIV, with end-stage liver disease contributing to 50% of all deaths in more recent years.⁹³ In a recent analysis from the D:A:D cohort study of over 23 000 HIV patients from Europe, HIV/AIDS remains the commonest cause of death (31%), but is followed by liver disease as the second commonest cause of mortality (15%), much of which is related to viral hepatitis co-infection.⁹⁴ Further recent evidence of the effect of co-infection on mortality appeared in a Taiwanese longitudinal study of patients on cART.⁹⁵ Participants with HBV co-infection were twice as likely to die during follow up when compared with patients with no history of HBV infection, with 30% of deaths of those with HBV co-infection recorded as liver-related, compared with no liver-related deaths in patients without HBV infection.

Conclusion

The presence of HIV infection, especially when associated with significant immunosuppression, has a negative impact on disease progression in both HBV and HCV infections and results in an increase in liver-related morbidity and mortality from conditions such as cirrhosis and hepatocellular carcinoma. The extent to which this effect can be avoided will depend both on the continuing successful treatment of HIV infection, and the early identification and appropriate monitoring and treatment of HBV and HCV infections.

References

1. Stubbe L, Soriano V, Antunes F, et al. Hepatitis C in the EuroSIDA Cohort of European HIV-infected patients: prevalence and prognostic value. 12th World AIDS Conference, Geneva, Switzerland, 1998. Abstract 22261.
2. Soriano V, Kirk O, Antunes F. The influence of hepatitis C on the prognosis of HIV: the EuroSIDA study. 13th International AIDS Conference, Durban, South Africa, 2000. Abstract ThOrB655.

3. Greub G, Ledergerber B, Battegay M, Grob P, Perrin L, Furrer H, et al. Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus co-infection: the Swiss HIV Cohort Study. *Lancet* 2000;356(9244):1800–5.
4. den Brinker M, Wit FW, Wertheim-van Dillen PM, Jurriaans S, Weel J, van Leeuwen R, et al. Hepatitis B and C virus co-infection and the risk for hepatotoxicity of highly active antiretroviral therapy in HIV-1 infection. *AIDS* 2000;14(18):2895–902.
5. Wit FW, Weverling GJ, Weel J, Jurriaans S, Lange JM. Incidence of and risk factors for severe hepatotoxicity associated with antiretroviral combination therapy. *J Infect Dis* 2002;186(1):23–31.
6. Sulkowski MS, Mast EE, Seeff LB, Thomas DL. Hepatitis C virus infection as an opportunistic disease in persons infected with human immunodeficiency virus. *Clin Infect Dis* 2000;30 Suppl 1:S77–S84.
7. Wright TL, Hollander H, Pu X, Held MJ, Lipson P, Quan S, et al. Hepatitis C in HIV-infected patients with and without AIDS: prevalence and relationship to patient survival. *Hepatology* 1994;20(5):1152–5.
8. Merrick ST, Sepkowitz KA, Boyle BA, et al. Seroprevalence of hepatitis C antibody and hepatitis B antigenaemia in a large urban HIV clinic. 12th World AIDS Conference, Geneva, Switzerland, 1998. Abstract 22263.
9. Sherman KE, Rouster SD, Chung RT, Rajcic N. Hepatitis C virus prevalence among patients infected with Human Immunodeficiency Virus: a cross-sectional analysis of the US adult AIDS Clinical Trials Group. *Clin Infect Dis* 2002;34(6):831–7.
10. Saha MK, Chakrabarti S, Panda S, Naik TN, Manna B, Chatterjee A, et al. Prevalence of HCV and HBV infection amongst HIV seropositive intravenous drug users and their non-injecting wives in Manipur, India. *Indian J Med Res* 2000;111:37–9.
11. Ahmed SD, Cuevas LE, Brabin BJ, Kazembe P, Broadhead R, Verhoeff FH, et al. Seroprevalence of hepatitis B and C and HIV in Malawian pregnant women. *J Infect* 1998;37(3):248–51.
12. Amin J, Kaye M, Skidmore S, Pillay D, Cooper DA, Dore GJ. HIV and hepatitis C co-infection within the CAESAR study. *HIV Medicine* 2004;5(3):174–179.
13. Alter MJ. Epidemiology of viral hepatitis and HIV co-infection. *J Hepatol* 2006;44(1 Suppl):S6–9.
14. Shukla NB, Poles MA. Hepatitis B virus infection: co-infection with hepatitis C virus, hepatitis D virus, and human immunodeficiency virus. *Clin Liver Dis* 2004(2):445–60, viii.
15. Matthews GV, Avihingsanon A, Lewin SR, Amin J, Rerknimitr R, Petcharapirat P, et al. A randomized trial of combination hepatitis B therapy in HIV/HBV co-infected antiretroviral naive individuals in Thailand. *Hepatology* 2008;48(4):1062–9.
16. HIV/AIDS, viral hepatitis and sexually transmissible infections in Australia: Annual Surveillance Report 2008. Sydney: National Centre in HIV Epidemiology and Clinical Research, The University of New South Wales; 2008.
17. Gidding HF, Warlow M, MacIntyre CR, Backhouse J, Gilbert GL, Quinn HE, et al. The impact of a new universal infant and school-based adolescent hepatitis B vaccination program in Australia. *Vaccine* 2007;25(51):8637–41.
18. Cowie BC, Karapanagiotidis T, Enriquez A, Kelly H. Markers of hepatitis B virus infection and immunity in Victoria, Australia, 1995 to 2005. *Aust NZ J Public Health*. 2010;34(1):72–8.
19. Lincoln D, Petoumenos K, Dore G, Australian HIV Observational Database. HIV-HBV and HIV-HCV co-infection, and outcomes following highly active antiretroviral treatment. *HIV Medicine* 2003;4(3):241–9.

1 The epidemiology of HIV and viral hepatitis co-infection

20. Bradshaw CS, Pierce LI, Tabrizi SN, Fairley CK, Garland SM. Screening injecting drug users for sexually transmitted infections and blood borne viruses using street outreach and self collected sampling. *Sex Transm Infect* 2005;81(1):53-8.
21. HIV/AIDS, viral hepatitis and sexually transmissible infections in Australia. Annual Surveillance Report 2008. Sydney: National Centre in HIV Epidemiology and Clinical Research, The University of New South Wales, 2008.
22. Troisi CL, Hollinger FB, Hoots WK, Contant C, Gill J, Ragni M, et al. A multicenter study of viral hepatitis in a United States hemophilic population. *Blood* 1993;81(2):412-8.
23. Dore GJ, Law M, MacDonald M, Kaldor JM. Epidemiology of hepatitis C virus infection in Australia. *J Clin Virol* 2003;26(2):171-84.
24. Leruez-Ville M, Kunstmann JM, De Almeida M, Rouzioux C, Chaix ML. Detection of hepatitis C virus in the semen of infected men. *Lancet* 2000;356(9223):42-3.
25. Dore GJ, Kaldor JM. Detection of HCV RNA in semen. *Lancet* 2000;356(9240):1520.
26. Eyster ME, Alter HJ, Aledort LM, Quan S, Hatzakis A, Goedert JJ. Heterosexual co-transmission of hepatitis C virus (HCV) and human immunodeficiency virus (HIV). *Ann Intern Med* 1991;115(10):764-8.
27. Thomas DL, Zenilman JM, Alter HJ, Shih JW, Galai N, Carella AV, et al. Sexual transmission of hepatitis C virus among patients attending sexually transmitted diseases clinics in Baltimore – an analysis of 309 sex partnerships. *J Infect Dis* 1995;171(4):768-75.
28. Brettler DB, Mannucci PM, Gringeri A, Rasko JE, Forsberg AD, Rumi MG, et al. The low risk of hepatitis C virus transmission among sexual partners of hepatitis C-infected hemophilic males: an international, multicenter study. *Blood* 1992; 80(2):540-3.
29. Osmond DH, Padian NS, Sheppard HW, Glass S, Shiboski SC, Reingold A. Risk factors for hepatitis C virus seropositivity in heterosexual couples. *J Am Med Assoc* 1993;269(3):361-5.
30. Gilleece YC, Browne RE, Asboe D, Atkins M, Mandalia S, Bower M, et al. Transmission of hepatitis C virus among HIV-positive homosexual men and response to a 24-week course of pegylated interferon and ribavirin. *J Acquir Immune Defic Syndr* 2005;40(1):41-6.
31. Gotz HM, van Doornum G, Niesters HG, den Hollander JG, Thio HB, de Zwart
- O. A cluster of acute hepatitis C virus infection among men who have sex with men--results from contact tracing and public health implications. *AIDS* 2005;19(9):969-74.
32. Gambotti L, Batisse D, Colin-de-Verdiere N, Delaroque-Astagneau E, Desenclos JC, Dominguez S, et al. Acute hepatitis C infection in HIV positive men who have sex with men in Paris, France, 2001-2004. *Euro Surveill* 2005;10(5):115-7.
33. Matthews GV, Hellard M, Kaldor J, Lloyd A, Dore GJ. Further evidence of HCV sexual transmission among HIV-positive men who have sex with men: response to Danta et al. *AIDS* 2007;21(15):2112-3.
34. Danta M, Brown D, Bhagani S, Pybus OG, Sabin CA, Nelson M, et al. Recent epidemic of acute hepatitis C virus in HIV-positive men who have sex with men linked to high-risk sexual behaviours. *AIDS* 2007;21(8):983-91.
35. Thomas DL, Villano SA, Riester KA, Hershov R, Mofenson LM, Landesman SH, et al. Perinatal transmission of hepatitis C virus from human immunodeficiency virus type 1-infected mothers. Women and Infants Transmission Study. *J Infect Dis* 1998;177(6):1480-8.
36. Granovsky MO, Minkoff HL, Tess BH, Waters D, Hatzakis A, Devoid DE, et al. Hepatitis C virus infection in the mothers and infants cohort study. *Pediatrics* 1998;102 (2 Pt 1):355-9.
37. Conte D, Fraquelli M, Prati D, Colucci A, Minola E. Prevalence and clinical course of chronic hepatitis C virus (HCV) infection and rate of HCV vertical transmission in a cohort of 15,250 pregnant women. *Hepatology* 2000;31(3):751-5.
38. Pembrey L, Newell ML, Tovo PA. The management of HCV infected pregnant women and their children European paediatric HCV network. *J Hepatol* 2005;43(3):515-25.
39. Gibb DM, Goodall RL, Dunn DT, Healy M, Neave P, Cafferkey M, et al. Mother-to-child transmission of hepatitis C virus: evidence for preventable peripartum transmission. *Lancet* 2000; 356(9233):904-7.
40. Cowie BC. Managing hepatitis B virus infection in complex situations. In: Matthews G, Robotin MC, editors. B positive - all you wanted to know about hepatitis B: a guide for primary care providers. Darlinghurst: Australasian Society for HIV Medicine 2008. p. 75-81.
41. Shukla NB, Poles MA. Hepatitis B virus infection: co-infection with hepatitis C virus, hepatitis D virus, and human immunodeficiency virus. *Clin Liver Dis* 2004;8(2):445-60
42. Weinbaum CM, Williams I, Mast EE, Wang SA, Finelli L, Wasley A, et al. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR Recomm Rep* 2008;57(RR-8):1-20.
43. Vento S, di Perri G, Luzzati R, Cruciani M, Garofano T, Mengoli C et al. Clinical reactivation of hepatitis B in anti-HBs-positive patients with AIDS. *Lancet* 1989; 1(8633):332-3.
44. Gilson RJ, Hawkins AE, Beecham MR, Ross E, Waite J, Briggs M, et al. Interactions between HIV and hepatitis B virus in homosexual men: effects on the natural history of infection. *AIDS* 1997;11(14):597-606.
45. Colin JF, Cazals-Hatem D, Lorient MA, Martinot-Peignoux M, Pham BN, Auperin A, et al. Influence of human immunodeficiency virus infection on chronic hepatitis B in homosexual men. *Hepatology* 1999; 29(4):1306-10.
46. Thio CL. Hepatitis B and human immunodeficiency virus co-infection. *Hepatology*. 2009;49(5 Suppl):S138-45.
47. Thomas DL, Astemborski J, Rai RM, Anania FA, Schaeffer M, Galai N, et al. The natural history of hepatitis C virus infection: host, viral, and environmental factors. *J Am Med Assoc* 2000;284(4):450-6.
48. Mehta SH, Cox A, Hoover DR, Wang XH, Mao Q, Ray S, et al. Protection against persistence of hepatitis C. *Lancet* 2002;359(9316):1478-83.
49. Cribier B, Rey D, Schmitt C, Lang JM, Kirn A, Stoll-Keller F. High hepatitis C viraemia and impaired antibody response in patients co-infected with HIV. *AIDS* 1995;9(10):1131-6.
50. Thomas DL, Shih JW, Alter HJ, Vlahov D, Cohn S, Hoover DR et al. Effect of human immunodeficiency virus on hepatitis C virus infection among injecting drug users. *J Infect Dis* 1996;174(4):690-5.
51. Sherman KE, O'Brien J, Gutierrez AG, Harrison S, Urdea M, Neuwald P et al. Quantitative evaluation of hepatitis C virus RNA in patients with concurrent human immunodeficiency virus infections. *J Clin Microbiol* 1993;31(10):2679-82.
52. Soto B, Sanchez-Quijano A, Rodrigo L, del Olmo JA, Garcia-Bengochea M, Hernandez-Quero J et al. Human immunodeficiency virus infection modifies the natural history of chronic parenterally-acquired hepatitis C with an unusually rapid progression to cirrhosis. *J Hepatol* 1997;26(1):1-5.

53. Poynard T, McHutchison J, Goodman Z, Ling MH, Albrecht J. Is an "a la carte" combination interferon alfa-2b plus ribavirin regimen possible for the first line treatment in patients with chronic hepatitis C? The ALGOVIRC Project Group. *Hepatology* 2000;31(1):211-8.
54. Fanning L, Kenny E, Sheehan M, Cannon B, Whelton M, O'Connell J et al. Viral load and clinicopathological features of chronic hepatitis C (1b) in a homogeneous patient population. *Hepatology* 1999;29:904-7.
55. Thio CL, Seaberg EC, Skolasky R Jr, Phair J, Visscher B, Muñoz A, et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). *Lancet* 2002;360(9349):1921-6.
56. Konopnicki D, Mocroft A, de Wit S, Antunes F, Ledergerber B, Katlama C, 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(6):593-601.
57. 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(15):2039-45.
58. Puoti M, Cozzi-Lepri A, Arici C, Moller NF, Lundgren JD, Ledergerber B, et al. Impact of lamivudine on the risk of liver-related death in 2,041 HBsAg- and HIV-positive individuals: results from an inter-cohort analysis. *Antivir Ther* 2006;11(5):567-74.
59. Monga HK, Rodriguez-Barradas MC, Breaux K, Khattak K, Troisi CL, Velez M, et al. Hepatitis C virus infection-related morbidity and mortality among patients with human immunodeficiency virus infection. *Clin Infect Dis* 2001;33(2):240-7.
60. Yee TT, Griffioen A, Sabin CA, Dusheiko G, Lee CA. The natural history of HCV in a cohort of haemophilic patients infected between 1961 and 1985. *Gut* 2000; 47(6):845-51.
61. Graham CS, Baden LR, Yu E, Mrus JM, Carnie J, Heeren T, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis
62. Thein HH, Yi Q, Dore GJ, Krahn MD. Natural history of hepatitis C virus infection in HIV-infected individuals and the impact of HIV in the era of highly active antiretroviral therapy: a meta-analysis. *AIDS* 2008;22:1979-1991
63. Pol S, Lamorthe B, Thi NT, Thiers V, Carnot F, Zylberberg H, et al. Retrospective analysis of the impact of HIV infection and alcohol use on chronic hepatitis C in a large cohort of drug users. *J Hepatol* 1999;30(2):347-8.
64. Cacciola I, Pollicino T, Squadrito G, Cerenzia G, Orlando ME, Raimondo G. Occult hepatitis B virus infection in patients with chronic hepatitis C liver disease. *N Engl J Med* 1999;341:22-6.
65. Benhamou Y, Di Martino V, Bochet M, Colombet G, Thibault V, Liou A et al. Factors affecting liver fibrosis in human immunodeficiency virus-and hepatitis C virus-co-infected patients: impact of 2001;34:283-7.
66. Brau N, Fox RK, Xiao P, Marks K, Naqvi Z, Taylor LE, et al. Presentation and outcome of hepatocellular carcinoma in HIV-infected patients: a U.S.-Canadian multicenter study. *J Hepatol* 2007;47(4):527-37.
67. Clifford GM, Rickenbach M, Polesel J, Dal Maso L, Steffen I, Ledergerber B, et al. Influence of HIV-related immunodeficiency on the risk of hepatocellular carcinoma. *AIDS* 2008;22(16):2135-41.
68. Salmon-Ceron D, Rosenthal E, Lewden C, Bouteloup V, May T, Burty C, et al. Emerging role of hepatocellular carcinoma among liver-related causes of deaths in HIV-infected patients: The French national Mortalite 2005 study. *J Hepatol* 2009;50(4):736-45.
69. Puoti M, Bruno R, Soriano V, Donato F, Gaeta GB, Quinzan GP, et al. Hepatocellular carcinoma in HIV-infected patients: epidemiological features, clinical presentation and outcome. *AIDS* 2004;18(17):2285-93.
70. Sulkowski MS, Thomas DL, Chaisson RE, Moore RD. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. *JAMA* 2000;283:74-80.
71. Drake A, Mijch A, Sasadeusz J. Immune reconstitution hepatitis in HIV and hepatitis B co-infection, despite lamivudine therapy as part of HAART. *Clin Infect Dis* 2004;39(1):129-32.
72. Rockstroh JK, Theisen A, Kaiser R, Sauerbruch T, Spengler U. Antiretroviral triple therapy decreases HIV viral load but does not alter hepatitis C virus (HCV) serum levels in HIV-HCV-co-infected haemophiliacs. *AIDS* 1998;12:829-30.
73. Garcia-Samaniego J, Bravo R, Castilla J, Gómez-Cano M, Laguna F, Muñoz F, et al. Lack of benefit of protease inhibitors on HCV viraemia in HIV-infected patients. *J Hepatol* 1998;28:526-7.
74. Zylberberg H, Chaix ML, Rabian C, Rouzioux C, Aulong B, Bréchet C, et al. Tritherapy for human immunodeficiency virus infection does not modify replication of hepatitis C virus in co-infected subjects. *Clin Infect Dis* 1998;26:1104-6.
75. Rutschmann OT, Negro F, Hirschel B, Hadengue A, Anwar D, Perrin LH. Impact of treatment with human immunodeficiency virus (HIV) protease inhibitors on hepatitis C viraemia in patients co-infected with HIV. *J Infect Dis* 1998;177:783-5.
76. Vento S, Garofano T, Renzini C, Casali F, Ferraro T, Concia E. Enhancement of hepatitis C virus replication and liver damage in HIV- co-infected patients on antiretroviral combination therapy. *AIDS* 1998;12:116-7.
77. Fialaire P, Payan C, Vitour D, Chenebault JM, Loison J, Pichard E et al. Sustained disappearance of hepatitis C viraemia in patients receiving protease inhibitor treatment for human immunodeficiency virus infection. *J Infect Dis* 1999;180:574-5.
78. Pascual-Pareja JF, Caminoa A, Larrauri C, Gonzalez-Garcia J, Montes ML, Diez J, et al. HAART is associated with lower hepatic necroinflammatory activity in HIV-hepatitis C virus-co-infected patients with CD4 cell count of more than 350 cells/microl at the time of liver biopsy. *AIDS* 2009;23(8):971-5.
79. Thein HH, Yi Q, Dore GJ, Krahn MD. Natural history of hepatitis C virus infection in HIV-infected individuals and the impact of HIV in the era of highly active antiretroviral therapy: a meta-analysis. *AIDS* 2008;22:1979-1991
80. Eskild A, Magnus P, Petersen G, Sohlberg C, Jensen F, Kittelsen P, et al. Hepatitis B antibodies in HIV-infected homosexual men are associated with more rapid progression to AIDS. *AIDS* 1992;6:571-4.
81. Schar Schmidt BF, Held MJ, Hollander HH, Read AE, Lavine JE, Veereman G, et al. Hepatitis B in patients with HIV infection: relationship to AIDS and patient survival. *Ann Intern Med* 1992; 117:837-8.
82. Thio, CL, Seaberg, CL, Kingsley, L, Phair, J, Visscher, B, and Munoz, A. The role of hepatitis B virus in the progression of HIV and the response to highly active antiretroviral therapy (HAART). 15th International AIDS Conference, 2002. Abstract WePeB6016.
83. Prins M, Hernández Aguado IH, Brettle RP, Robertson JR, Broers B, Carré N, et al. Pre-AIDS mortality from natural causes associated with HIV disease progression: evidence from the European Seroconverter Study among injecting drug users. *AIDS* 1997;11:1747-56.

