

# HIV, HBV, HCV and STIs: similarities and differences

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## Introduction

The three major blood-borne viruses, human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV), are members of different virus families but have one thing in common: their major mode of transmission is via blood or bodily fluids. Sexually transmitted infections (STIs) are a diverse group of infections caused by widely differing micro-organisms (viruses, protozoa, bacteria, yeasts, ectoparasites and even a nematode), whose common characteristic is that they are transmitted from person to person by sexual contact such as deep kissing, vaginal sex, anal sex, oral sex, oro-anal sex or just close intimate physical contact.

Table 1.1 provides a list, probably not exhaustive, of the causative agents and their accompanying infections which are capable of being sexually transmitted (i.e. sexually transmissible infections). The distinction between the terms 'sexually transmitted' and 'sexually transmissible' is a fine one and there is little consensus about the correct usage—in this monograph the terms will be used interchangeably, with 'sexually transmitted' being favoured.

Some infections (e.g. gonorrhoea, chlamydia and syphilis) are readily recognisable as being STIs while others (e.g. hepatitis A and the enteric infections) are only sexually transmitted under certain circumstances, namely where sexual activity facilitates oro-anal transmission (Table 1.1). The three major blood-borne viruses mentioned above are all capable of sexual transmission so can also be categorised as STIs, with HIV and HBV very readily sexually transmitted, but HCV only rarely sexually transmitted (see below). Despite their diversity, STIs share two other common characteristics which justify considering them as a group:

- Similar behavioural characteristics lead to people contracting, and being at risk of, STIs—so control strategies are similar for all of them

- Most STIs, in their early stages, are asymptomatic or so mildly symptomatic as to be easily overlooked, yet are infectious—screening at-risk people is essential for population management.

## Key points

- Human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) are distinct viruses with different epidemiological profiles, modes of transmission, natural histories and treatments.
- All three viruses lead to chronic infection in many infected individuals and are characterised by hypermutability and quasispecies.
- The microbiological and virological agents which cause STIs are highly diverse, having specific epidemiological profiles, varied modes of sexual transmission, different natural histories and individual treatment modalities.
- HIV is transmitted through sexual contact, blood-to-blood contact and mother-to-child transmission. Without treatment, most infected individuals develop severe immune deficiency within ten years. Combination antiretroviral therapy has transformed the course of the disease, extending the life expectancy of infected individuals by many years.
- STIs have a complex synergistic relationship with HIV. Most STIs play an enhancing role in the acquisition and transmission of HIV, while HIV may alter the natural history and response to treatment of some STIs.
- HBV is transmitted through mucous membrane contact (including unprotected sexual contact), blood-to-blood contact, mother-to-child transmission and intrafamilial transmission. A safe and effective vaccine against HBV is available. The age of infection is crucial in determining the natural history of HBV. For people who develop chronic active hepatitis B, treatment is effective in a substantial minority of patients. Chronic active hepatitis B may progress to cirrhosis and hepatocellular carcinoma.  
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**TABLE 1.1 Sexually Transmissible Infections (i.e. those capable of sexual transmission)**

STI	Causative micro-organism	Mode of sexual transmission	Commonly found in:
<b>BACTERIA</b>			
bacterial vaginosis (probably NOT a true STI)	<i>Gardnerella vaginalis</i> , <i>Atopobium vaginae</i> , <i>Mobiluncus sp</i> and other anaerobic bacteria	unknown	WSW, but also any sexually active woman
chancroid	<i>Haemophilus ducreyi</i>	genital skin to skin and mm to mm contact	individuals who have unprotected sex in endemic areas
donovanosis	<i>Klebsiella granulomatis</i>	uncertain	remote Indigenous communities in Australia
enteric infections	<i>Campylobacter spp</i>	oral faecal contamination during sex	mostly MSM
	<i>Shigella spp</i>	oral faecal contamination during sex	mostly MSM
	<i>Salmonella spp</i>	oral faecal contamination during sex	mostly MSM
	<i>Yersinia enterocolitica</i>	oral faecal contamination during sex	mostly MSM
chlamydia infection	<i>Chlamydia trachomatis</i> serovars D-K	genital, rectal and oropharyngeal mm to mm contact	all sexually active people
lymphogranuloma venereum (LGV)	<i>Chlamydia trachomatis</i> serovars L1-L3	genital and rectal skin to skin and mm to mm contact	MSM and individuals who have unprotected sex in endemic areas
mycoplasma infection	<i>Mycoplasma genitalium</i>	genital mm to mm contact	probably all sexually active people
	<i>Mycoplasma hominis</i>	role uncertain	role in genital infection uncertain
Neisseria infection (gonorrhoea)	<i>Neisseria gonorrhoeae</i>	genital, rectal and oropharyngeal mm to mm contact	all sexually active people
urethritis, pharyngeal colonisation	<i>Neisseria meningitidis</i>	oropharyngeal mm to urethral mm (rarely)	mostly, but not exclusively MSM
ureaplasma infection	<i>Ureaplasma urealyticum</i> (some subtypes)	genital mm to mm contact	probably all sexually active people
syphilis	<i>Treponema pallidum</i>	genital, rectal and oropharyngeal mm to mm and skin to skin contact	all sexually active people
<b>ECTOPARASITES</b>			
pubic lice	<i>Phthirus pubis</i>	close body contact, sharing a bed	everyone
scabies	<i>Sarcoptes scabiei</i>	close body contact, sharing a bed, plus institution and household contact	everyone
<b>NEMATODES</b>			
thread worms	<i>Enterobius vermicularis</i>	oral faecal contamination during sex	predominantly MSM

