

21.1 Hepatitis B co-infection

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Hepatitis B virus (HBV) infection is an important infection in people with HIV because of the influence of HIV on the natural history of HBV infection. Antiviral therapies with activity against both viruses have enabled targeted therapy in individuals with co-infection without an increase in pill burden.

21.1.1 Epidemiology and pathogenesis

It is estimated that over 300 million people worldwide, or approximately 5% of the global population, are chronically infected with HBV. Areas of high endemicity for HBV infection, such as sub-Saharan Africa and Asia, are also most affected by the HIV pandemic.¹ HIV and HBV infections occur commonly together owing to shared routes of transmission. The prevalence of chronic HBV infection in people with HIV in Australia is approximately 5%.²

HBV is not directly cytopathic, and viral pathogenesis is largely immune-mediated. Necro-inflammatory changes in liver tissue that characterise chronic HBV infection are a result of cellular immune responses to viral antigens.³ In immunocompromised individuals, the greater the extent of deficiency in the immunological response to the HBV antigens, the more likely that the host will be immunotolerant to the virus and lack significant histological disease.³ The converse is also true – the more robust the immunological response to these antigens, the greater the likelihood of substantial inflammatory changes, damage to the hepatocytes and progressive fibrosis. These factors have implications for individuals initiating combination antiretroviral therapy (cART).

21.1.2 Diagnosis Serology

All individuals with HIV infection should be screened for HBV infection. Although the detection of hepatitis B surface antigen (HBsAg) is usually sufficiently sensitive to establish the presence of chronic infection in the normal host, immunodeficient individuals may be negative for HBsAg, but still have active HBV replication.⁴ It is therefore recommended that individuals with HIV with advanced immunodeficiency (CD4 cell counts <200 cells/ μ L) also be tested for the presence of anticore antibody (anti-HBc). Patients found to be HBsAg-positive should also have their e-antigen (HBeAg) status evaluated. Individuals who are HBeAg positive usually have active replication, but some individuals who are negative for HBeAg and positive for anti-HBe may also have active replication and active liver disease. The failure to synthesise HBeAg is due to the presence of mutations in the precore or core promoter regions.

HBV DNA

If either HBsAg or anti-HBc is detected, patients should be evaluated for active HBV replication using an assay for HBV DNA. The level of HBV DNA determines whether patients are at risk for transmission, progressive disease and immune reconstitution flares. HBV DNA should ideally be quantified by nucleic acid amplification assays, usually polymerase chain reaction (PCR).

In HBV mono-infection, strong evidence indicates that the incidence of cirrhosis is related to the level of HBV DNA. The REVEAL-HBV study group demonstrated that individuals with HBV DNA of >200 000 IU/mL (10^6 copies/mL) were ten times more likely to develop cirrhosis than those with undetectable HBV DNA (<370 IU/mL) at baseline, over a mean follow-up period of 11 years.⁵ Individuals with HBV DNA >2000 IU/mL (10^4 copies/mL) had a 2.5 times increased risk of cirrhosis. Whether this is relevant in HIV-HBV co-infection, where HBV DNA levels are frequently higher, is unclear.

21.1.3 Disease progression Effect of HIV on HBV disease progression

HIV co-infection results in considerable modification of the natural history of HBV infection.⁶⁻⁸ Persistent HBV infection is more common in individuals with HIV, with the prevalence of chronic HBV infection estimated at 25%⁹ compared with a prevalence of 3-5% in HIV-seronegative men who have sex with men.^{10,11} Rarely, reactivation of infection may occur in the setting of profound CD4 cell deficiency despite seroconversion to anti-HBs.¹² Furthermore, during chronic co-infection, the HBV DNA levels are substantially higher than in HIV-seronegative individuals and rates of seroconversion from HBeAg to anti-HBe are lower.^{6,12-14}

Despite the high levels of viral replication seen in people with HIV infection with chronic HBV infection, these patients have significantly lower serum alanine aminotransferase levels than people with chronic hepatitis B alone^{6,12-14} and liver biopsies usually demonstrate milder necroinflammatory activity.¹² Despite this, progression to cirrhosis is more common, indicating accelerated fibrosis.¹² The reasons for progression are unclear, and may relate to factors such as flares associated with immune restoration, the toxicity of antiretroviral medication, increased direct pathogenicity of HBV in this patient group and possible direct effects of HIV on fibrosis.

Rarely, in severely immunocompromised patients, HBV may exert direct cytopathic effects that are not immune-mediated and result in a unique condition called fibrosing cholestatic hepatitis. This condition is associated with very high levels of HBV DNA and has been described in people with HIV infection.¹⁵ The histological features of fibrosing cholestatic hepatitis include a paucity of cellular infiltrates and rapidly progressive,

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cholestatic injury with very high levels of intracellular virus, which accelerate fibrosis and hepatic decompensation. The condition has a high mortality rate, although recent treatment approaches have resulted in successful outcomes.

An increased rate of hepatocellular carcinoma has not been described in those with HIV-HBV co-infection, although this may be related to the high mortality associated with HIV infection prior to the availability of antiretroviral therapy. It is not yet apparent whether prolonged survival due to cART will result in an increased rate of hepatocellular carcinoma.

Effect of HBV on HIV disease progression

In contrast to the effect of HIV on HBV infection, most studies have not detected a significant effect of HBV infection on the clinical course of HIV infection.^{16,17}

Effect of cART on HBV disease

Antiretroviral hepatotoxicity

Severe hepatotoxicity occurs in up to 10% of all patients commenced on cART.^{18,19} HIV-HBV co-infection is an independent risk factor for the development of cART-related hepatotoxicity.¹⁸⁻²⁰ Although all antiretroviral agents have been associated with abnormal liver function, ritonavir, nevirapine and tipranavir^{21,22} are especially implicated in severe hepatotoxicity^{18,19} and thus should be used cautiously in the patient with HIV-HBV co-infection.

21.1.4 Immune restoration disease

In patients with HIV-HBV co-infection, immune restoration following cART has been associated with acute rises in levels of serum aminotransferases known as hepatic flares.²³⁻²⁵ Risk factors include high pretreatment HBV viral loads and alanine aminotransferase (ALT) levels.^{18,20,23,26} Hepatic flares related to cART have also been reported in other circumstances, including re-activation of HBV infection,^{23,27} development of lamivudine resistance²⁸ and following withdrawal of lamivudine.²⁹ This highlights the need to test all patients for chronic HBV infection prior to the initiation of cART. Patients with cirrhosis are particularly at risk of hepatic decompensation, and require careful observation after the initiation of cART. The role of corticosteroids in this situation is unproven and cannot be recommended outside of a clinical trial.

21.1.5 The role of liver biopsy

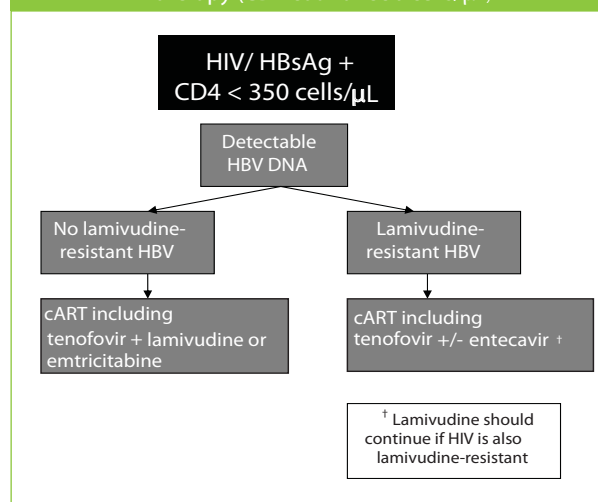
The role of liver biopsy is controversial. Most treatment guidelines base treatment decisions on HBV DNA and ALT levels and do not recommend liver biopsy routinely.³⁰ In Australia, a liver biopsy is not required to initiate HBV active agents that also have anti-HIV activity. However, other experts recommend that most patients should have a liver biopsy to determine the grade and stage of disease unless there are strong contraindications such as a bleeding disorder. Liver biopsy is the only accurate method of determining the degree of hepatic fibrosis and necroinflammatory activity, as well as being a means of excluding other factors which may contribute to liver dysfunction, particularly drug toxicity. While a number of non-invasive methods to evaluate liver pathology are being developed, none so far has a sufficiently acceptable performance to replace biopsy.

21.1.6 Management

General principles

Sustained suppression of serum HBV DNA to below the level of detection by the most sensitive available assay should be the goal of therapy, and, at present, treatment of HBV in HIV-HBV co-infection is lifelong. If antiretroviral therapy is required, then two agents with anti-HBV activity should be incorporated into the regimen (Figure 21.1). If antiretroviral therapy is not required, then the treatment chosen should have no anti-HIV activity (Figure 21.2). Current therapeutic options in this setting are pegylated interferon, adefovir or the early introduction of

Figure 21.1 Proposed algorithm for treatment of HBV in people with HBV-HIV co-infection already on or immediately requiring antiretroviral therapy (CD4 count <350 cells/ μ L)



cART, even when the CD4 count is >350 cells/ μ L.³¹ However, recent guidelines from IAS have recommended treatment of HIV at any CD4 cell count in the setting of HIV-HBV co-infection. This remains an area where further research is needed.