1 The epidemiology of HIV and viral hepatitis co-infection

84. Dorrucchi M, Pezzotti P, Phillips AN, Alliegro MB, Rezza G. Antiretroviral treatment and progression to AIDS in HIV seroconverters from different risk groups. HIV Italian Seroconversion Study. *AIDS* 1997;1:461–7.
85. Dorrucchi M, Pezzotti P, Phillips AN, Lepri AC, Rezza G. Co-infection of hepatitis C virus with human immunodeficiency virus and progression to AIDS. Italian Seroconversion Study. *J Infect Dis* 1995;172:1503–8.
86. Quan CM, Krajden M, Grigoriew GA, Salit IE. Hepatitis C virus infection in patients infected with the human immunodeficiency virus. *Clin Infect Dis* 1993;17:117–9.
87. Staples CT, Jr, Rimland D, Dudas D. Hepatitis C in the HIV (human immunodeficiency virus) Atlanta V.A. (Veterans Affairs Medical Center) Cohort Study (HAVACS): the effect of co-infection on survival. *Clin Infect Dis* 1999;29:150–4.
88. Piroth L, Duong M, Quantin C, Abrahamowicz M, Michardiere R, Aho LS et al. Does hepatitis C virus co-infection accelerate clinical and immunological evolution of HIV-infected patients? *AIDS* 1998;12:381–8.
89. Sabin CA, Telfer P, Phillips AN, Bhagani S, Lee CA. The association between hepatitis C virus genotype and human immunodeficiency virus disease progression in a cohort of hemophilic men. *J Infect Dis* 1997;175:164–8.
90. Daar ES, Lynn H, Donfield S, Gomperts E, O'Brien SJ, Hilgartner MW, et al. Hepatitis C virus load is associated with human immunodeficiency virus type 1 disease progression in hemophiliacs. *J Infect Dis* 2001;183:589–95.
91. Sulkowski MS, Moore RD, Mehta SH, Chaisson RE, Thomas DL. Hepatitis C and progression of HIV disease. *J Am Med Assoc* 2002;288:199–206.
92. Peters L, Mocroft A, Soriano V, Rockstroh JK, Losso M, Valerio L, et al. Hepatitis C virus co-infection does not influence the CD4 cell recovery in HIV-1-infected patients with maximum virologic suppression. *J Acquir Immune Defic Syndr* 2009;50(5):457–63.
93. Bica I, McGovern B, Dhar R, Stone D, McGowan K, Scheib R et al. Increasing mortality due to end-stage liver disease in patients with human immunodeficiency virus infection. *Clin Infect Dis* 2001;32:492–7.
94. Weber R, Sabin CA, Friis-Moller N, Reiss P, El-Sadr WM, Kirk O, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. *Arch Intern Med* 2006;166(15):1632–41.
95. Sheng WH, Kao JH, Chen PJ, Huang LM, Chang SY, Sun HY, et al. Evolution of hepatitis B serological markers in HIV-infected patients receiving highly active antiretroviral therapy. *Clin Infect Dis* 2007;45(9):1221–9.

The management of HIV and hepatitis C virus co-infection

2

Gregory Dore
Joe Sasadeusz

National Centre in HIV Epidemiology and Clinical Research, The University of New South Wales, Sydney, NSW
Victorian Infectious Diseases Service, Royal Melbourne Hospital and Infectious Diseases Unit, The Alfred Hospital, Melbourne, VIC

KEY POINTS

- All people with HIV infection should be tested for hepatitis C virus (HCV); however, those with a history of injecting drug use or elevated serum transaminase (ALT) levels are most likely to be infected.
- HCV RNA should be measured to confirm active infection in all people positive on anti-HCV antibody testing.
- HCV genotype analysis will help to determine the likelihood of response to antiviral therapy.
- Adverse effects of both HCV antiviral therapy and HIV antiretroviral therapy (ART) are increased in people with HIV–HCV co-infection.
- Efficacy of HCV antiviral therapy, particularly in people with HCV genotype 1, is suboptimal. A strategy of prioritisation of HIV and HCV therapy based on respective risks of HIV and liver disease-related complications is required.

Introduction

The declining incidence of HIV-related opportunistic disease due to improved antiretroviral therapy (ART) has shifted the emphasis of HIV clinical management towards prevention and treatment of comorbidities, especially liver disease. Significant advances in antiviral therapy for hepatitis B virus (HBV) and hepatitis C virus (HCV) infection^{1–4} provide the opportunity for more effective management of underlying chronic viral hepatitis in people with HIV infection. This chapter will cover clinical management of people with HIV–HCV co-infection and propose a therapeutic strategy based on current evidence.

Important virological, epidemiological and clinical interactions between HIV and HCV have been described over the last decade.⁵ People with HIV–HCV co-infection have a lower clearance rate of HCV infection, higher HCV viral load and accelerated liver disease progression.^{6,7} However, evidence is starting to emerge that immune restoration through combination antiretroviral therapy (cART) may slow liver disease progression in people with HIV–HCV co-infection.⁸ Accelerated HIV disease progression in people with HIV–HCV co-infection was suggested in some earlier studies, although more recent research has refuted this association (see Chapter 1).^{9–11}

Diagnosis and assessment of HCV infection in people with HIV infection

Overlapping modes of transmission, and the higher prevalence of HCV in HIV infected individuals¹² (see Chapter 1) suggest that HCV antibody testing should be recommended for all people living with HIV.

Groups at risk of an underlying HCV infection include:

- Injecting drug users;
- Men who have sex with men (MSM) having high-risk contact with other MSM living with HIV;

- Individuals with elevated serum transaminase (ALT) and aspartate aminotransferase levels (AST).

An HCV testing algorithm for people with HIV infection is shown in Figure 2.1. The sensitivity of HCV antibody testing is lower in people with HIV infection, particularly for those with advanced immunodeficiency. HCV RNA assessment by polymerase chain reaction (PCR) is recommended if HCV antibody testing is negative but risk factors suggest an increased likelihood of HCV infection.

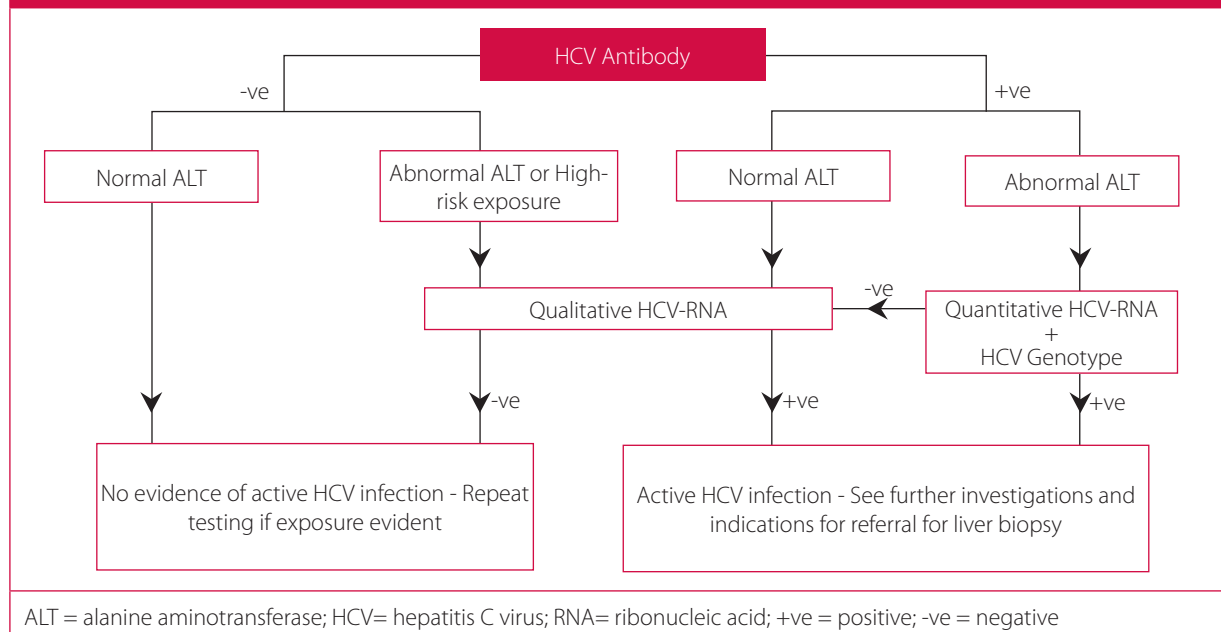
In 20–30% of cases, HCV infection does not lead to viral persistence¹³ although progression to chronic HCV infection is more common in people with HIV infection.¹⁴ HCV RNA testing for co-infected individuals allows confirmation of chronic HCV infection. Negative qualitative HCV RNA results from tests performed on two or more occasions, separated by several months, indicate the absence of active acute or chronic HCV infection.

Chronic HCV infection is highly likely in people with a positive HCV antibody and elevated ALT levels. Baseline testing for these people generally includes viral genotype and quantitative HCV RNA viral load as efficacy of HCV antiviral therapy is associated with both parameters.^{2,3,4} HCV viral load however, has no prognostic value in terms of disease progression (unlike HIV or HBV viral load), and does not require regular monitoring.

Possible explanations for elevated ALT levels and a negative HCV RNA test include hepato-toxic ART agents, hepatic steatosis and heavy alcohol intake.

As the vast majority of people are asymptomatic at the time of HCV acquisition, people with HIV infection who are at ongoing risk should have regular (12 monthly) HCV antibody testing. People diagnosed with newly acquired HCV infection (positive HCV antibody with negative HCV antibody within the

Figure 2.1 HCV testing algorithm for people with HIV



previous two years, or acute clinical hepatitis with positive HCV antibody or HCV PCR) should be referred for assessment and consideration of early antiviral therapy.

It is important to note that several outbreaks of acute HCV have been reported among HIV-positive MSM. In these outbreaks sexual transmission was the predominant form of transmission with practices such as fisting and toy sharing playing a role.^{15,16} It is thus important to consider HCV as a potential diagnosis in these populations and screening for the infection is warranted.

Further assessment and referral for treatment consideration

Further assessment in people with HIV–HCV co-infection should include a drug and alcohol history, psychiatric history, and hepatitis A virus (HAV) and HBV serology with vaccination of all patients susceptible to these infections. HCV genotype and viral load are important in determining the likelihood of response to antiviral therapy. A psychiatric history is particularly important, given the high rates of depression that are experienced with interferon (IFN)-based therapy. Any patients with a psychiatric history should be considered for referral for formal psychiatric assessment and management prior to therapy.

In people with HIV–HCV co-infection, the risk of progressive liver disease is relatively high. Although mandatory liver biopsy as a requirement for access to Section 100 PBS funding for chronic hepatitis C treatment was removed in 2006, the staging of liver disease remains an important tool during prognosis and treatment decision-making. Liver biopsy-based staging of disease should be considered for individuals with confirmed chronic HCV infection who are candidates for treatment.¹⁷ Individuals with an estimated duration of infection longer than ten years should be particularly encouraged to undergo liver biopsy.

Non-invasive alternatives to biopsy such as transient elastography (Fibroscan[®]) have been developed and are available in some centres. Limited information regarding the reliability of alternatives to biopsy, in the setting of HCV-HIV co-infection, is currently available. Although initial evidence suggests that transient elastography accurately predicts cirrhosis in these patients,¹⁸ the ability to discriminate between lesser degrees of fibrosis has been questioned.¹⁹

Apart from consistently normal ALT levels being associated with slow disease progression, the ALT level is only weakly correlated with risk of hepatic fibrosis.²⁰ The lack of correlation between elevated serum transaminases and severity of HCV-associated liver disease is particularly noted in HIV-HCV co-infection.¹⁷ In a recent Spanish study, nearly one quarter of co-infected patients with persistently normal ALT demonstrated advanced fibrosis (F3-4) by transient elastography.²¹ It is therefore clear that normal ALT levels should not preclude further assessment of liver disease in patients with HIV-HCV co-infection.

Although a prior negative HCV antibody test is often not available, and symptomatic acute hepatitis C is uncommon, an assessment of HCV risk factors can often help determine the likely duration of HCV infection. For example, a person presenting as HCV anti-body positive and having a two year history of injecting drug use 18 to 20 years ago can be assumed to have been infected at that time if no other risk factors are determined. This can be correlated with disease activity on biopsy and aid in decisions regarding therapy.

Indications for liver biopsy

Assessing the degree of fibrosis in patients with chronic HCV infection (including those co-infected with HIV) is important when making decisions about treatment. This is because treatment may be safely deferred (if necessary) for patients with minimal fibrosis, whereas more significant fibrosis is an

indication for more timely intervention. The other important reason for investigating the stage of fibrosis is to enable detection of patients with cirrhosis, in whom (provided they have compensated cirrhosis) treatment should be initiated as soon as possible. Patients with cirrhosis also have additional care requirements such as ultrasound surveillance for Hepatocellular carcinoma and endoscopic surveillance for oesophageal varices, and maximal attention to modifiable risk factors for progression such as alcohol and other hepatotoxic drugs is required.

However liver biopsy is invasive, associated with attributable morbidity and mortality, and is no longer required prior to therapy to attract s100 funding. It is likely Fibroscan and other non-invasive modalities will become increasingly incorporated into care of patients with HIV-HCV co-infection. As discussed, robust data regarding the reliability of this test in co-infected patients is lacking, which complicates the incorporation of such technology into diagnostic algorithms.

Non-invasive technologies such as Fibroscan can be considered for all co-infected patients, preferably as part of a formal research program designed to assess the performance of these tools in such patients. While further evidence is gathered regarding the reliability of such alternative modalities, liver biopsy should be considered if there is any discordance between results of non-invasive testing and other evidence such as clinical presentation.

In particular, the following categories of patients should be recommended for assessment of fibrosis:

- Patients with an estimated duration of HCV infection greater than 10 years;
- Patients aged 35 years and over;
- Patients with features suspicious of more advanced disease, including clinical evidence (e.g. hepatomegaly and spider naevi) or findings on other investigations (such as thrombocytopenia or hypoalbuminaemia on laboratory tests, or ultrasound evidence of portal hypertension).

The removal of mandatory liver biopsy from s100 guidelines for hepatitis C treatment means that the only major requirement for access to treatment is the demonstration of chronic hepatitis C. This is generally confirmed by a positive antibody test for greater than six months, in the presence of evidence of active HCV infection, as determined by a positive qualitative or quantitative HCV RNA test.

Therapeutic strategies for people with HIV-HCV co-infection

In the current environment of rapidly evolving HIV and HCV antiviral therapy and expanding knowledge regarding HIV-HCV co-infection, the therapeutic decision-making process for people with HIV-HCV co-infection and their clinicians is complex. Several factors contribute to this increasing complexity:

- There is evidence that introduction of cART has enhanced life expectancy for people with HIV infection, including those with HIV-HCV co-infection;

- Although cART can in general be deferred until progressive immune deficiency develops, there is an increasing move towards early initiation of therapy, particularly in the setting of comorbidities such as HCV co-infection;
- HCV in the setting of HIV has a faster progression to complications, including both cirrhosis and hepatocellular carcinoma;
- Declining morbidity and mortality from HIV-related opportunistic disease has increased the proportion of non HIV-related morbidity and mortality including those from advanced liver disease;
- Large-scale trials using pegylated interferon (PEG) and ribavirin (RBV) demonstrate enhanced HCV antiviral response rates for people with HIV-HCV co-infection. These are similar to the situation seen in patients with HCV infection alone;
- Response rates to PEG and RBV in people with HIV-HCV co-infection are 10–20% lower than the rates observed in people with HCV infection alone. This is particularly the case in the setting of more advanced immunodeficiency;
- Toxicity may be enhanced in people with HIV-HCV co-infection with concurrent cART plus the combination of IFN and RBV.