**TABLE 1.1 Sexually Transmissible Infections (i.e. those capable of sexual transmission) continued**

STI	Causative micro-organism	Mode of sexual transmission	Commonly found in:
<b>PROTOZOA</b>			
enteric infections	<i>Entamoeba spp</i>	oral faecal contamination during sex	MSM
	<i>Giardia duodenale</i>	oral faecal contamination during sex	MSM
trichomoniasis	<i>Trichomonas vaginalis</i>	mm to mm contact during peno-vaginal sex	heterosexually active people
<b>VIRUSES</b>			
adenoviral urethritis	<i>Adenoviruses</i>	genital and oropharyngeal mm to mm contact	all sexually active people
cytomegalovirus infection	<i>Cytomegalovirus (CMV)</i>	oral mm to mm contact, saliva exchange	all sexually active people
infectious mononucleosis	Epstein-Barr virus (EBV)	oral mm to mm contact, saliva exchange	all sexually active people
genital herpes	Herpes simplex virus types 1 and 2 (HSV-1 and HSV-2)	genital, rectal and oropharyngeal skin to skin and mm to mm contact	all sexually active people
genital human papillomavirus infection (genital warts and squamous intraepithelial lesions - SIL)	Human papillomavirus (HPV) (many types, but especially 6 and 11 for genital warts; and 16 and 18 for SIL)	genital, rectal, mouth and oropharyngeal skin to skin and mm to mm contact oral faecal contamination during sex	all sexually active people
hepatitis A	<i>Hepatitis A virus (HAV)</i>	oral faecal contamination during sex	predominantly MSM
hepatitis B	<i>Hepatitis B virus (HBV)</i>	exchange of body fluids during sex	all sexually active people
hepatitis C (rarely)	<i>Hepatitis C virus (HCV)</i>	blood exchange during sex	potentially all sexually active people, but rare*
human immunodeficiency virus infection	Human immunodeficiency virus types 1 and 2 (HIV-1 and HIV-2)	exchange of body fluids during sex	all sexually active people
Kaposi's sarcoma (KS)	Human herpes virus 8 (HHV-8)	uncertain, probably exchange of body fluids	predominantly MSM
molluscum contagiosum	<i>Molluscum contagiosum (pox) virus (MCV)</i>	direct skin to skin contact	all sexually active people
<b>YEASTS</b>			
candidiasis	<i>Candida spp</i> (ubiquitous commensals, only incidentally sexually transmitted)	genital mm to mm contact	all sexually active people

\* There is increasing evidence for the sexual transmission of HCV in HIV-positive MSM<sup>1</sup>

mm = mucous membrane

MSM = men who have sex with men

WSW = women who have sex with women

## Key points

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- HCV is transmitted primarily through blood-to-blood contact. The sharing of equipment during injecting drug use is the most common mode of transmission in Australia. A minority of people clear HCV from the body but the majority develop a chronic infection. Some chronically infected individuals will develop symptoms such as fatigue and nausea. A small proportion of individuals will progress to liver failure or hepatocellular carcinoma. Combination therapy may be effective, although HCV genotype significantly influences response to treatment.
- Early diagnosis and treatment of non-viral STIs is an effective intervention for the population control of STIs generally, while suppressive anti-viral therapy for genital herpes decreases onward transmission of this virus and may indirectly assist in reducing the spread of HIV.

This chapter describes the blood-borne viral and sexually transmitted micro-organisms, specifically focusing on their biology, transmission, pathogenesis and natural history. It also provides an introduction to the principles of therapy and discusses the effects of therapy on the natural history of each of these infections. This chapter will discuss only the following STIs as representative of the group as a whole. These six infections are included because of their serious long-term sequelae or because they are common in Australia and New Zealand:

- Genital chlamydial infection (including lymphogranuloma venereum [LGV])
- Genital herpes (herpes simplex virus, or HSV)
- Genital warts (human papillomavirus, HPV)
- Gonorrhoea (*Neisseria gonorrhoeae*)
- Syphilis (*Treponema pallidum*)
- Trichomoniasis (*Trichomonas vaginalis*)

In addition, there will be a brief discussion about bacterial vaginosis because it is very common. Bacterial vaginosis may not be a true STI as it can occur in celibate women on rare occasions and treating the sexual partners of women with bacterial vaginosis has no effect on recurrence rates in index patients.

## Biology (virology and microbiology)

### HIV

The manifestations of HIV were first apparent in the early 1980s when an epidemic of unexplained cases of immunodeficiency was reported in the western world. Evidence suggested the cause to be a transmissible agent, and in 1984 the agent was confirmed to be a retrovirus now known as human immunodeficiency virus (HIV). Human infection may date back to the early part of the twentieth century and the virus may have originally been transmitted zoonotically to humans from primates in Africa.