HBV DNA

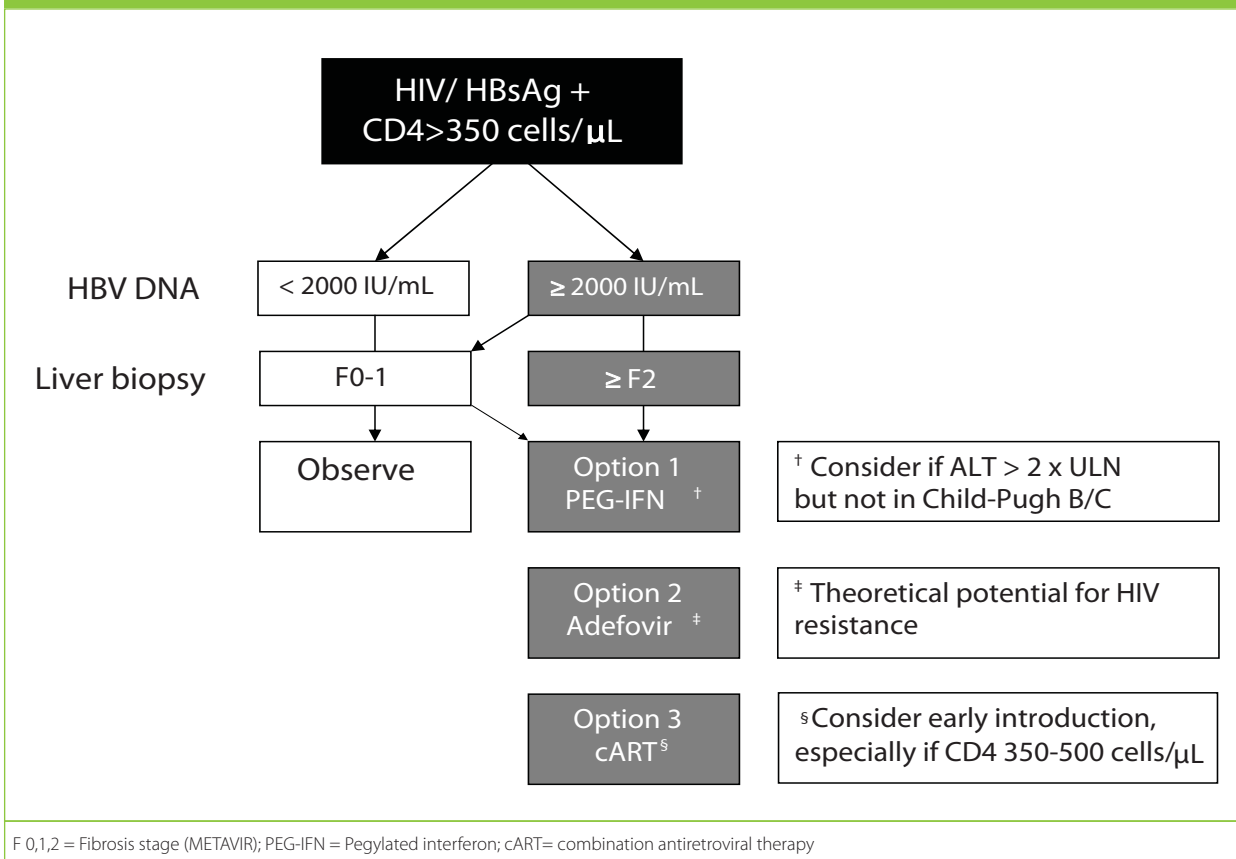
Previous guidelines for initiation of treatment for HIV-HBV co-infection recommended the same thresholds of HBV DNA used for HBV mono-infection,^{31,32-35} i.e. HBeAg-positive disease: greater than 20 000 IU/mL (10^5 copies/mL); HBeAg-negative disease: greater than 2000 IU/mL (10^4 copies/mL); and underlying cirrhosis: greater than 200 IU/mL (10^3 copies/mL).

However, since people with HIV-HBV co-infection are at greater risk of liver disease, it is now recommended that treatment is initiated in individuals with HBV DNA >2000 IU/mL (10^4 copies/mL) for all non-cirrhotic individuals and >200 IU/mL (10^3 copies/mL) in the presence of cirrhosis.³⁰ Monitoring of HBV DNA should ideally take place every three to six months where possible.^{36,37}

Anti-HBV therapy

There are six currently licensed treatments available for the management of HBV. These include interferons, nucleoside reverse transcriptase inhibitors (lamivudine, emtricitabine, entecavir and telbivudine) and nucleotide reverse transcriptase inhibitors (tenofovir and adefovir).

Figure 21.2 Proposed algorithm for treatment of HBV in people with HBV-HIV co-infection when antiretroviral therapy is not yet required (CD4 count > 350 cells/ μ L). If biopsy is contraindicated, then treatment of people with HBV DNA >2000 IU/mL is usually only initiated if ALT levels are abnormal



Interferons

In immunocompetent individuals, interferon-alfa (alphaIFN) therapy may result in HBeAg seroconversion and induce a clinical remission in 20-40% of patients with chronic HBV.³² Treatment of individuals with HIV-HBV co-infection is significantly less effective.^{36,38,39} In particular, patients with advanced immunodeficiency usually have poorer responses to therapy.⁴⁰ It thus seems reasonable to attempt alphaIFN therapy in individuals with preserved CD4 cell counts (>500 cells/ μ L) who are not candidates for cART. This enables drugs such as lamivudine to be reserved for HIV therapy so that monotherapy does not result in HIV resistance. There is currently no data on pegylated interferon in the setting of co-infection.

Lamivudine / emtricitabine

Lamivudine and emtricitabine are both nucleoside analogue reverse transcriptase inhibitors that suppress both HIV and HBV replication by inhibition of viral RNA-dependent DNA polymerases.^{41,42} In HIV-negative individuals, the reduction in plasma HBV DNA secondary to lamivudine therapy is associated with HBeAg seroconversion, normalisation of liver function and improved histological activity. Unfortunately the long-term effectiveness of lamivudine is diminished by the development of HBV resistance mutations.⁴³ Resistance to lamivudine develops because 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 also been demonstrated in people with HIV-HBV co-infection.^{23,33,44,45} Approximately 20%

of patients with HIV-HBV co-infection develop HBV resistance to lamivudine annually, with projected rates of resistance after four years of lamivudine therapy of approximately 90%.^{46,47} This frequency of lamivudine resistance is higher to that seen in patients with HBV mono-infection.⁴⁶ Prolonged lamivudine therapy has been identified as the major risk factor for the development of drug-resistant HBV. Given that lamivudine, when used as a component of cART, is administered lifelong in patients with co-infection, it is inevitable that HBV monotherapy in this population will result in resistance.⁴⁶

Adefovir dipivoxil

Adefovir dipivoxil is a nucleotide analogue which, at a dose of 10 mg daily, has demonstrated efficacy against HBV. Higher doses of 30 mg or greater have been associated with nephrotoxicity, which has been rarely observed with the 10-mg dose. Adefovir, like alphaIFN, may also be an alternative option for patients with high CD4 cell counts who do not require cART, so that lamivudine may be preserved for HIV therapy.⁴⁸ However, studies to date have been performed on small numbers of patients and the structural similarity of adefovir to tenofovir may potentially lead to the possibility of cross resistance to tenofovir.⁹

Tenofovir disoproxil

Tenofovir is a nucleotide analogue with the ability to inhibit both HIV and HBV DNA polymerases. It demonstrates activity against viral strains that contain polymerase gene mutations including common lamivudine-resistant mutations.

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When added to a lamivudine-containing regimen in patients with documented HBV lamivudine resistance, tenofovir has demonstrated a $>3 \log_{10}$ reduction in HBV DNA after 12 weeks.⁴⁹ One small randomised control study has demonstrated its efficacy in patients with HIV-HBV co-infection with superior virological suppression compared to lamivudine.^{47,50} Tenofovir is now commonly used as combination therapy in conjunction with lamivudine or emtricitabine for the treatment of HBV in patients with co-infection. In addition, the coformulation of tenofovir and emtricitabine allows convenient single-daily dosing.

Entecavir

Entecavir is a guanosine analogue which has well documented, potent anti-HBV activity both *in vitro* and clinically and has a high barrier to HBV antiviral resistance.⁵¹⁻⁵³ Although entecavir was initially reported to have no anti-HIV activity, a recent report of three patients with HIV-HBV co-infection who were treated with entecavir monotherapy demonstrated significant reductions of HIV RNA despite no concomitant HIV therapy. Furthermore, one of these patients was shown to develop an M184V mutation, the signature HIV resistance mutation for lamivudine.⁵⁴ In a larger cohort of 17 patients with HIV-HBV co-infection treated with entecavir monotherapy a significant reduction in HIV RNA (defined as $> .05 \log_{10}$) was observed in 13 of them (76%), including treatment-naïve patients. The M184V mutation was also identified in six individuals including three who were antiretroviral-naïve.⁵⁵ Therefore, entecavir should no longer be used as monotherapy for the treatment of HBV in the setting of HIV co-infection.

Telbivudine

There have been no studies to date of telbivudine in HIV-HBV co-infection, however, HBV resistance develops rapidly when telbivudine is used as monotherapy and should therefore not be used in the setting of HIV-HBV co-infection.⁵⁶

Conclusion

HBV infection in individuals with HIV may result in significant morbidity and mortality. People with HIV-HBV co-infection have higher rates of chronic HBV infection and accelerated hepatic fibrosis and cirrhosis compared with individuals with HBV infection who do not have HIV. Management of each viral infection is complicated by the presence of the other virus. Sustained suppression of serum HBV DNA to below the level of detection by the most sensitive available assay should be the goal of therapy, and, at present, treatment of HBV in HIV-HBV co-infection is lifelong. Close monitoring is necessary to detect treatment failure or hepatic flares, particularly following initiation of cART. Further studies of newer anti-HBV agents in individuals with HIV-HBV co-infection are still needed.

