Coinfection

HIV & Viral Hepatitis

a guide for clinical management

ashm
Australasian Society for HIV Medicine Inc

Edited by Gregory Dore
and Joe Sasadeusz

REVISED EDITION

About ASHM

The Australasian Society for HIV Medicine is the peak representative professional body for medical practitioners and other health care workers in Australasia who work in HIV, viral hepatitis and related disease areas.

It was formed in 1988 (as the Australian Society of AIDS Physicians). It changed its name in 1989 to reflect a broader membership base and was incorporated in New South Wales in 1990. ASHM became a registered charity in 2003.

ASHM is a key partner in the Australasian and regional response to HIV, viral hepatitis and related diseases. It works closely with government, advisory bodies, community agencies and other professional organisations in Australia and the Asia Pacific region. It conducts broad education programs in HIV and viral hepatitis for medical practitioners, health care providers and allied health workers and manages programs of continuing medical education.

ASHM is governed by an elected voluntary board and managed by a secretariat. It receives support from the Australian Government Department of Health & Ageing, the Australian Government's Agency for International Development (AusAID), State and Territory Departments of Health and the private sector, and has established the ASHM Foundation which raises funds in support of educational activities. ASHM convenes committees on a range of issues affecting its members, including education, HIV treatment, viral hepatitis, international/development issues and professional affairs. ASHM conducts an annual medical scientific conference, and the conference team provides professional conference organisation to third parties in the sector.

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Foreword

The advent of highly active antiretroviral therapy has brought with it a great sense of optimism for people living with HIV and their clinicians. Improved life expectancy, reductions in risk of opportunistic disease and enhanced quality of life are a reality for the vast majority of people living with HIV in settings with broad access to improved HIV treatments. Advances in HIV clinical management, however, are associated with increased therapeutic complexity and the emergence of new morbidities. In this sense, HIV and viral hepatitis coinfection and antiretroviral therapy-related hepatotoxicity are areas of emerging clinical concern.

The prevalence of HIV and viral hepatitis coinfection has considerable geographic and demographic variability. In Australia, close to 20% of people living with HIV are estimated to be coinfected with either chronic hepatitis B or chronic hepatitis C. Other countries, in particular those with larger proportions of injecting drug use-related HIV, have a higher prevalence of coinfection. An understanding of the natural history of HIV and viral hepatitis coinfection underpins clinical management. For this reason, Chapter 1 covers the epidemiology of HIV and viral hepatitis coinfection, including important interactions between these blood-borne viruses.

Accelerated liver disease progression in people with HIV and chronic hepatitis C coinfection, and improving efficacy of hepatitis C antiviral therapy form the basis for recommendations for clinical management of HIV and hepatitis C coinfection as outlined in Chapter 2. Despite improved hepatitis C antiviral therapy, efficacy remains suboptimal particularly for people with hepatitis C genotype 1 and those with advanced immune deficiency. Interactions between hepatitis C antiviral therapy and antiretroviral therapy increase the difficulty in therapeutic decisions. For these reasons, a strategy of clinical management based on an assessment of HIV and hepatitis C prognosis, and the likelihood of response to hepatitis C antiviral therapy is suggested.

Several hepatitis B antiviral therapies, some of which have dual activity against HIV and hepatitis B, have either been recently introduced or are in development. These advances in hepatitis B therapeutic management will undoubtedly enhance prospects for clinical management of HIV and hepatitis B coinfection as outlined in Chapter 3. The dual activity of some of these agents should improve the overall feasibility of managing both chronic viral infections.

The prevention and management of antiretroviral therapy-related toxicity is a major aspect of clinical care for people living with HIV. Hepatotoxicity is an important component of this emerging clinical management area. In Chapter 4, a review of studies of antiretroviral-therapy related hepatotoxicity is presented including incidence and predictors of such events. In addition, a practical management algorithm for hepatotoxicity is provided.

The revised edition of this monograph includes therapeutic advances, especially those in the area of Hepatitis C and HIV coinfection.

We hope that this monograph will provide HIV clinicians with the tools to improve their confidence in management of both HIV and viral hepatitis coinfection and antiretroviral therapy-related hepatotoxicity.

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The epidemiology of HIV and viral hepatitis coinfection

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Key points

- Both hepatitis B virus (HBV) and hepatitis C virus (HCV) are more common in people with 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 coinfection.
- In the setting of both HBV and HCV infections, coinfection with human immunodeficiency virus (HIV) results in a greater likelihood of chronicity and enhanced viral replication.
- Current evidence suggests that HIV infection may have a negative effect on HBV-related liver disease progression, although the reasons are unclear. HBV appears to have little effect on the progression of HIV disease.
- HIV infection hastens HCV-related liver disease with faster progression to cirrhosis, decompensated liver disease and earlier occurrence of hepatocellular carcinoma.
- The evidence for the effect of HCV on HIV progression is conflicting, with inconsistent results from cohort studies. Long-term follow up of people on highly-active antiretroviral therapy (HAART) is therefore required.
- Antiretroviral agents have little long-term effect on HCV viraemia, although some have significant anti-HBV activity.
- Morbidity and mortality from end-stage liver disease in people with HIV infection are increasing; every effort should be made to identify, educate and appropriately treat those people with HBV or HCV coinfection.

Introduction

There is now wide recognition that infections with hepatitis B virus (HBV) and hepatitis C virus (HCV) will contribute significantly to continuing morbidity and mortality among people with HIV in the coming years. Natural history studies examining the effect of HIV on outcomes in those 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 HIV infection continues to evolve and develop. This chapter reviews the available epidemiology of HIV and viral hepatitis coinfection and the consequences of coinfection 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 coinfection rates within certain groups, particularly for HIV–HCV coinfection.

In Europe rates of HIV–HCV coinfection show distinct geographical variation. In the EuroSIDA cohort of over 3000 patients, the prevalence of HIV–HCV coinfection 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 coinfection with around 240 000 people with HIV–HCV coinfection (a prevalence of 30%)[6] but this rate varies considerably in studies from different states.[7]

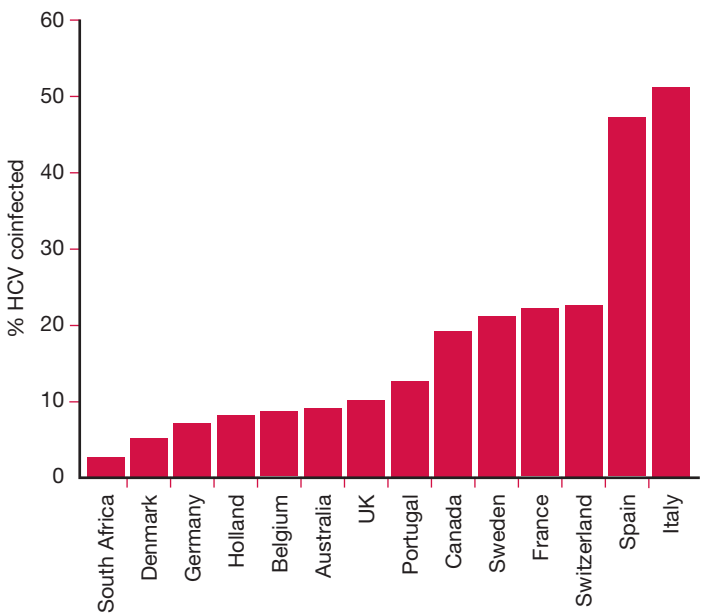
A study from New York estimated seroprevalence of HCV as 40% in people with HIV infection,[8] whereas a study from San Francisco estimated prevalence at only 14%.[7] Within a large AIDS Clinical Trials Group (ACTG) study, HCV prevalence was 16%.[9] As in European studies variability in HCV prevalence

relates to different proportions of high-risk groups such as injecting drug users and people with haemophilia within study populations.

Elsewhere, similar patterns are seen with prevalence rates being determined primarily by risk factors. In Manipur, India, 92% of injecting drug users with HIV are estimated to be coinfected with HCV.[10] In Malawi, where the predominant mode of HIV transmission is through heterosexual spread, the HCV prevalence (approximately 16.5%) is similar in women with and without HIV.[11]

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

Figure 1.1 Prevalence of HCV coinfection by country: CAESAR study



Source: Amin J, Kaye M, Skidmore S, Pillay D, Cooper DA, Dore GJ. HIV and hepatitis C coinfection within the CAESAR study. *HIV Medicine* 2004;5:174–179.

Among people with HIV, the prevalence of active HBV infection does not reach the same levels as HCV but it is still significantly higher than in the general population. Prevalence of HBsAg positivity is usually in the range of 6–10%,[5,13] with less geographical and HIV risk category variation than HCV prevalence.

The mechanism behind this higher risk for HBV infection in people with HIV is related to shared routes of sexual and parenteral transmission.

Australian prevalence

By the end of 2004 the total number of people living in Australia with HIV was estimated at 14,840, whilst approximately 194,000 were living with chronic hepatitis C infection.[14] A further 65,000 were estimated to have been exposed to hepatitis C with documented HCV antibodies but no evidence of active infection. The exact prevalence of chronic hepatitis B infection is unknown, with most recent estimates suggesting that between 90,000 and 160,000 people in Australia are HBsAg positive.[15]

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.[16] Seventy-seven per cent of this cohort have been tested for HBV surface antigen 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 than 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 is estimated to be between 50% and 60% whereas the prevalence of HIV infection is only 1%.[17] The proportion of injecting drug users with HIV–HCV coinfection is therefore also no more than 1%. This coinfection rate is in contrast to other countries such as the USA and Spain where the prevalence of coinfection 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.

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 injecting drug use and unscreened blood products, and HBV parenterally and through sexual transmission.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 screening were exposed to large quantities of hep-

atitis C virus on multiple occasions. Thus, rates of HCV infection in this group may reach 80–90% and virtually all people with haemophilia and HIV will also be HCV infected.[18]

Globally, injecting drug use 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 coinfection. In studies of injecting drug users with HIV, rates of HCV infection vary from 40%[7] to over 90%.[1,19] Although prevalence of HIV is lower among injecting drug users and other populations with HCV,[18] it should always be suspected.