Current therapeutic options

The current standard of care for treatment of chronic HCV infection is pegylated interferon plus ribavirin. Experience with this combination extends over eight years and response rates are significantly higher than those achieved with standard interferon regimens in both HCV mono-infected, and HIV-HCV co-infected patients.²²⁻²⁵ A sustained virologic response (SVR - defined by the absence of HCV viraemia six months following completion of antiviral therapy) appears to equate to complete viral clearance (cure) in the vast majority of cases,²⁶ and is associated with reversibility of hepatic fibrosis, even in the setting of cirrhosis.²⁷ As is the case in HCV mono-infection, in patients co-infected with HIV the predominant factors associated with SVR remain HCV viral load and genotype.²⁸

In HCV-monoinfected patients, SVR rates for genotype 1 and 4 infections are of the order of 55% after 48 weeks of therapy while SVR rates in genotype 2 and 3 infections are as high as 85% after 24 weeks of therapy.²⁻⁴ However the likelihood of attaining SVR in people with HIV-HCV co-infection is typically 10–20% lower, particularly in the setting of more advanced immunodeficiency.²²⁻²⁵

The duration of therapy in HIV-HCV co-infected patients has traditionally been 48 weeks, regardless of genotype. This contrasts with HCV mono-infected patients, in whom 24 weeks of combination therapy is given for patients with genotype 2 or 3 (and often for those with genotype 1, low viral load and a rapid virological response) unless bridging fibrosis or cirrhosis is present. Depending on the rapidity of viral response, it has been suggested that treatment duration for genotype 2 and 3 HCV co-infected patients could be reduced;²⁹ the data supporting this approach is currently limited, and most guidelines suggest treating for 48 weeks in the absence of more compelling evidence that shorter treatment durations are equivalent.

Increasingly treatment courses are adapted to the individual patient and this will be even more relevant when new protease and polymerase inhibitors become available in the next two to three years. It is likely that these advances will also be of benefit to patients living with HIV-HCV co-infection, although it will take longer for clinical studies to be performed in this setting, and other considerations such as interactions between new HCV agents and cART regimens may add further complexity.

Increased therapeutic toxicity in HIV-HCV co-infection

A major past consideration of treatment of co-infection has been safety of treatment regimens and in particular potential interactions between cART and HCV therapy. The overall discontinuation rates in the above studies in the PEG + RBV arms were 25% for APRICOT, 42% for RIBAVIC and 12% for ACTG. The APRICOT study demonstrated no difference in withdrawal rates or serious adverse events between groups. Furthermore, the spectrum and rate of adverse events reported was similar for all three groups. This data suggests that the safety profile of PEG is similar to standard IFN.

In addition, there was no negative impact on HIV replication. On the contrary, the PEG + RBV arms resulted in a 1 log reduction in HIV viral load in patients with detectable HIV RNA at baseline. This allays many previously held fears that RBV may have impaired the phosphorylation of nucleoside analogues such as zidovudine and stavudine and compromised HIV control.

Despite the above assurances there are two important cautionary observations, which need to be heeded from these studies. The RIBAVIC study reported mitochondrial toxicity (as defined by hyper-lactataemia or pancreatitis) in 13 patients. This occurred in 16% of patients on didanosine therapy in whom the risk was increased 18 fold. This may be due to RBV enhancing phosphorylation of didanosine; thereby increasing drug concentration.³⁰ The second important finding was that of hepatic decompensation in the APRICOT study. This occurred in 14 patients resulting in 6 deaths. All cases occurred in cirrhotic patients in whom the risk was 10.5%. On closer examination of these cases didanosine therapy was also an independent risk factor but, contrary to RIBAVIC, they were not related to lactic acidosis. The majority of these patients had a Child's Pugh score of six or greater at baseline indicating at least early hepatic decompensation.

These data suggest that there needs to be careful selection of patients and cART regimens. Patients with decompensated cirrhosis need to be excluded, and RBV should not be administered with didanosine due to the significant risk of drug interaction leading to lactic acidosis and pancreatitis.¹⁷ With a number of less toxic alternatives available Didanosine containing regimens are less common than was previously the case in well resourced settings, a patient with HIV-HCV co-infection who remains on didanosine should be switched to an alternative regimen prior to commencing therapy with PEG and RBV. Another concern with respect to interactions between RBV and cART is the potential for zidovudine to exacerbate RBV-associated anaemia, and this combination should also be avoided when possible.¹⁷

Close monitoring is also required for people with cirrhosis following commencement of IFN and RBV therapy, including regular coagulation testing, and any evidence of hepatic decompensation necessitates cessation of therapy. Concerns about an increased risk of mitochondrial toxicity in people with HIV-HCV co-infection, commenced on IFN and RBV therapy, also make regular lactate measurements a reasonable monitoring strategy. However, cases of lactic acidosis may be particularly rapid in onset and are not always precluded by detectable hyperlactataemia on regular lactate monitoring.

These issues also highlight the need for early identification and referral of such patients to specialist centres so that they can be seen earlier in the course of their HCV infection, especially prior to the onset of cirrhosis when responses to therapy are further impaired.

Influence of disease staging on therapy decision-making

A number of interrelated issues determine the therapeutic strategy in the setting of HIV-HCV co-infection, including immune function, degree of liver disease, and the potential for adverse drug reactions and interactions. The complexity of these factors, and the lack of strong data to guide clinicians and patients, have resulted in ongoing debate regarding whether to initiate therapy for these viruses concurrently or sequentially, and if the latter, which should be treated first.³¹

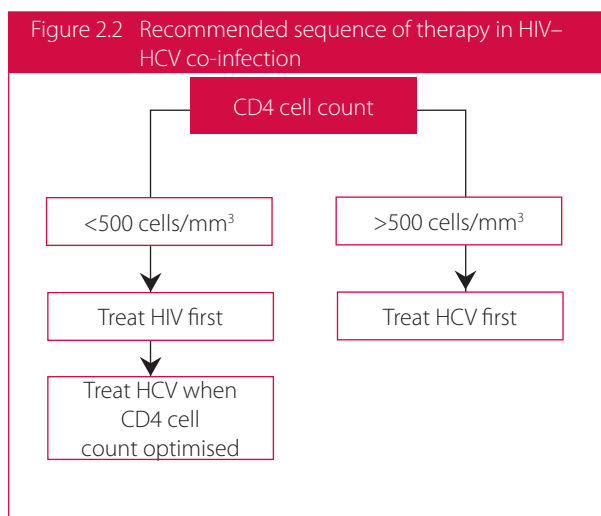
HIV therapy is now clearly indicated when the CD4 cell count falls below 350 cells/ul, with recent suggestions that earlier treatment initiation (below 500 cells/ul) should be considered.^{17,32} Recent international recommendations specifically cited HCV co-infection as a circumstance in which initiation of cART should be considered irrespective of the patients' CD4 cell count.³³ Evidence in support of this approach can be found in a recent study, which demonstrated that the use of cART in patients with CD4 cell counts above 350 cells/ul was associated with lower necroinflammatory activity on liver biopsy.³⁴ Further clinical studies are needed to assess whether cART is indeed associated with improved outcomes in HIV-HCV co-infected individuals with preserved immune function.

The other consideration affecting treatment decisions is that in people with more advanced immunodeficiency, HCV therapy is likely to be less effective.^{17,35} For these reasons it seems logical to use the CD4 threshold of 500 cells/ul to determine therapeutic priority. Below this level, response rates may be compromised by immuno-suppression and HIV therapy clearly assumes priority. Above 500 cells/ul, immune function is relatively well preserved and the absence of ART reduces the incidence of hepatotoxicity. Furthermore, successful treatment of chronic HCV in co-infected patients has been demonstrated to reduce the hepatotoxicity of subsequent cART regimens.³⁶

If both infections are to be treated simultaneously, it is advisable to initially commence cART, using minimally hepatotoxic agents that are not associated with significant interactions with RBV. Treatment of HCV can commence once stably taking cART. One to two months after commencement of cART maybe required if toxicities and adherence needs to be minimised or improved,

Liver biopsy remains an important component of the process of therapy decision-making for people with HIV–HCV co-infection. However, removal of mandatory liver biopsy means that staging of liver disease may be less important for individuals with more favourable treatment characteristics (e.g. HCV genotype 2/3 with higher CD4 cell counts).

A recommended sequence for HIV and HCV treatment is outlined in Figure 2.2.



The duration of therapy in HIV-HCV co-infected patients has traditionally been 48 weeks, regardless of genotype. This contrasts with HCV mono-infected patients, in whom 24 weeks of combination therapy is given for patients with genotype 2 or 3 (and often for those with genotype 1, low viral load and a rapid virological response) unless bridging fibrosis or cirrhosis is present. Depending on the rapidity of viral response, it has been suggested that treatment duration for genotype 2 and 3 HCV co-infected patients could be reduced;²⁹ the data supporting this approach is currently limited, and most guidelines suggest treating for 48 weeks in the absence of more compelling evidence that shorter treatment durations are equivalent.

HIV–HCV co-infection and decompensated liver disease

People with HIV–HCV co-infection and established liver failure should not be commenced on IFN-based therapy because of the greatly increased risk of toxicity and further hepatic decompensation. A person with stable HIV disease and HCV-related liver failure should be considered for liver transplantation. Current evidence suggests promising outcomes, in particular, in persons able to tolerate cART post-transplantation.³⁷

Other management issues

Management of hepatotoxicity and choice of antiretroviral therapy in people with HIV–HCV co-infection is discussed in Chapter 4. Drug and alcohol intake is the other major management issue for people with HIV–HCV co-infection. The higher risk of HCV-related progressive liver disease in people

with HIV infection means that other co-factors for progression take on increased importance.

For example, a person with HIV–HCV co-infection and a heavy alcohol intake would be at greatly increased risk of progressive liver disease. In general, people with HIV–HCV co-infection should moderate their alcohol intake to no more than 20 grams (two standard drinks) per day and have at least three alcohol-free days per week. In the case of severe hepatic fibrosis or cirrhosis, complete abstinence from alcohol should be advised.

It is also important to highlight that individuals on cART have an improved overall mortality and also an improved liver-related mortality when compared to individuals not receiving cART.⁸

The requirement for haemopoietic growth factors to manage IFN-associated neutropenia and RBV-associated anaemia is not uncommon,¹⁷ and appropriate use of these agents can avoid the necessity for dose reduction of HCV therapy. There is some evidence to suggest that the use of growth factors is associated with improved rates of SVR and histological outcomes³⁸ and their use may therefore be preferable to reduction in RBV or IFN dosage.

An association between cannabis use and progression of liver disease in the setting of HCV mono-infection has now been described in a number of studies.³⁹ Patients should be advised to moderate exposure to cannabis, particularly in the setting of daily use. There is no evidence to suggest that other recreational drug use per se increases the risk of progressive liver disease in people with HCV infection. However, moderation of recreational drug use, particularly injecting drug use, would seem an appropriate strategy for people with HIV–HCV co-infection. Re-infection following therapeutic HCV clearance is well documented, thus increasing the importance of prevention of HCV exposure in people who continue to inject recreational drugs.^{40,41}

Conclusion

The much-improved prognosis for people living with HIV, along with increasing toxicity associated with the complex therapy required to sustain control of HIV replication and immune function, have seen liver disease emerge as a major clinical management issue. Due to overlapping transmission routes for HIV and HCV, people with HIV infection should be counselled and recommended for HCV testing. For those with underlying chronic hepatitis, improved treatment outcomes provide an opportunity for HCV viral clearance (cure). Assessment of the activity and the stage of liver disease will remain an important tool in therapeutic decision-making, particularly for those with less favourable treatment characteristics.

Acknowledgments

Dr David Koorey, Mr Paul Harvey and Dr Darren Russell provided valuable comments on an earlier draft of this chapter.

References

- Torresi J, Locarnini S. Antiviral chemotherapy for the treatment of hepatitis B virus infections. *Gastroenterology* 2000;118(Suppl 1):S83–S103.
- Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001;358(9286):958–65
- Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Gonçales FL Jr, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med*. 2002;347(13):975–82.
- Hadziyannis SJ, Sette H Jr, Morgan TR, Balan V, Diago M, Marcellin P, et al. PEGASYS International Study Group. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med*. 2004;140(5):167
- Dore GJ, Cooper DA. The impact of HIV therapy on co-infection with hepatitis B and hepatitis C viruses. *Curr Opin Infect Dis* 2001;14(6):749–55.
- Benhamou Y, Bochet M, Di Martino V, Charlotte F, Azria F, Coutellier A, et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus co-infected patients. The Multivirc Group. *Hepatology* 1999;30(4):1054–8.
- Graham CS, Baden LR, Yu E, Mrus JM, Carnie J, Heeren T, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. *Clin Infect Dis* 2001;33(4):562–9.
- Qurishi N, Kreuzberg C, Luchters G, Effenberger W, Kupfer B, Sauerbruch T, et al. Effect of antiretroviral therapy on liver-related mortality in patients with HIV and hepatitis C virus co-infection. *Lancet*. 2003, 362 (9397):1708–13.
- Rockstroh JK, Mocroft A, Soriano V, Tural C, Losso MH, Horban A, et al. Influence of hepatitis C virus infection on HIV-1 disease progression and response to highly active antiretroviral therapy. *J Infect Dis* 2005;192(6):992–1002.
- Kaufmann GR, Perrin L, Pantaleo G, Opravil M, Furrer H, Telenti A, et al. CD4 T-lymphocyte recovery in individuals with advanced HIV-1 infection receiving potent antiretroviral therapy for 4 years: the Swiss HIV Cohort Study. *Arch Intern Med* 2003;163(18):2187–95.
- Peters L, Mocroft A, Soriano V, Rockstroh JK, Losso M, Valerio L, et al. Hepatitis C virus co-infection does not influence the CD4 cell recovery in HIV-1-infected patients with maximum virologic suppression. *J Acquir Immune Defic Syndr* 2009;50(5):457–63.
- Lincoln D, Petoumenos K, Dore GJ. HIV/HBV and HIV/HCV co-infection, and outcomes following highly active antiretroviral therapy. *HIV Med* 2003;4(3):241–9.
- Dore G. Natural history of hepatitis C virus infection. In: *Hepatitis C: an Australian perspective*. Crofts N, Dore GJ, Locarnini S, editors. Melbourne: IP Communications, 2001. p82–100.
- Daar ES, Lynn H, Donfield S, Gomperts E, Hilgartner MW, Hoots WK, et al. Relation between HIV-1 and hepatitis C viral load in patients with hemophilia. *J Acquir Immune Defic Syndr* 2001;26(5):466–72.
- Gilleece YC, Browne RE, Asboe D, Atkins M, Mandalia S, Bower M, et al. Transmission of hepatitis C virus among HIV-positive homosexual men and response to a 24-week course of pegylated interferon and ribavirin. *Journal of Acquired Immune Deficiency Syndromes: JAIDS*. 2005;40(1):41–6.
- Serpaggi J, Chaix ML, Batisse D, Dupont C, Dupont C, Vallet-Pichard A, Fontaine H, et al. Sexually transmitted acute infection with a clustered genotype 4 hepatitis C virus in HIV-1-infected men and inefficacy of early antiviral therapy. *JAIDS*. 2006 ; 20(2)233–40.
- Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1, 2009;1–161. Available at <http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf> (cited December, 2009)
- de Ledinghen V, Douvin C, Kettaneh A, Zioli M, Roulot D, Marcellin P, et al. Diagnosis of hepatic fibrosis and cirrhosis by transient elastography in HIV/hepatitis C virus-co-infected patients. *J Acquir Immune Defic Syndr* 2006;41(2):175–9.
- Vergara S, Macias J, Rivero A, Gutierrez-Valencia A, Gonzalez-Serrano M, Merino D, et al. The use of transient elastometry for assessing liver fibrosis in patients with HIV and hepatitis C virus co-infection. *Clin Infect Dis* 2007;45(8):969–74.
- Danta M, Dore GJ, Hennessy L, Li Y, Vickers CR, Harley H, et al. Factors associated with severity of hepatic fibrosis in people with chronic hepatitis C infection. *Med J Aust* 2002;177(5):240–5.
- Maida I, Soriano V, Barreiro P, Rivas P, Labarga P, Nunez M. Liver fibrosis stage and HCV genotype distribution in HIV-HCV co-infected patients with persistently normal transaminases. *AIDS Res Hum Retroviruses* 2007;23(6):801–4.
- Torriani FJ, Rodriguez-Torres M, Rockstroh JK, Lissen E, Gonzalez-Garcia J, Lazzarin A, et al. Peginterferon Alfa-2a plus Ribavirin for Chronic Hepatitis C Virus Infection in HIV-Infected Patients. *N Engl J Med*, 2004;351(5):438–50.
- Perronne C, Carrat F, Bani-Sadr F et al. Final Results of ANRS HC02-RIBAVIC: A Randomized Controlled Trial of Pegylated-Interferon-alfa-2b plus Ribavirin vs Interferon-alfa-2b plus Ribavirin for the Initial Treatment of Chronic Hepatitis C in HIV Co-infected Patients. Abstract # 117LB. 11th Conference on Retroviruses and Opportunistic Infections. Feb 8-11 2004. San Francisco, CA
- Chung RT, Andersen J, Volberding P, Robbins GK, Liu T, Sherman KE, et al. Peginterferon Alfa-2a plus Ribavirin versus Interferon i. Alfa-2a plus Ribavirin for Chronic Hepatitis C in HIV-Co-infected Persons. *N Engl J Med*, ii. 2004;351(5): 451–59.
- Nunez M, Marino A, Miralles C, Berdun MA, Sola J, Hernandez-Burruezo JJ, et al. Baseline serum hepatitis C virus (HCV) RNA level and response at week 4 are the best predictors of relapse after treatment with pegylated interferon plus ribavirin in HIV/HCV-co-infected patients. *J Acquir Immune Defic Syndr* 2007;45(4):439–44
- Desmond CP, Roberts SK, Dudley F, Mitchell J, Day C, Nguyen S, et al. Sustained virological response rates and durability of the response to interferon-based therapies in hepatitis C patients treated in the clinical setting. *J Viral Hepat* 2006;13(5):311–5.
- Shiratori Y, Imazeki F, Moriyama M, Yano M, Arakawa Y, Yokosuka O, et al. Histological improvement of fibrosis in patients with hepatitis C who have sustained response to interferon therapy. *Ann Intern Med* 2000;132(7):517–24.
- Dore GJ, Torriani FJ, Rodriguez-Torres M, Brau N, Sulkowski M, Lamoglia RS, et al. Baseline factors prognostic of sustained virological response in patients with HIV-hepatitis C virus co-infection. *AIDS* 2007;21(12):1555–9.
- Soriano V, Puoti M, Sulkowski M, Cargnel A, Benhamou Y, Peters M, et al. Care of patients co-infected with HIV and hepatitis C virus: 2007 updated recommendations from the HCV-HIV International Panel. *AIDS* 2007;21(9):1073–89.
- Lafeuillade A, Hittinger G, Chadapaud S. Increased mitochondrial toxicity with ribavirin in HIV/HCV co-infection. *Lancet* 2001;357(9252):280–1
- Cooper CL. De-“Liver”-ing HIV/hepatitis C virus-co-infected patients from antiretroviral hepatotoxicity. *J Infect Dis* 2007;196(5):656–8.