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21.2 Hepatitis C co-infection

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The significance of hepatitis C virus co-infection in populations with HIV infection has become apparent since HIV-related mortality has reduced in the era of combination antiretroviral therapy (cART). While the total number of HIV-related deaths has reduced, the proportion of liver-related deaths among people with HIV has increased in cohort studies from around the world.¹⁻⁴

21.2.1 Epidemiology

HCV is transmitted by the parenteral route, with most new infections reported in injecting drug users. People with haemophilia were at high risk of HCV until universal screening of blood products in 1990: HCV transmission from HCV-infected blood products has affected significant numbers of people with haemophilia, although new HCV infections via this route are rarely reported. HCV is transmitted perinatally, and co-infection with HIV increases the likelihood of HCV vertical transmission. HCV transmission via sexual intercourse is uncommon, although more recently transmission has been postulated to occur via the sexual route among men who have sex with men (MSM) in association with HIV co-infection.^{5,6} Although rates of HIV infection are low among Australian injecting drug users, the prevalence of HCV infection is high, such that injecting drug users with HIV are likely to have HCV co-infection.⁷ HCV co-infection was present in 7.6% of individuals with HIV infection at one Australian tertiary referral centre.⁸ In Australia, HCV infection is more prevalent among MSM than in the general population. One study from Sydney reported an HCV prevalence of 7.6% in MSM,⁹ with an association between HCV infection and both injecting drug use and HIV infection. The prevalence of HCV co-infection in subjects undergoing cART in the Australian HIV Observational Database was approximately 12%.¹⁰

21.2.2 Diagnosis

The diagnosis of HCV infection is made by the detection of HCV antibody and the detection of HCV RNA by polymerase chain reaction (PCR) in serum. Detection of HCV antibody by enzyme-linked immunosorbent assay (ELISA) should be confirmed with another serological assay, usually a different ELISA. HCV RNA testing should be undertaken to establish persistence of viral replication. Although false-negative assays are uncommon with third-generation HCV ELISA in HIV-negative individuals, failure to detect HCV antibody by HCV ELISA in persons with HIV has been reported.¹¹ Patients who are HCV-antibody-negative with evidence of liver disease (e.g. elevated serum transaminase levels), or a history of high-risk behaviours, should be evaluated for HCV infection with HCV RNA testing. Cases diagnosed on the basis of a positive serum HCV RNA assay alone should be confirmed by repeating the test. HCV genotyping is important, as some genotypes are relatively resistant to therapy and prolonged treatment is required.

The incubation period for hepatitis secondary to HCV is between two and 26 weeks. HCV RNA testing should be undertaken in seronegative cases of possible acute HCV infection, as the

antibody response may be delayed by several months. HCV RNA may be measured by quantitative PCR. A high HCV RNA has been associated with poor response to therapy.

21.2.3 Disease progression

Effects of HIV on HCV disease progression

Studies of the natural history of HCV infection reveal that less than 50% of people with HCV infection (in the absence of HIV infection) clear HCV, with most people developing persistent HCV infection and chronic hepatitis. HIV co-infection is associated with a reduced HCV clearance rate.¹² Chronic HCV infection with chronic hepatitis is complicated by hepatic fibrosis, which may ultimately progress to cirrhosis and liver failure. Hepatocellular carcinoma (HCC) is another potentially fatal complication of advanced HCV infection, usually occurring in people with established cirrhosis. The progression to cirrhosis in individuals with HCV infection alone occurs in 10% of persons after 20 years of infection.¹³ Cross-sectional studies have demonstrated higher rates of cirrhosis in persons with HIV-HCV co-infection compared with individuals with HCV infection. After ten years, the prevalence of cirrhosis in persons with co-infection was 14.9% (versus 2.6% in HCV mono-infection) in one study and 25% (versus 6.5%) at 15 years in another study.^{14,15} HIV accelerates the progression of liver disease in people with haemophilia with HIV infection as well as in other populations.¹⁶ A small case-control study suggested that HCC occurs at a younger age and sooner in the course of HCV infection in individuals with co-infection.¹⁷ Progression of HIV-related immunodeficiency is associated with HCV disease progression, with lower CD4 cell counts being associated with hepatic fibrosis and liver failure.^{18,19} Significant levels of alcohol consumption are associated with greater disease progression in persons with HIV-HCV co-infection.²⁰ People with HIV-HCV co-infection and mild fibrosis on liver biopsy may experience significant progression of hepatic fibrosis over a three-year period.²¹

Effects of HCV on HIV disease progression

Studies of the influence of HCV infection on the progression of HIV infection have been contradictory, with some studies suggesting an increase in HIV disease progression in people with HIV-HCV co-infection and others demonstrating no influence on disease progression.^{22,23}

Effects of cART on HCV disease

Although cART has no direct antiviral activity on HCV replication, cART results in an initial increase and subsequent decline in HCV RNA,^{24,25} yet HCV clearance with cART has rarely been reported.²⁶ The changes in HCV RNA following cART are largely thought to be secondary to improvement in HCV-specific immunity resulting in better control of HCV replication. Individuals with HIV-HCV co-infection have higher HCV RNA than persons with HCV mono-infection,²⁷ but in contrast to HIV RNA, HCV RNA is not predictive of HCV disease progression. High HCV RNA, however, is associated with reduced response

to treatment in individuals with HCV infection.²⁸ It is unlikely that cART alone is sufficiently effective as a primary treatment strategy for HCV infection in people with co-infection.

Antiretroviral hepatotoxicity

cART-associated hepatotoxicity in the setting of HIV-HCV co-infection may be directly related to multiple antiretroviral agents. In addition, nucleoside reverse transcriptase inhibitor therapy may be specifically associated with hepatic steatosis in patients with HIV-HCV co-infection.

Immune restoration disease

Hepatotoxicity can also occur secondary to immune restoration disease.²⁹ This is typically manifest as an elevation of serum hepatic transaminases levels in the first few months after the introduction of cART, and may take months to spontaneously resolve. The association between a rise in CD4 cell count of 50 cells/ μ L and severe hepatotoxicity is evidence that immune reconstitution may contribute to hepatic injury.³⁰ It is unclear what threshold should be used regarding withdrawal of cART in this setting or whether HCV therapy should be instituted. One small study suggested that subjects with symptomatic drug-induced liver injury could successfully recommence cART if pegylated interferon and ribavirin were used, although rates of HCV clearance with this strategy were low.³¹ Others have suggested that treating HCV before HIV may reduce the risk of cART-associated hepatotoxicity.³² No studies of corticosteroid therapy in the setting of possible cART-induced immune reconstitution hepatic injury in HIV-HCV co-infection have been reported.

Liver disease progression

cART may be associated with improvement in, or rapid progression of, liver disease, but larger controlled studies are required to determine the predictors of such disparate outcomes.^{20,33} Although HCV co-infection is a risk factor for a blunted CD4 cell response after cART,²² the clinical significance of this is unclear. cART is associated with a reduction in the mortality rate in people with decompensated cirrhosis when initiated after the first episode of decompensation.³⁴

21.2.4 The role of liver biopsy

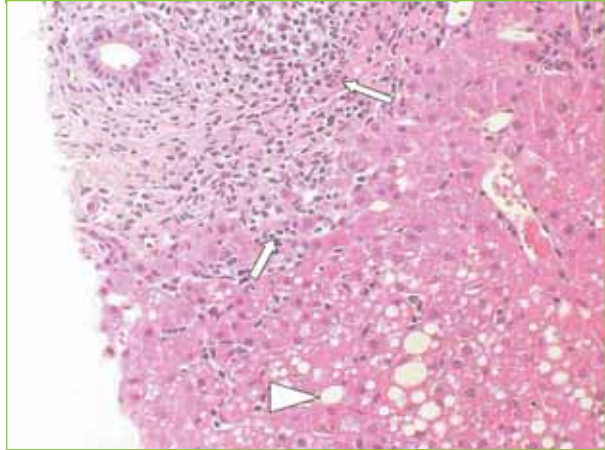
A liver biopsy is not required to access HCV therapy under the Australian Government's Highly Specialised Drugs Program Section 100 reimbursement guidelines. A liver biopsy demonstrates the degree of fibrosis in chronic HCV infection, and it may guide decisions regarding therapy as people with more significant fibrosis or compensated cirrhosis should be encouraged to undergo HCV therapy. It may also help exclude other hepatic disorders and assist in the assessment of multifactorial liver injury (e.g. drug toxicity and HCV). Several systems have been devised for the staging and grading of liver histology in chronic HCV infection. Fundamentally, the degree of architectural change or fibrosis is the most important histological aspect that guides treatment decisions. More recently, non invasive markers of liver fibrosis have been investigated and may find a role in clinical practice to exclude or predict the presence of significant fibrosis or cirrhosis.^{35,36}

21.2.5 Management

General principles

Decisions regarding the priority and relative urgency of HCV therapy versus HIV therapy are complex. The progression

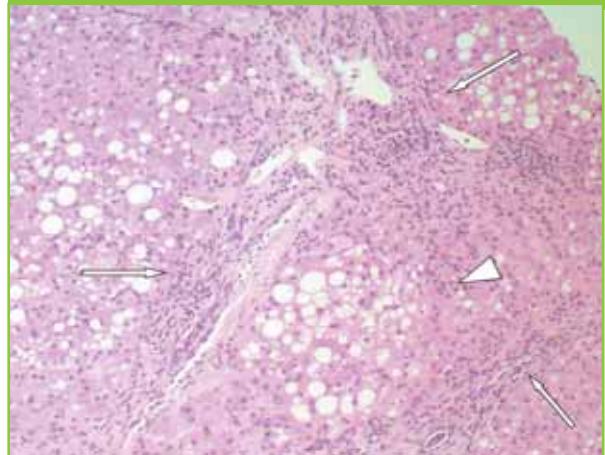
Image 21.1 Chronic inflammation of the liver



Note: Chronic inflammation with interface hepatitis (arrows) on the edge of a portal tract (with bile ductule in upper left-hand corner) identified in a patient with chronic hepatitis C infection. The micro and macrovesicular steatosis (arrowhead) are typically seen in hepatitis C infected liver tissue.