HIV is a single-stranded ribonucleic acid (RNA) virus. It has an outer envelope that surrounds two copies of single-stranded RNA as well as a number of viral proteins. From its outer envelope protrudes the 120 glycoprotein (gp 120). The HIV replication cycle commences when gp 120 attaches to the CD4 receptor and the chemokine co-receptor CCR5. (These receptors are expressed on the surface of the CD4 lymphocyte, the cell that HIV predominantly infects.) Attachment precipitates the fusion of the membranes of virus and cell via the HIV envelope 41 glycoprotein (gp 41), allowing the virus to enter the cell. The RNA then undergoes reverse transcription, a process whereby RNA is converted to deoxyribonucleic acid, (DNA)

using the viral-encoded reverse transcriptase. The resulting viral DNA, called the provirus, migrates to the nucleus and integrates into the host chromosome.

The provirus acts as a template to allow production of messenger RNA to produce the components of new virus particles, including the RNA genome of new virions. The viral proteins are processed and cleaved by another virus-specific enzyme known as HIV protease. Viral proteins and RNA are then assembled and bud from the cell membrane, forming mature HIV particles that can infect other cells. Some of the CD4 cells are irreparably damaged by HIV infection. Premature cell death of damaged CD4 cells in part contributes to the immunosuppression characteristic of advanced HIV disease.<sup>2</sup>

### HBV

HBV is a non-cytopathic virus and contains a partially double-stranded DNA genome. This virus predominantly infects hepatocytes and belongs to the hepadnavirus family. HBV has an outer envelope containing hepatitis B surface antigen (HBsAg) and a core containing hepatitis B core antigen (HBcAg). Excess HBsAg is produced as sub-viral particles which circulate in the blood and permit serological diagnosis of HBV. The core contains the genomic DNA as well as the viral-encoded DNA polymerase, which is detected in liver tissue. HBV also produces hepatitis B 'e' antigen or HBeAg, which is secreted into the blood and is detected by serological assay. The presence of circulating HBeAg and serum HBV DNA is indicative of ongoing viral replication and increased infectivity. Resolution of HBV infection is accompanied by clearance of HBeAg and HBsAg and seroconversion to anti-HBe-positivity (anti-HBe+) and anti-HBs-positivity (anti-HBs+).

Soon after entering the hepatocyte, the genomic DNA is converted in the nucleus to a form known as supercoiled or covalently closed circular (ccc) DNA. This serves as a template to yield two types of RNA: a pregenomic RNA that ultimately undergoes reverse transcription to yield DNA for progeny virus and messenger RNA for structural proteins. The former is assembled into mature virions that are then released from the cell.

In long-term, chronic infection, HBV DNA may integrate into the host cell genome but integration is typically incomplete and a full life cycle cannot occur from these integrated sequences. Viral integration does play a role in the development of hepatocellular carcinoma, especially in the setting of cirrhosis. Supercoiled HBV DNA in the liver cell nucleus is long-lived and resistant to all current antiviral therapies, resulting in lifelong chronic infection.<sup>3</sup>

## HCV

HCV is a single-stranded, enveloped RNA virus belonging to the flavivirus family. It causes most cases of what was previously known as non-A, non-B hepatitis. HCV was discovered when infected serum was injected into a number of chimpanzees, whose sera were then used to identify a clone that reacted with an infected serum panel from patients with non-A, non-B hepatitis. This finding ultimately formed the basis of the first antibody test for detection of HCV. The virus has only recently been cultivated in cell culture systems.

The HCV replication cycle has been partially elucidated. The viral receptor has not been conclusively demonstrated on the hepatocyte. Following infection of the hepatocyte and internalisation of the virus, HCV RNA is translated by the host cell ribosomes to produce a large viral polyprotein, which is cleaved and processed by both host cellular and virus-specific (NS-2 and NS-3) enzymes. The viral polymerase/replicase (NS-5B) copies the viral RNA in the cytoplasm and, as soon as a pool of progeny RNA molecules and core proteins is present, assembly of the nucleocapsids occurs. Mature HCV virions then develop and bud through the plasma membrane.

## Chlamydia trachomatis

*Chlamydia trachomatis* is a common human pathogen divided into 15 different serovars. Serovars A, B, Ba and C cause trachoma; serovars D to K cause genital (and sometimes conjunctival) infection; serovars L1-L3 are associated with lymphogranuloma venereum (LGV) and tend to be more virulent and invasive showing a predilection for lymphatic vessels and tissue. *C. trachomatis* is a bacterium, but an obligate intracellular one, so can only be isolated and grown in suitable host cells. There are two main structures in the life cycle of *C. trachomatis*, the elementary body (EB) and the reticulate body (RB). The EB is a rigid-walled structure packed with DNA and is the infectious particle. It infects a potential host cell by adhering to its surface.

The EBs enter the cell by endocytosis and soon begin the second phase of their life cycle as metabolically active reticulate bodies. The RBs use adenosine triphosphate (ATP) derived from the host cell to replicate by binary fission, each producing several hundred progeny. The RBs become larger and form inclusions in the cytoplasm of infected cells which can be detected by staining (e.g. with iodine). A microscopist can see these intracytoplasmic inclusions in some infected cells draped around the nucleus like a cloak; the word 'chlamys' is Greek for 'cloak', so this gave the micro-organism its name. After about 20 hours some of the RBs undergo reorganisation to form new EBs that with cell lysis, burst out of the old cell ready to infect other susceptible cells. The whole life cycle takes about 72 hours. Chlamydial disease confined to epithelial surfaces tends to produce only a mild immune response, whereas more serious sequelae (e.g. salpingitis) and systemic disease such as LGV, elicit a vigorous antibody reaction.<sup>4</sup>