32. Guidelines for the use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents (with Australian Commentary): DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents; 2008 (updated November 3).
33. Hammer SM, Eron JJ, Jr, Reiss P, Schooley RT, Thompson MA, Walmsley S, et al. Antiretroviral treatment of adult HIV infection: 2008 recommendations of the International AIDS Society-USA panel. *Jama* 2008;300(5):555-70.
34. Pascual-Pareja JF, Caminoa A, Larrauri C, Gonzalez-Garcia J, Montes ML, Diez J, et al. HAART is associated with lower hepatic necroinflammatory activity in HIV-hepatitis C virus-co-infected patients with CD4 cell count of more than 350 cells/microl at the time of liver biopsy. *AIDS* 2009;23(8):971-5.
35. Soriano V, Vispo E, Martin-Carbonero L, Labarga P, Garcia-Samaniego J, Barreiro P. Management and therapy of chronic hepatitis C in HIV. *Curr Opin HIV AIDS* 2007;2(6):482-8.
36. Labarga P, Soriano V, Vispo ME, Pinilla J, Martin-Carbonero L, Castellares C, et al. Hepatotoxicity of antiretroviral drugs is reduced after successful treatment of chronic hepatitis C in HIV-infected patients. *J Infect Dis* 2007;196(5):670-6.
37. Ragni MV, Belle SH, Im K, et al. Survival of human immunodeficiency virus-infected liver transplant recipients. *J Infect Dis*. 2003; 188:1412-20.
38. Behler CM, Vittinghoff E, Lin F, Chung RT, Peters MG, Robbins GK, et al. Hematologic toxicity associated with interferon-based hepatitis C therapy in HIV type 1-co-infected subjects. *Clin Infect Dis* 2007;44(10):1375-83.
39. Hezode C, Roudot-Thoraval F, Nguyen S, Grenard P, Julien B, Zafrani ES, et al. Daily cannabis smoking as a risk factor for progression of fibrosis in chronic hepatitis C. *Hepatology* 2005;42(1):63-71.
40. Asselah T, Vidaud D, Doloy A, Boyer N, Martinot M, Vidaud M, et al. Second infection with a different hepatitis C virus genotype intravenous drug user during interferon therapy. *Gut* 2003;52(6):900-2.
41. Dalgard O, Bjoro K, Hellum K, Myrvang B, Skaug K, Gutigard B, et al. Treatment of chronic hepatitis C in injecting drug users: 5 years' follow-up. *Eur Addict Res* 2002;8(1):45-9.

The management of HIV and hepatitis B virus co-infection

3

Joe Sasadeusz

Victorian Infectious Diseases Service, Royal Melbourne Hospital and Infectious Diseases Unit, The Alfred Hospital, Melbourne, VIC

Benjamin Cowie

Victorian Infectious Diseases Service, Royal Melbourne Hospital, Victorian Infectious Diseases Reference Laboratory, VIC and Department of Medicine, The University of Melbourne, VIC

KEY POINTS

- ▶ Hepatitis B virus (HBV) infection in people with HIV infection may result in significant morbidity and mortality.
- ▶ People with HIV-HBV co-infection have lower clearance rates of HBV infection and accelerated hepatic fibrosis and cirrhosis than those with HBV infection alone.
- ▶ Management of each viral infection is complicated by the presence of the other virus.
- ▶ The presence of hepatitis B surface antigen should indicate monitoring of HBV DNA viral load by a sensitive assay to determine significant levels.
- ▶ Antiviral monotherapy against HBV in the setting of co-infection carries the proven or theoretical risk of induction of resistance mutations in HIV and is best avoided.
- ▶ Initiation of antiretroviral therapy may lead to clinically significant hepatic inflammation (hepatic flares) and hepatic decompensation.
- ▶ Current recommendations support the commencement of combination antiretroviral therapy including tenofovir and either emtricitabine or lamivudine in the setting of HIV-HBV co-infection where either virus requires treatment. Another option in the setting of preserved immune function is to use pegylated interferon.

Introduction

It is estimated that approximately 5% of the world's population, or over 350 million people have chronic Hepatitis B virus (HBV) infection. Areas of high endemicity for HBV infection such as sub-Saharan Africa and Asia are also the areas most affected by the HIV pandemic.¹ The occurrence of both HIV and HBV infections is related to shared routes of transmission. The prevalence of chronic HBV infection in people with HIV varies in accordance with epidemiological patterns of transmission, and has been estimated at 6% in Australia (see Chapter 1).

HBV is not directly cytopathic, and viral pathogenesis is largely immune-mediated. Necro-inflammatory changes in liver tissue that characterise chronic hepatitis B are a result of cellular immune responses to viral antigens.² In people who are immunocompromised, a weak immunological response to HBV antigens results in relatively low levels of hepatic inflammatory disease. Despite this effect, liver disease progression through development of hepatic fibrosis is accelerated in people with HIV-induced immunosuppression.² The pathogenesis of chronic liver disease in people with HIV-HBV co-infection, in particular, the relationship between immunosuppression and disease progression, has important implications for the development of antiretroviral therapeutic strategies.

Diagnosis

An algorithm for diagnosis when co-infection is suspected is shown in Figure 3.1. All people with HIV should be screened for HBV infection by testing for a panel of hepatitis B serology including hepatitis B surface antigen (HBsAg), antibody to hepatitis B surface antigen (anti-HBs), and antibody to hepatitis B core antigen (anti-HBc). By ordering these three tests, a

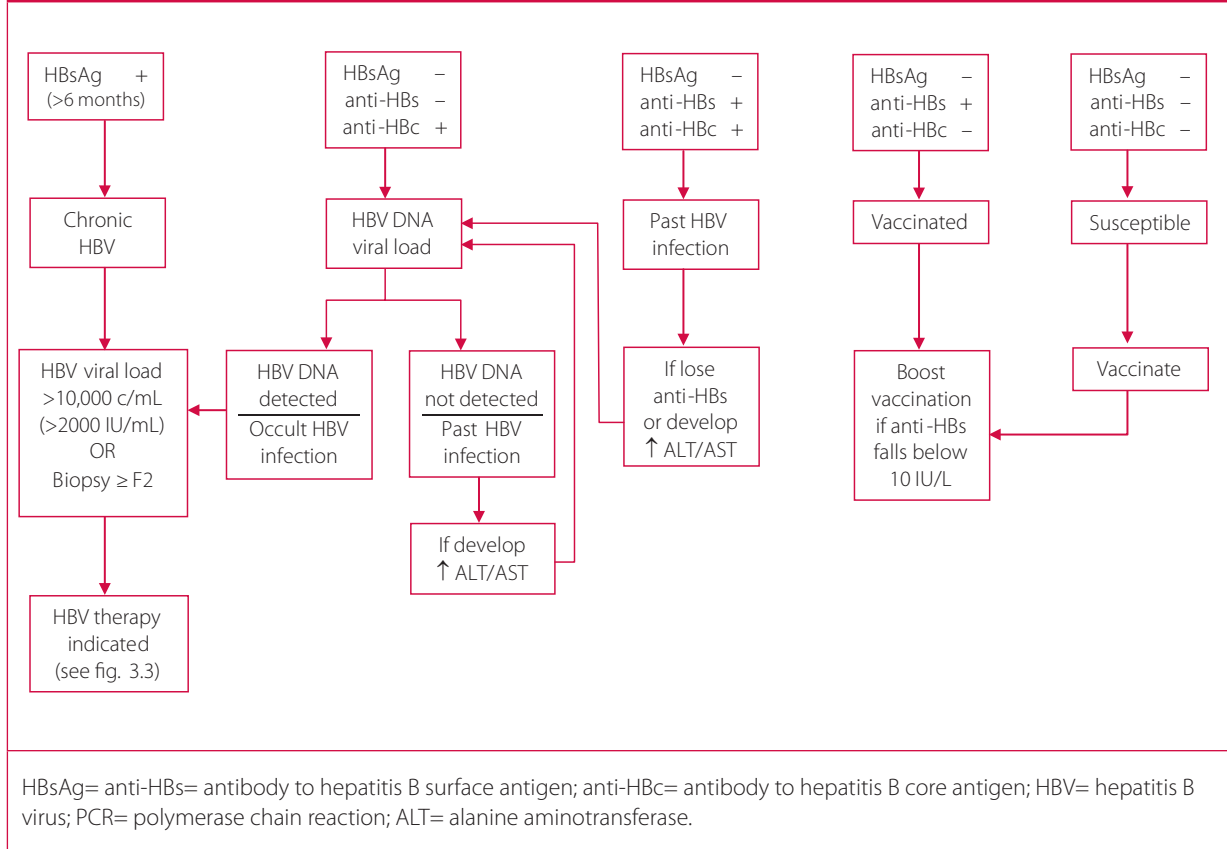
patient's HBV status can be ascertained, and the need for vaccination can be determined. All people with HIV infection who are susceptible to HBV should be vaccinated with double the usual dose of vaccine. Following completed vaccination, unlike the case for patients with normal immune function, those infected with HIV should have regular tests of anti-HBs titre, and receive booster doses of vaccine when their titre falls below 10 mIU/mL.³

If HBsAg is detected, the presence of active HBV replication should be assessed through a quantitative assay for HBV DNA (viral load) by polymerase chain reaction or other sensitive assay. HBV DNA level is associated with risk of transmission, progression to cirrhosis and hepatocellular carcinoma (HCC),⁴ and in the setting of HIV co-infection immune reconstitution inflammation (hepatic flares). HBV viral load testing became Medicare rebatable in July 2008, and allowed once per year for any HBsAg positive patient and up to four times per year for individuals on antiviral medication.

It is also important to determine HBV e antigen (HBeAg) status as this helps determine the phase of chronic HBV infection and influences treatment decisions. Current recommendations for patients with HBV mono-infection suggest that, in HBeAg-positive patients, a level of > 100 000 copies/mL (20 000 IU/mL) is clinically significant whereas in HBeAg-negative patients > 10 000 copies/mL (2000 IU/mL) is significant.^{1,5} Sufficient data for similar thresholds are not available in the setting of co-infection, but a HBV DNA level of 10 000 copies/mL for treatment initiation for HIV infected patients has been proposed.^{6,7}

The failure to synthesise HBeAg in HBeAg-negative infection is due to the presence of mutations in the precore and core

Figure 3.1 Initial serological assessment: HBsAg/anti-HBs/anti-HBc in HIV infected individuals



promoter regions.¹ People with significantly elevated HBV DNA levels should be further assessed and considered for antiviral therapy.

All people who are HBsAg positive should have regular liver function tests performed to determine the presence of necro-inflammatory activity. If biochemical evidence of hepatic inflammation (defined by an alanine aminotransferase (ALT) level exceeding the upper limit of the laboratory reference range) is detected, a liver biopsy to determine the grade and stage of disease would generally be recommended (unless there are strong contraindications such as a bleeding disorder).

Normal ALT values, however, do not preclude significant hepatic fibrosis, especially in patients with HIV co-infection.^{7,8} Liver biopsy therefore remains the gold standard for assessing the stage of HBV disease,⁷ and enables assessment of other factors contributing to liver dysfunction, particularly drug toxicity. Non-invasive alternatives to biopsy have been developed and are available in some Australian centres, such as transient elastography (Fibroscan[®]). However this technique has not been as widely validated in chronic HBV infection as it has for hepatitis C virus infection, and no information regarding reliability in the context of HBV-HIV co-infection is currently available. This is a priority area for future research.

Clinical manifestations

HIV co-infection results in considerable modification of the natural history of HBV infection.^{7,8} Persistent HBV infection

is more common in people with HIV, with studies among men who have sex with men exposed to HBV showing evidence of chronic HBV infection in almost 25%^{7,8} of individuals compared to 3–5% in those without HIV.^{9,10} Rarely, reactivation of HBV infection may occur in the setting of advanced immunodeficiency despite seroconversion to anti-HBs positive.¹¹ Furthermore, in people with HIV-HBV co-infection, HBV DNA levels are substantially higher, and rates of seroconversion from HBeAg to anti-HBe are lower than in people with HBV alone.^{11,12}

The high levels of HBV viral replication seen in people with HIV-HBV co-infection are associated with significantly lower serum aminotransferase^{11,12} and liver biopsies usually demonstrate milder necro-inflammatory activity.¹² This situation is consistent with the model of immunopathogenic injury of HBV infection. However, progression to cirrhosis is more common, indicating accelerated fibrosis.¹² It is unclear why this occurs and may relate to factors such as higher levels of HBV replication, hepatic inflammation associated with immune restoration, toxicity of antiretroviral medication, immune dysregulation causing fibrosis or increased direct pathogenicity of HBV in people with HIV-HBV co-infection.

In people with immunodeficiency, HBV may rarely exert direct cytopathic effects that are not immune-mediated resulting in a unique condition called fibrosing cholestatic hepatitis (FCH). FCH is a serious condition associated with very high levels of HBV DNA and has been described in people with HIV.¹³

It is well established that HBV markedly increases the risk of primary HCC,¹⁴ and is second only to tobacco amongst known human carcinogens.¹⁵ An increased risk of HCC with falling CD4 cell counts has also recently been described in people with HIV-HBV co-infection.¹⁶ Regular screening with six monthly abdominal ultrasound and alpha-fetoprotein protein is strongly recommended in individuals at elevated risk. In HBV mono-infected individuals, these include Asian males over 40 and females over 50 years of age, Africans over 20 years of age, patients with a family history of HCC, patients with cirrhosis, and adults with high HBV viral loads and ongoing hepatic inflammation.¹⁷

It is not certain whether HIV infection in itself is associated with sufficiently increased incidence of HCC to warrant surveillance for all co-infected individuals. Although some experts recommend this approach,⁷ established guidelines recommend using the same criteria for enrolling co-infected patients that apply to HBV mono-infected patients.¹⁷ Until further data become available to better inform this decision, a reasonable approach is to use conventional HCC surveillance criteria (as above) in co-infected patients, and to also consider screening patients with lower CD4 cell counts (< 500/mm³). This is based on the Swiss HIV Cohort Study findings suggesting a significantly increased risk of developing HCC in co-infected patients with cell counts below this number.¹⁶

In contrast to the effect of HIV on the natural history of chronic HBV infection, there is little evidence for a significant effect of HBV on the clinical course of HIV infection.¹⁸

Hepatitis D virus infection

Hepatitis D virus (HDV) is a defective virus which only occurs as a co-infection with HBV. It is estimated that approximately 5% of people living with chronic HBV infection worldwide are co-infected with HDV, although notable diversity in the geographic distribution of HDV is observed among areas with high HBV prevalence.^{19,20}

In Australia, as in other non-endemic countries, HBV-HDV co-infection has previously been associated in particular with a history of injecting drug use,²¹ with this finding also reported amongst men who have sex with men.²² However with increasing migration from HDV-endemic regions such as Sub-Saharan Africa and parts of the Asia-Pacific region,^{19,20} the epidemiology of HDV in Australia may be changing, reflecting similar trends reported internationally.²⁰

All patients diagnosed with chronic HBV infection, including those co-infected with HIV, should have baseline serology to determine whether HDV infection is present. Chronic HBV-HDV co-infection has been associated with faster progression to cirrhosis and increased incidence of mortality.²³ Current nucleoside analogue therapies for HBV and HIV are ineffective against HDV, with the only available treatment being interferon-alpha, conventional or pegylated.²⁴ However interferon therapy is effective in only a minority of patients, and relapse is common.²³

Management

Anti-HBV therapy

There are seven therapeutic agents currently licensed for the treatment of chronic HBV, with the majority of these being approved in the last five years (Table 3.1). Emtricitabine, although active against HBV, is only licensed for use in the treatment of HIV.

Agent	Year of approval
Interferon α-2a/b	1997
Lamivudine	1999
Adefovir	2004
Pegylated interferon α-2a	2005
Entecavir	2006
Telbivudine	2006
Tenofovir	2009

Interferon-alpha

Interferon-alpha therapy has long been known to be able to induce HBeAg seroconversion and sustained reduction in viral replication in a minority of immunocompetent patients with chronic HBV infection.²⁵ Equally well established is the knowledge that interferon-alpha treatment of people with HIV, particularly those with advanced immunodeficiency, is significantly less effective.^{26,27}

Pegylated interferon (PEG) (see Chapter 2) is superior to conventional interferon in the treatment of HBV mono-infection²⁸⁻³¹ and may offer an advantage in HIV co-infection¹ although this has not been adequately assessed. It seems reasonable to consider therapy with PEG in people with preserved immune function (CD4 cell counts > 500/mm³)¹ who are not candidates for combination antiretroviral therapy (cART). Drugs such as lamivudine and tenofovir disoproxil fumarate or tenofovir (TDF) can therefore be preserved, with avoidance of both HIV and HBV resistance. If interferon is considered, a liver biopsy is critical as people with cirrhosis may decompensate on therapy.

Lamivudine

Lamivudine (3TC) is a nucleoside analogue that suppresses both HIV and HBV replication by inhibition of the viral reverse transcriptase.^{32,33}

In people with HBV mono-infection, reduction in plasma HBV viral load secondary to 3TC therapy is associated with HBeAg seroconversion, normalisation of liver function and improved histological activity in approximately 20% of those treated for 12 months. Unfortunately, the long-term effectiveness of 3TC is diminished by the development of HBV-resistant mutations (in up to 70% of patients after five years)³⁴ and variable durability of HBeAg seroconversion.³⁵ Resistance to 3TC develops as a result of mutations in the tyrosine-methionine-aspartate-aspartate (YMDD) motif of the catalytic domain of the HBV polymerase gene.