Source: Photomicrograph kindly provided by Simpson I, Ryan A, Monash Medical Centre, Melbourne, VIC.

Image 21.2 Cirrhosis of the liver



Note: Broad bands of fibrosis (arrows) surround a nodule of steatotic hepatocytes (arrowhead) in a patient with hepatitis C infection with cirrhosis.

Source: Photomicrograph kindly provided by Simpson I, Ryan A, Monash Medical Centre, Melbourne, VIC.

of each disease, overlapping and possibly synergistic drug toxicities, effects of immunodeficiency on the effectiveness of HCV treatment, patient preference and adherence may all influence decisions regarding therapy (Table 21.1). In general, people with significant HIV-associated immunodeficiency should be treated with cART, and treatment for HCV should be considered after effective immune reconstitution. Others with preserved CD4 cell counts (>350 cells/ μ L) may be treated for HCV before the initiation of cART becomes necessary. However, recent guidelines from IAS recommend treatment of HIV at any CD4 cell count for all patients with HIV-HCV co-infection. Recent reports of successful liver transplantation in small numbers of people with HIV-HCV co-infection are encouraging, but cholestatic hepatitis is a complication that may limit the widespread application of transplantation in the population with co-infection.^{37,38}

Pegylated interferon and ribavirin

The response to treatment for HCV appears similar in immunocompetent persons with HIV-HCV co-infection and individuals with HCV mono-infection. Treatment responses probably decline with increasing immunodeficiency, although not all studies have found an association between CD4 count and treatment response.^{39,40}

The aim of HCV therapy is the normalisation of alanine aminotransferase (ALT) and eradication of HCV RNA from serum. This is referred to as a sustained virological response (SVR) and is defined as a normal ALT and negative serum HCV RNA six months after completion of therapy. Typically, HCV genotypes 2 and 3 have better response rates than genotypes 1 or 4. Other factors associated with higher response rates are: less hepatic fibrosis and low HCV viral load. Treatment with cART, race and body mass are less significant predictors of treatment response.⁴¹ The response to therapy is predicted by changes in HCV viral load as early as four weeks after therapy commencement in people with HIV-HCV co-infection.^{42,43}

In HCV mono-infection, pegylated interferon with ribavirin treatment is associated with a SVR in 54% of all patients treated, and 80% of those with genotypes 2 or 3 HCV infection.⁴⁴ In HCV mono-infection, therapy is recommended for 12 months in persons with genotypes 1 or 4 HCV infection and six months for persons with genotypes 2 or 3 HCV infection, unless there is advanced fibrosis, as response rates are higher with genotypes 2 and 3. More recently, shorter courses of therapy have been investigated in HCV mono-infection, but have not yet been demonstrated to be effective in HIV-HCV co-infection. In HIV-HCV co-infection, the rates of SVR after treatment with pegylated interferon-alfa and ribavirin are lower than those in HCV people with HCV mono-infection, but overall SVR rates of 49%, with 72% for genotypes 2 and 3 and 35% for genotypes 1 and 4, have recently been reported.⁴⁵ This study was different to earlier studies of HCV treatment in HIV co-infection as weight-based ribavirin dosing and a longer duration of therapy (up to 72 weeks in some cases) was used. People with HIV co-infection and genotypes 2 or 3 who have an undetectable HCV viral load at week 4 may be able to be treated for 24 weeks, rather than 48 weeks as has been previously recommended (Figure 21.3).⁴⁶

Table 21.1 Approach to management of a person with HIV-HCV co-infection

1. Evaluation of cofactors

- Alcohol abuse – worsens HCV disease progression
- Ongoing injection drug use – consider methadone maintenance if opiate user; risk of re-infection if HCV treatment effective
- HBV co-infection
- Immunity to HAV and HBV – vaccinate if not immune as co-infection may worsen liver disease in persons with chronic HCV infection
- Depression – assess and manage before consideration of interferon-alfa therapy
- Likely adherence to dual methods of contraception – ribavirin is teratogenic
- Significant cardiopulmonary disease that may be exacerbated by ribavirin-induced haemolytic anaemia

2. Evaluation of HIV infection

- Determine prognosis of HIV disease based on surrogate markers and clinical status to help determine relative importance of HIV treatment compared with HCV treatment
- If already stable on cART, then addition of HCV therapy should depend on assessment of HCV disease

3. Evaluation of HCV infection

- Duration of infection
- Clinical assessment for signs of chronic liver disease or cirrhosis
 - If cirrhotic, classify as compensated or decompensated – decompensated cirrhosis is a contraindication to interferon
 - If decompensated cirrhosis – referral to centre experienced in management of liver failure
- Liver function tests:
 - Alanine aminotransferase (ALT) – persistently normal serum ALT levels on three occasions over six months unlikely to be associated with significant hepatic fibrosis, although normal serum ALT level does not exclude the possibility
 - Markers of cirrhosis – reduced serum albumin level, elevated INR, thrombocytopenia - may be difficult to interpret as some of these markers occur in HIV disease
- HCV genotype – determines likelihood of therapeutic success and duration of therapy
- HCV viral load – high viral load reduces chance of successful therapy
- Consider liver biopsy to assess degree of fibrosis (F0-F4) if HCV treatment being considered and if decision about treatment would be altered (e.g. patient uncertain about treatment)
- Management may be altered on the basis of biopsy result:
 - F0 – consider repeat biopsy in three years to assess disease progression, or treat to eliminate infection
 - F1-F2 – consider treatment if not immunodeficient – if no treatment, consider repeat biopsy in three years to assess disease progression
 - F3-F4 – recommend treatment unless patient has decompensated cirrhosis

4. Treatment strategy

- The sequence of HIV or HCV therapy depends on the relative severity of the two conditions, the likelihood of adherence and response to therapy, behaviours that may result in HCV re-infection, current co-existing conditions, and prior drug toxicities

HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus; cART = combination antiretroviral therapy.

Management of pegylated interferon-alfa and ribavirin toxicity

As there are overlapping toxicities between cART and pegylated interferon-alfa plus ribavirin (Table 21.2), the best strategy may be to treat HCV early in the course of HIV infection, so that toxicity and potential drug interactions are minimised. As ribavirin causes a haemolytic anaemia and zidovudine may also cause anaemia, this combination should be avoided if possible. However, avoiding this combination is not always possible, and it is not an absolute contraindication. Ribavirin enhances the phosphorylation of didanosine and is associated with an increased risk of lactic acidosis and is contraindicated.^{47,48} Interferon therapy is associated with a reversible reduction in CD4 cell count.

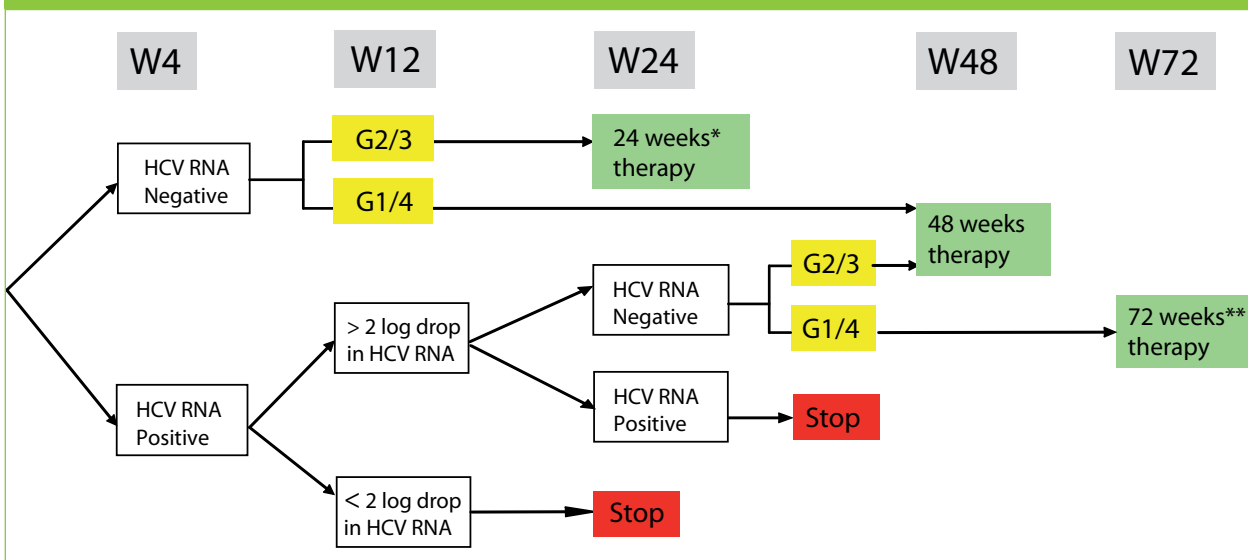
Depression induced by pegylated interferon-alfa can be managed with counselling with or without oral paroxetine 20 mg daily.⁴⁹ Severe depression with suicidal ideation requires cessation of interferon therapy, as suicide has been reported as a complication of therapy for HCV infection. Prophylactic paracetamol or non-steroidal anti-inflammatory drugs and treatment of symptoms may improve the tolerability of side-effects secondary to pegylated interferon-alfa. It is important to warn patients of the likely toxicities of these agents to maximise treatment adherence.