## Herpes simplex virus-types 1 and 2 (HSV-1 and HSV-2)

The herpes simplex viruses are double-stranded DNA viruses, members of the human herpesvirus family and are exceptionally successful human pathogens. Like the varicella-zoster virus, HSV-1 and HSV-2 are neurotropic viruses but have the ability to cause infection in many other cell types. HSV-1 and HSV-2 are widely prevalent and tend to cause only mild and self-limited disease. A characteristic which they share with other members of the human herpesvirus family is the ability to establish latent infection, so that they are able to persist throughout the life of the host. During latency, the genome of the invading virus is maintained in stable form in the infected neural cell with no production of progeny virus for variable periods of time and no apparent cytotoxic effects. Periodically, reactivation of virus replication occurs with virus migrating back down axons to surface sites. The clinical severity of herpes simplex infections and the host's capacity to control viral replication depends very much on cell-mediated immunity, although humoral immune mechanisms also play an important part.<sup>5</sup>

## Human papillomavirus (HPV)

The human papillomaviruses (HPV) are small DNA viruses which induce proliferation of epithelial cells with the production of papillomas. More than 35 HPV types infect genital skin and mucous membrane. So far HPV has not been grown in tissue culture and typing is dependent on detection of the genome by molecular cloning and sequencing. Genital HPV types are divided into high-risk and low-risk depending on their potential to promote the development of squamous cell cancers in infected cells. Types 6 and 11 are low-risk types as they are rarely associated with cancers and tend to cause typical genital warts.

Types 16, 18, 31, 33, 35 and 45 are high-risk types. About 50% of invasive squamous cell cancers of the cervix carry the HPV DNA of type 16. HPV has a highly significant role in the development of anogenital cancers whether they be cervical, vulval, penile or anal cancers.<sup>6</sup> Genital HPV is ubiquitous in the community; an American study published in 2006 found that in women aged 18 to 25 years, the overall HPV frequency of detection was 26.9% and there was detectable high-risk HPV DNA in 20%<sup>7</sup>, while another recent study from a very broad cross-section of the population in the USA found that the prevalence of HPV DNA in young women aged 14 to 24 years was 33.8%.<sup>8</sup> Infection usually occurs in adolescence and young adulthood soon after the beginning of sexual activity. Because of the asymptomatic nature of much HPV genital infection and the lack of any specific antiviral treatment, up until now control of high-risk HPV type infection in the community has depended entirely on cervical cancer screening and follow-up with surgical ablation of high grade squamous intraepithelial lesions. The recent development and licensing in Australia of two prophylactic vaccines (Gardasil and Cervarix) for girls and young women against the commonest high-risk and low-risk genital HPV types is therefore a considerable step forward, although it should be noted that only one of the vaccines (Gardasil) is active against HPV types causing genital warts.<sup>9</sup> Studies of the vaccine in young gay men will now proceed to inform possible future use of the vaccine to prevent anal cancer in this group.

### **Neisseria gonorrhoeae**

*Neisseria gonorrhoeae*, or the gonococcus, the causative agent of gonorrhoea, is perhaps the best known sexually transmitted agent and has caused considerable morbidity in human beings since the earliest recorded history. Gonococci are gram-negative bacteria which characteristically grow in pairs as diplococci. Under the light microscope they are indistinguishable from meningococci and indeed meningococci, on occasions, have been demonstrated to cause urethritis—hence the need for accurate microbiological identification of urethral isolates. Like *C. trachomatis*, gonococci have a predilection for the mucous membrane surfaces of the urethra, endocervical canal, rectum, pharynx and conjunctiva. Sequelae of untreated infections can be serious and severe. Some uncommon strains of gonococci cause little inflammatory response on mucosal surfaces but have the ability to invade, leading to bacteraemia and more systemic disease.

Gonococci possess surface molecules called pili which are largely responsible for adhesion to mucosal surfaces and also for invasion into the submucosa. Pili also serve as targets for host defences but have an amazing ability to undergo swift antigenic change. This accounts for the almost complete absence of acquired natural immunity against attacks of mucosal gonorrhoea. A person can be successfully treated for

gonococcal urethritis or cervicitis today and if exposed to infection again tomorrow is completely susceptible to re-infection. A great deal is known now about the pathogenicity of *N. gonorrhoeae* and associated host-bacterial interactions. Despite all this accumulated knowledge, gonorrhoea remains a considerable problem around the world. There has been a notable lack of progress towards vaccine development and the gonococcus has an extraordinary capacity to acquire resistance to antibiotics very rapidly. This ability continues to present a formidable challenge. Medical science always seems to be only one step ahead of this doughty Darwinian survivor.<sup>10</sup>

### **Treponema pallidum**

*Treponema pallidum* is the bacterial agent which causes syphilis, another well known and once feared STI. *T. pallidum* is a spirochaetal organism related to *Borrelia* and *Leptospira*. It is a long, thin, tightly coiled bacterium, just beyond the resolution of the light microscope, although it can be demonstrated in a microscope with a dark field condenser. Here, in a wet preparation, it distinguishes itself from other spirochaetes by its regular tight spirals and its characteristic motility. Both the corkscrew shape and the mobility of the organism play important roles in its invasion and dissemination. The body mounts an immune response against invading treponemes, both humoral and cell-mediated, and many of the unique clinical features of syphilis are due to the immune response. Bacteria are able to establish latency in lymphatic and splenic tissue and during this period of latency, which may last for many years in untreated patients, the infected person will be resistant to reinfection from a new challenge with *T. pallidum*.<sup>11</sup>