Sexual transmission is responsible for the majority of HIV–HBV coinfections and up to 77% of MSM with HIV have evidence of past or chronic HBV infection.[21] The extent to which sexual transmission of HCV occurs remains somewhat uncertain. Although it is not a major route of infection, sexual HCV transmission does occur and is responsible for a small proportion of new infections. HCV has been detected at low levels in semen.[22] Factors that may be associated with sexual HCV transmission include multiple partners and HIV infection.[23,24,25] Several studies have confirmed that the risk of HCV transmission between sexual partners in stable long-term relationships is low (< 2%),[26-28] although the risk may be facilitated by the presence of HIV infection.[23] It has been suggested[29] but not yet proven that this increased risk is related to higher levels of HCV viraemia seen in people with HIV coinfection.

A retrospective analysis of HCV prevalence among people with HIV enrolled in the CAESAR study was recently undertaken (Table 1.1) (National Centre in HIV Epidemiology and Clinical Research, unpublished data). Rates of coinfection were significantly linked to risk factors for HIV acquisition: 92% in heterosexual injecting drug users, 44% in MSM injecting drug users and only 3% in MSM. This low HCV prevalence in MSM with HIV is similar to that in MSM without HIV and suggests low efficiency of sexual HCV transmission, even in people with HIV. However, longitudinal cohort studies of discordant couples and MSM with detailed risk behaviour assessment are needed to more clearly define rates of sexual transmission.

All three viruses may be transmitted via the maternal-fetal route. Most countries have universal infant vaccination but only a few have antenatal HBV screening. Maternal-fetal transmission of HCV is infrequent, occurring in 3–5% of infants born to women with HCV infection.[30-32] Coinfection with HIV increases the rate of HCV transmission by up to three to four fold,[30,33] presumably due to higher levels of maternal viraemia.[31] Caesarean section and avoidance of breast-feeding are advocated for mothers with coinfection to reduce the risk of perinatal HIV infection.

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

	CAESAR	AHOD[13]
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

Source: Amin J, Kaye M, Skidmore S, Pillay D, Cooper DA, Dore GJ. HIV and hepatitis C coinfection within the CAESAR study. *HIV Medicine* 2004;5:174–179

The natural history of HIV and viral hepatitis coinfection

The effect of HIV on viral load, transmission and chronicity

HIV–HBV

People infected with hepatitis B 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.[34] As routes of transmission for HBV and HIV are similar, a high prevalence of HIV–HBV coinfection exists, particularly in MSM, and markers of past or present HBV can be found in over 50% of MSM with HIV.[35] Reactivation of HBV in people who have previously lost detectable HBsAg may be associated with increasing immunosuppression in the context of HIV infection.[36,37] People with untreated HIV–HBV coinfection 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.[38,39] Despite this state of apparent immune tolerance, progression to advanced liver disease including cirrhosis and hepatocellular carcinoma is probably enhanced.[40]

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.[41,42]

As with HIV–HBV coinfection, people with HIV–HCV coinfection have been shown to have higher levels of viraemia than those with HCV alone[43,44,45] and in some studies increased levels have been correlated with more advanced immunosuppression.[46] High levels of HCV viraemia are likely to result in a greater risk of transmission and a reduction in success of therapy.[47] It is however unlikely that the increased HCV viraemia in people with HIV–HCV coinfection is responsible for greater rates of disease progression and fibrosis. There is no correlation between quantitative HCV and progression of fibrosis[41,50] in either people with HCV or HIV–HCV coinfection.

Effect of HIV on liver disease progression

HIV–HBV

In the pre-HAART era, mortality from other HIV-related causes and small study populations led to difficulties in defining the true extent of HBV-related liver disease.[49,50] A recent analysis of the Multicentre AIDS Cohort Study (MACS) cohort however demonstrated an increased risk of liver-related mortality in people with HIV–HBV coinfection, particularly those with the greatest degree of immunosuppression.[51] In this study of 5293 MSM, of whom 6% were HBsAg positive and 41% HIV-1 positive, liver-related mortality was more than eight times as likely in those with HIV–HBV coinfection 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/mm^3 were at the highest risk of liver-related mortality and there was a trend for mortality to increase in the years after HAART became available.

Table 1.2 Meta-analysis of studies showing the relative risks (RR) for decompensated liver disease (DLD) and cirrhosis in people with HIV-HCV coinfection relative to those with HCV alone.[54]

Study	No of patients (HIV +/total)	RR of DLD (95% CI)	RR of cirrhosis (95% CI)
Makris et al[55]	36/138	4.21 (0.96-18.41)	3.9 (1.4-10.8)
Soto et al[46]	116/547		1.94 (0.92-4.1)
Pol et al[60]	52/514		2.6 (1.1-5.9)
Benhamou et al[59]	122/244		1.46 (0.76-2.83)
Eyster et al[57]	98/156	3.2 (0.6-17)	
Telfer et al[56]	103/255	21.4 (2.6-174.5)	
Lesens et al[58]	81/134	7.4 (2.2-25.5)	

HIV–HCV

There is convincing evidence that coinfection 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.[52,53,54] A recent meta-analysis examining the risk of cirrhosis and DLD in people with HIV–HCV coinfection found the combined relative risk of progression to histological cirrhosis to be 2.07 (95% CI:1.40-3.07) and that of DLD to be 6.14 (95% CI: 2.86-13.20) compared to people with HCV alone (Table 1.2).[55] This meta-analysis included studies of people with haemophilia with HIV–HCV coinfection,[57,58,59] people predominantly infected through injecting drug use[60,61] and mixed populations.[46,62]

Factors associated with increased risk of liver disease progression in people with HIV–HCV coinfection include heavy alcohol intake (> 50 grams/day), older age at HCV acquisition, low CD4 count,[60] increased quasispecies variability,[63] and occult HBV infection.[64] In a recent French study, it has been suggested that therapy with protease inhibitor (PI)-containing HAART may delay fibrosis progression, although the mechanisms behind this effect are not yet defined.[65]

Evidence is now emerging that the development of hepatocellular carcinoma may also be accelerated in people with HIV–HCV coinfection.[66]

Effect of HAART on HBV–HCV progression

Hepatotoxicity with HAART occurs in a significant number of people initiating therapy and the risk is two- to three-fold higher for those with HBV or HCV coinfection.[4,67] The prevalence, mechanisms and management of HAART-related hepatotoxicity are dealt with in Chapter 4.

With effective immune restoration, some individuals with chronic HBV may mount an immune response to circulating HBV resulting in a flare in hepatitis and clearance of HBeAg from serum.[68] On the other hand, if seroconversion does not occur, enhanced immunological recognition of HBV may

result in worsening of necro-inflammatory activity within the liver and enhanced progression to cirrhosis. The inclusion of lamivudine, a nucleoside analogue with both anti-HIV and anti-HBV activity, in many HAART regimens results in a small but significant HBV seroconversion rate.[69] The development of increasing HBV resistance with duration of therapy, however, limits the usefulness of this strategy in the long term.[70] The emphasis is now focused on the development of more effective combination therapies for the treatment of HIV–HBV coinfection (see Chapter 3).

Several studies have examined the effect of HAART on HCV viraemia; results are conflicting. Most of these studies have found no evidence for an effect of HAART on HCV viremia[71,72,73] although two have reported significant transient increases after HAART initiation, along with elevations in serum transaminases.[74,75] Despite having little direct effect on HCV viremia, the commencement of antiretroviral therapy has occasionally been reported to cause HCV clearance, presumably through immune-mediated mechanisms.[76] This situation does not occur for the majority of people and, unlike HBV, treatment of HCV is unlikely to be possible with anti-HIV agents alone. Aspects of clinical management of HIV–HCV coinfection are covered in Chapter 2.

Effect of viral hepatitis on HIV disease progression

HIV–HBV

The interaction between HIV and HBV and the resultant effect on HIV disease progression have been debated. Before the availability of HAART, some studies suggested that the presence of HBsAg could hasten progression to AIDS.[77] This was refuted in other studies that demonstrated no difference in time to AIDS development[38] or survival times after AIDS diagnosis[78] 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 HAART.[79]

In the AHOD, individuals who commenced HAART with HBV coinfection were no more likely to progress to AIDS or death than those without HBV coinfection.[14] Similarly, both virological response to HAART and CD4 count increases were unaffected by HBsAg. It therefore seems likely that HBV coinfection 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 coinfection 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,[80] as well as in attitudes and adherence patterns to antiretroviral therapy,[81] compared to populations with HIV alone. Failure to properly control for these differences has a marked impact on study findings.

Before the introduction of HAART, many longitudinal and cross-sectional studies failed to show any significant effect of HCV on HIV progression[82,83,84] while some studies were able to demonstrate a more rapid clinical progression to AIDS in people with HCV[85,86,87] More recently, two large cohort studies examining the effect of HCV in people receiving HAART 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 coinfection (hazard ratio 1.7; 95% CI: 1.26-2.30).[4] Despite similar virological responses, people with HCV were also less likely to achieve increases in CD4 counts of at least 50 cells/mm^3 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 coinfection with regard to incidence of AIDS, death or change in CD4 count over time.[88] In particular, increases in CD4 cell count after HAART were unimpaired in individuals with HIV–HCV coinfection. Findings from the AHOD support the lack of evidence for greater risk of HIV disease progression in people with HIV–HCV coinfection but, similar to the Swiss HIV Cohort Study results, were able to demonstrate marginally poorer CD4 count responses to HAART in those with HCV.[16]

Contribution of liver disease to HIV-related morbidity and mortality

The widespread availability of HAART 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 shows 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.[89] Similar high rates of hospital admission and deaths have been reported from other countries with high rates of coinfection such as Spain, where chronic viral hepatitis is now the fifth most common cause of mortality in people with HIV.[90]

Data from other cohort studies are contradictory. In the Swiss HIV Cohort Study, mortality data were analysed to estimate the relative contribution of liver-related deaths. End-stage liver disease accounted for only 0.52% of deaths in the population with HIV–HCV coinfection. The failure of this and other studies[40] to report increased mortality rates from chronic viral hepatitis may be due to an insufficient period of follow-up, especially given the long natural history of HCV and HBV infection. The full effect of viral hepatitis on HIV-related morbidity and mortality still remains to be understood.