Efficacy of 3TC against HBV has been demonstrated in people with HIV^{36,37} however; HBV resistance develops in approximately

20% per year, with projections of 90% after four years of 3TC therapy.³⁸ Thus the frequency of 3TC resistance in people with HIV-HBV co-infection is slightly higher than in those with HBV mono-infection.

Prolonged 3TC therapy and high HBV viral loads have been identified as the major risk factors for the development of resistant HBV.³⁸ Given that 3TC, when used as a component of cART, is administered lifelong in people with HIV-HBV co-infection who commonly have high HBV viral loads, it is inevitable that 3TC monotherapy in this population will result in resistance.

Adefovir dipivoxil

Adefovir dipivoxil (ADV) is a nucleotide analogue, with demonstrated efficacy against HBV at doses of 10 mg daily, with a 4-log₁₀ reduction in plasma HBV DNA. ADV also inhibits replication of 3TC-resistant HBV. An open-label study of 35 people with HIV and 3TC-resistant HBV infection reported a 4-log₁₀ reduction in serum HBV DNA levels at week 48, comparable to antiviral activity in people without HIV.³⁹ When followed to four years, 26 of the patients remaining on ADV continued to achieve further reductions in HBV viral load with no emergence of HBV or HIV-associated ADV mutations.⁴⁰

Adefovir is licensed in Australia and is available under the s100 scheme but its use is restricted to 3TC-resistant HBV infection. Higher doses of ADV (≥30 mg daily) have been associated with nephrotoxicity, which is rare with the 10-mg daily dose. Due to lack of HIV activity at this dose, ADV has been considered a reasonable option for therapy in people not requiring cART. However, there is a significant concern regarding the potential for inducing HIV cross-resistance between ADV and the structurally related nucleotide analogue TDF.

Entecavir

Entecavir is a nucleoside analogue, which has been available for first-line treatment of HBV in Australia since late 2006. Entecavir is more potent than either 3TC or ADV in terms of suppression of viral replication. It also has a higher barrier to the development of HBV resistance mutations than either of these agents with a 1% incidence of resistance mutation after five years.⁴¹ Lamivudine resistant HBV has a much higher rate of development of resistance to entecavir, of the order of 50% at five years.⁴¹

Entecavir was originally thought not to have any anti-HIV activity and was therefore promoted as a monotherapy for co-infected patients not receiving cART. However, it has subsequently been demonstrated that this drug does suppress HIV replication and selects for antiviral resistance mutations.⁴² Therefore entecavir should not be used in co-infected patients who are not receiving fully suppressive cART regimens.

Telbivudine

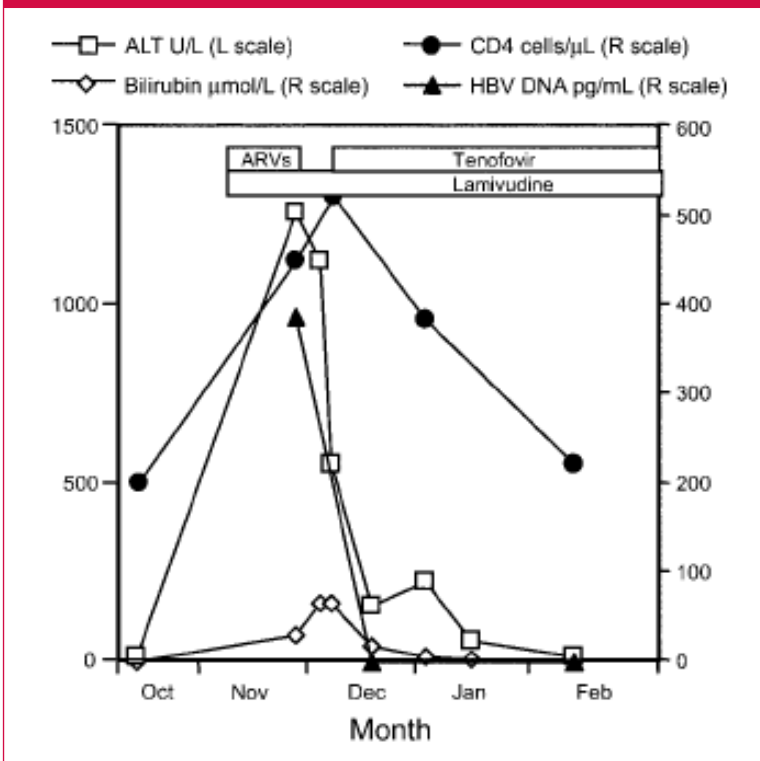
Telbivudine is a potent nucleoside analogue which has been demonstrated to be superior to 3TC in terms of virological response.⁴³ However, significant emergence of resistance mutations on treatment, which also mediate 3TC resistance, has limited the appeal of telbivudine in the treatment of chronic HBV infection.^{1,44}

Tenofovir disoproxil fumarate

Tenofovir is a nucleotide analogue, which like 3TC has the ability to inhibit both HIV and HBV DNA polymerases. Like entecavir, TDF has potent activity against HBV replication and a high barrier to the selection of resistance mutations. It also demonstrates excellent activity against virus strains that contain 3TC-associated polymerase gene mutations at baseline,⁴⁵ making TDF perhaps the best candidate agent for therapy following viral breakthrough on 3TC.

Clinical efficacy was demonstrated in a report of substudies,⁴⁶ which were part of two larger registration studies (study 907⁴⁷ and study 903⁴⁸) evaluating TDF for the treatment of HIV.⁴⁶ Although these substudies had very low sample sizes, they provided valuable prospective data to support the retrospective and in vitro evidence of TDF activity data previously published.⁴⁶ Twelve participants, 10 on TDF and two on placebo fulfilled the criteria for substudy 907. There was a 4.9 log₁₀ overall reduction in HBV DNA after 24 weeks of therapy in the TDF-treated patients. More importantly, the

Figure 3.2 Example of the introduction of cART leading to a marked flare of hepatitis due to immune reconstitution in the presence of high HBV DNA levels. ALT, alanine aminotransferase; bilirubin levels, CD4 counts, and HBV DNA levels during treatment with antiretroviral agents (ARVs).



Source: Drake A, Mijch A, Sasadeusz J. Immune reconstitution hepatitis in HIV and hepatitis B co-infection, despite lamivudine therapy as part of HAART. Clin Infect Dis. 2004 Jul 1;39(1):129-32. © 2004 by the Infectious Diseases Society of America

reduction in HBV DNA was equivalent, regardless of whether the virus was 3TC-resistant or wild type. Eleven patients fulfilled the criteria for the 903 study; six were randomised to receive 3TC alone as HBV-active therapy while five received 3TC+TDF. This study demonstrated that the reduction of HBV DNA after 48 weeks was greater for patients treated with combination TDF+3TC (median decline of 4.7 log₁₀ copies/mL) compared to patients on 3TC as the only HBV active agent (median decline of 3.0 log₁₀ copies/mL). More importantly, only the 3TC monotherapy arm demonstrated genotypic evidence of 3TC resistance, which occurred in four of the five subjects. This was the first suggestion that combination therapy in HBV can prevent antiviral resistance in a manner analogous to HIV. In both substudies there was no emergence of TDF genotypic resistance.⁴⁶

These promising findings were followed by the report of a 48-week prospective, randomised, multicentre study in HBV co-infected patients, comparing 3TC with TDF and 3TC+TDF as a component of cART to evaluate anti-HBV activity.⁴⁹ HBV DNA was suppressed to < 1000 copies/mL in approximately double the proportion of patients receiving TDF containing regimens compared to those receiving 3TC (91-92% vs 46%). Furthermore, drug resistance emerged in two patients; both in the 3TC only arm. In terms of efficacy, HBeAg loss occurred in 33% of patients who were positive at baseline, and 8% of patients lost HBsAg, with these results not significantly differing between groups. The superiority of TDF to 3TC in terms of virological suppression and avoidance of induction of resistance was thus confirmed, in the setting of HIV co-infection, by this trial.

Emtricitabine

Emtricitabine (FTC) is a nucleoside analogue, which is structurally related to 3TC and shares a similar efficacy and resistance profile.⁴⁴ It is approved for treatment of people with HIV infection in Australia and is available alone and as a combined formulation with TDF. The combined formulation is particularly attractive as the nucleoside analogue backbone of cART regimens in the treatment of co-infected individuals because these two agents are from different structural groups and have different resistance mutation profiles.⁴⁴ The combined formulation also helps reduce the pill burden, which can promote treatment adherence.

Immune reconstitution

In people with HIV-HBV co-infection, immune reconstitution following the introduction of cART has been associated with acute rises in serum aminotransferase levels (Figure 3.2), and known as hepatic flares.^{36,50,51} These flares usually occur in the first 4-8 weeks after commencing cART in people who had high HBV viral loads pretreatment, and are usually accompanied by a rapid fall in HIV RNA levels and rise in CD4 cell count.^{6,36,52,53} Hepatitis flares can result in significant liver disease and mortality, particularly in patients with advanced liver disease and poor hepatic reserve. Conversely, flares can also lead to HBeAg clearance and the suppression of viral replication in some patients⁹ leading to immune reconstitution hepatitis during co-infection. This has been described as a double-edged sword.⁵⁴

Immune reconstitution flares can occur despite the inclusion of HBV active agents such as 3TC as part of the initial cART regimen.⁵⁵ In a randomised trial of combination therapy for co-infected individuals,⁴⁹ 25% of patients experienced a hepatic flare following treatment initiation, with all except one occurring within 12 weeks of commencement of cART. An important finding was that of the HBeAg positive patients experiencing a flare, 80% subsequently experienced anti-HBe seroconversion and HBsAg loss, although one cirrhotic patient died.⁴⁹

Acute hepatic inflammation in co-infected patients has also been reported in a number of other circumstances, including reactivation of HBV infection,^{36,56} development of 3TC resistance and following withdrawal of 3TC⁵⁷. With regard to withdrawal of treatment, recent retrospective data from a Swiss cohort of 147 co-infected patients who ceased 3TC demonstrated that 29% experienced an elevation of their liver enzymes, with three cases of fulminant hepatitis and one death recorded.⁵⁸ This highlights the need for caution when changing cART regimens in co-infected patients, and that HBV-active agents should be continued even if they add little to the patient's HIV therapy regimen.²³

It is important to assess HBV status before starting cART in order to identify people at risk of hepatic flares. Individuals with clinically significant levels of HBV DNA (>10 000 copies/ml), especially those with cirrhosis or those with low nadir CD4 cell counts, may be particularly at risk of hepatic decompensation during flares.⁴⁹ In this setting, some experts advise initial treatment of HBV with a combination of ADV and telbivudine (agents with no proven induction of HIV resistance mutations at the prescribed dosages), with subsequent commencement of cART including TDF and FTC or 3TC once HBV replication is fully suppressed. This approach has not been evaluated clinically, and should only be undertaken in consultation with a clinician with expertise in the management of HIV-HBV co-infection.

The use of corticosteroids in this situation is also highly controversial. Theoretical concerns include the known effect of corticosteroids in increasing HBV replication through direct promotion of viral transcription⁵⁹ and the augmentation of existing immunosuppression. However, it is known that hepatic inflammation is immune-mediated and there are anecdotal reports⁶⁰ and a retrospective comparison of outcomes (in non-HIV infected patients), which support the role of early use of steroids in reducing mortality in life threatening exacerbations of chronic HBV infection.⁶¹

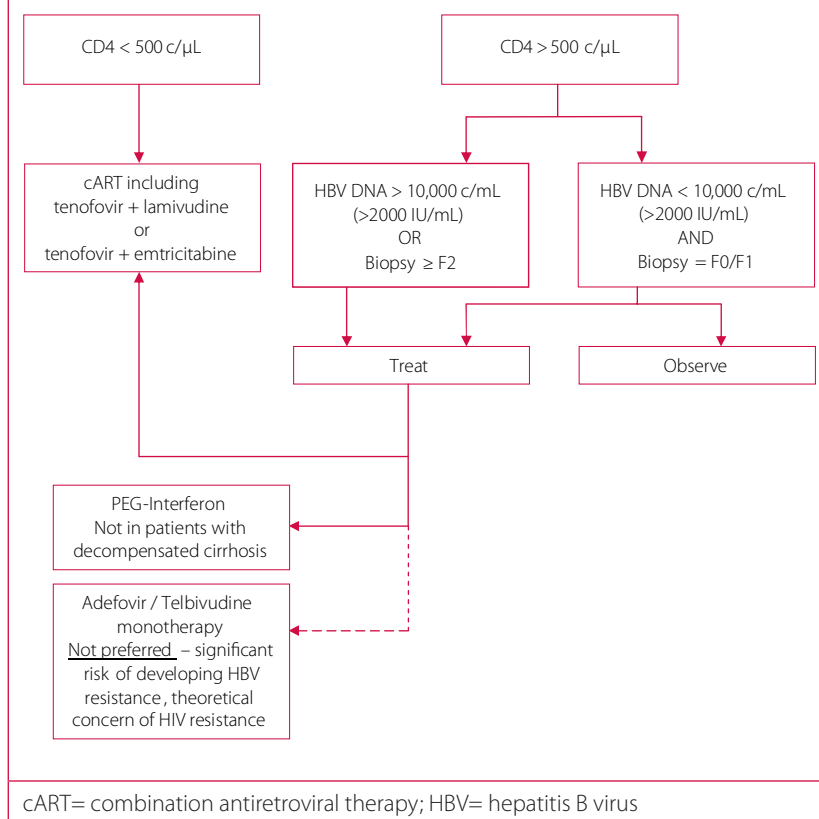
Strategies for therapy

An algorithm highlighting therapy management strategies for co-infected individuals is shown in Figure 3.3.

The person who requires antiretroviral therapy

The preferred option in treatment-naïve patients requiring cART is to include TDF plus either FTC or 3TC in the antiretroviral regimen. This is currently the optimal approach in treatment-experienced patients, including those with 3TC resistant virus.⁶² As discussed previously, care must be taken with treatment initiation as immune reconstitution hepatitis flares are

Figure 3.3 Management algorithm



common,⁴⁹ and in those with advanced immune suppression, high HBV DNA viral load, and significant hepatic fibrosis, such flares can be fatal.⁵⁵

If for some reason TDF cannot be used, another strategy is to use entecavir in addition to the cART regimen, as this is also a potent anti-HBV agent with a high barrier to resistance (although viral breakthrough is more common in patients with 3TC resistant HBV at baseline). If this strategy is used, the HIV antiretroviral regimen must fully suppress HIV replication because of recent evidence showing the induction of HIV resistance mutations by entecavir.^{7,42}

The person who does not require antiretroviral therapy

Monotherapy with nucleoside/nucleotide analogue drugs in HBV infected people carries the proven or theoretical risk of inducing resistance if they are co-infected with HIV and is best avoided in the absence of long-term follow up virological data confirming the safety of this approach. Although telbivudine does not appear to be active against HIV *in vitro*, no *in vivo* data in the setting of high levels of HIV replication is available. Furthermore, rapid development of telbivudine resistance in HBV limits the utility of this approach.^{1,46}

Early commencement of cART incorporating TDF plus either FTC or 3TC is an increasingly attractive option in this situation, a recommendation which is reflected in Australian and international guidelines.^{1,7,63,64}

Alternatively, in patients with preserved immune function (e.g. CD4 cell count $>500/\text{mm}^3$), pegylated interferon can be considered. This agent has the advantage of a limited treatment duration (12 months), and no potential for inducing antiviral resistance in either HBV or HIV, but side effects can be problematic.

Antiretroviral hepatotoxicity

Severe hepatotoxicity occurs in up to 10% of people who commence cART^{53,66} and HBV co-infection is an independent risk factor for the development of cART-related hepatotoxicity.⁶⁵⁻⁶⁸

Although all antiretroviral agents have been associated with abnormal liver function, full-dose ritonavir and nevirapine are especially implicated in severe hepatotoxicity⁶⁶ and should be used cautiously in those with HIV-HBV co-infection (see Chapter 4).

Conclusion

Improved life expectancy for people with HIV, together with cART-related hepatotoxicity and accelerated liver disease progression highlight the need to address liver-related outcomes in people with HIV-HBV co-infection.

In co-infected individuals, HBV monotherapy with available antiviral agents is associated with the proven or theoretical risk of induction of resistance in either or both infections. The focus is now on optimal initiation of combination therapy fully suppressing both viruses. Further research is needed to guide the prevention and management of treatment-related complications such as hepatic flares following immune reconstitution, the emergence of resistance, and hepatotoxicity from the antiviral agents themselves (see Chapter 4).

Acknowledgments

Professor Stephen Locarnini, Associate Professor Anne Mijch and Dr Darren Russell provided valuable comments on an earlier draft of this chapter.

References

- Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology*. 2009;50(3):661-2
- Perrillo R. Acute flares in chronic hepatitis B: the natural and unnatural history of an immunologically mediated liver disease. *Gastroenterology* 2001;120(4):1009-22.
- National Health and Medical Research Council. The Australian Immunisation Handbook. 9th Ed. 2008. Chapter 2.3 Groups with Special Vaccination Requirements. Available at: <http://www.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook-copyright> (cited October 2009)
- Chen CJ, Yang HI, Iloeje UH. Hepatitis B virus DNA levels and outcomes in chronic hepatitis B. *Hepatology* 2009;49(5 Suppl):S72-84.