### **Trichomonas vaginalis**

*Trichomonas vaginalis* is a flagellated protozoan which lives only in the human genitourinary tract. As long ago as 1836 Donné demonstrated trichomonads as motile organisms in a preparation of fresh vaginal discharge, and for the next hundred years *T. vaginalis* was regarded as a harmless inhabitant of the vagina. It causes symptomatic infection (vaginitis in women and urethritis in men) but more often is carried asymptotically in both sexes. It is highly infectious and almost invariably sexually transmitted.<sup>12</sup>

### **Bacterial vaginosis**

Bacterial vaginosis is a common, complex, clinical syndrome of which the characteristic feature is an alteration in the normal vaginal flora. Normal lactobacilli are absent or greatly reduced and a swarm of gram-variable, small, mostly anaerobic microorganisms including *Gardnerella vaginalis*, *Atopobium vaginae*, *Mobiluncus sp.*, and *Prevotella sp.* replace them. Some of these organisms are highly motile and tend to cluster around shed epithelial cells in vaginal fluid. Microscopists describe such cells as 'clue cells' and they are a hallmark of bacterial vaginosis. The normal

acidic milieu of the vagina is lost with the pH rising to 7 or above. The cause of this curious condition is still unknown and while it has some features in common with other STIs, namely strong association with sexual activity, the lack of any similar condition or conjunction of micro-organisms in males, whether symptomatic or not, makes its classification as an STI suspect in our present state of ignorance. However, the condition is very common in women who have sex with women (WSW) and in this group bacterial vaginosis certainly seems to be acting like an STI.<sup>13</sup>

## Quasispecies and hypermutability of blood-borne viruses

The replicase enzymes of all three blood-borne viruses, the HIV reverse transcriptase, the HBV DNA polymerase and the HCV RNA polymerase, are hypermutable. Mutation, particularly under immunological and therapeutic pressure, leads to the presence in a given individual of a number of closely related, but genetically distinct, viral variants known as quasispecies. The emergence of quasispecies is the likely reason why infection with these viruses results in chronic infection in most individuals despite a host immune response. Each one of the virus-specific enzymes previously discussed is the focus of intense research to develop potent and selective inhibitors of key viral functions, which could result in significant gains in managing the health of people persistently infected with these viruses.<sup>14</sup>

## Transmission

While each blood-borne virus has distinct transmission patterns, HIV, HBV and HCV can all be transmitted parenterally through the sharing of injecting equipment, needle-stick injuries, or piercing and tattooing with contaminated equipment. On the other hand, efficiency of sexual transmission differs markedly between viruses. STIs are by definition transmitted through sexual contact but the precise mode of transmission varies from infection to infection—different sexual activities favour the transmission of different sexually transmissible agents: individuals don't acquire pubic lice and gonorrhoea in quite the same way (see Table 1.1).

## HIV

HIV is predominantly transmitted sexually, with efficiency being greatest through receptive anal intercourse. In Australia, transmission is most commonly seen in homosexual men, whereas in developing countries, especially in Africa, HIV is predominantly acquired through vaginal intercourse. Transmission through injecting drug use is uncommon in Australia, accounting for 4% of HIV cases, but is particularly prevalent in parts of Europe and Asia (including countries of the former Soviet Union) and the USA. Transmission by blood products largely occurred before the introduction of antibody screening in 1985 in Australia and was responsible for

the high incidence of HIV among multiply-transfused people, such as those with haemophilia. It is now exceedingly rare in countries where blood is screened. Transmission by needle-stick injury occurs in 0.3% of exposures from HIV-infected individuals. Perinatal transmission occurs in 20–45% of infants born to infected mothers, but this rate can be reduced to 1–2% with the administration of antiretroviral therapy during pregnancy, labour and after delivery, and other interventions, such as caesarean section and avoidance of breast-feeding.<sup>15</sup> In Australia there have been 22,785 new diagnoses of HIV infection, with 9,827 cases of AIDS to the end of June 2006 and 6,621 AIDS-related deaths.<sup>16</sup>

## HBV

Most HBV cases result from perinatal transmission, which accounts for high prevalence in people from endemic countries, particularly China and South East Asian and Pacific nations. Transmission is effectively prevented by HBV vaccination and administration of hepatitis B immunoglobulin (HBIG) to newborns of hepatitis B surface antigen positive women, but such programs are not currently available in many developing countries where most cases occur.

Among adults, HBV transmission is predominantly via sexual contact and injecting drug use. In Australia, the overall prevalence of HBV infection has been estimated to be 90,000 to 160,000.<sup>17</sup> The risk of transmission by percutaneous exposure such as a needle-stick injury is approximately 30% if the person with HBV infection has replicative disease (defined as HBV DNA+ by hybridisation assay or HBsAg+ and HBeAg+), compared with 3% for those with HBV infection with non-replicative disease (that is, people without HBeAg or HBV DNA but with HBsAg+).<sup>3</sup>

## HCV

HCV transmission is predominantly parenteral. The most common mode of transmission in Australia remains injecting drug use, which is responsible for approximately 80% of the estimated 225,000 prevalent cases nationally and is reported as the predominant risk factor in over 90% of the estimated 16,000 annual incident cases.<sup>18</sup> Among particular immigrant populations, poor infection-control practices during procedures such as vaccination (European and Asian) and chemoprophylaxis programs for schistosomiasis (Egyptian) may have been responsible for many cases. The role of sexual transmission is still controversial. If sexual transmission of HCV does occur, it is at a very low level that makes it inappropriate to routinely recommend safe sex among long-term monogamous couples.