Conclusion

Uncertainties remain regarding the real effect of coinfection with HIV and HBV or HCV on the progression and outcomes of these viral infections. This situation is largely due to difficulties in performing accurate natural history studies, particularly in the constantly developing field of HIV medicine. Still, it seems likely that 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 treatment of HBV and HCV infections.

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2 The management of HIV and hepatitis C virus coinfection

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Introduction

The declining incidence of HIV-related opportunistic disease due to improved antiretroviral therapy has shifted the emphasis of HIV clinical management towards prevention and treatment of comorbidities, especially liver disease. Recent advances in antiviral therapy for HBV and HCV infection[1-4] provide the opportunity for more effective management of underlying chronic viral hepatitis in people with HIV. This chapter will cover clinical management of people with HIV–HCV coinfection 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 coinfection have a greater rate of chronic HCV infection, higher HCV viral load and accelerated liver disease progression. However, increasing evidence is starting to emerge that immune restoration through HAART may slow liver disease progression in people with HIV–HCV coinfection.[6] While accelerated HIV disease progression in people with HIV–HCV coinfection has also been shown in some studies, it has been refuted by others (see Chapter 1).

Diagnosis and assessment of HCV infection in people with HIV

Overlapping transmission modes of HIV and HCV suggest that all people with HIV should be recommended for HCV antibody testing.

However, groups in whom the likelihood of underlying HCV infection is highest are those who:

- have ever injected drugs;
- received blood product transfusions before 1990;
- have elevated serum transaminase levels (ALT, AST).

Key points

- All people with human immunodeficiency virus (HIV) should be tested for hepatitis C virus (HCV); however, those with a history of injecting drug use or elevated serum transaminase 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 are increased in people with HIV–HCV coinfection.
- 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.

An HCV testing algorithm for people with HIV is shown in Figure 2.1. People with HIV, particularly those with advanced immunodeficiency, have a lower sensitivity of HCV antibody testing. HCV RNA assessment, by polymerase chain reaction (PCR) or an alternative method, is recommended if HCV antibody testing is negative but there is an increased likelihood of HCV infection. In 20–30% of cases, HCV infection does not lead to viral persistence.[7] Thus, another indication for HCV RNA testing is confirmation of chronic HCV infection. Negative qualitative HCV RNA testing – preferably performed on two occasions – indicates the absence of active acute or chronic HCV infection.

Chronic HCV infection is highly likely in people with a positive HCV antibody and elevated serum transaminase levels. Baseline testing generally includes viral genotype and quantitative HCV RNA test (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 viral load), and does not require regular monitoring.

Explanations for elevated serum transaminase levels and a negative HCV RNA test include hepatotoxic antiretroviral therapy agents, hepatic steatosis and heavy alcohol intake.

As the vast majority of people are asymptomatic at the time of HCV acquisition, people with HIV who are at ongoing risk should have regular (12 monthly) HCV antibody testing. All people diagnosed with newly-acquired HCV infection (positive HCV anti body with negative HCV antibody within the previous two years, or acute clinical hepatitis with positive HCV antibody or HCV PCR) should be referred for assessment for early antiviral therapy.

It is important to note that several outbreaks of acute HCV have been reported among HIV-positive men who have sex with men. In these outbreaks sexual transmission seems to be the predominant form of transmission with practices such as fisting and toys playing a role.[8,9] It is thus important to consider HCV as a potential diagnosis in such populations and screening such individuals regularly may be warranted.

Further assessment and referral for treatment consideration

Further assessment in people with HIV–HCV coinfection should include a drug and alcohol history, psychiatric history, and hepatitis A virus (HAV) and hepatitis B virus (HBV) serology and vaccination status. 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-based therapy, thus enabling early referral prior to therapy.

In people with HIV–HCV coinfection, the risk of progressive liver disease is relatively high. Although mandatory liver biopsy has been recently removed (April 2006) as a requirement for access to Australian Government Section 100 chronic hepatitis C treatment, the staging of liver disease will remain an important tool for prognosis determination and treatment decision-making. Liver biopsy-based staging of disease should be considered for those with confirmed chronic HCV infection and elevated transaminase levels. Those with an estimated duration of infection longer than ten years should be particularly encouraged to undergo liver biopsy.

Apart from consistently normal ALT levels being associated with slow disease progression, the ALT level is only weakly correlated with risk of hepatic fibrosis.[10] Thus, within the abnormal range, ALT is a poor discriminator of stage of liver disease.

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 who is HCV antibody positive and has a brief injecting history of two years 18 to 20 years ago with no other risk factors can be assumed to have been infected at that time. This can be correlated with disease activity on biopsy and aid in decisions regarding therapy.

Indications for liver biopsy

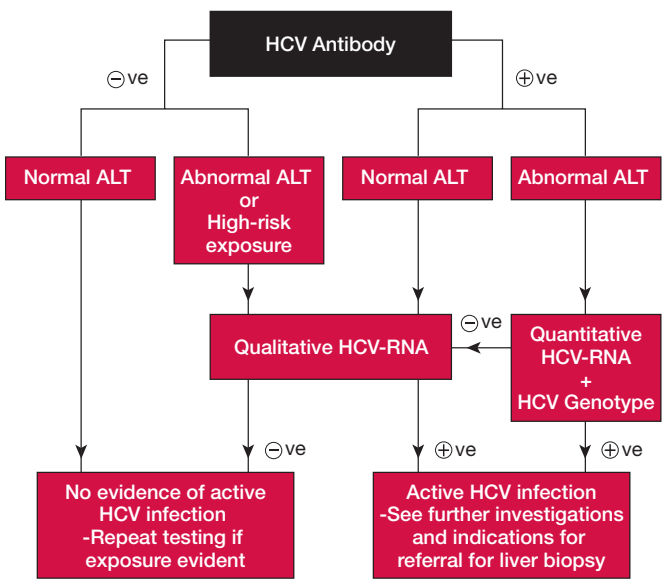
The following categories of people with HIV-HCV coinfection should be recommended for liver biopsy

- Abnormal ALT levels and estimated duration of infection greater than 10 years
- Abnormal ALT levels and unknown duration of infection, particularly in those aged 35 years and over
- Normal ALT levels but clinical evidence of chronic liver disease such as hepatomegaly, and spider naevi.
- Less responsive HCV genotype/viral load, particularly those with genotype 1 and high viral load.

Individuals with HIV–HCV coinfection for whom liver biopsy may be less important for treatment decision-making include:

- those with greater treatment response rates, particularly individuals with HCV genotype 2 and 3. Treatment responses are also considerably higher among individuals with genotype 1 and low viral load compared to high viral load;
- those with shorter durations of HCV infection or persistently normal liver function tests, in whom early liver disease is likely;
- those who wish to commence treatment, irrespective of the extent of liver damage.

Figure 2.1 HCV testing algorithm for people with HIV



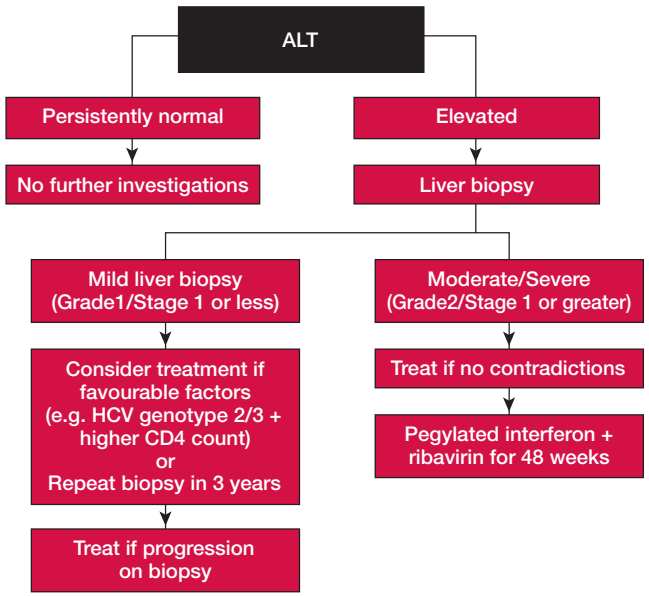
The removal of mandatory liver biopsy from s100 guidelines for hepatitis C treatment means that the only major requirement for access to treatment is the demonstration of chronic hepatitis C – generally a positive antibody for greater than six months in the presence of evidence of active HCV infection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

Therapeutic strategies for people with HIV–hepatitis C coinfection

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

- There is evidence that introduction of HAART has enhanced life expectancy for people with HIV, including those with HIV–HCV coinfection, but that this therapy may be deferred until progressive immune deficiency develops;
- HCV in the setting of HIV has a faster progression to complications, 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 from advanced liver disease;
- Large-scale trials using pegylated interferon and ribavirin demonstrate enhanced HCV antiviral response rates for people with HIV–HCV coinfection, similar to the situation seen in those with HCV alone;
- Response rates to pegylated interferon and ribavirin in people with HIV–HCV coinfection are 10–20% lower than rates in people with HCV, particularly in the setting of more advanced immunodeficiency;
- HCV may impair immune responsiveness following the introduction of HAART in people with HIV–HCV coinfection;
- Toxicity may be enhanced in people with HIV–HCV coinfection with concurrent HAART and the combination of interferon and ribavirin.

Figure 2.2 Therapeutic strategies for the management of people with HIV–HCV coinfection in HCV RNA positive individuals*



* Treatment of mild fibrosis is not funded by some jurisdictions, including Australian s100 restrictions.

Current therapeutic options

Improvements in HIV antiviral therapy during the mid-1990s were followed by improved HCV antiviral therapy in the late 1990s. Although not containing potent direct HCV antiviral action as monotherapy, the guanosine analogue, ribavirin, when combined with standard interferon produced sustained virological response (SVR) rates of approximately 40% in people with HCV infection. The major determinant of SVR was shown to be HCV genotype, and rates of 25–30% for genotype 1 and 60–70% for genotypes 2 and 3 were demonstrated with these regimens. HCV viral load, age, gender and adherence to therapy were also shown to influence response rates.[11,12] An 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, and is associated with reversibility of hepatic fibrosis, even in the setting of cirrhosis.[13]

These rates were further improved over recent years with reports of studies using pegylated interferons in combination with ribavirin which achieved overall SVRs of 54 to 63%, rising to 75–80% for genotype 2 and 3 infections.[2-4] Pegylated interferons are a longer-acting formulation and have the advantage of administration by weekly subcutaneous injections rather than thrice weekly for standard interferon. Ribavirin is administered orally twice a day. The com-bination of pegylated interferon and ribavirin has now become standard of care for chronic HCV.