3 The management of HIV and hepatitis B virus co-infection

5. Crawford D, Ryan R, Phung N. Clinical assessment of patients with hepatitis B virus infection. In: Matthews G, Robotin M, editors. B positive - all you wanted to know about hepatitis B: a guide for primary care providers. Darlinghurst: Australasian Society for HIV Medicine; 2008. p. 51-6. Available at: http://www.ashm.org.au/images/publications/monographs/b%20positive/b_positive-all_you_wanted_to_know.pdf (cited October 2009)
6. Keeffe EB, Dieterich DT, Han SH, Jacobson IM, Martin P, Schiff ER, et al. A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: 2008 update. *Clin Gastroenterol Hepatol* 2008;6(12):1315-41; quiz 286.
7. Thio CL. Hepatitis B and human immunodeficiency virus co-infection. *Hepatology* 2009;49(5 Suppl):S138-45.
8. Shukla NB, Poles MA. Hepatitis B virus infection: co-infection with hepatitis C virus, hepatitis D virus, and human immunodeficiency virus. *Clin Liver Dis* 2004;8(2):445-60, viii.
9. Hyams K. Risks of chronicity following acute hepatitis B virus infection: a review. *Clin Infect Dis* 1995;20(4):992-1000.
10. Richards M, Lucas C, Gust I. Hepatitis in male homosexuals in Melbourne. *Med J Aust* 1983;2(10):474-5.
11. Bodsworth N, Cooper D, Donovan B. The influence of human immunodeficiency type 1 infection on the development of the hepatitis B carrier state. *J Infect Dis* 1991;163(5):1138-40.
12. Colin JF, Cazals-Hatem D, Lioriot MA, Martinot-Peignoux M, Pham BN, Auperin A, et al. Influence of human immunodeficiency virus infection on chronic hepatitis B in homosexual men. *Hepatology* 1999;29(4):1306-10.
13. Fang J, Wright T, Lau J. Fibrosing cholestatic hepatitis in a patient with human immunodeficiency virus and hepatitis B virus co-infection. *Lancet* 1993;342(8880):1175.
14. Liang TJ, Jeffers LJ, Reddy KR, De Medina M, Parker IT, Cheinquer H, et al. Viral pathogenesis of hepatocellular carcinoma in the United States. *Hepatology* 1993;18(6):1326-33.
15. Previsani N, Lavanchy D. Hepatitis B. Geneva: Department of Communicable Diseases Surveillance and Response, World Health Organisation; 2002. Available at: http://www.who.int/csr/disease/hepatitis/HepatitisB_whocdscsrlyo2002_2.pdf (cited October 2009)
16. Clifford GM, Rickenbach M, Polesel J, Dal Maso L, Steffen I, Ledergerber B, et al. Influence of HIV-related immunodeficiency on the risk of hepatocellular carcinoma. *Aids* 2008;22(16):2135-41.
17. Bruix J, Sherman M. Management of hepatocellular carcinoma. *Hepatology* 2005;42(5):1208-36.
18. Scharschmidt B, Held M, Hollander H, Read AE, Lavine JE, Veereman G, et al. Hepatitis B in patients with HIV infection: relationship to AIDS and patient survival. *Ann Intern Med* 1992;117(10):837-8.
19. Abbas Z, Jafri W, Raza S. Hepatitis D: Scenario in the Asia-Pacific region. *World J Gastroenterol*. 2010 Feb 7;16(5):554-62.
20. Wedemeyer H. Re-emerging interest in hepatitis delta: new insights into the dynamic interplay between HBV and HDV. *J Hepatol*. 2010 May;52(5):627-9.
21. Dimitrakakis M, Waters MJ, Wootton AL, Gust ID. Epidemiology of hepatitis D virus (delta) infection in Melbourne over a 15-year period. *Med J Aust*. 1986 Aug 4-18;145(3-4):128-30.
22. Bodsworth NJ, Donovan B, Gold J, Cossart YE. Hepatitis delta virus in homosexual men in Sydney. *Genitourin Med*. 1989 Aug;65(4):235-8.
23. Cowie BC. Managing hepatitis B virus infection in complex situations. In: Matthews G, Robotin MC, editors. B positive - all you wanted to know about hepatitis B: a guide for primary care providers. Darlinghurst: Australasian Society for HIV Medicine 2008. p. 75-81. Available at: http://www.ashm.org.au/images/publications/monographs/b%20positive/b_positive-all_you_wanted_to_know.pdf (cited October 2009)
24. European Association For The Study Of The Liver. EASL Clinical Practice Guidelines: management of chronic hepatitis B. *J Hepatol*. 2009 Feb;50(2):227-42.
25. Di Bisceglia A. Interferon therapy for chronic viral hepatitis. *N Engl J Med* 1994;330(2):137-8.
26. Wong D, Cheung A, O'Rourke K, Naylor C, Detsky A, Heathcote J. Effect of alpha-interferon treatment in patients with hepatitis B e antigen-positive chronic hepatitis B. A meta-analysis. *Ann Intern Med* 1993;119(4):312-23.
27. Chen D, Yim C, O'Rourke K, Kraiden M, Wong D, J H. Long-term follow-up of a randomized trial of interferon therapy for chronic hepatitis B in a predominately homosexual male population. *J Hepatol* 1999;30(4):557-63.
28. Lau GK, Piratvisuth T, Luo KX, Marcellin P, Thongsawat S, Cooksley G, et al. Peginterferon Alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. *N Engl J Med* 2005;352(26):2682-95.
29. Marcellin P, Lau GK, Bonino F, Farci P, Hadziyannis S, Jin R, et al. Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B. *N Engl J Med* 2004;351(12):1206-17.
30. Cooksley WG, Piratvisuth T, Lee SD, Mahachai V, Chao YC, Tanwandee T, et al. Peginterferon alpha-2a (40 kDa): an advance in the treatment of hepatitis B e antigen-positive chronic hepatitis B. *J Viral Hepat* 2003;10(4):298-305.
31. Janssen HL, van Zonneveld M, Senturk H, Zeuzem S, Akarca US, Cakaloglu Y, et al. Pegylated interferon alfa-2b alone or in combination with lamivudine for HBeAg-positive chronic hepatitis B: a randomised trial. *Lancet* 2005;365(9454):123-9.
32. Coates J, Cammack N, Jenkinson H, Jowett AJ, Jowett MI, Pearson BA, et al. 2',3'-dideoxy-3'-thiacytidine is a potent, highly selective inhibitor of human immunodeficiency virus type 1 and type 2 replication in vitro. *Antimicrob Agents Chemother* 1992;36(4):733-9.
33. Doong S, Tsai C, Schinazi R, Liotta D, Cheng Y. Inhibition of the replication of hepatitis B virus in vitro by 2',3'-dideoxy-3'-thiacytidine and related analogues. *Proc Natl Acad Sci USA* 1991;88(19):8495-9.
34. Locarnini S. Molecular virology and the development of resistant mutants: implications for therapy. *Semin Liver Dis* 2005;25(Suppl 1):9-19.
35. Leung N, Lai CL, Chang T, Guan R, Lee CM, Ng KY, et al. Extended lamivudine treatment in patients with chronic hepatitis B enhances hepatitis B e antigen seroconversion rates: results after 3 years of therapy. *Hepatology* 2001;33(6):1527-32.
36. Hoff J, Bani-Sadr F, Gassin M, Raffi P. Evaluation of chronic hepatitis B virus (HBV) infection in co-infected patients receiving lamivudine as a component of anti-human immunodeficiency virus regimens. *Clin Infect Dis* 2001;32(6):963-9.
37. Dore G, Cooper D, Barrett C, Goh L, Thakrar, Atkins M. Dual efficacy of lamivudine treatment in human immunodeficiency virus/hepatitis B virus-co-infected persons in a randomized, controlled study (CAESAR). The CAESAR Coordinating Committee. *J Infect Dis* 1999;180(3):607-13.
38. Benhamou Y, Bochet M, Thibault V, Di Martino V, Caumes E, Bricaire F, et al. Long-term incidence of hepatitis B virus resistance to lamivudine in human immunodeficiency virus-infected patients. *Hepatology* 1999;30(5):1302-6.
39. Benhamou Y, Bochet M, Thibault V, Calvez V, Fievet MH, Vig P, et al. Safety and efficacy of adefovir dipivoxil in patients co-infected with HIV-1 and lamivudine-resistant hepatitis B virus: an open label study. *Lancet* 2001;358(9283):718-23.

40. Benhamou Y, Thibault V, Vig P, Valantin MA, Guyon P, Katlama C, Lu B, Currie G, Brosgart CL, Poynard T. Long term treatment with adefovir dipivoxil 10 mg (ADV) in patients with lamivudine-resistant (LAM-R) HBV and HIV co-infection results in significant and sustained clinical improvement. Abstract #1329 XVI Int AIDS conference Bangkok July 11-16 2004
41. Tenney DJ, Rose RE, Baldick CJ, Pokornowski KA, Eggers BJ, Fang J, et al. Long-term monitoring shows hepatitis B virus resistance to entecavir in nucleoside-naïve patients is rare through 5 years of therapy. *Hepatology* 2009;49(5):1503-14.
42. McMahon MA, Jilek BL, Brennan TP, Shen L, Zhou Y, Wind-Rotolo M, et al. The HBV drug entecavir - effects on HIV-1 replication and resistance. *N Engl J Med* 2007;356(25):2614-21.
43. Liaw YF, Gane E, Leung N, Zeuzem S, Wang Y, Lai CL, et al. 2-Year GLOBE trial results: telbivudine is superior to lamivudine in patients with chronic hepatitis B. *Gastroenterology*. 2009;136(2):486-95.
44. Dienstag JL. Benefits and risks of nucleoside analog therapy for hepatitis B. *Hepatology* 2009;49(5 Suppl):S112-21.
45. Ghany MG, Doo EC. Antiviral resistance and hepatitis B therapy. *Hepatology* 2009;49(5 Suppl):S174-84.
46. Dore GJ, Cooper DA, Pozniak AL, DeJesus E, Zhong L, Miller MD, Lu B, Cheng AK, 903 Study Team; 907 Study Team. Efficacy of tenofovir disoproxil fumarate in antiretroviral therapy-naïve and -experienced patients co-infected with HIV-1 and hepatitis B virus. *Journal of Infectious Diseases* 2004;189(7):1185-1192.
47. Squires K, Pozniak AL, Pierone G, Jr, Steinhart CR, Berger D, Bellos NC, et al. Tenofovir disoproxil fumarate in nucleoside-resistant HIV-1 infection: a randomized trial. *Ann Intern Med*. 2003 Sep 2;139(5 Pt 1):313-20.
48. Gallant JE, Staszewski S, Pozniak AL, DeJesus E, Suleiman JM, Miller MD, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naïve patients: a 3-year randomized trial. *Jama*. 2004 Jul 14;292(2):191-201.
49. Matthews GV, Avihingsanon A, Lewin SR, Amin J, Rerknimitr R, Petcharapirat P, et al. A randomized trial of combination hepatitis B therapy in HIV/HBV co-infected antiretroviral naïve individuals in Thailand. *Hepatology* 2008;48(4):1062-9.
50. Carr A, Cooper D. Restoration of immunity to chronic hepatitis B infection in HIV-infected patient on protease inhibitor. *Lancet* 1997;346(9057):995-6.
51. Proia L, Ngui S, Kaur S, Kessler H, Trenholme G. Reactivation of hepatitis B in patients with human immunodeficiency virus infection treated with combination antiretroviral therapy. *Am J Med* 2000;108(3):249-51.
52. Savès M, Raffi F, Clevenbergh P, Marchou B, Waldner-Combernoux A, Morlat P, et al. Hepatitis B or hepatitis C virus infection is a risk factor for severe hepatocytolysis after initiation of a protease inhibitor-containing antiretroviral regimen in human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother* 2000;44(12):3451-5.
53. Sulkowski M, Thomas D, Chaisson R, Moore R. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. *J Am Med Assoc* 2000;283(1):74-80.
54. McGovern B. What drives hepatitis B virus-related hepatic flares? Virus, T cells--or a bit of both? *Clin Infect Dis* 2004;39(1):133-5.
55. Drake A, Mijch A, Sasadeusz J. Immune Reconstitution Hepatitis in HIV and Hepatitis B Co-infection, Despite Lamivudine Therapy as Part of HAART. *Clin Infect Dis* 2004;39(1):129-13.
56. Manegold C, Hannoun C, Wywiol A, Dietrich M, Polywka S, Chiwakata CB, et al. Reactivation of hepatitis B virus replication accompanied by acute hepatitis in patients receiving highly active antiretroviral therapy. *Clin Infect Dis* 2001;32(1):144-8.
57. Bessesen M, Ives D, Condreay L, Lawrence S, Sherman R. 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(5):1032-5.
58. Bellini C, Keiser O, Chave JP, Evison J, Fehr J, Kaiser L, et al. Liver enzyme elevation after lamivudine withdrawal in HIV-hepatitis B virus co-infected patients: the Swiss HIV Cohort Study. *HIV Med* 2009;10(1):12-8.
59. Tur-Kaspa R, Burk RD, Shaul Y, Shafritz DA. Hepatitis B virus DNA contains a glucocorticoid-responsive element. *Proc Natl Acad Sci U S A* 1986;83(6):1627-31.
60. Masuhara M, Yagawa T, Aoyagi M, Suzuki C, Sakaguchi E, Segawa M, et al. HBV-related fulminant hepatic failure: successful intensive medical therapy in a candidate for liver transplantation. *J Gastroenterol* 2000;36(5):350-53.
61. Fujiwara K, Yokosuka O, Kojima H, Kanda T, Saisho H, Hirasawa H, et al. Importance of adequate immunosuppressive therapy for the recovery of patients with "life-threatening" severe exacerbation of chronic hepatitis B. *World J Gastroenterol* 2005;11(8):1109-14.
62. Matthews G, Seaberg E, Dore G, Bowden S, Lewin S, Sasadeusz J, et al. Combination of HBV-active antiretroviral therapy influences HBV virological suppression in an international cohort of 120 HIV/HBV co-infected individuals. 42nd Annual Meeting of the European Association for the Study of the Liver; 2007; Barcelona, April 11-15; 2007.
63. Hammer SM, Eron JJ, Jr, Reiss P, Schooley RT, Thompson MA, Walmsley S, et al. Antiretroviral treatment of adult HIV infection: 2008 recommendations of the International AIDS Society-USA panel. *Jama* 2008;300(5):555-70.
64. Guidelines for the use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents (with Australian Commentary): DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents; 2008 (updated November 3). Panel on Antiretroviral Guidelines for Adult and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. January 29, 2008;1-128. Available at: <http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf> (cited October 2009).
65. Savès M, Vandendorren S, Daucourt V, Marimoutou C, Dupon M, Couzigou P, et al. Severe hepatic cytolysis: incidence and risk factors in patients treated by antiretroviral combinations. Aquitaine Cohort, France, 1996-1998. *AIDS* 1999;13(17):F115-F121.
66. Sulkowski M, Thomas D, Mehta S, Chaisson R, Moore R. Hepatotoxicity associated with nevirapine or efavirenz-containing antiretroviral therapy: role of hepatitis C and B infections. *Hepatology* 2002;35(1):182-9.
67. Cooper CL. HIV antiretroviral medications and hepatotoxicity. *Curr Opin HIV AIDS*. 2007 Nov;2(6):466-73.
68. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1, 2009;1-161. Available at <http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf> (cited December, 2009)

Antiretroviral therapy-related hepatotoxicity: predictors and clinical management

Gregory Dore
Benjamin Cowie

National Centre in HIV Epidemiology and Clinical Research, The University of New South Wales, Sydney, NSW
Victorian Infectious Diseases Service, Royal Melbourne Hospital,
Victorian Infectious Diseases Reference Laboratory, VIC and
Department of Medicine, The University of Melbourne, VIC

KEY POINTS

- Severe hepatotoxicity develops in 5-10% of people with HIV infection in the first 12 months following initiation of combination antiretroviral therapy (cART), with continuing risk in subsequent years.
- The major risk factors for severe hepatotoxicity are underlying chronic viral hepatitis, abnormal baseline levels of serum hepatic transaminases, and nevirapine or high-dose ritonavir-containing antiretroviral therapy regimens.
- The vast majority of severe hepatotoxicity cases are not associated with development of symptoms of acute hepatitis or other adverse hepatic outcomes and resolve within a few months.
- Antiretroviral therapy should be discontinued in association with grade 4 elevations in serum hepatic transaminase measurements, hyperlactataemia, symptoms of acute hepatitis, or features of drug hypersensitivity.

Introduction

Prevention and management of antiretroviral therapy (ART)-related toxicity have emerged as major issues for HIV/AIDS treatment and care.^{1,2} Hepatotoxicity is now well described as a component of the broad spectrum of toxicity associated with ART.³⁻¹⁵ Elevations in serum hepatic enzymes have been described in association with all major classes of ART,³⁻¹⁵ with several underlying mechanisms proposed:

- mitochondrial toxicity in association with several nucleoside analogue reverse transcriptase inhibitors (NRTIs);
- hypersensitivity reaction in association with non-nucleoside reverse transcriptase inhibitors (NNRTIs);
- immune restoration disease in association with underlying chronic viral hepatitis.

This chapter will present an overview of ART-related hepatotoxicity, including incidence and predictors, and propose an algorithm for its clinical management.

Definitions of severe hepatotoxicity

Studies examining rates of hepatotoxicity have employed various case definitions. However, most studies have defined elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in accordance with the AIDS Clinical Trials Group criteria.¹⁶

AIDS Clinical Trials Group criteria¹⁶

Grade 1: 1.25-2.5 times the upper limit of normal (x ULN)
Grade 2: 2.6-5.0 x ULN
Grade 3: 5.1-10 x ULN
Grade 4: > 10 x ULN.