Dose reduction is effective in controlling many of the adverse events associated with pegylated interferon-alfa and ribavirin therapy, but efficacy may be compromised. There are suggestions that haematopoietic factors (e.g. erythropoietin and granulocyte-colony-stimulating factor) are associated with improved treatment outcomes, although funding for such treatments is problematic.⁵⁰

Table 21.2 Toxicities of pegylated interferon-alfa and ribavirin

Pegylated interferon-alfa	
Systemic	Flu-like symptoms Fevers Chills Weight loss Poor appetite Fatigue Nausea and vomiting Headache Myalgia Arthralgia
Neuropsychiatric	Depression Irritability Anxiety Mood swings Neuropathy
Dermatological	Alopecia Rash Dry skin
Haematological	Neutropenia Thrombocytopenia
Autoimmune	Thyroid disease Exacerbation of other autoimmune disorders (e.g. psoriasis, rheumatoid arthritis, inflammatory bowel disease)
Ribavirin	
	Haemolytic anaemia (e.g. tiredness, breathlessness, myocardial ischaemia) Teratogenicity

Figure 21.3 Proposed optimal duration of hepatitis C virus (HCV) therapy in patients with HVI/HCV-coinfection



W = week; G = genotype.

*In patients with baseline low viral load (<400 000 IU/L) and minimal liver fibrosis.

** 72 weeks of treatment is not currently funded in Australia under Pharmaceutical Benefits Scheme (PBS) s100.

Source: Rockstroh JK, Bhagani S, Benhamou Y, Bruno R, Mauss S, Peters L, et al; EACS Executive Committee. European AIDS Clinical Society (EACS) guidelines for the clinical management and treatment of chronic hepatitis B and C in HIV-infected adults. HIV Med 2008;9(2):82-8. Reproduced with permission.

Non-pharmacological management

Reduction in alcohol consumption is recommended, given the association between excessive alcohol consumption and progression of chronic liver disease in people with HIV-HCV co-infection.²⁰ Vaccination against other hepatotropic viruses (HBV and hepatitis A virus) is recommended. Chronic HBV co-infection is associated with more progressive chronic liver disease in people with HIV-HCV co-infection and immunisation against HBV is important for this population.

21.2.6 Prevention

Addressing safer injecting practices and referral to drug and alcohol services may reduce the risk of re-infection in injecting drug users who successfully eliminate HCV infection with treatment. Recent reports of sexual acquisition of HCV in MSM infected with HIV also highlights the importance of safe sex for prevention of re-infection.

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21.3 HIV and syphilis

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Syphilis in patients with HIV infection generally presents with typical clinical manifestations. Response to therapy is equivalent to that seen in patients without HIV, although anecdotal reports of the failure of syphilis treatment in persons with HIV infection have led to conservative guidelines both in treatment and follow-up. Controlled data are usually not available to support the more conservative guidelines.

21.3.1 Epidemiology

There is a bi-directional relationship between HIV transmission and syphilis which remains incompletely understood. Cross-sectional studies demonstrate that a history of syphilis or genital ulcer disease is associated with an increased risk of HIV infection.¹ Therefore, all patients with HIV should undergo syphilis testing and vice versa.

Changes in the prevalence of syphilis have mirrored changes in prevalence of HIV infection. High rates of syphilis recorded in homosexual men in the USA in the late 1970s coincided with unrecognised HIV transmission. Decreased rates of syphilis were observed after the introduction of safe sex HIV prevention campaigns during the 1980s. Rates of infectious syphilis reached a nadir in approximately 2000 in most developed countries including Australia.² Since that time, an increase in rates of early syphilis has been observed. Rates of notification of infectious syphilis rose 10 fold from 1999 to 2003 in inner Sydney.³ The increased infections have predominantly been in men who have sex with men (MSM). This has increased from 1.2 per 100 000 population in 2000 to 5.7 per 100 000 population in 2005 in the USA. This epidemiological shift is more marked in cities with large MSM populations. California has experienced a 700% increase in notifications of infectious syphilis between 1999 and 2005, of which 80% were documented in MSM. Rates of HIV infection within MSM with early syphilis have varied from 20-60%.⁴

HIV-clinic-based studies have also demonstrated increases in rates of asymptomatic syphilis. One study showed an increased rates from 2.8 to 7.8 per 1000 patient years from 2002 to 2003.⁵

Multiple reasons for the observed increases in syphilis in MSM have been suggested.⁶ An increase in unsafe sex underlies the increase in infectious syphilis, and this increase has been reflected in rising rates of other sexually transmissible infections in MSM.⁷ Factors which have been suggested to cause this behavioural change includes: the success of combination antiretroviral therapy (cART); use of the internet to source sex partners; serosorting (finding sex partners with the same HIV status); and the use of illicit (e.g. amphetamines) and licit (e.g. sildenafil) recreational drugs.⁸ Finally, oral sex is established as an efficient method of syphilis transmission but not HIV infection. Cohort data suggest that changes in risk behaviour may favour syphilis versus HIV transmission.⁹

A role of early syphilis as a cofactor in the apparent increases in HIV infection in western MSM populations has been suggested by some but not all studies.¹⁰

21.3.2 Clinical manifestations

The majority of patients with HIV and syphilis co-infection present with typical manifestations of syphilis. There is some debate regarding the manifestations and progression of syphilis in patients with HIV; some studies have suggested an altered clinical presentation and rate of disease progression,¹¹ while other studies have shown no difference.^{12,13} However, studies of syphilis in individuals with HIV prior to the introduction of cART are limited by the short-term survival of patients, and there are no longitudinal studies of syphilis manifestations following the introduction of cART. Reports of unusual manifestations of syphilis in patients with HIV are likely to represent traditionally uncommon rather than unique complications of syphilis.⁶

Syphilis is classified according to early versus late phases and symptomatic versus asymptomatic (Table 21.3).

Stage	Symptomatic	Asymptomatic
Early	Primary, secondary ¹	Early latent ¹
Late	Tertiary	Late latent

¹ Similar treatment and follow-up required.

Primary syphilis

The classic lesion of primary syphilis, the chancre, is a single, painless, indurated ulcer with a clean base. Chancres are more likely to be larger, deeper and multiple in persons with HIV.^{13,14} Chancres usually appear 14-21 days following infection, but may occur up to 90 days later. There is significant variability in the appearance of the chancre, which makes clinical diagnosis unreliable. Induration is the single most specific sign, and purulence involving less than 30% of the ulcer base is the most sensitive sign.¹⁵ Classically, the margin is sharp. While the lesion is painless, tenderness upon palpation is common. Painless regional lymphadenopathy occurs in up to 80% of patients.

Chancres occur at the site of inoculation. The most common inoculation sites are the coronal sulcus, glans penis, anus and rectum in men, and the labia major, labia minor, fourchette and perineum in women. Extragenital lesions are uncommon and occur in less than 2% of patients. In contrast to genital lesions, extragenital chancres are classically nonindurated and painful.

Secondary syphilis

Typically, the primary lesion heals eight weeks before the onset of secondary syphilis. However, primary and secondary manifestations of syphilis may co-exist in up to one-quarter of patients with HIV infection with secondary syphilis.¹⁴ Conversely, up to 60% of patients with secondary syphilis do not recall a primary lesion. Individuals with HIV are more likely to present with secondary syphilis than those without concurrent HIV infection.¹⁶

Clinical features of secondary syphilis include rash, fever and malaise. A widespread maculopapular rash is the cardinal feature. Involvement of the palms and soles is classically described. Painless lymphadenopathy involving suboccipital, posterior cervical, posterior auricular and epitrochlear nodes occurs in up to 85% of cases. Mouth ulcers, condyloma lata, alopecia, hepatitis, glomerulonephritis and nephrotic syndrome have been reported. Systemic symptoms include malaise, headache, nausea and anorexia. Arthralgia and jaundice have been reported in a subset of patients.

Headache without meningism is commonly reported however other neurological manifestations may also occur in persons with HIV. The occurrence of neurological symptoms portends a poorer prognosis. This is described as early neurosyphilis and is described later.

Rarely, after a prodrome of fever, malaise and headache, disseminated papular-nodular eruptions develop and evolve into pustules with ulcerated necrotic centres. This phenomenon is referred to as **malignant secondary syphilis**. An association between this rare manifestation of secondary syphilis and HIV infection has been suggested, as 11 of the 12 cases of malignant secondary syphilis reported since 1989 have occurred in persons with HIV infection or those at high risk of HIV infection.¹⁷ Classically, patients with this condition experience a severe Jarisch-Herxheimer reaction (see below) following initiation of treatment.

Effect of early syphilis on CD4 cell count and HIV viral load

Early syphilis is associated with transient decreases in CD4 cell count and increases in HIV viral load.⁶ These markers return to baseline following treatment of syphilis. The significance of HIV surrogate-marker changes induced by early syphilis remains speculative. Increases in plasma viral load may contribute to the observed increases in HIV transmission in persons with genito-ulcerative disease secondary to syphilis. There is no evidence that these transient alterations in HIV surrogate markers accelerate HIV disease progression. Unexplained alterations in these markers may prompt syphilis testing in persons with HIV.⁶

Latent syphilis

The latent period of syphilis is defined as the period between the early symptomatic period (which may be unrecognised) and the development of tertiary manifestations. Serological evidence of syphilis in the absence of signs or symptoms is referred to as latent-stage disease. This period is divided into early latent and late latent periods. This distinction is made because of the likelihood of spontaneous mucocutaneous (and infectious) relapse in untreated patients.