Studies of HIV–HCV coinfection have lagged behind those in monoinfected populations, however, the findings from three pivotal studies evaluating

pegylated interferon with ribavirin in HCV-HIV coinfection have recently been published: the APRICOT study, the RIBAVIC study and the ACTG 5071 study.[14–16] All studies clearly demonstrated the superiority of pegylated interferon formulations (PEG) combined with ribavirin (RBV) against standard interferon (IFN) with ribavirin.

The APRICOT study was an international multicentre trial involving 860 patients and is the only registration study performed in this patient population. It was designed as a three-armed study comparing PEG + RBV vs PEG monotherapy vs standard IFN + RBV. It achieved the highest-yet reported SVR rate in HIV–HCV coinfected patients, with PEG + RBV producing a SVR of 40% compared to IFN + RBV of 12% and PEG monotherapy of 20%. The APRICOT study utilised pegylated interferon alpha-2a (PEGASYS) 180 ug with 800 mg ribavirin for 48 weeks.[14] Patients with genotype-1 infection treated with PEG + RBV had a considerably lower SVR (29%) than those with genotype 2/3 infections (62%).

The French RIBAVIC study was a multicentre trial which enrolled 412 patients and conducted a comparison of pegylated interferon 2b (PEGINTRON) 1.5 ug/kg/day and standard IFN both in combination with RBV 800mg/day. The SVR for the PEG + RBV arm in this study was again significantly higher than the IFN + RBV arm (26% versus 18%).[15]

The United States ACTG 5071 Study as another multicentre trial which enrolled 134 patients who were randomised to two arms: Pegylated interferon 2a (PEGASYS) 180 ug/week vs IFN using 6MU for 12 weeks followed by 3MU to a total of 48 weeks of therapy. RBV dose in this study ranged between 600–1000 mg/day. Patients underwent an additional liver biopsy at 24 weeks and were continued in the study only if they met predetermined improvements in histology. SVR in this study was 27% for the PEG + RBV arm vs 12% for the IFN + RBV arm.[15]

SVR rates may have differed between studies for a variety of reasons. Patient populations were different between studies. In particular, the proportion of patients with cirrhosis, a factor associated with lower SVR rates was higher in the RIBAVIC (39%) compared to the APRICOT (15%) study. Also more patients in RIBAVIC discontinued therapy prematurely compared to those in APRICOT. The ACTG study used a lower dose of RBV now known to be less effective. Additionally, the requirement of a histological improvement in the ACTG study may have caused premature discontinuation of therapy in patients who may have ultimately achieved an SVR.

Taken together, these trials clearly demonstrate the improved efficacy of pegylated interferon and ribavirin combination therapy. However, treatment responses remain sub-optimal, particularly for individuals with HCV genotype 1.

Increased therapeutic toxicity in HIV–HCV coinfection

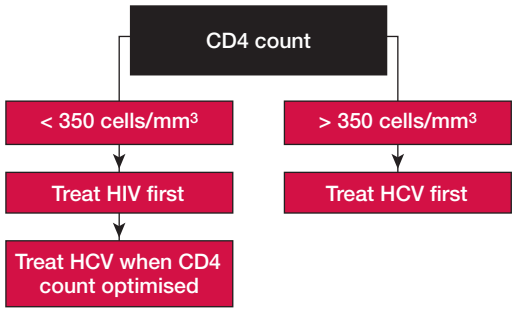
A major past consideration of treatment of coinfection has been safety of treatment regimens and in particular potential interactions between HAART and HCV therapy. The overall discontinuation rates in these studies in the PEG + RBV arms were: 25% for APRICOT, 42% for RIBAVIC and 12% for ACTG. The APRICOT 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 similiar to standard IFN.

In addition, there was no negative impact on HIV control. On the contrary, the PEG + RBV arms resulted in an almost 1 $\log_{10}$ 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 hyperlactataemia 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 the factthat ribavirin enhances phosphorylation of didanosine, thereby increasing drug levels.[17] 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 6 or greater at baseline indicating at least early hepatic decompensation.

These data suggest that there needs to be careful selection of patients and HAART regimens. Patients with decompensated cirrhosis are excluded and didanosine avoided during HCV therapy. The current recommendation is to use didanosine with extreme caution when combinedwith ribavirin. eople with HIV–HCV coinfection who start interferon and ribavirin cmbination therapy and who are receiving didanosine should probably either switch to a non-didanosine containing regimen or reduce the dose of didanosine if alternative regimens are not readily available. Close monitoring is also required for people with cirrhosis following commencement of interferon and ribavirin theapy, including regular

Figure 2.3 Recommended sequence of therapy in HIV–HCV coinfection



coagulation testing, and any evidence of hepatic decompensation should necessitate cessation of therapy. Concerns about an increased risk of mitochondrial toxicity in people with HIV–HCV coinfection commenced on interferon and ribavirin 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. Absolute CD4 cell counts often decline during interferon therapy and this is related to interferon-induced leucopenia, however, CD4 percentages are generally stable.

Influence of disease staging on therapy decision-making

A strategy for management of HCV infection has been to delay antiviral therapy until evidence of progressive hepatic fibrosis (generally stage 2: moderate fibrosis). This deferred therapeutic approach may not be as appropriate for people with HIV–HCV coinfection, given their accelerated liver disease progression. Efficacy of HCV therapeutic intervention in coinfection is greatest when immune function is relatively preserved. These issues beg the question of timing of therapy: should these two blood-borne viruses be treated concurrently, or separately, and if the latter, which virus should be the initial focus? Given that HIV therapy is now recommended when the CD4 count falls below 350 cells/ul[18] it would seem logical to use this threshold to determine therapeutic priority. Below this level response rates are compromised by immuno-suppression, CD4 counts fall further on therapy and HIV therapy assumes priority. Above 350 cells/ul, immune function is relatively well preserved and the absence of antiretroviral therapy reduces the incidence of hepatotoxicity. Whichever is started first, HIV and HCV therapies should be staggered by at least a month and preferably two to minimise toxicities and improve adherence.

A suggested therapeutic strategy for people with HIV–HCV coinfection is outlined in Fig 2.2. As this strategy is based on the stage of liver disease, liver biopsy remains an important component of the process of therapy decision-making for people with HIV–HCV coinfection. 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 counts).

A recommended sequence for HIV and HCV treatment is outlined in Figure 2.3.

HIV–HCV coinfection and decompensated liver disease

People with HIV–HCV coinfection and established liver failure should not be commenced on interferon-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 HAART post-transplantation.[19]

Other management issues

Management of hepatotoxicity and choice of antiretroviral therapy in people with HIV–HCV coinfection is discussed in Chapter 4. Drug and alcohol intake is the other major management issue for people with HIV–HCV coinfection. The higher risk of HCV-related progressive liver disease in people with HIV means that other co-factors for progression take on increased importance.

For example, a person with HIV–HCV coinfection and a heavy alcohol intake would be at greatly increased risk of progressive liver disease. In general, people with HIV–HCV coinfection 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 is preferable.

It is also important to highlight that individuals on HAART have been shown to have not only an improved overall mortality but also improved liver-related mortality when compared to individuals not receiving HAART.[6]

There is no evidence to suggest that recreational drug use per se increases the risk of progressive liver disease in people with HCV infection. In fact, there

are no specific drug and alcohol exclusion criteria for access to HCV antiviral therapy. However, moderation of recreational drug use, particularly injecting drug use, would seem an appropriate strategy for people with HIV–HCV coinfection. Re-infection following therapeutic HCV clearance appears possible, thus increasing the importance of prevention of HCV exposure in people who continue to inject recreational drugs.[20,21]

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.

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3 The management of HIV and hepatitis B virus coinfection

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Key points

- Hepatitis B virus (HBV) infection in people with human immunodeficiency virus (HIV) infection may result in significant morbidity and mortality.
- People with HIV–HBV coinfection have higher rates of chronic 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 HBsAg should indicate monitoring of HBV viral load, preferably by PCR to determine significant levels.
- Current HBV therapy is limited by development of drug resistance and low rates of HBeAg seroconversion.
- Initiation of antiretroviral therapy may lead to clinically significant hepatic inflammation (hepatic flares) and hepatic decompensation.
- Further clinical studies are required to determine therapeutic strategies, in particular optimum combination regimens.

Introduction

It is estimated that approximately 5% of the world's population, or over 350 million people worldwide have chronic 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 recently 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 coinfection, in particular, the relationship between immunosuppression and disease progression, has important implications for the development of antiretroviral therapeutic strategies.

Diagnosis

All people with HIV should be screened for HBV infection, initially with hepatitis B surface antigen (HBsAg).