Sexual transmission is likely to be more efficient, however, where there is HIV co-infection and high HCV viral load.<sup>19</sup> Risk of sexual transmission may also be increased when blood is present in the genital tract, such as during menstruation. Perinatal transmission

occurs in approximately 5% of deliveries, although this may be higher in women who have HIV co-infection or high levels of viraemia. Elective caesarean section in women with HIV/HCV co-infection is usually advocated, although its role in reducing perinatal transmission in women with HCV mono-infection is unclear and is generally not recommended as routine in this context.<sup>21</sup>

### **Chlamydia trachomatis**

*Chlamydia trachomatis* tends to infect columnar epithelium rather than squamous epithelium. Direct mucous membrane-to-mucous membrane contact facilitates transmission and chlamydial elementary bodies in infected genital secretions and discharges readily seed uninfected mucous membrane and cause infection in columnar cells. During birth, transmission occurs from a mother with cervical chlamydial infection to the child very efficiently (overall risk is 50–75%).

Indirect transmission of chlamydial infection by fomites appears to be extremely uncommon. Lymphogranuloma venereum (LGV) serovars are transmitted similarly by direct surface to surface contact or contamination of susceptible genital surfaces by contaminated secretions. The recent LGV outbreak in men who have sex with men (MSM) appears to be predominantly via anal intercourse with multiple partners, fisting and use of contaminated sex toys. For all practical purposes, transmission of the genital serovars of *C. trachomatis* is sexual and vertical only, and conjunctival infection in the adult results from auto-inoculation with infected secretions from genitals to eye by the patient's own fingers.<sup>22</sup>

### **HSV-1 and HSV-2**

Sexual transmission is a highly significant method of transmission of these viruses.<sup>23</sup> However, most people with oral and labial cold sores are infected with HSV-1 in childhood usually by being kissed on or near the mouth by family or relatives. Once they grow up and become sexually active, they can pass HSV-1 on to various anatomical sites in one or other of their sexual partners by kissing or by oro-vulval, oro-penile or oro-anal sex. A significant proportion of anogenital herpes is due to HSV-1 infection (30% or more in many studies).<sup>25</sup>

All that is required for transmission of HSV-1 or HSV-2 is for the virus from an infected person to come in contact with a mucosal surface (vaginal, cervical, rectal, pharyngeal, buccal, labial, conjunctival) or a slightly abraded skin surface anywhere on the body of a susceptible person.

People never exposed to either virus are most susceptible and may develop a severe primary attack when infected; those with antibodies to one or other HSV, demonstrating previous exposure, are still capable of being infected by the alternative virus but have some degree of protection and may

suffer a less severe infection. The two viruses exhibit different tropism for anatomic sites; HSV-1 can infect both oral and genital sites but tends to thrive better in the mouth area, in that it reactivates more commonly there with viral shedding and sometimes with clinically obvious recurrences; HSV-2 can also infect both oral and genital sites but thrives better in the genital region.

However, surprisingly, a study published in 2006 of men seropositive for HSV-2 (about half of whom were also HIV positive), showed that 40% of the men shed HSV-2 from both genital and oral sites. Oral shedding was always asymptomatic, it usually occurred at the same time as genital shedding and it occurred more commonly in HIV-positive men.<sup>26</sup>

All these facts explain why HSV infection is so common in sexually active people and why control of the spread of infection in communities presents such a challenge. Transmission rates can be reduced with careful and consistent condom use, and suppressive therapy with antiviral drugs for those who suffer frequent recurrences. Only an effective vaccine will make a significant impact on the problem of herpes simplex virus infection at population level.

All forms of sexual contact can lead to transmission of HSV-1 or HSV-2 and mother-to-child transmission can occur at the time of birth. Neonatally acquired herpes can be a devastating and life-threatening disease. Fortunately mothers who are already infected with herpes provide their own antibodies transplacentally which substantially protect the infant from infection, even if HSV is shed by the mother around the time of delivery. However, if a pregnant woman is infected in the anogenital region with HSV-1 or HSV-2 in the last trimester of pregnancy and fails to develop significant HSV antibody levels (as shown by testing prior to delivery), the baby is at significant risk of acquiring neonatal herpes. In this situation obstetricians recommend a caesarean section birth.<sup>4</sup>

### **Human papillomavirus**

Sexual contact of all types accounts for all genital HPV infection. This includes the low-risk HPV types which result in the growth of genital warts and the high-risk HPV types that are associated with anogenital cancers. Genital HPV is a sexually transmitted infection demonstrated by the now well established fact that women without a present or prior sex partner tend to have a very low yield of HPV DNA in cervico-vaginal secretions, women with only one sex partner have a slightly higher yield and women with a history of more than one partner have a substantially higher yield.