Severe hepatotoxicity or liver enzyme elevation has been defined as either grade 3 and grade 4 ALT and AST elevations, or, occasionally, only grade 4 elevations. In addition, several

studies have included the requirement of an absolute ALT and AST increase of greater than 100 U/L from baseline to avoid selection bias in favour of people with baseline ALT and AST elevations. Other more clinically relevant endpoints, such as any interruption of ART due to symptomatic elevations in transaminases regardless of the peak level, have more recently been used.¹⁷

Incidence and predictors of severe hepatotoxicity

Many studies have now examined the issue of ART-related hepatotoxicity (Table 4.1),⁴⁻¹⁵ particularly since the introduction of combination antiretroviral therapy (cART also termed highly active antiretroviral therapy HAART), which generally describes combinations of two NRTIs and either an NNRTI or one or more protease inhibitors (PI). The majority of these studies have been retrospective or prospective clinic-based cohort studies, with incidence of hepatotoxicity generally assessed following commencement of a new ART regimen. Contrasts in study populations, definitions of hepatotoxicity, and rates of clinical monitoring make comparisons across studies somewhat problematic, however, broad patterns in hepatotoxicity have emerged. Some of the major findings with regard to severe hepatotoxicity include:

- a wide range in cumulative risk (1–30%), with a median incidence of 5–10/100 person years over the initial 12 months of therapy;
- co-infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) as the strongest risk factors, with a 3–5 fold increase in risk in several studies;
- increased risk associated with elevated baseline ALT and AST levels;
- increased risk associated with cART regimens compared to dual NRTI regimens;
- nevirapine (NVP) and ritonavir (RTV) as the ART agents most commonly implicated;

Table 4.1 Incidence and predictors of severe hepatotoxicity following commencement of antiretroviral therapy

Study	Definition of hepatotoxicity	Subjects	Antiretroviral regimens	Median follow-up (weeks)	Incidence of hepatotoxicity	Median time to hepatotoxicity (weeks)	Predictors of hepatotoxicity
Savès et al 1999 (France) ⁴	Grade 3 or 4 ALT	748	Initiation of PI- containing cART	56	7.3/100 py (5.5% at 6 months, 8.0% at 12 months, 13.2% at 24 months)	23	HBV, HCV, baseline ALT
Savès et al 1999 (France) ⁴	Grade 3 or 4 ALT	1249	Dual NRTI regimen	52	5.7/100 py (3.0% at 6 months, 4.8% at 12 months, 12.7% at 24 months)	36	HBV, HCV
Den Brinker et al 2000 (The Netherlands) ⁵	Grade 3 or 4 ALT or AST + 100 U/L increase	394	Initiation of cART	65	18%	25	HBV, HCV, elevated baseline ALT
Gisolf et al 2000 (The Netherlands) ⁶	Grade 3 or 4 +100 U/L increase	208	RCT of RTV/ SQV +/- d4T	NA	9%	12	HBV, baseline ALT, d4T-containing regimen
Sulkowski et al 2000 (USA) ⁷	Grade 3 or 4 ALT or AST	298(87 NA, 211 PI)	Initiation of new ART regimens	24 (NA) 26 (PI)	10.4% (37/100 py)	17	RTV-containing regimen CD4 increase > 50/ mm3
Monforte et 2001 (Italy) ⁸	ALT > 200 U/L	1,255	Initiation of cART	NA	8% (based on K-M estimate at 24 months)	NA	HCV, HBV/HCV, elevated baseline ALT
Martinez et al 2001 (Spain) ⁹	ALT or AST > 3 x increase from baseline	610	Initiation of NVP- containing combination ART regimen	38	12.5% or 13.1/100 py	NA	HCV, baseline ALT, duration of prior ARV
Nunez et al 2001(Spain) ¹⁰	Grade 3 or 4 ALT or AST or 3.5 x baseline (if abnormal)	222	Initiation of cART	35	9%	NA	HCV, heavy alcohol intake, older age
Aceti et al 2002 (Italy) ¹¹	Grade 3 or 4 ALT	1325	PI-containing cART	NA	2.8% after 12 months, 3.7% after 24 months	NA	HBV, HCV, RTV- containing regimen (first 6 months)
Palmon et al 2002 (USA) ¹²	Grade 3 or 4 ALT or AST and >5x baseline and >5x baseline	272	Initiation of NNRTI- containing regimen	54	1.1%	14	Nil
Wit et al 2002 (The Netherlands) ¹³	Grade 4 ALT or AST + 200 U/L elevation	560	Initiation of cART	156	8%	NA	HBV, HCV, elevated baseline ALT, no prior ART, recent NPV or RTV commencement, female, 3TC discontinuation (HBV)
Cooper et al 2002 (Canada) ¹⁴	Grade 3 or 4 x	66 HIV/ HCV	Initiation of PI- containing cART	56	26% (single-PI) 19% (dual-PI)	NA	Nil
Sulkowski et al 2002(USA) ¹⁵	Grade 3 or 4 x ALT of AST	568 (256 NVP, 312 EFV)	Initiation of NNRTI- containing cART	45 (NVP) 37 (EFV)	15.6/100 py (NVP) 8.0/100 py (EFV)	20 (NVP) 14 (EFV)	HBV, HCV, concurrent PI)

ALT = alanine aminotransferase; AST= aspartate aminotransferase; NVP= nevirapine; EFV= efavirenz; NNRTI= non-nucleoside reverse transcriptase inhibitors; cART= combination antiretroviral therapy; HBV= hepatitis B virus; HCV= hepatitis C virus; PI= protease inhibitor; NA= not available; 3TC= lamivudine; RTV= ritonavir; U/L= ; ART= antiretroviral therapy; SQV= saquinavir; d4T= stavudine; NRTI= nucleoside analogue reverse transcriptase inhibitors; RCT= ; py= .

- increased risk within the initial 12 weeks of therapy, particularly in relation to NVP;
- a low risk of symptomatic hepatitis, and extremely low risk of fulminant hepatitis;
- an incidence of clinically apparent hepatotoxicity requiring treatment interruption of 2–4%;¹⁸
- resolution of hepatotoxicity, generally within three months, and often despite continued ART.

Co-infection with hepatitis B virus or hepatitis C virus

Co-infection with HBV or HCV is clearly associated with ART hepatotoxicity.^{4,6–11,13,15,19} Immune restoration disease is one of the underlying mechanisms for this increased risk,²⁰ supported by the association between CD4 cell count change following commencement of ART and risk of severe hepatotoxicity observed in some studies.⁷ A further explanation for an increased risk in association with hepatitis co-infection is that established liver inflammation may increase the risk of direct toxicity from ART agents.¹⁸ As described in Chapter 3, in the setting of HIV-HBV co-infection, cessation of lamivudine (3TC) has been associated with hepatotoxicity,^{13,21} with recurrence of HBV viraemia and associated hepatic inflammation (hepatic flare) being the underlying mechanism. Such episodes have been associated with hepatic decompensation and death in people with more advanced liver disease.²¹

Non-nucleoside reverse transcriptase inhibitors

Hepatotoxicity is well described in people with HIV receiving any NNRTI-containing regimen, with evidence for particular toxicity associated with NVP therapy.^{9,13,15,18,19,22} The incidence of NVP related hepatotoxicity varies in published studies, although in general, symptomatic hepatitis and adverse clinical outcomes are uncommon (2.5–11% in different trials).^{10,12,22} Differences in prevalence of other risk factors, in particular co-infection with HBV or HCV, may be responsible for contrasting findings from these studies.

Although NVP-associated hepatotoxicity appears to be most common in the initial six weeks of therapy, it can occur up to 18 weeks after initiation.²² Clinical features of this apparent hypersensitivity syndrome may include fever, flu-like symptoms, abdominal pain and jaundice, with a rash occurring in approximately 50% of patients.^{18,22} Risk factors include relatively preserved immune function (CD4 cell count > 250 cells/ml in women and > 400 cells/ml in men, and particularly in people with normal immunity when NVP was used in post-exposure prophylaxis), treatment naïveté, and possibly high drug concentrations (in the 2NN study, daily dosing of NVP was associated with a higher risk of grade 3/4 transaminase elevations).^{18,19,22,23}

Cases of cholestatic hepatitis – with a mixed picture of hepatic transaminitis and cholestasis – have also been described in association with NVP,²⁴ and would appear to be related to direct drug-induced cholestasis. Asymptomatic elevations in gamma glutamyl transferase are relatively common in people receiving NVP-containing ART regimens.^{25,26} Efavirenz (EFV) has also been associated with adverse

hepatobiliary events of both a clinical and biochemical nature, although both are significantly less common than is the case with NVP¹⁹ perhaps because these are not manifestations of the hypersensitivity syndrome which appears to be specific to NVP.²² This is supported by the observation that after the first 16 weeks of treatment incidence of hepatotoxicity is similar between EFV and NVP.¹⁸ Evidence for the safety of initiating therapy with other NNRTIs following significant hepatotoxicity due to NVP is lacking and should be undertaken with caution.²²

Thus, the pathogenesis of NNRTI-associated hepatotoxicity is almost certainly multifactorial, with direct drug-induced toxicity, hypersensitivity in the setting of NVP, immune restoration and exacerbation of underlying chronic viral hepatitis all potential contributing factors.

Protease inhibitors

Protease inhibitor therapy, in particular RTV, has been associated with severe hepatotoxicity in several studies.^{7,11,13,15,27} As with NNRTI-associated hepatotoxicity, chronic viral hepatitis co-infection increases the risk of grade 3/4 transaminase elevation, with immune restoration also proposed as a pathogenic mechanism.²⁰ RTV is a potent inhibitor of the cytochrome P450 system, therefore elevated concentrations of other drugs may be a contributing factor to hepatotoxicity. The risk of RTV associated hepatotoxicity is greatest in the setting of high-dose therapy which is no longer recommended. The current use of low and boosting doses of RTV (100–200 mg daily) with a second PI does not appear to be associated with high rates of hepatotoxicity, with grade 3/4 transaminase rises generally below 5% in treatment naïve patients (although higher in the setting of co-infection).^{18,28,29}

Amongst other protease inhibitors, tipranavir (TPV) appears to have a higher incidence of clinically relevant hepatotoxicity¹⁸ particularly in the setting of underlying liver disease. This has led to cautions against the use of this agent in the setting of moderate to severe hepatic insufficiency.²²

The protease inhibitors atazanavir and indinavir both cause indirect hyperbilirubinaemia that can lead to jaundice. Although this is of no clinical significance, it can cause cosmetic concerns and patients should be counselled about this reaction prior to treatment initiation.^{11,18,22}

Nucleoside analogue reverse transcriptase inhibitors

Risk of severe hepatotoxicity appears to be relatively low in association with NRTIs. Incidence of hepatotoxicity associated with dual NRTI combination therapy is lower than NRTI and NNRTI dual combination therapy²⁶ and either NNRTI or PI-containing cART regimens.^{4,7} Despite a relatively low risk of severe hepatotoxicity, NRTIs have certainly been associated with adverse hepatic outcomes. Such adverse hepatic outcomes, including cases of hepatic failure, have been associated with the development of steatohepatitis and hyperlactataemia ascribed to mitochondrial toxicity.^{30–33}

It has been recognised for some time that the NRTIs most commonly associated with this mitochondrial toxicity syndrome are the dydeoxynucleoside analogues stavudine

(d4T) and didanosine (ddl).¹⁸ This was reinforced in the setting of HCV co-infection in a Spanish study of patients undergoing HCV treatment, where the only independent predictors of hepatotoxicity following interferon therapy were lack of SVR (sustained virologic response, see Chapter 2) and the use of dydeoxynucleosides.¹⁷ A further concern in the setting of treatment of HCV is that concomitant use of ribavirin and ddl substantially increases the risk of mitochondrial toxicity^{18,22} and this combination should therefore not be used. Zidovudine (ZDV) is the other NRTI drug which has been associated with mitochondrial toxicity, although the incidence is less than for d4T and ddl. Other NRTIs including abacavir (ABC), tenofovir disoproxil fumarate or tenofovir (TDF), 3TC and emtricitabine (FTC) are much less likely to induce mitochondrial toxicity.²²

Symptoms such as increasing lethargy, abdominal discomfort, and unexplained nausea and vomiting may indicate increasing serum lactate levels. Hyperventilation and neuromuscular dysfunction are generally late signs associated with lactic acidosis. Mitochondrial toxicity appears to be the underlying mechanism for both steatohepatitis and symptomatic hyperlactataemia; however, these syndromes do not always coexist. Normal liver function tests may be present, even in cases of NRTI-associated lactic acidosis, and lactate levels may be normal despite severe steatohepatitis.³⁰⁻³³

The continuing risk of severe hepatotoxicity beyond the initial few months of cART, and the latent phase prior to the clinical appearance of mitochondrial toxicity-related adverse events, mean that longer-term follow-up is required to fully assess the risk of adverse hepatic outcomes associated with NRTI-containing cART. It is possible that chronic low level hyperlactataemia may be associated with progressive liver damage, even following cessation of antiretroviral therapy.³⁰ This syndrome is less commonly seen in developed economies due to the availability of alternative NRTIs which are associated with less metabolic toxicity on prolonged therapy. However these agents are expensive, and ongoing use of ddl and d4T in developing countries will result in a substantial burden of the mitochondrial toxicity syndrome into the future.^{18,34}

Other antiretroviral agents

Fusion inhibitors

Enfuvirtide is not commonly associated with hepatotoxicity. Elevated transaminases are seen in the rare setting (<1% of patients) of an enfuvirtide hypersensitivity reaction.²²

CCR5 antagonists

Although maraviroc has been associated with hepatotoxicity,²² clinical trial data published in 2008 demonstrated that grade 3/4 transaminase elevations were no different between the intervention and control arms.³⁵ Excess hepatotoxicity was not observed in patients with chronic viral hepatitis co-infection was not observed in these trials although the number of co-infected patients was low.³⁶ Clinical trials of another member of this class, aplaviroc, were ceased in 2005 when four patients (one of whom was co-infected with HBV) developed elevated transaminases and bilirubin.³⁷

Integrase inhibitors

No increase in hepatotoxicity compared with placebo has been reported as yet for raltegravir.^{22,38}

Management of antiretroviral therapy-related hepatotoxicity

Several features of ART-related hepatotoxicity should be kept in mind when making clinical management decisions. First, severe hepatotoxicity is generally not symptomatic or associated with adverse hepatic outcomes. Second, serum hepatic transaminase levels almost always return to normal or baseline levels, even when therapy is continued. Third, most ART agents have been associated with severe hepatotoxicity. Fourth, ART can in many cases be interrupted for at least a few months without adverse outcomes in relation to HIV disease progression.

Exclusion of other causes of acute and chronic hepatitis

Although most cases of new onset severe serum hepatic transaminase elevation in people receiving cART are related to one or more antiretroviral therapeutic agent, other causes of acute and chronic hepatitis need to be excluded. The following conditions should be considered, with appropriate investigations:

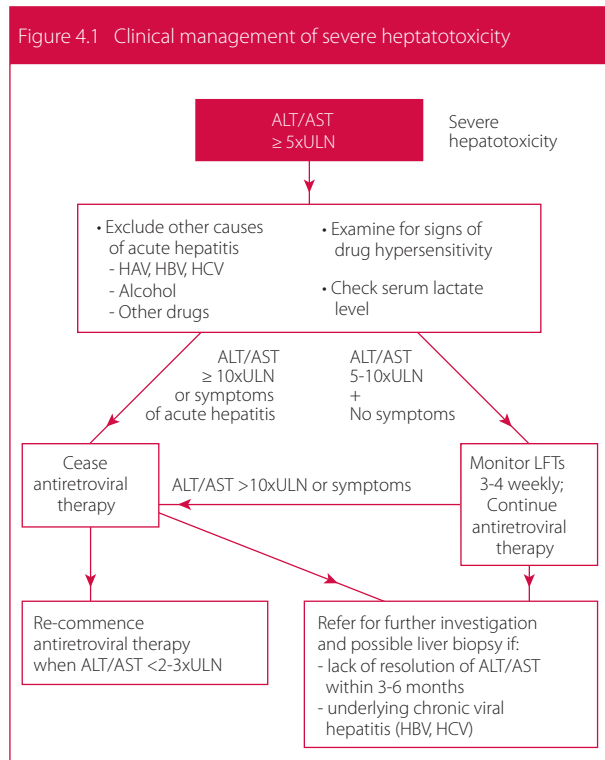
- Acute viral hepatitis – anti-HAV IgM/IgG, HBsAg/anti-HBc IgM, anti-HCV Ab/HCV RNA (if either unknown or previous negative serology);
- Flare of chronic viral hepatitis – immune reconstitution hepatitis, cessation of antivirals active against HBV in the setting of chronic infection or development of antiviral resistance in HBV;
- Other infectious causes – anti-CMV IgM/IgG, anti-EBV IgM/IgG, anti-toxoplasma IgM/IgG, syphilis serology;
- Autoimmune liver disease – anti-nuclear antibodies, anti-smooth muscle antibodies, anti-mitochondrial antibodies, anti-liver kidney microsomal antibodies;
- Alcoholic hepatitis – history of recent heavy alcohol intake;
- Use of recreational drugs – both injecting and non-injecting related administration;
- Other drug toxicity – in particular anti-mycobacterials, other antibiotics and lipid lowering agents;
- Hereditary and metabolic conditions – such as haemochromatosis, Wilson's disease, non-alcoholic steatohepatitis (NASH).

Viral hepatitis and alcohol and recreational drug use are also factors that may contribute to an increased risk of ART-related hepatotoxicity.

Initial management and monitoring

An algorithm for management of severe hepatotoxicity is outlined in Figure 4.1. In general, ART can be continued if ALT and AST elevations are less than grade 4 (> 10 x ULN) and symptoms of acute hepatitis are absent. Liver function test monitoring and assessment of international normalised ratio (INR) should be performed approximately every two weeks until levels return towards normal or baseline. Indications for cessation of ART include:

- symptomatic hepatitis – anorexia, nausea, malaise, diarrhoea, abdominal discomfort, increasing lethargy, jaundice;
- tender hepatomegaly;
- ALT and AST elevations greater than 10 x ULN;



- signs of drug hypersensitivity – rash, hypereosinophilia – or suspected hypersensitivity reaction following initiation of NVP (most within 6 weeks but can occur as late as 18 weeks after commencement);
- hyperlactataemia – lactate levels above 3 mmol/L;
- evidence of synthetic dysfunction such as elevated INR.

In people who require ART cessation, the period of treatment interruption may be partly guided by level of immune function, but should be at least until the ALT and AST levels decline to less than 2–3 x ULN and any symptoms subside.

A special consideration in the setting of HBV co-infection is that cessation of all ART may induce a viral hepatitis flare with further liver injury likely (see Chapter 3). As anti-HBV active agents such as TDF, 3TC and FTC are unlikely causes of liver disease, consideration should be given to continuing these antivirals,²² particularly in the setting of advanced underlying liver disease, although without fully suppressive cART the potential for development of HIV resistance mutations over time is significant. Consultation with a physician with expertise in the management of HIV/HBV co-infection is advised in this situation.

Further investigation of hepatic enzyme elevations

In people who have ALT and AST elevations of less than 10 x ULN, no features of hyperlactataemia or drug hypersensitivity, and no symptoms or signs of acute hepatitis, ART can be continued with liver function test monitoring every two weeks initially. Further elevations of ALT and AST (above 10 x ULN) and development of symptoms warrant discontinuation of antiretroviral therapy. Specialist referral for further investigations and possible liver biopsy is recommended if there is lack of ALT

and AST resolution (to < 2–3 x ULN) or in the context of chronic viral hepatitis co-infection. Investigations for alternative causes of chronic liver disease and a liver ultrasound could be initiated prior to referral.