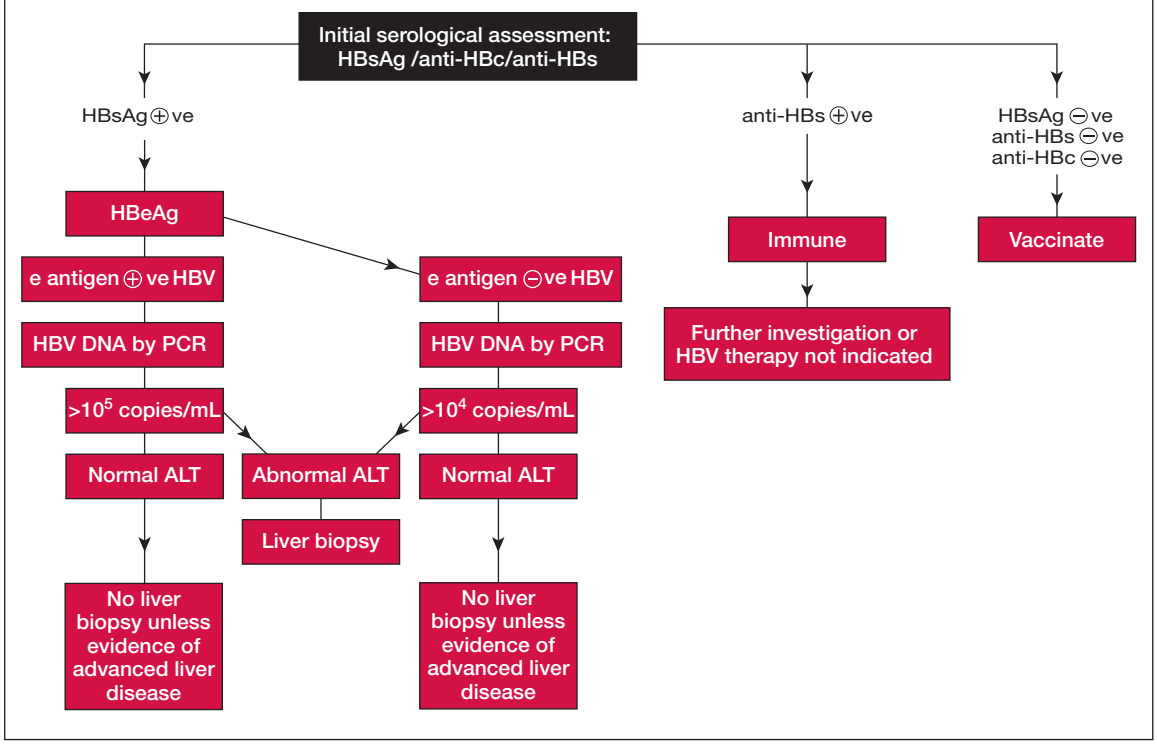
If HBsAg is detected, the presence of active HBV replication should be assessed through a quantitative assay for HBV DNA (viral load). HBV DNA level is associated with risk of transmission, progressive liver disease and immune reconstitution inflammation (hepatic flares). HBV DNA can be quantified by nonamplification (usually hybridisation) assays or amplification assays (PCR or branched DNA (bDNA)).

It is also important to determine HBV e antigen (HBeAg) status as the clinically significant level of HBV DNA is uncertain and varies according to HBeAg status. Current recommendations suggest that, in HBeAg-positive patients, a level of $> 10^5$ copies/mL is clinically significant whereas in HBeAg-negative patients $> 10^4$ copies/mL is said to be significant.[1]

There is a preference for amplification assays such as PCR in the assessment of replication, especially in HBeAg-negative infections, as nonamplification assays only have a sensitivity of 10^5 copies/mL. The failure to synthesise HBeAg in HBeAg-negative infection is due to the presence of mutations in the precore and core 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 sequential liver function tests performed to determine if significant necro-inflammatory activity is

Figure 3.1 Proposed investigation algorithm for evaluation of HBV in HIV coinfected individuals



present or evolves. If biochemical evidence of hepatic inflammation (defined by an ALT level exceeding the upper limit of the laboratory reference range) is present, 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). Liver biopsy is crucial to management as it is the only accurate method to determine the degree of hepatic fibrosis and necroinflammatory activity, as well as being able to exclude other factors contributing to liver dysfunction, particularly drug toxicity.

Clinical manifestations

HIV coinfection results in considerable modification of the natural history of HBV infection.[3-5] Persistent HBV infection is more common in people with HIV, with studies among MSM exposed to HBV showing evidence of chronic HBV infection in almost 25%[6] of individuals compared to 3–5% in those without HIV.[7,8] Rarely, reactivation of HBV infection may occur in the setting of advanced immunodeficiency despite seroconversion to hepatitis B surface antibody (HBsAb) positive.[9] Furthermore, in people with HIV–HBV coinfection, HBV DNA levels are substantially higher, and rates of seroconversion from HBeAg to anti-HBe are lower than in people with HBV alone.[4,9-11]

The high levels of HBV viral replication seen in people with HIV–HBV coinfection are associated with significantly lower serum aminotransferase levels[4,9-11] and liver biopsies usually demonstrate milder necroinflammatory activity.[4] This situation is consistent with the model of immunopathogenic injury of HBV infection. However, progression to cirrhosis is more common, indicating accelerated fibrosis.[4]

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 coinfection.

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 associated with very high levels of HBV DNA and has been described in people with HIV.[12]

The histological features of FCH include a paucity of cellular infiltrate, proliferating bile ducts and rapidly progressive cholestatic injury with very high levels of intracellular virus, resulting in accelerated fibrosis and hepatic decompensation. The condition has a high mortality, although recent treatment approaches have been responsible for successful outcomes.

It is well established that HBV markedly increases the risk of primary hepatocellular carcinoma (HCC).[13] Although an increased rate of HCC has yet to be described in people with HIV, the known overall increased risk of malignancy in this population suggests a risk at least as high if not higher. Regular screening with 6–12 monthly abdominal ultrasound and alpha-fetoprotein protein is thus strongly recommended.

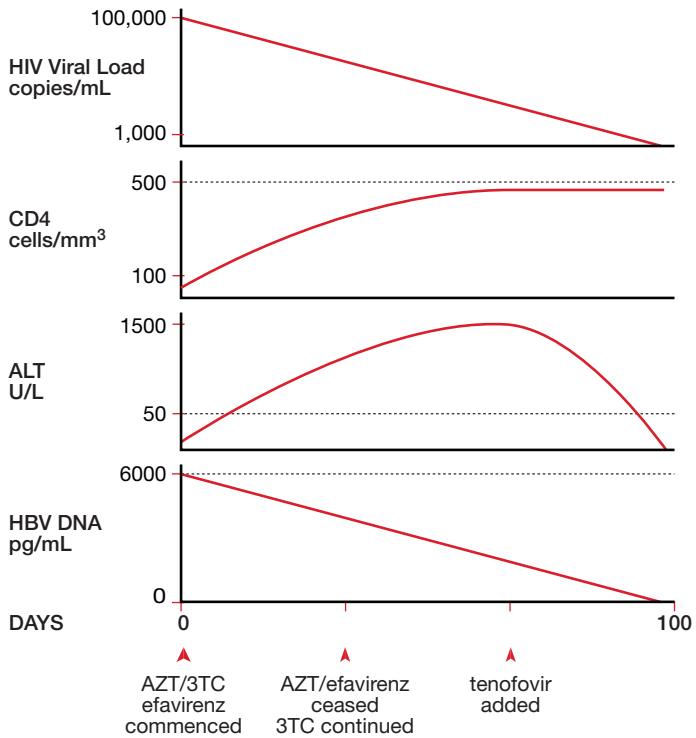
In contrast to the effect of HIV on the natural history of chronic HBV infection, a significant effect of HBV on the clinical course of HIV has not yet been found.[14,15]

Management

Anti-HBV therapy

There are five therapeutic agents currently licensed for the treatment of chronic HBV: interferon-alpha, lamivudine, adefovir dipivoxil, tenofovir disoproxil and entecavir. A number of newer agents are also in development.

Figure 3.2 Diagram showing how introduction of HAART causes a marked ALT flare due to immune reconstitution in the presence of high HBV DNA levels



*HBV therapy only indicated for individuals with significant levels of replication.

Interferon-alpha

Interferon-alpha (aIFN) therapy may successfully result in HBeAg seroconversion and may induce a clinical remission in 20–40% of immunocompetent people with chronic HBV monoinfection.[16] Treatment of people with HIV is, however, significantly less effective.[17-19] People with advanced immunodeficiency, in particular usually have poorer responses to therapy.[20]

Studies of a new longer-acting formulation of interferon called pegylated interferon (PEG) (see Chapter 2) has suggested improved outcomes in treatment of monoinfected HBV.[21] and may offer an advantage in HIV coinfection although this has not been examined in randomised, controlled trials.

However, it seems reasonable to consider therapy with aIFN or PEG in people with preserved immune function (CD4 counts > 500/mm^3) who are not candidates for HAART. Drugs such as lamivudine could 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. Adefovir and entecavir both have potent anti-HBV activity, and may also be appropriate therapeutic options for people with HIV–HBV coinfection and preserved immune function (see Fig 3.3).

Lamivudine

Lamivudine is a nucleoside analogue that suppresses both HIV and HBV replication by inhibition of the viral reverse transcriptase.[22,23]

In people with HBV monoinfection, reduction in plasma HBV viral load secondary to lamivudine therapy is associated with HBeAg seroconversion, normalisation of liver function and improved histological activity in approximately 20% of those treated. Unfortunately, the long-term effectiveness of lamivudine is diminished by the development of HBV-resistant mutations and variable durability of HBeAg seroconversion.[24]

Resistance to lamivudine 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 lamivudine against HBV has been demonstrated in people with HIV[35,25-27] however, HBV resistance develops in approximately 20% per year, with projections of 90% after four years of lamivudine therapy.[28] This frequency of lamivudine resistance in people with HIV–HBV coinfection is slightly higher than in people with HBV monoinfection.

Prolonged lamivudine therapy and high HBV viral loads have been identified as the major risk factors for the development of resistant HBV.[28] Given that

lamivudine, when used as a component of HAART, is administered lifelong in people with HIV–HBV coinfection who commonly have high HBV viral loads, it is inevitable that lamivudine monotherapy in this population will result in resistance.

Adefovir dipivoxil

Adefovir dipivoxil (ADV) is a nucleotide analogue, with demonstrated efficacy at doses of 10 mg daily, against HBV, with a 4-$\log_{10}$ reduction in plasma HBV DNA. Adefovir also inhibits replication of lamivudine-resistant HBV. An open-label study of 35 people with HIV and lamivudine-resistant HBV infection reported a 4-$\log_{10}$ reduction in serum HBV DNA levels at week 48, comparable to antiviral activity in people with-out HIV.[29] When followed to four years, 26 of these patients remaining on ADV continued to achieve further reductions in HBV viral load with no emer ence of HBV or HIV-associated ADV mutations.[30]

Adefovir has recently been licensed in Australia and is available under the s100 scheme but its use is restricted to lamivudine-resistant HBV infection. Higher doses (ADV 30 mg or more daily) have been associated with nephrotoxicity, rarely observed with the 10-mg daily dose. Due to lack of HIV activity at this dose, adefovir may also be a reasonable option for therapy in people not requiring HAART although theoretical concerns about HIV cross-resistance to tenofovir disoproxil remain (see below).