Each time a person acquires a new sex partner, that person's risk of acquiring genital HPV increases considerably. The consequence is that most sexually active adults have acquired one or more of the plethora of genital HPV types by the time they reach their fourth decade. Direct skin-to-skin, skin-

to-mucous membrane and mucous membrane-to-mucous membrane contact is all that is required for transmission to occur. HPV infection with one or more genital types of HPV does occur around the mouth and lips as a result of oral sex but is only a problem in an immunosuppressed patient. Similarly mother-to-child transmission of HPV at the time of birth sometimes does occur resulting in genital or laryngeal infection in the infant, but fortunately these infections rarely cause clinical problems.<sup>6</sup> *Laryngeal papillomatosis*, while extremely rare, can be a very significant clinical problem in young children.

### **Neisseria gonorrhoeae**

The gonococcus is highly infectious but is a fragile organism outside the human body, being poorly resistant to environmental changes such as heat and drying. Transmission is therefore almost exclusively by sexual contact or from mother to infant at the time of birth. Transmission by fomites is extremely unlikely. Gonorrhoea transmission is fairly efficient, with a prevalence of infection of 50–90% in female sex contacts of a man with urethral gonorrhoea.

Transmission is by direct mucous membrane-to-mucous membrane contact or via infected genital secretions on a susceptible mucosal surface. Transmission from male to female via vaginal sex is slightly more efficient than from female to male and, similarly, transmission from the male partner to the receptive partner in anal sex is more efficient than vice versa. The pharyngeal mucosa is readily infected from an infected urethral meatus via oral sex while transmission from infected pharynx to urethra is less common but well documented, especially among MSM. Adult gonococcal conjunctivitis (a sight-threatening infection) is almost always acquired by auto-inoculation via the person's own fingers from his or her infected genitals, while neonatal conjunctivitis is acquired by direct inoculation of the baby's conjunctivae during transit through the infected maternal endocervical canal.<sup>10</sup>

### **Treponema pallidum**

Syphilis is only acquired by sexual contact or by transplacental transmission of *Treponema pallidum*, i.e. from an infected mother to her foetus in utero. An old study suggested that the risk of acquiring syphilis from an infectious partner was about 30% per sexual exposure.<sup>26</sup> A woman infected with syphilis has a potential risk of transmitting syphilis transplacentally during many years of untreated infection (8–10 years at least, although the risk decreases with every passing year). However, people with syphilis seem only able to transmit it to sexual partners during the first two years of untreated infection. This suggests that for sexual transmission to occur, moist mucosal or cutaneous lesions (i.e. those that appear in primary and secondary syphilis) must be present, so that active treponemes on those surfaces of an infected person have an opportunity of reaching and penetrating moist mucosal or cutaneous surfaces of the sexual partner.

Infectious lesions include the primary chancre and all the mucosal manifestations of secondary syphilis, e.g. snail track ulcers, condylomata lata, mucous patches, and split papules. Even microscopic and non-clinically obvious mucosal lesions, as may occur in the vagina, the mouth, under the foreskin and perianally, in early latent syphilis, are infectious to sexual partners and probably account for most of the transmission that occurs in areas where syphilis is endemic.<sup>26</sup>

### **Trichomonas vaginalis**

*Trichomonas vaginalis* is transmitted almost exclusively by sexual contact. There has been a long debate about the possibility of transmission by contaminated fomites such as face cloths, towels, and toilet seats. While it is true that the organism is hardier than *T. pallidum* and *N. gonorrhoeae* and may survive 45 minutes or so outside the body, epidemiological evidence to support non venereal transmission is slim. *T. vaginalis* is not known to infect rectal mucosa, the conjunctiva or the pharynx. In this respect it differs from the gonococcus and *C. trachomatis*. Vaginal intercourse appears to be the main way trichomoniasis is spread, with oral sex and anal sex having no part to play.<sup>12</sup>