Choice of antiretroviral therapy regimen

If severe hepatotoxicity requires ART cessation, the choice of regimen for re-commencement will depend on a number of factors:

- an assessment of the likelihood of an association with particular ART agents – probable increased risk with NVP, high-dose RTV, and some NRTIs including ddI, stavudine, and ZDV (particularly when hyperlactataemia is present);
- presence of drug hypersensitivity features – patients should not be rechallenged with ABC or NVP following a suspected hypersensitivity reaction, and other agents possibly associated with a severe skin eruption should also not be re-commenced;
- ensuring that anti-HBV active agents are continued in the setting of HBV co-infection;
- in the setting of moderate to severe hepatic insufficiency, TPV should be avoided;
- remaining choice of ART– re-challenge (except in the situation of ABC or NVP hypersensitivity as above) may be more appropriate where choices are limited.

Re-commencement of ART, particularly when re-challenging with agents in the previous regimen, should be monitored with one to two weekly liver function tests for the first few months at least.

Conclusion

Although severe hepatotoxicity among people receiving ART is generally not associated with adverse hepatic outcomes, careful monitoring and investigation of alternative and contributing factors are required. This is especially the case in the setting of co-infection with chronic viral hepatitis. In this context, clinicians should take particular care to counsel patients prior to initiating ART regarding the need for regular clinical and biochemical monitoring. Patients should also be educated regarding the possible symptoms of hepatotoxicity such as lethargy, anorexia, nausea, vomiting, abdominal pain and jaundice. The relationship between laboratory test abnormalities including elevated serum hepatic transaminase levels and increased medium-term mortality^{39,40} is further reason to monitor and appropriately investigate potential liver disease co-morbidities in people with HIV infection, especially in the setting of co-infection with chronic viral hepatitis.

Acknowledgments

Professor Geoffrey Farrell and Professor Martyn French provided valuable comments on an earlier draft of this chapter.

References

1. Powderly WG, Carr A. AIDS 2001. Clinical treatment. Overview. *AIDS* 2001;15(Suppl 5):S159–S160.
2. Carr A, Workman C, Smith DE, Hoy J, Hudson J, Doong N, et al. Mitochondrial Toxicity (MITOX) Study Group. Abacavir substitution for nucleoside analogs in patients with HIV lipotrophy: a randomized trial. *J Am Med Assoc* 2002;288(2):207–15.
3. Rodriguez-Rosado R, Garcia-Samaniego J, Soriano V. Hepatotoxicity after introduction of highly active antiretroviral therapy. *AIDS* 1998;12(10):1256.
4. Savès M, Vandentorren S, Daucourt V, Marimoutou C, Dupon M, Couzigou P, et al. Severe hepatic cytolysis: incidence and risk factors in patients treated by antiretroviral combinations. Aquitaine Cohort, France, 1996–1998. *AIDS* 1999; 13(17):F115–F121.
5. den Brinker M, Wit WNM, Wertheim-van Dillen PME, Jurriaans S, Weel J, van Leeuwen R, et al. Hepatitis B and C virus co-infection and the risk for hepatotoxicity of highly active antiretroviral therapy in HIV-1 infection. *AIDS* 2000;14(18):2895–2902.
6. Gisolf EH, Dreezen C, Danner SA, Weel JLF, Weverling GJ, Promethus Study Group. Risk factors for hepatotoxicity in HIV-1-infected patients receiving ritonavir and saquinavir with or without stavudine. *Clin Infect Dis* 2000;31(5):1234–9.
7. Sulkowski MS, Thomas DL, Chaisson RE, Moore RD. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. *J Am Med Assoc* 2000, 283(1):74–80.
8. Monforte Ade A, Bugarini R, Pezzotti P, De Luca A, Antinori A, Mussini C, et al. The ICONA (Italian Cohort of Naive for Antiretrovirals) Study Group. Low frequency of severe hepatotoxicity and association with HCV co-infection in HIV-positive patients treated with cART. *J AIDS* 2001;28(2):114–23.
9. Martinez E, Blanco JL, Arnaiz JA, Pérez-Cuevas JB, Mocroft A, Cruceta A, et al. Hepatotoxicity in HIV-1-infected patients receiving nevirapine-containing antiretroviral therapy. *AIDS* 2001; 15(10):1261–8.
10. Nunez M, Lana R, Mendoza JL, Martin-Carbonero L, Soriano V. Risk factors for severe hepatic injury after introduction of highly active antiretroviral therapy. *J AIDS* 2001;27(5):426–31.
11. Aceti A, Pasquazzi C, Zechini B, De Bac C. The LIVERHAART Group. Hepatotoxicity development during antiretroviral therapy containing protease inhibitors in patients with HIV: the role of hepatitis B and C virus infection. *J AIDS* 2002;29(1):41–8.
12. Palmon R, Koo BC, Shoultz DA, Dieterich DT. Lack of hepatotoxicity associated with nonnucleoside reverse transcriptase inhibitors. *J AIDS* 2002;29(4):340–5.
13. Wit FW, Weverling GJ, Weel J, Jurriaans S, Lange JM. Incidence of and risk factors for severe hepatotoxicity associated with antiretroviral combination therapy. *J Infect Dis* 2002;186(1):23–31.
14. Cooper CL, Parbhakar MA, Angel JB. Hepatotoxicity associated with antiretroviral therapy containing dual versus single protease inhibitors in individuals co-infected with hepatitis C virus and human immunodeficiency virus. *Clin Infect Dis* 2002;34(9):1259–63.
15. Sulkowski MS, Thomas DL, Mehta SH, Chaisson RE, Moore RD. Hepatotoxicity associated with nevirapine or efavirenz-containing antiretroviral therapy: role of hepatitis C and B infections. *Hepatology* 2002; 35(1):182–9.
16. AIDS Clinical Trials Group criteria, division of AIDS. Table for grading severity of adult adverse experiences, August 1992.
17. Labarga P, Soriano V, Vispo ME, Pinilla J, Martin-Carbonero L, Castellares C, et al. Hepatotoxicity of antiretroviral drugs is reduced after successful treatment of chronic hepatitis C in HIV-infected patients. *J Infect Dis* 2007;196(5):670–6.
18. Cooper CL. HIV antiretroviral medications and hepatotoxicity. *Curr Opin HIV AIDS* 2007;2(6):466–73.
19. van Leth F, Phanuphak P, Ruxrungtham K, Baraldi E, Miller S, Gazzard B, et al. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. *Lancet* 2004;363(9417):1253–63.
20. John M, Flexman J, French MA. Hepatitis C virus-associated hepatitis following treatment of HIV-infected patients with HIV protease inhibitors: an immune restoration disease? *AIDS* 1998;12(17):2289–93.
21. Bellini C, Keiser O, Chave JP, Evison J, Fehr J, Kaiser L, et al. Liver enzyme elevation after lamivudine withdrawal in HIV-hepatitis B virus co-infected patients: the Swiss HIV Cohort Study. *HIV Med* 2009;10(1):12–8.
22. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. November 3, 2008; 1–139. Available at <http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf> (cited September, 2009)
23. Anonymous. From the Centers for Disease Control and Prevention. Serious adverse events attributed to nevirapine regimens for postexposure prophylaxis after HIV exposures—worldwide, 1997–2000. *J Am Med Assoc* 2001;285(4):402–3.
24. Clarke S, Harrington P, Condon C, Kelleher D, Smith OP, Mulcahy F. Late onset hepatitis and prolonged deterioration in hepatic function associated with nevirapine therapy. *Int J STD AIDS* 2000;11(5):336–7.
25. Carr A, Vella S, de Jong MD, Sorice F, Imrie A, Boucher CA, et al. A controlled trial of nevirapine plus zidovudine versus zidovudine alone in p24 antigenaemic HIV-infected patients. *AIDS* 1996;10(6):635–41.
26. Montaner JS, Reiss P, Cooper D, Vella S, Harris M, Conway B et al. A randomized, double-blind trial comparing combinations of nevirapine, didanosine, and zidovudine for HIV infected patients – The INCAS Trial. *J Am Med Assoc* 1998; 279(12):930–7.
27. Arribas JR, Ibáñez C, Ruiz-Antoran B, Peña JM, Esteban-Calvo C, Frías J, et al. Acute hepatitis in HIV-infected patients during ritonavir treatment. *AIDS* 1998;12(13):1722–4.
28. Murphy RL, Brun S, Hicks C, Eron JJ, Gulick R, King M, et al. ABT-378/ritonavir plus stavudine and lamivudine for the treatment of antiretroviral-naïve adults with HIV-1 infection: 48 week results. *AIDS* 2001;15(1):1–9.
29. Vora S, Michon C, Junet C, Balavoine JF, Renold-Moynier C, Yerly S, et al. Switch from indinavir to ritonavir-indinavir regimen in patients treated with highly active antiretroviral therapy co-infected with hepatitis C is not associated with alteration of liver function tests. *AIDS* 2000;14(17):2795–7.
30. Carr A, Morey A, Mallon P, Williams D, Thorburn C. Fatal portal hypertension, liver failure, and mitochondrial dysfunction after HIV-1 nucleoside analogue-induced hepatitis and lactic acidemia. *Lancet* 2001;357(9266):1412–4.
31. Lonergan JT, Behling C, Pfander H, Hassanein TI, Mathews WC. Hyperlactataemia and hepatic abnormalities in 10 human immunodeficiency virus-infected patients receiving nucleoside analogue combination regimens. *Clin Infect Dis* 2000;31(1):162–6.
32. Coghlan ME, Sommadossi J-P, Jhala NC, Many WJ, Saag MS, Johnson VA. Symptomatic lactic acidosis in hospitalized antiretroviral therapy-treated patients with human immunodeficiency virus infection: a report of 12 cases. *Clin Infect Dis* 2001;33(11):1914–21.

4 Antiretroviral therapy-related hepatotoxicity: predictors and clinical management

33. Boubaker K, Flepp M, Sudre P, et al. Hyperlactataemia and antiretroviral therapy: The Swiss HIV Cohort Study. *Clin Infect Dis* 2001;33(11):1931–7.
34. Cooper CL. De-“Liver”-ing HIV/hepatitis C virus-co-infected patients from antiretroviral hepatotoxicity. *J Infect Dis*. 2007;196(5):656-8.
35. Gulick RM, Lalezari J, Goodrich J, Clumeck N, DeJesus E, Horban A, et al. Maraviroc for previously treated patients with R5 HIV-1 infection. *N Engl J Med*. 2008;359(14):1429-41.
36. Fatkenheuer G, Nelson M, Lazzarin A, Konourina I, Hoepelman AI, Lampiris H, et al. Subgroup analyses of maraviroc in previously treated R5 HIV-1 infection. *N Engl J Med*. 2008;359(14):1442-55.
37. Crabb C. GlaxoSmithKline ends aplaviroc trials. *AIDS*. 2006 Mar 21;20(5):641.
38. Hicks C, Gulick RM. Raltegravir: the first HIV type 1 integrase inhibitor. *Clin Infect Dis*. 2009;48(7):931-9.
39. Lewden C, Raffi F, Cuzin L, Cailleton V, Vildé JL, Chêne G, et al. Factors associated with mortality in human immunodeficiency virus type 1-infected adults initiating protease inhibitor-containing therapy: role of education level and of early transaminase level elevation (APROCO-ANRS EP11 Study). *J Infect Dis* 2002;186(5):710–4.
40. Keiser O, Fellay J, Opravil M, Hirsch HH, Hirschel B, Bernasconi E, et al. Adverse events to antiretrovirals in the Swiss HIV Cohort Study: effect on mortality and treatment modification. *Antivir Ther*. 2007;12(8):1157-64.

Glossary of terms

Abbreviation	Denotation
3TC	lamivudine
Ab	antibody
ABC	abacavir
ADV	adefovir dipivoxil or adefovir
ALT	alanine aminotransferase
AIDS	AIDS Acquired immune deficiency syndrome
ART	ART antiretroviral therapy
AST	aspartate aminotransferase
AHOD	Australian HIV Observational Database
CAESAR	Canada, Australia, Europe, South Africa study
cART	combination antiretroviral therapy
CCR5	chemokine co receptor on the surface of cells
CD4 cell	helper T-cell that carries the CD4 surface antigen. CD4 cells are the primary target of HIV and CD4 cell numbers decline during HIV disease.
CMV	cytomegalovirus
d4T	stavudine
ddI	didanosine
DLD	decompensated liver disease
DNA	deoxyribonucleic acid
EBV	Epstein Barr virus
EFV	efavirenz
FTC	emtricitabine
FCH	fibrosing cholestatic hepatitis
HAART	highly active antiretroviral therapy (see cART, now preferred terminology)
HAV	hepatitis A virus
HBc	antibody to hepatitis B core antigen
HBeAg	HBV e antigen, an antigen associated with the viral nucleocapsid
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus-1
IDU	injecting drug use
IgG	immunoglobulin G

IgM	immunoglobulin M
IFN	interferon
INR	international normalised ratio
MACS	Multicenter AIDS Cohort Study
MSM	men who have sex with men
NASH	non-alcoholic steatohepatitis
NNRTIs	Non nucleoside reverse transcriptase inhibitor
NRTI s	nucleoside reverse transcriptase inhibitors
NVP	nevirapine
PEG	pegylated interferon
PI	protease inhibitors
PCR	polymerase chain reaction
RBV	ribavirin
RNA	ribonucleic acid
RTV	ritonavir
s100	Section of the Pharmaceutical Benefits Scheme, which provides access to highly specialised drugs
SVR	sustained virologic response
TDF	tenofovir disoproxil fumarate or tenofovir
TPV	tipranavir
YMDD	tyrosine-methionine-aspartate-aspartate motif of the catalytic domain of the HBV polymerase gene
ULN	Upper Limit of Normal
ZDV	zidovudine

List of drugs

abacavir (ABA, ABC)

adefovir dipivoxil (ADV)

didanosine (ddl)

emtricitabine (FTC)

entecavir

indinavir (IDV)

interferon (IFN)

interferon-alpha (α IFN)

lamivudine (3TC)

nevirapine (NVP)

pegylated interferon (PEG)

ribavirin (RBV)

ritonavir (RTV)

stavudine (D4T)

tenofovir disoproxil fumarate (TDF)

zidovudine (AZT, ZDV)

Index

A

abacavir.....31
adefovir dipivoxil (ADV).....23
Africa.....20
alcohol.....8, 13, 14, 17, 31
antiretroviral naïve24, 25
aplaviroc.....31
atazanavir30
Australian prevalence6

B

blood products.....6
breast-feeding.....7

C

caesarean section.....7
cannabis.....17
cART (combined anti-retroviral therapy)
.....8, 9, 15–17, 28, 31
 commencement.....24, 25
CCRS antagonists.....31
cholestatic hepatitis.....30
chronic HCV infection.....7, 13–15
cirrhosis.....8, 9, 15–17, 20–22, 24
corticosteroids.....24

D

decompensated liver disease (DLD).....8
didanosine16, 31, 32
disease staging16, 17
drug hypersensitivity.....28, 30–32

E

efavirenz (EFV)30
emtricitabine24, 31
end-stage liver disease.....9
enfuvirtide.....31
entecavir.....23, 25
epidemiology.....5–9

F

fibrosing cholestatic hepatitis21
fibrosis7, 14, 15, 17, 21, 24
fulminant hepatitis24
fusion inhibitors.....31

G

global prevalence.....5, 6

H

harm reduction programs6

HBV

clinical manifestations.....21, 22
diagnosis20, 21
progression8
therapy22–25
transmission6, 7

HCV

chronic infection7, 13–15
diagnosis13–15
and disease staging.....16, 17
management issues17
progression8
therapeutic toxicity.....16
therapy14–16
transmission6, 7

HDV

hepatic decompensation.....8, 16, 17, 24

hepatic enzyme elevations.....32

hepatic inflammation21, 22, 24, 30

hepatic steatosis.....13

hepatocellular carcinoma8, 9, 15, 20, 22

hepatotoxicity.....8, 13, 16, 25, 28
 definitions.....28

 incidence and predictions.....28–31
 management.....31, 32

heterosexual5, 7

HIV

contribution of liver disease to HIV-related

morbidity and mortality9

effect on liver disease progression.....7, 8

effect on viral load, transmission and chronic
infection.....7

HCV diagnosis and assessment in HIV-infected
individuals.....13, 14

natural history7, 8

prevalence.....5–7

viral hepatitis effects on HIV disease progression
.....8, 9

HIV–HBV co-infection.....20

anti-HBV therapy22, 23

clinical manifestations.....21, 22

diagnosis20, 21

immune reconstitution.....24

strategies for therapy.....24, 25

HIV–HCV co-infection
 and decompensated liver disease 17
 influence of disease staging on therapy decision-
 making 16, 17
 management issues 17
 therapeutic strategies 15, 16
 therapeutic toxicity 16
 hyperbilirubinemia 30
 hyperlactatemia 30–32

I

immune reconstitution (hepatic flares) 8, 20, 24
 immune restoration 13, 21, 28, 29
 indinavir 30
 injecting drug use/rs 5–8, 14, 22
 integrase inhibitors 31
 interferon 15–17, 22, 25

L

lactic acidosis 16, 31
 lamivudine 22, 23, 30
 liver biopsy 14–17, 21, 22, 32
 liver disease progression 7, 8, 13, 20, 25

M

management of antiretroviral therapy-related
 toxicity 28, 31, 32
 maraviroc 31
 maternal-foetal route 7
 men who have sex with men (MSM) 7, 14, 21, 22
 mitochondrial toxicity 16, 28, 30, 31

N

natural history 5, 7–9, 21, 22
 necro-inflammatory activity 7, 16, 21
 nevirapine 25, 30
 non-nucleoside reverse transcriptase inhibitors
 (NNRTIs) 28, 29
 nucleoside analogue reverse transcriptase
 inhibitors (NRTIs) 28, 30, 31

P

pegylated interferon (PEG) 15, 22, 25
 polymerase chain reaction 13, 20
 polymerase inhibitors 16
 post-exposure prophylaxis 30
 progressive liver disease 14, 17
 protease inhibitors (PIs) 16, 28, 30
 psychiatric history 14

R

re-infection 17
 ribavirin (RBV) 15–17, 31
 ritonavir (RTV) 25, 30

S

sexual transmission 6, 7, 14
 stavudine 16, 31, 32
 steatohepatitis 30, 31

T

telbivudine 23, 25
 tenofovir disoproxil fumarate (TDF) 23, 24, 31
 time to AIDS 8
 tipranavir (TPV) 30
 transient elastography (Fibroscan) 14, 15, 21

Z

zidovudine (ZDV) 16, 31, 32

ashm

Supporting the HIV, Viral Hepatitis and Sexual Health Workforce

www.ashm.org.au



9 781920 773816