Tenofovir disoproxil

Tenofovir disoproxil (TDF) is also a nucleotide analogue which, like lamivudine, has the ability to inhibit both HIV and HBV DNA polymerases. It also demonstrates activity against virus strains that contain lamivudine-associated polymerase gene mutations.

Clinical efficacy has been demonstrated in two substudies which were part of two large randomised, multinational, registration studies evaluating TDF for the treatment of HIV. Although these substudies have very low sample sizes, they provide us with valuable prospective, evidence-based support to the retrospective and in vitro evidence of TDF activity already published. Twelve participants, 10 on TDF and 2 on placebo fulfilled the criteria for substudy 907.

There was a 4.9 $\log_{10}$ overall reduction in HBV DNA after 24 weeks of therapy in the TDF-treated patients. More importantly, the reduction in HBV DNA was equivalent, regardless of whether the virus was lamivudine-resistant or wild-type.

Eleven patients fulfilled criteria for the 903 study; 6 were randomised to receive lamivudine alone as HBV-active therapy while 5 received lamivudine+TDF.

This study demonstrated that the reduction of HBV DNA after 48 weeks was greater for patients treated with combination TDF+lamivudine (4.7 $\log_{10}$) compared to patients on lamivudine as the only HBV active agent (3.0 $\log_{10}$). More importantly still, only the lamivudine monotherapy arm demonstrated genotypic evidence of lamivudine resistance which occurred in four of the five subjects. This is 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 which is analogous to the very low level of HBV resistance seen with adefovir therapy.[31]

These promising findings have been followed up with a 48-week prospective, randomised, multicentre study in HBV-coinfected patients, comparing lamivudine with TDF and lamivudine+TDF as a component of HAART to evaluate anti-HBV activity. This study is currently under way.

Entecavir

Entecavir is a purine-derived nucleoside analogue which has completed phase III registration clinical trials for HBV infection and has demonstrated an almost 7 $\log_{10}$ reduction in HBV DNA with no observed resistance over 48 weeks in treatment-naive patients.[32] It also has activity against lamivudine-resistant HBV isolates, but in vitro cross-resistance with lamivudine-resistant HBV has been reported.[33, 34] Studies in people with HIV–HBV coinfection are soon to be released. It has no anti-HIV activity and may also be a reasonable alternative in people not requiring HAART or in those in whom immune reconstitution is a concern where HBV DNA can be reduced prior to the introduction of full HAART.

Combination therapy

The role of lamivudine, adefovir, tenofovir and entecavir as combination therapy with or without immune modulators such as aIFN is appealing. Clinical studies of these combinations to assess safety and efficacy are currently ongoing.

Immune reconstitution

In people with HIV–HBV coinfection, immune reconstitution following the introduction of highly active antiretroviral therapy (HAART) has been associated with acute rises in serum aminotransferase levels known as hepatic flares[35-37] These flares usually occur soon after commencing HAART in people who had high HBV viral loads pretreatment.[35,38,39] Furthermore, reconstitution flares have been reported to occur despite the inclusion of HBV active agents such as lamivudine as part of the initial HAART regimen due to immune reconstitution occurring prior to effective reduction in HBV DNA.[40]

Hepatic inflammation related to HAART has also been reported in a number of other circumstances,

including reactivation of HBV infection,[35,41] development of lamivudine resistance[42] and following withdrawal of lamivudine in individuals who have experienced immune reconstitution.[43]

It is important to assess HBV status before starting HAART in order to identify people at risk of hepatic flares. Individuals with clinically significant levels of HBV DNA ($>10^4$-10^5 copies/ml), especially those with cirrhosis or those with low nadir CD4 counts, may be particularly at risk of hepatic decompensation with such flares. Strategies that require further investigation to minimise this risk include the use of dual HBV active therapy with tenofovir prior to the addition of a third HAART agent after HBV DNA levels drop to non-significant levels (e.g. $<10^5$ copies/ml). An alternative approach which will soon be available in Australia is to use a potent anti-HBV drug which has no anti-HIV activity up front prior to the introduction of HAART. Entecavir has such potential and will also alleviate any concerns about the development of HIV resistance while reducing HBV DNA levels. After this is achieved, full HAART with HBV active drugs can then be safely instituted.

The use of corticosteroids in this situation is highly controversial. Theoretical concerns include their known effect in increasing HBV replication and the potential augmentation of existing immunosuppression. On the other hand, it is known that hepatic inflammation is immune-mediated and there are anecdotal reports of good outcomes with their use.[44] Furthermore, there is recent evidence from a retrospective study that when used in patients with decompensation within 10 days of onset they improve mortality.[45]

Strategies for therapy

The antiretroviral naïve person

In a person with no prior antiretroviral therapy, immune restoration resulting in hepatic inflammation following commencement of HAART may lead to hepatic decompensation. Hepatic decompensation is most likely when both cirrhosis and advanced immunodeficiency are present. Entecavir results in a profound reduction of HBV DNA with a very favourable resistance profile[32] and can be used to reduce HBV DNA prior to the introduction of full HAART (see below). The role of initial combination anti-HBV therapy with lamivudine and tenofovir is currently under investigation, although most authorities would use combination lamivudine and TDF in all coinfected individuals.

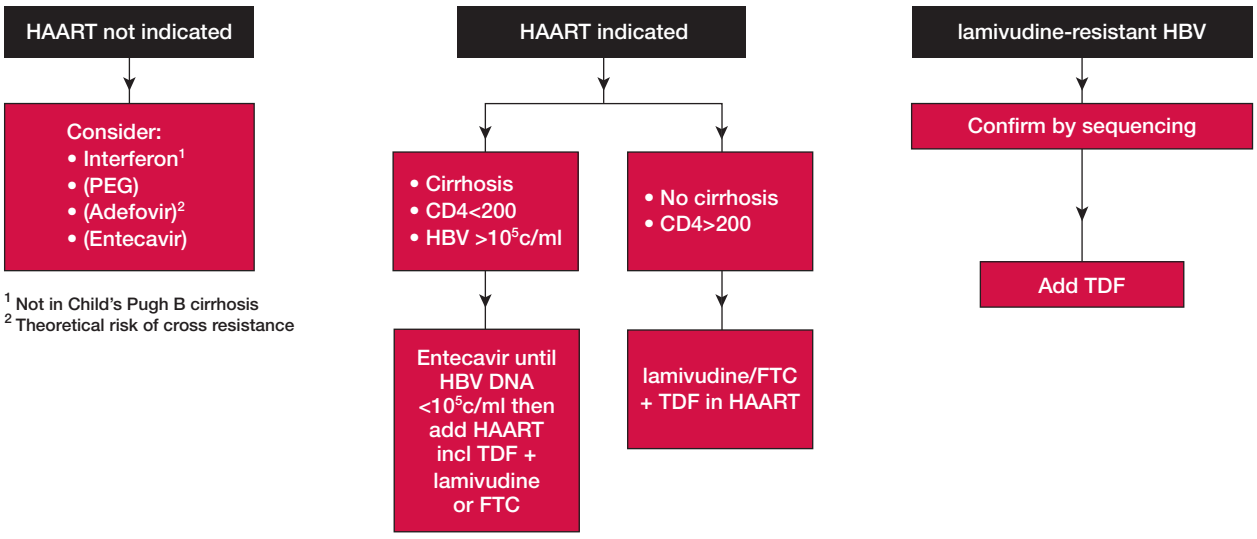
The person who does not require antiretroviral therapy

People who do not require HIV therapy should generally not receive therapy for HBV infection that also has activity against HIV; early HIV resistance is likely, with consequent limitations of HIV therapeutic options. Under these circumstances HBV therapy should consist of interferon, adefovir or entecavir.

The person with lamivudine-resistant HBV

Lamivudine-resistant HBV among people with HIV–HBV coinfection is frequent; active HBV is often unrecognised at the time HIV therapy is commenced, and lamivudine is a common component of HIV therapy. Resistance is suspected in a person

Figure 3.3 Management algorithm



receiving lamivudine therapy when ALT levels are persistently elevated in association with high HBV replication. Resistance must be differentiated from non-adherence by confirming the presence of classical mutations associated with lamivudine resistance. This test is available in specialised laboratories. Once classical mutations are confirmed, therapeutic options include the addition of tenofovir, adefovir or entecavir, all of which have documented activity against lamivudine-resistant HBV in this setting.[29,46]

Antiretroviral hepatotoxicity

Severe hepatotoxicity occurs in up to 10%[20,34] of people who commence HAART. HBV coinfection is an independent risk factor for the development of HAART-related hepatotoxicity,[47-48] and the rate in people with HIV and with HBV coinfection is approximately three times higher than in people who are HBV negative.

Although all antiretroviral agents have been associated with abnormal liver function, full-dose ritonavir and nevirapine are especially implicated in severe hepatotoxicity[46] and thus should be used cautiously in those with HIV–HBV coinfection (see Chapter 4).

Conclusion

Improved life expectancy for people with HIV, together with HAART-related hepatotoxicity and accelerated liver disease progression highlight the need to address liver outcomes in people with HIV–HBV coinfection. Therapeutic response to HBV monotherapy, with either interferon or lamivudine remains suboptimal. New therapeutic agents should provide the means to develop strategies that reduce liver disease-related morbidity and mortality.

Acknowledgments

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4 Antiretroviral therapy-related hepatotoxicity: predictors and clinical management

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Key points

- Severe hepatotoxicity develops in 5-10% of people with HIV infection in the first 12 months following initiation of highly-active antiretroviral therapy (HAART), 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-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 antiretroviral therapy.[3-15] Elevations in serum hepatic enzymes have been described in association with all major classes of antiretroviral therapy,[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 antiretroviral therapy-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 criteria[16]
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 (LEE) 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.