About 25% of patients with untreated early symptomatic syphilis will experience a relapse: 90% of relapses occur within one year, 94% occur within two years and 100% occur within four years. Therefore, a patient with early latent syphilis is considered infectious because they have about a 25% chance of relapse to secondary syphilis.¹⁸

In contrast, patients with late latent syphilis are not considered infectious and the primary aim of treatment in this context is to reduce the risk of disease progression.

Tertiary syphilis

There have been many reports suggesting that neurosyphilis is more common, more likely to present with atypical signs and more rapidly progressive in patients with HIV infection compared with patients without HIV.¹⁹⁻²¹ However, longitudinal comparative studies have not been performed. Asymptomatic neurosyphilis, defined as the presence of cerebrospinal fluid (CSF) abnormalities in the absence of neurological symptoms or signs, is the most common form of tertiary syphilis.²² Meningovascular syphilis affects about 10% of patients with neurosyphilis and peaks at four to seven years after infection. The typical clinical scenario is one of a diffuse encephalitic presentation with superimposed focal features.²³ Headache usually precedes the vascular injury.

Neurosyphilis

Despite early case reports^{24,25} suggesting that neurosyphilis may be more common and more aggressive in persons with HIV infection, it is not known if in fact this is the case. Cohort studies have failed to demonstrate a difference. Surveillance studies found no increase in neurosyphilis from 1985 to 1992 despite increases in HIV infection in California.²⁶ However recent reports of neurosyphilis have generally occurred in persons with HIV. No contemporary comparative studies have been conducted. One recent cohort study reported 41 cases of neurosyphilis in 231 cases of newly diagnosed syphilis in patients with HIV spanning a period of 16 years.⁹² Immune dysfunction was suggested to predict neurosyphilis as both low CD4 cell count and absence of antiretroviral therapy both predicted neurosyphilis (as did rapid plasma reagin (RPR) > 1:128) in this cohort.

There are three distinct entities of neurosyphilis. These include early, asymptomatic and tertiary neurosyphilis.

1. Early neurosyphilis

Early neurosyphilis (ENS) is defined as neurological disease occurring in persons with early syphilis.²⁷ It must be distinguished from uncomplicated secondary syphilis and thorough neurological examination is mandatory for all patients presenting with secondary syphilis. ENS is thought to primarily involve the meninges and blood vessels (meningovascular syphilis).

ENS is increasingly recognised as a serious complication of syphilis in persons with HIV infection. The risk of having neurosyphilis in MSM with HIV who have early syphilis has been estimated to be 1-2%.^{27,28} The risk of having persistent neurological deficit at six months despite treatment was estimated to be 0.5%. These data underscore the importance of preventing syphilis in MSM with HIV infection.

Symptoms of early neurosyphilis include cranial nerve dysfunction, acute meningitis, cerebrovascular accident, headache or altered mental status of recent onset. Cranial nerve dysfunction occurs in more than 50% of cases. Ocular, auditory and facial nerves are most commonly affected. Ocular abnormalities, including optic neuritis and iritis, may also occur.

ENS may be the only manifestation of syphilis in over 50% of patients. Therefore any MSM presenting with cranial nerve defects or other unexplained neurological deficit should be evaluated for syphilis and HIV.

2. Asymptomatic neurosyphilis

It is estimated that between 10-25% of asymptomatic patients with HIV and late latent syphilis have CSF findings suggestive of neurosyphilis.^{29,30} It is unclear if rates of asymptomatic neurosyphilis are increased in persons with HIV infection. Treponemal central nervous system penetration occurs in early syphilis in many patients regardless of HIV status.¹³ Most cases of early clinical neurosyphilis have been reported in persons with HIV infection²⁷ and a correlation between CSF findings suggestive of neurosyphilis and advanced HIV disease^{31,30} have led to the hypothesis that HIV-induced immunological defects result in reduced treponemal CNS clearance with subsequent development of clinical neurosyphilis. This is supported by the observation that patients with HIV and CD4 cell counts less than 200 cells/ μ L were 3.7 times less likely to normalise CSF abnormalities after being treated for neurosyphilis than persons with HIV infection and CD4 cell counts above 200 cells/ μ L.³²

Ocular syphilis

Ocular involvement has been reported in 4.6% of cases with secondary syphilis and 2.6% of persons presenting with uveitis have syphilis.³³ It is not known if patients with HIV are more likely to present with ocular manifestations of syphilis although some authors have suggested that this may be the case.³⁴ Patients with syphilitic uveitis present with decreased vision, redness, pain, photophobia, visual field defects and floaters. The most common ocular manifestations are anterior uveitis, vitritis and optic disc oedema. Retinitis, periopic and retrobulbar neuritis are less commonly described.^{35,36} Cutaneous manifestations can occur in up to 40% of patients with ocular syphilis. Nontreponemal titres are generally high (>1:16). CSF abnormalities have been reported in 30-70% of cases.^{36,37} HIV testing should be offered in all patients who present with ocular syphilis. Delays in diagnosis can lead to irreversible vision loss secondary to optic nerve or retinal atrophy.³⁵

Benzathine penicillin is inadequate for ocular syphilis. Procaine penicillin or intravenous penicillin treatment as for neurosyphilis is required.³⁸

Otologic syphilis

This complication may present with asymmetrical hearing loss, tinnitus or vestibular disturbances.³⁹ All patients diagnosed with syphilis should be assessed for otologic complications. Neurosyphilis treatment is recommended as permanent otological deficits can persist after benzathine treatment. It is not known if these manifestations are more common in persons with HIV infection.

3. Tertiary neurosyphilis

Pathologically this type of neurosyphilis involves the blood vessels and brain parenchyma. The classic presentations include general paresis which is a chronic, insidious meningoencephalitis and tabes dorsalis which is a deficit of the posterior columns of the spinal cord causing sensory ataxia, bowel and bladder dysfunction.

Re-infection

Re-infection is possible with syphilis and is detected by an increasing nontreponemal assay titre.⁴⁰ Regular syphilis testing is recommended for all sexually active patients with HIV infection and prior syphilis to detect re-infection or relapse. It is difficult to distinguish re-infection from relapse of treated syphilis. This can usually only be done using molecular-based methodology

which is generally not available in routine clinical practice.⁴¹ A rare form of relapsing syphilis, chancre redux or monorecive, has been described in which the chancre reappears in the same anatomical site in untreated or inadequately treated patients.⁴⁰

21.3.3 Diagnosis

The diagnosis depends on clinical findings, examination of lesions for treponemes and serology. The diagnosis of syphilis is the same for patients with and without HIV infection.⁴² Syphilis is usually diagnosed on serological grounds (Table 21.4). Detection of treponemes is reserved for cases where serological diagnosis can not be confirmed.

Detection of treponemes

Darkfield microscopy of lesion exudate was the previous gold-standard test for the diagnosis of lesions suggestive of syphilis. However its role is limited by the need for specialised equipment and training. It is also not useful for the diagnosis of oral or rectal lesions due to the possibility of contaminating non-pathogenic treponemal species. Syphilis polymerase chain reaction (PCR) assays have been developed for lesional syphilis diagnosis and is now the most common assay used in this context. Sensitivity and specificity greater than 90% and 95% have been reported.^{43,44}

Serological diagnosis of syphilis

Screening tests for syphilis involve enzyme immunosorbent assays (EIA), which have high sensitivity and specificity.⁴⁵ Syphilis EIA have higher sensitivity (93% v 86%) and equal specificity to traditional assays. There is an appreciable false-positive rate for syphilis EIA, especially in low prevalence settings. Rates of biological false-positive rapid plasmin reagin (RPR) tests are higher in patients with HIV (1-5.8%) compared with the general population (0.2-0.8%) and more common in injecting drug users with HIV infection.⁴⁶⁻⁴⁸

Positive EIA are then confirmed by traditional serological syphilis assays, which are based on the combination of nontreponemal and treponemal assays. The nontreponemal serological screening tests (Venereal Disease Research Laboratory - VDRL) and RPR are reactive in secondary and untreated latent and tertiary syphilis. The sensitivity of serological tests for the diagnosis of syphilis increases with the duration of infection. It ranges from 75% in primary syphilis to 100% in secondary and later syphilis.⁴⁹ These assays perform equally well in patients with HIV infection. There is no conclusive evidence to suggest that patients with HIV infection are more likely to have false-negative results despite some isolated case reports over a decade ago.^{50,51}

The most commonly used treponemal assays are the serum fluorescent treponemal antibody absorption test (FTA-Abs) and the microhaemagglutination test for *Treponema pallidum* particle agglutination (TP-PA). There are some data to suggest that nontreponemal titres are higher in patients with primary syphilis who also have HIV disease.¹⁶ These results are not influenced by CD4 cell count. Patients with HIV who do not have suppressed viral replication may have higher nontreponemal titres although this is not well studied.

Patients with HIV infection have higher titres of nontreponemal assays.¹³ This may be secondary to the characteristic polyclonal B-cell activation which characterises HIV infection. However, the occurrence of a false-positive RPR is not related to the degree of immunodeficiency.

Table 21.4 Expected serology

	Untreated				Treated	
	Primary	Secondary	Early latent	Late latent	Recent	Distant
EIA	+/-	+	+	+	+	+
Non-treponemal assay e.g. RPR	+/-	+	+	+/-	+/-	-
Treponemal assay e.g. TP-PA or FTA-Abs	-	+	+	+	+*	+*

+ = reactive; +/- = may or may not be reactive; - = usually non-reactive; * = treponemal titres may revert to non-reactive in up to 10% of patients (see text)
EIA = enzyme immunoassay; RPR = rapid plasma reagin assay; TP-PA = *Treponema pallidum* particle agglutination test; FTA-Abs = fluorescent treponemal antibody absorption test.

Clinicians should be aware of the prozone effect which may account for a false-negative RPR. This occurs when a high concentration of treponemal antigen does not permit the antigen-antibody complex formation. This is corrected by diluting the sample to reveal a reactive RPR. Most laboratories do not routinely dilute serum in this context. Therefore, the clinician must specifically request dilution to detect a prozone effect.

Treponemal reactivity may also be lost in patients with HIV disease, giving rise to biological false-negative results. In one study, loss of specific treponemal reactivity occurred in 10% to 14% of patients with HIV compared with no HIV-negative patients.⁵² Loss of reactivity was associated with symptomatic HIV disease, a single episode of syphilis and a low initial VDRL titre ($\leq 1:32$). Time since treatment did not influence loss of treponemal reactivity rates. The role of syphilis EIA in identifying false-negative results is yet to be determined.⁵³ All patients with negative nonspecific tests and positive specific tests should be treated if they have not received appropriate treatment in the past.

In 2008, three-monthly sexually transmissible infection screening is recommended for all sexually active MSM who have multiple partners or frequent sex on premises venues, in an attempt to curb the marked increase in sexually transmissible infections including syphilis.^{42,54}

Diagnosis of neurosyphilis

Symptomatic or asymptomatic late latent (or unknown duration) syphilis

CSF analysis is required for the diagnosis of neurosyphilis. Lumbar punctures are required in all patients with neurological symptoms and positive serum syphilis serology and in all patients with asymptomatic late latent syphilis or syphilis of unknown duration.⁵⁵ At least 10% of persons with HIV infection with latent syphilis will have a positive CSF-VDRL, a specific marker for neurosyphilis.¹⁹ Patients with symptomatic neurosyphilis have more CSF abnormalities than patients with asymptomatic neurosyphilis.⁶

Asymptomatic early syphilis

The definition of asymptomatic neurosyphilis has been problematic in persons with HIV infection with early syphilis. A presumptive diagnosis is made generally on the basis of CSF abnormalities.

CSF markers suggestive of neurosyphilis

The CSF abnormalities seen in neurosyphilis include an elevated lymphocyte count, increased protein and a reactive CSF VDRL. This latter assay has high specificity but lower sensitivity (22–69%), so that the test may be negative in one-third of patients with neurosyphilis.⁵⁶ However, there is no consensus as to what particular CSF markers should be used to diagnose neurosyphilis. Most studies use CSF VDRL, which lacks sensitivity, and elevated white cell counts. CSF-FTA Abs and TP-PA have been suggested to be useful in some recent studies.^{57,58} The intrathecally produced *T. pallidum* antigen index may be used to diagnose neurosyphilis when the CSF VDRL is negative.^{19,59,60} Most recent studies have not included an elevated CSF protein in the definition of neurosyphilis because there are many other causes of high CSF protein in patients with HIV infection. It should be noted that an increased leukocyte count and increased protein in the CSF are observed in up to 40% of patients with HIV infection without co-existent syphilis. Some studies have defined CSF findings consistent with neurosyphilis as having a high white cell count (>20 cells/hpf) in an attempt to increase the specificity of the diagnosis of neurosyphilis.^{31,61} Detection of treponemes in the CSF by PCR is currently not recommended due to the low sensitivity of the available assays.⁶² Patients with RPR $\geq 1:32$ were six times more likely than patients with RPR $< 1:32$ to have neurosyphilis.³¹

Prognostic significance of CSF abnormalities in asymptomatic patients with HIV infection with early syphilis

The prognostic significance of the CSF abnormalities has not been validated in persons with HIV infection, nor in those with early syphilis, in whom elevated protein and cell counts may occur, but may not develop clinical neurosyphilis.^{61,63} In fact, no correlation between CSF abnormalities and clinical manifestations of neurosyphilis was observed in one study.³¹ This report supported earlier studies which suggested that CSF findings in early syphilis did not predict the development of clinical neurosyphilis.^{13,19} A weak correlation between CSF treponemal detection by PCR and CSF abnormalities was reported in one study,⁵⁷ while another study demonstrated a correlation between clinical neurological abnormalities and CSF abnormalities and serum RPR.⁶⁴

There is debate in the literature regarding the association between neurosyphilis and CD4 cell count. Some studies have found that patients with low CD4 cell counts (<350 cells/ μ L) are more likely to have CSF abnormalities suggestive of neurosyphilis^{31,6} while other studies have not been able to confirm this association.

The role of lumbar puncture in asymptomatic patients with HIV infection with early syphilis

Given the uncertainties outlined above a variety of approaches exist. The exact approach taken, in large part, depends on the intended treatment plan.

A. Lumbar puncture in all asymptomatic patients with HIV and early syphilis

Some authors have recommended that all patients with HIV and syphilis should undergo lumbar puncture to identify those patients with asymptomatic neurosyphilis who are at risk of developing symptomatic neurosyphilis and require enhanced treatment (see below).^{29,31,60}

B. Lumbar puncture in no asymptomatic patients with HIV and early syphilis

This approach is supported by the observation that invasion of the central nervous system (CNS) is common during this stage of the infection and the CNS findings are not predictive of the development of neurosyphilis.¹³

C. Lumbar puncture only in asymptomatic patients with HIV and early syphilis who are at high risk of neurosyphilis

Some authors have advocated targeting asymptomatic patients who have been identified to be at increased risk of neurosyphilis for lumbar punctures. Those found to have CSF findings suggestive of neurosyphilis should then receive intravenous penicillin based treatment (see later). Some authors suggest that patients with HIV infection with early syphilis and a CD4 cell count <350 cells/ μ L and RPR >1:32 should undergo lumbar puncture and receive treatment for neurosyphilis if CSF findings support this diagnosis.^{31,64} However, this is not universally accepted.^{6,42}

D. Lumbar puncture in no patients with asymptomatic neurosyphilis but treat all patients with procaine penicillin

Alternatively, all asymptomatic patients should be treated with procaine penicillin (see later) avoiding the need for lumbar punctures in persons with early neurosyphilis. However the benefit of identifying patients with asymptomatic laboratory-defined neurosyphilis for enhanced penicillin treatment has not been proven. An earlier study using non-contemporary enhanced treatment for patients with early syphilis found no advantage in enhanced treatment over conventional treatment.¹³

It is not known if the risk for the development of neurosyphilis can be further stratified by CD4 cell count or serum non-treponemal titre. While persons with CD4 cell counts <350 cells/ μ L and RPR >1:32 are more likely to have CSF abnormalities suggestive of neurosyphilis^{31,64} there is no data to suggest that they are at increased risk of symptomatic neurosyphilis. These studies grouped patients with early and late syphilis together which may have overcalled those patients with significant CSF abnormalities. These studies were retrospective in nature and thus their findings are limited.

The lack of longitudinal data to support the use of enhanced treatment for neurosyphilis over conventional treatment for early syphilis in patients with HIV infection has lead some to reject these recommendations. Conversely proponents

argue that there are no data to suggest that CSF-VDRL is less predictive of neurosyphilis in patients with early versus late syphilis. Similarly there are no data to suggest that a reactive CSF-VDRL in patients with early syphilis is likely to become nonreactive. Using the very strict definition of neurosyphilis (i.e. CSF-VDRL reactive): no asymptomatic patient with a serum RPR of less than 1:32 had a reactive CSF-VDRL and while 15/42 (36%) asymptomatic patients with an RPR \geq 1:32 met the broader definition of neurosyphilis, 5/42 (12%) had a reactive CSF-VDRL.^{64,66}

21.3.4 Treatment

Primary, secondary and early latent syphilis

There is great diversity of opinion amongst different published guidelines and practice for the treatment of early syphilis in patients with HIV (Table 21.5).