Incidence and predictors of severe hepatotoxicity

Many studies have now examined the issue of antiretroviral therapy-related hepatotoxicity (Table 4.1),[4-15] particularly since the introduction of 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 antiretroviral

therapy 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;
- coinfection with HBV or HCV as the strongest risk factors, with a 3–5 fold increase in risk in several studies;

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)	Grade 3 or 4 ALT	748	Initiation of PI-containing HAART	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)	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
Brinker et al 2000 (The Netherlands)	Grade 3 or 4 ALT or AST + 100 U/L increase	394	Initiation of HAART	65	18%	25	HBV, HCV, elevated baseline ALT
Gisolf et al 2000 (The Netherlands)	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)	Grade 3 or 4 ALT or AST	298 (87 NA, 211 PI)	Initiation of new ARV regimens	24 (NA) 26 (PI)	10.4% (37/100 py)	17	RTV-containing regimen, CD4 increase > 50/mm^3
Monforte et 2001 (Italy)	ALT > 200 U/L	1,255	Initiation of HAART	NA	8% (based on K-M estimate at 24 months)	NA	HCV, HBV/HCV, elevated baseline ALT
Martinez et al 2001 (Spain)	ALT or AST > 3 x increase from baseline	610	Initiation of NVP-containing combination ARV regimen	38	12.5% or 13.1/100 py	NA	HCV, baseline ALT, duration of prior ARV
Nunez et al 2001 (Spain)	Grade 3 or 4 ALT or AST or 3.5 x baseline (if abnormal)	222	Initiation of HAART	35	9%	NA	HCV, heavy alcohol intake, older age
Aceti et al 2002 (Italy)	Grade 3 or 4 ALT	1325	PI-containing HAART	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)	Grade 3 or 4 ALT or AST and >5x baseline ALT/AST if elevated	272	Initiation of NNRTI-containing regimen	54	1.1%	14	Nil
Wit et al 2002 (The Netherlands)	Grade 4 ALT or AST + 200 U/L elevation	560	Initiation of HAART	156	8%	NA	HBV, HCV, elevated baseline ALT, no prior ARV, recent NPV or RTV commencement, female, 3TC discontinuation (HBV)
Cooper et al 2002 (Canada)	Grade 3 or 4 x	66 HIV/HCV	Initiation of PI-containing HAART	56	26% (single-PI) 19% (dual-PI)	NA	Nil
Sulkowski et al 2002 (USA)	Grade 3 or 4 x ALT of AST	568 (256 NVP, 312 EFV)	Initiation of NNRTI-containing HAART	45 (NVP) 37 (EFV)	15.6/100 py (NVP) 8.0/100 py (EFV)	20 (NVP) 14 (EFV)	HBV, HCV, concurrent PI

- increased risk associated with elevated baseline ALT and AST levels;
- increased risk associated with HAART regimens compared to dual NRTI regimens;
- nevirapine and ritonavir as the antiretroviral therapy agents most commonly implicated;
- increased risk within the initial 12 weeks of therapy, particularly in relation to nevirapine;
- a low risk of symptomatic hepatitis, and extremely low risk of fulminant hepatitis;
- resolution of hepatotoxicity, generally within three months, and often despite continued antiretroviral therapy.

Coinfection with hepatitis B virus or hepatitis C virus

Coinfection with HBV or HCV is clearly associated with hepatotoxicity.[4-6,8-11,13,15] Immune restoration disease has been hypothesised as one of the underlying mechanisms for this increased risk.[22] An association between CD4 cell count change following commencement of antiretroviral therapy and risk of severe hepatotoxicity has been present in some studies,[7] a finding in favour of immune restoration as a causative mechanism. A further explanation for an increased risk in association with hepatitis coinfection is that established liver inflammation may increase the risk of direct toxicity from antiretroviral therapy agents. In relation to HBV coinfection, cessation of lamivudine has been associated with hepatotoxicity,[13] with recurrence of HBV viraemia and associated hepatic inflammation (hepatic flare) the likely mechanism. Such episodes may also be associated with hepatic decompensation in people with more advanced liver disease.

Non-nucleoside reverse transcriptase inhibitors

Hepatotoxicity is now well described in people with HIV receiving NNRTI-containing regimens, in particular nevirapine.[9,13,15] Despite the relatively high incidence of nevirapine-associated hepatotoxicity in some studies, symptomatic hepatitis and other adverse clinical outcomes are uncommon. Furthermore, risk of nevirapine-associated hepatotoxicity has been low in other studies.[10,12] Differences in prevalence of other risk factors, in particular coinfection with HBV or HCV, may be responsible for contrasting findings from these studies. Although nevirapine-associated hepatotoxicity appears to be more common in the initial 12 weeks of therapy, other features of drug hypersensitivity reactions such as rash are generally not present, suggesting that other pathogenic mechanisms may be involved. Despite an extremely low risk of fulminant hepatitis in association with nevirapine, cases have been documented in association with use within post-exposure prophylaxis regimens.[17]

Cases of cholestatic hepatitis – with a mixed picture of hepatic transaminitis and cholestasis – have also been described in association with nevirapine,[18] and would appear to be related to direct drug-induced cholestasis. Asymptomatic elevations in gamma glutamyl transferase (GGT) are relatively common in people receiving nevirapine-containing antiretroviral therapy regimens.[19,20]

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

Protease inhibitors

Protease inhibitor therapy, in particular ritonavir, has been associated with severe hepatotoxicity in several studies.[7,11,13,15,21] As with NNRTI-associated hepatotoxicity, underlying chronic HCV infection appears to increase the risk with immune restoration also proposed as a pathogenic mechanism.[22] Ritonavir is a potent inhibitor of the cytochrome P450 system, therefore elevated concentrations of other drugs may be a contributing factor to hepatotoxicity. The association between ritonavir and hepatotoxicity has generally been described in studies of high-dose therapy. The recent use of low and boosting doses of ritonavir (100–200 mg daily) with a second PI does not appear to be associated with high rates of hepatotoxicity.[23,24]

Compared with ritonavir, elevations of hepatic transaminases appear to be uncommon in association with indinavir. On the other hand, cases of isolated hyperbilirubinemia are more commonly associated with indinavir therapy.[11]

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 therapy[20] and either NNRTI or PI-containing HAART 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, and generally ascribed to mitochondrial toxicity.[25-28] NRTIs most commonly associated with steatohepatitis and hyperlactataemia are the thymidine analogues,

stavudine and didanosine, although cases have also been associated with zidovudine. 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.[25-28]

The continuing risk of severe hepatotoxicity beyond the initial few months of HAART, 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 HAART. It is possible that chronic low level hyperlactataemia may be associated with progressive liver damage, even following cessation of antiretroviral therapy.[25] Further studies involving liver biopsy and quantitative mitochondrial DNA assessment are also required to more closely examine the underlying pathogenesis of such toxicity.

Management of antiretroviral therapy-related hepatotoxicity

Several features of antiretroviral therapy-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 antiretroviral therapy agents have been associated with severe hepatotoxicity. Fourth, antiretroviral therapy can generally 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 HAART 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:

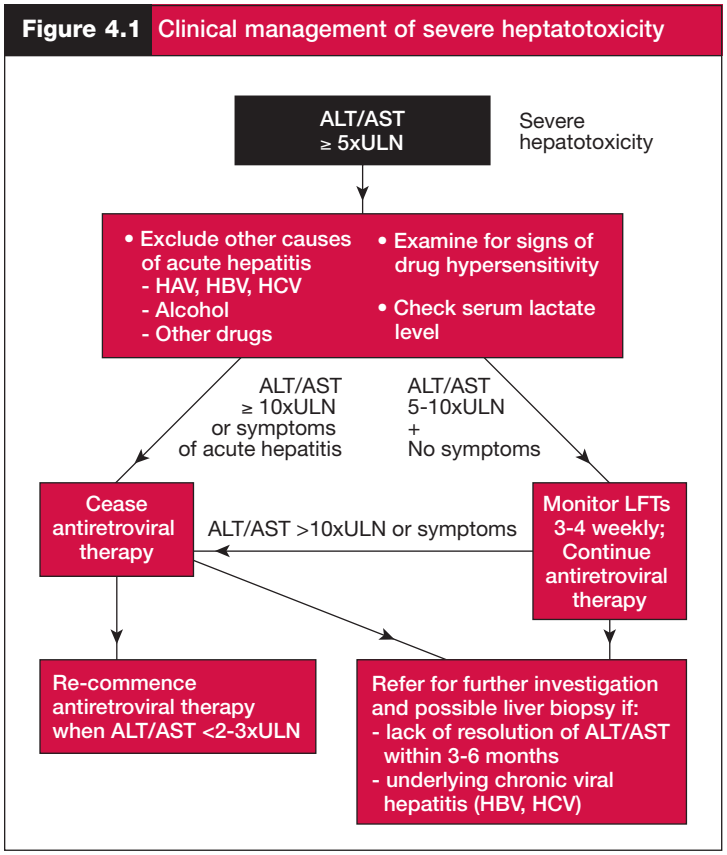
- Acute viral hepatitis – hepatitis A, IgM/IgG, HBcAbIgM/sAg, HCV Ab/HCV RNA (if either unknown or previous negative serology);
- Other viral causes – CMV IgM/IgG, EBV IgM/IgG, toxoplasmosis IgM/IgG, syphilis serology;
- Autoimmune hepatitis – anti-nuclear antibodies, anti-smooth muscle antibodies, anti-mitochondrial 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-mycobacterial and anti-cholesterol agents.

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

Initial management and monitoring

An algorithm for management of severe hepatotoxicity is outlined in Figure 4.1. In general, antiretroviral therapy 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 should be performed every

Figure 4.1 Clinical management of severe heptatotoxicity



3–4 weeks until levels return towards normal or baseline. Indications for cessation of antiretroviral therapy 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;
- hyperlactataemia – lactate levels above 3 mmol/L.

In people who require antiretroviral therapy 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 symptoms subside.

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, antiretroviral therapy can be continued with liver function test monitoring every 3–4 weeks. Further elevations of ALT and AST (above 10 x ULN) and development of symptoms should warrant antiretroviral therapy discontinuation. 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 there is underlying chronic viral hepatitis (HBV or HCV). Investigations for alternative causes of chronic liver disease and a liver ultrasound could be performed prior to referral.

Choice of antiretroviral therapy regimen

If severe hepatotoxicity requires antiretroviral therapy 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 antiretroviral therapy agents – probable increased risk with nevirapine and high-dose ritonavir;
- presence of drug hypersensitivity features – abacavir should never be re-commenced when hypersensitivity develops, and other agents possibly associated with a severe skin eruption should also not be re-commenced;
- other associated features – for example, when hyperlactataemia is present, stavudine and didanosine should not be re-commenced;
- remaining choice of antiretroviral therapy – re-challenge may be more appropriate where choices are limited.

Re-commencement of antiretroviral therapy, particularly when re-challenging with agents in the previous regimen, should be monitored with 3–4 weekly liver function tests for the first few months at least.

Conclusion

Although severe hepatotoxicity among people receiving antiretroviral therapy is generally not associated with adverse hepatic outcomes, careful monitoring and investigation of alternative and contributing factors are required. The relationship between elevated serum hepatic transaminase levels and increased medium-term mortality in a recent study[29] is further reason to monitor and appropriately investigate potential liver disease co-morbidities in people with HIV infection.

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Glossary of terms

Alanine aminotransferase (ALT)	a protein which generally indicates liver damage when found in the blood in elevated quantities
CD4 count nadir	the lowest level of immune function, generally prior to starting antiretroviral treatment
Cholestatic hepatitis	jaundice with bile stasis in inflamed intrahepatic bile ducts; often due to drug toxicity
Chronic viral hepatitis	liver disease caused by viral infection (e.g. hepatitis B or C) that continues for more than six months
Cirrhosis	extensive scarring of the liver, with architectural distortion
Combination therapies	two or more drugs used together to achieve maximum impact against infection
Fibrosing cholestatic hepatitis (FCH)	inflammation and scarring of the liver which affects the flow of bile
Fibrosis	formation of scar tissue to replace normal tissue lost through injury and infection
Fulminant hepatitis	severe and rapidly progressive form of hepatitis accompanied by hepatocellular death and hepatic failure
Genotype	the specific genetic structure of a virus
HCV genotype testing	test to establish the genotype of hepatitis C virus (currently six major genotypes and many sub-types)
Harm reduction programs	programs aiming to reduce the harm of drug use to users and to society
HBV core antibody	antibodies directed against the core antigen of the hepatitis B virus
HBV 'e' antigen	a protein associated with rapid replication of the hepatitis B virus
HBV surface antigen	the outer surface of the hepatitis B virus which triggers an immune response
Hepatic decompensation	the failure of a damaged liver to meet minimum functional requirements, which manifests as easy bruising/bleeding, abdominal fluid retention (ascites), and hepatocellular carcinoma
Hepatitis	inflammation of the liver
Hepatocellular carcinoma	the most common primary malignant liver tumour
Hepatomegaly	enlargement of the liver
Hepatotoxic	damaging or destroying liver cells
Hyperbilirubinemia	excessive levels of bilirubin in blood
Hyperlactataemia	elevated lactic acid levels in the blood
Hypersensitivity	an exaggerated immune response to a foreign substance
Immune restoration	rebuilding of a damaged or compromised immune system
Immune restoration disease	unusual manifestations of opportunistic infections following commencement of HIV treatment, caused by excessive responses by the recovering immune system
Interferon-alpha	an immune-modulating agent used in the treatment of chronic viral hepatitis and certain malignancies
Lactic acidosis	severe build-up of lactic acid in the body
Leucopenia	a reduction in the number of white blood cells in the blood
Liver biopsy	removal of a small amount of liver tissue for microscopic analysis
Mitochondrial toxicity	damage to the small intracellular organelle responsible for energy production and cellular respiration
Natural history	study of natural development and outcomes of disease over time
Necro-inflammatory	inflammation leading to cell death

Glossary of terms (cont.)

Parenteral	introduced subcutaneously, intravenously or by any other route other then the digestive tract
Pegylated Interferon	slow release interferon, administered once a week
Phenotype	the organism itself as opposed to its genetic constitution, the genotype
Polymerase chain reaction (PCR)	a laboratory technique that amplifies the genetic material of a virus to a level that can be detected, so that the presence or absence of the virus can be determined
Protease inhibitor (PI)	antiviral drug that inhibits the virus' protease enzyme, thereby preventing viral replication
Re-infection	describes a second HCV infection, generally in a person with resolved HCV infection
Seroconversion	describes the conversion from antibody negative to positive following exposure
Steatohepatitis	fatty infiltration of the liver, associated with inflammation
Viral pathogenesis	the way in which a virus causes disease
Viraemia	presence of virus in the blood stream

Acronyms

Ab	antibody
AHOD	Australian HIV Observational Database
aIFN	interferon-alpha
AIDS	acquired immune deficiency syndrome
ALT	alanine aminotransferase
Anti-HBc	antibody to the hepatitis B core antigen
AST	aspartate aminotransferase
bDNA	branched DNA
CAESAR	multicentre study conducted in Canada, Australia, Europe, South Africa
CMV	cytomegalovirus
DLD	decompensated liver disease
DNA	deoxyribonucleic acid
EBV	Epstein Barr virus
EuroSIDA	large cohort study of people with HIV infection in Europe
ETR	end-of-treatment virological response
FCH	fibrosing cholestatic hepatitis
GGT	gamma glutamyltransferase
HAART	highly-active antiretroviral therapy
HAV	hepatitis A virus
HBcAg	hepatitis B core antigen
HBeAg	hepatitis B e antigen
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IDU	injecting drug use
Ig	immunoglobin
LEE	liver enzyme elevation
MACS	Multicentre AIDS Cohort Study
MSM	men who have sex with men
NNRTIs	non-nucleoside reverse transcriptase inhibitors
NRTIs	nucleoside analogue reverse transcriptase inhibitors
PCR	polymerase chain reaction
PI	protease inhibitor
RNA	ribonucleic acid
RR	relative risk
SVR	sustained virological response
ULN	upper limit of normal
US ACTG	United States AIDS Clinical Trials Group

List of drugs

abacavir (ABA, ABC)
adefovir dipivoxil (ADV)
didanosine (ddI)
emtricitabine (FTC)
entecavir
indinavir (IDV)
interferon (IFN)
interferon-alpha (a-IFN)
lamivudine (3TC)
nevirapine (NVP)
pegylated interferon (PEG)
ribavirin (RBV)
ritonavir (RTV)
stavudine (D4T)
tenofovir disoproxil fumarate (TDF)
zidovudine (AZT, ZDV)

Index

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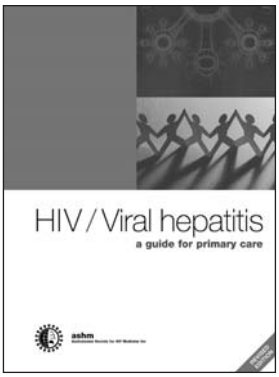
HIV/Viral Hepatitis

a guide for primary care



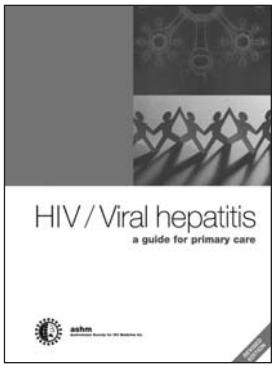
This monograph explores patterns of risk and the intersections and differences in the management of these illnesses in the primary care setting. It addresses risk assessment, diagnosis, management and professional issues, presenting guiding principles for care and practical examples to help inform service delivery. Information for patients is also provided.

Copies are available free of charge to primary care providers, medical registrars, other health care workers, academics at medical faculties and other education providers in Australasia.

Revised edition 2004, ISBN 1 920773 12 6

HIV Management in Australasia:

a guide for clinical care



Intended predominantly for registrars, medical students, specialists, general practitioners and nurses, this respected monograph is divided into three sections.

The first deals with basic HIV virology, immunology and the tools used to monitor HIV disease.

The second discusses antiretroviral therapy.

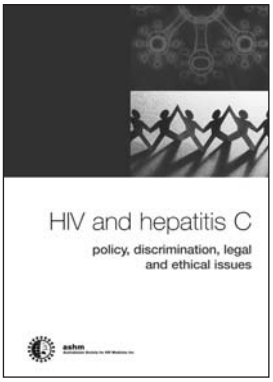
The third section focuses on clinical presentations, including diagnostic features, treatment, prevention and outcome.

The 2003 edition was described as: *'a cornerstone resource in HIV education for HIV clinicians. The concise, yet authoritative and clear, style of this publication makes it an ideal educational tool.'* (Professor Michael Kidd)

Published 2004, ISBN 1 920773 10 X

HIV and hepatitis C:

policy, discrimination, legal and ethical issues



This collection of nine essays describes legal, ethical and discrimination issues presented by two important challenges to global public health: HIV and hepatitis C.

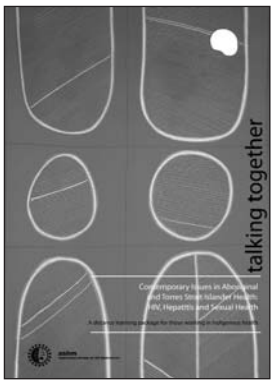
Topics covered include discrimination and workers, pregnancy and HIV, immigration, the AIDS vaccine, and Australia's response to HIV among injecting drug users.

This book is in part a history, in part a text on social activism, in part a description of applicable laws and current problems and in part, an exploration of how Australians can do better in the future than they have done in the past. Easy-to-read and informative, it is of particular interest to medical and legal practitioners, as well as policy analysts and human rights professionals. The Foreword is written by The Hon Justice Michael Kirby AC CMG.

Published 2005 ISBN 1 920773 20 7

'Talking Together'

contemporary issues in Aboriginal and Torres Strait Islander health: HIV, hepatitis and sexual health



This distance learning kit focuses on issues related to sexual health, HIV and HCV for Indigenous communities in Australia.

Metropolitan, rural and remote settings are covered in the material, as well as the importance of delivering information about sensitive topics in culturally appropriate ways to diverse Indigenous communities.

Published 2005 ISBN 1 90773 19 3

ASHM produces resources on HIV and viral hepatitis.
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