Procaine penicillin

Procaine penicillin regimens (1.0 and 1.5 g plus probenecid 500 mg four times daily for 10 days) have largely superseded benzathine penicillin regimens. This regimen is well tolerated and adherence is easily achieved.⁷² Numerous lines of evidence converge to support this shift. High rates of early neurosyphilis (1.7%) with significant long-term sequelae despite treatment (0.5%) occur in persons with HIV.²⁷ This suggests that treatment should achieve treponemocidal CSF levels of penicillin in all patients with HIV infection with early syphilis. Procaine penicillin at doses \geq 0.5 g (i.e. \geq 5 000 000 units) intramuscularly daily with probenecid 500 mg four times daily has been demonstrated to achieve treponemocidal levels within the CSF.^{71,91}

Arguments against this approach are that 75% of patients with early syphilis (who have been referred for lumbar puncture in retrospective clinical trials) do not have CSF findings suggestive of neurosyphilis and may not require enhanced treatment above a single dose of benzathine penicillin.^{6,66}

A compromise position has been suggested that asymptomatic patients with early syphilis who may be at increased risk of neurosyphilis should undergo CSF analysis (see earlier). Two retrospective studies have reported that patients with RPR >1:32 have an increased risk of CSF findings suggestive of neurosyphilis.^{31,64} These authors suggest that patients with RPR >1:32 (and/or CD4 cell count <350 cells/ μ L) should undergo CSF analysis. With this approach, approximately 25% of patients will be found to have CSF findings suggestive of neurosyphilis and may benefit from intravenous penicillin therapy. Conversely 75% of patients would only require benzathine penicillin therapy. The Centers for Disease Control and other authors reject this approach.^{6,42}

Comparative trials between procaine penicillin and benzathine penicillin have not been performed.⁷³

Benzathine penicillin

Some guidelines recommend benzathine penicillin (2.4 MU or 1.8 g intramuscularly once) for all patients with HIV and early syphilis.⁴² However there are concerns that this treatment may be inadequate given the insufficient CSF penetration of penicillin administered in this formulation and reports of clinical failure following benzathine penicillin treatment.⁶⁷ Some authorities recommend giving benzathine penicillin weekly for three weeks to enhance the perceived inadequate neurological effect of a single dose of benzathine penicillin.⁶⁸

Table 21.5 Management of syphilis in non-penicillin allergic patients with HIV

Syphilis stage		Drug	Dose	Follow-up	Comments
Early	Primary Secondary Early latent	Procaine penicillin ¹	1.0 - 1.5 g daily for 10 days	Clinical and serological review at 3, 6, 12, and 24 months	As for non-HIV patients
Late	Late latent	Procaine penicillin ²	1.5 g IM daily plus probenecid 500 mg 4 times daily for 10-14 days	Clinical and serological review at 6, 12 and 24 months	LP indicated (NB: different from non-HIV patients)
Late	Non- neurological tertiary	As for late latent disease	As for late latent disease except duration extended to 20 days	Clinical and serological review at 6, 12 and 24 months	LP indicated
Late	Neurosyphilis (including ocular disease)	Aqueous penicillin G	3 - 4 MU every 4 hours IV for 15 days	Clinical and serological review at 6, 12 and 24 months	As for non-HIV patients Failures have been reported in HIV patients treated with recommended doses
1 Alternative benzathine penicillin 2.4 MU x1 2 Alternative benzathine penicillin 2.4 MU IM for three weekly doses					
LP= lumbar puncture; IM= intramuscularly; IV= intravenously.					

Anecdotal reports of neurosyphilis in people with HIV treated with benzathine penicillin (suggesting failure of this regimen)⁶⁹ and neurological relapse has been reported in up to 10% of patients with HIV with primary or secondary syphilis treated with benzathine penicillin.⁷⁰

Jarisch-Herxheimer reaction

This is an acute systemic reaction which occurs two to six hours after the initial dose of penicillin. It is thought to be secondary to the release of treponemal antigens and endotoxin, although the exact pathogenesis is unknown.⁷⁴ It is characterised by fever, malaise, arthralgia and worsening rash. It has been reported to occur at variable rates from 10-80% of patients.¹³ Patients with HIV infection are twice as likely to experience Jarisch-Herxheimer reaction (JHR) than patients without HIV infection.¹³ In patients being treated with neurosyphilis, administration of prednisolone 20 mg 12 hourly for three doses may prevent JHR.

Late latent syphilis

The recommended treatment is procaine penicillin 1-1.5 g (cf 1.5 gm) intramuscularly daily and probenecid 500 mg four times daily for 15 days or benzathine penicillin 2.4 MU intramuscularly weekly for three doses.

The recommendations for prolonged therapy in patients with late latent syphilis are made for two reasons. Prolonged therapy is required in latent syphilis, because it is assumed that spirochetes are dividing more slowly during this phase of the illness and that treponemical CSF levels of penicillin are required to ensure adequate treatment and to prevent neurosyphilis. Previously, standard therapy for late latent syphilis was benzathine penicillin (2.4 MU intramuscularly weekly for three weeks). However, based on the failure to demonstrate treponemical levels of penicillin after the administration of benzathine penicillin⁷⁵, as well as anecdotal reports of failure of this regimen, treatment with daily procaine penicillin is preferred.

However, it should be noted that these recommendations are not based on clinical trial data.

Neurosyphilis

The Centers for Disease Control recommended treatment in patients without HIV infection is aqueous benzylpenicillin (4 MU every four hours for 15 days intravenously), or procaine penicillin (2.4 gm intramuscularly daily) and probenecid (500 mg four times daily) for 20 days.

While there is no consensus in the literature regarding the appropriate treatment of neurosyphilis in patients with HIV most Australian experts would use intravenous penicillin.

The role of non-penicillin-based therapies

As the role of non-penicillin-based therapy for syphilis has not been validated, penicillin desensitisation is recommended in all patients with HIV with a history of non-anaphylactoid penicillin hypersensitivity. A variety of schedules is available, which have been recently reviewed.⁷⁶ Desensitisation should not be considered in persons with prior anaphylactoid reactions to penicillin and non-penicillin based therapies should only be used in this context. All other patients with historical penicillin allergies should be referred for penicillin desensitisation. While a number of non-penicillin-based regimens have been used, there are little data to support their use in persons with HIV infection. Lumbar puncture is mandated to exclude neurosyphilis and provide a baseline of CSF markers to assess response to treatment.⁴² Patients and clinical staff should be aware of the need for careful clinical follow-up in patients with HIV infection who receive non-penicillin-based regimens to treat syphilis.

Non-penicillin-based regimens include:

1. Doxycycline (100 mg twice daily for 14 days for early syphilis or 200 mg twice daily for 28 days for late syphilis).^{77,78} These studies were not adequately powered to detect a difference in treatment response between patients with and without HIV infection.
2. Ceftriaxone (1 g intramuscularly for 10 days) has also been used to treat early syphilis.⁷⁹⁻⁸¹ On the basis of pharmacokinetic data alone, a single dose of ceftriaxone would not be expected to provide adequate therapy for early syphilis.⁸² Ceftriaxone (2 g intravenously) daily for 10 to 14 days has been suggested as an alternative to penicillin for neurosyphilis.⁸³ An open-labelled study compared ceftriaxone with standard intravenous penicillin in patients with CSF abnormalities consistent with neurosyphilis. Serological responses were similar in both groups. Higher rates of prior neurosyphilis in the intravenous penicillin group and higher rates of secondary syphilis in the ceftriaxone group may have obscured a difference in treatment responses.
3. Azithromycin can no longer be considered, given high rates of resistance, and high levels of treatment failure compared with penicillin-based therapy.⁸⁴⁻⁸⁶

Assessing treatment response

The assessment of an adequate response to treatment in syphilis is generally the same for patients with HIV infection and those without HIV infection. Clinical failure is defined as the persistence of clinical manifestations three months after appropriate therapy, or the development of a new clinical manifestation following therapy. Patients who experience clinical failure require CSF analysis and should receive a second round of treatment.

Appropriate serological responses to syphilis treatment is more difficult to define. A four-fold decline in nontreponemal titre over a six-12 month period is considered satisfactory in patients with and without HIV infection. Serological failure has been recently reported to occur in up to 40% of HIV-infected patients treated for syphilis.⁹² Patients with low CD4 cell counts and those not receiving antiretroviral therapy were more likely to experience serological failure in this study.

Patients with high baseline nontreponemal titres are more likely to be defined as having treatment failure on serological grounds independent of HIV status.⁸⁷ Previously reported increased rates of treatment failure on serological grounds in persons with HIV infection treated for early syphilis were likely to be secondary to an apparent slower decline from high baseline nontreponemal titres and to be of no clinical significance. A persistent low level (<1:8) nontreponemal titre occurs more commonly in patients with HIV.¹³ This is not thought to be clinically significant. There are no data to suggest that such patients benefit from further treatment.

A satisfactory response to treatment of neurosyphilis involves resolution of symptoms, a four-fold reduction in serum nontreponemal titres and a normalisation of CSF pleocytosis by six months and all other CSF parameters by 24 months.⁴²

Unsatisfactory treatment responses to neurosyphilis have been reported in up to 30% of patients.⁸⁸ CSF serological response to therapy and normalisation of CSF markers for asymptomatic

neurosyphilis has been slower in patients with HIV-infection versus those without HIV in some uncontrolled studies.^{12,32,89}

CSF re-evaluation and retreatment are indicated in patients with persistent or new clinical disease, rising titres or failure of initially high, nontreponemal-specific titres ($\geq 1:32$) to decrease by 12 to 24 months after therapy. In light of the observation of the delayed serological responses to syphilis treatment in persons with HIV, some authors have suggested that serological responses should be observed for 12 months for early syphilis and 24 months for late syphilis before considering treatment has failed.⁶

21.3.5 Contact tracing

Early identification and treatment of partners of patients with HIV and syphilis potentially limits the spread of both infections. Given high rates of syphilis among MSM with HIV and the significant rates of early neurosyphilis in this group, renewed efforts to contact trace are warranted in an attempt to reduce the transmission of both infections and reduce the incidence of permanent neurological morbidity in MSM with HIV following early syphilis.

Presumptive treatment is recommended for any sexual contact within the past 90 days of a person with early syphilis. Treatment is one dose of benzathine penicillin 2.4 MU intramuscularly. If the contact was more than 90 days ago, presumptive treatment is not necessary unless follow-up is problematic. There is increasing use of the internet to assist contact tracing. This is via contacting internet-based sexual networks by public health agencies.⁶ Alternatively, individuals can leave anonymous messages for contacts (e.g. www.whytest.com.au). These patients should be offered testing for HIV and other sexually transmissible diseases.⁷³

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