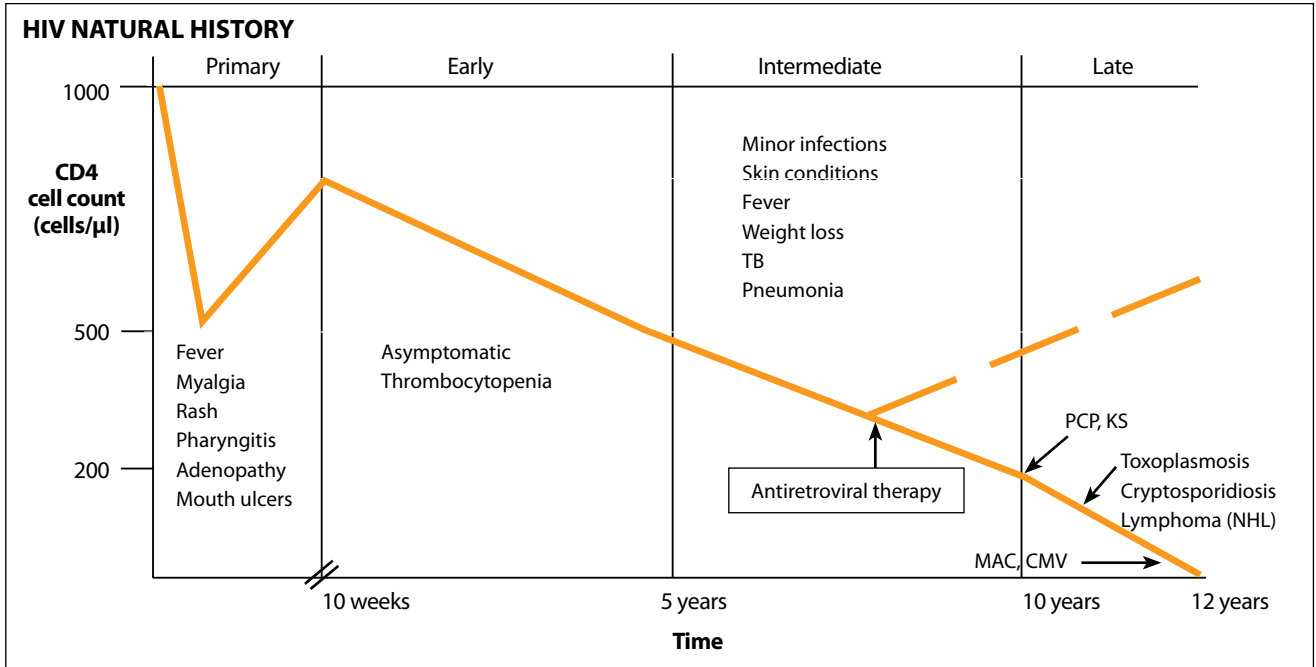
### **Bacterial vaginosis**

The aetiology of this condition is unknown. It remains uncertain whether sexual transmission of agents (known and unknown) plays a part in its aetiology.

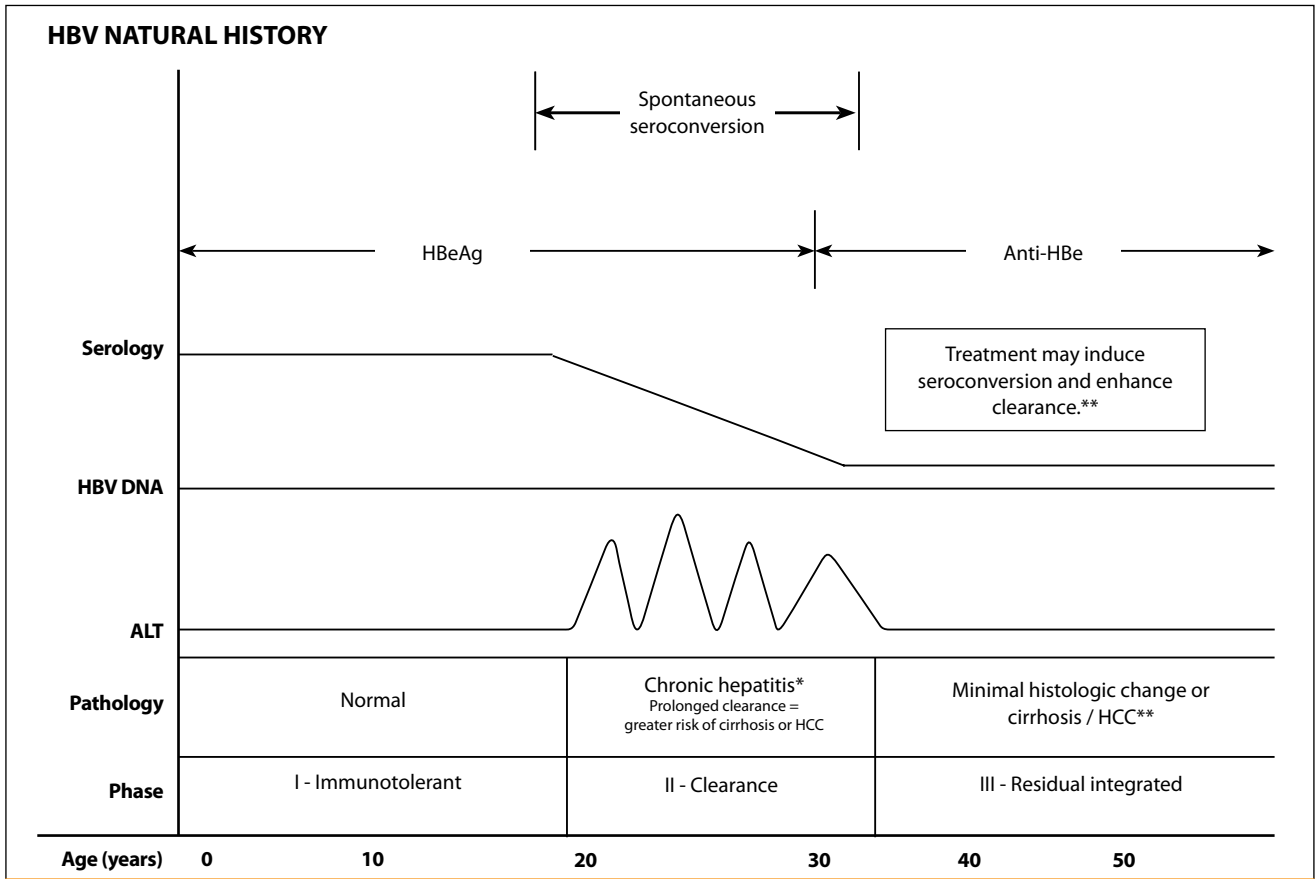
## **Natural history**

### **HIV**

Following inoculation with HIV, there is a period of high-level viraemia associated with a reduction in the CD4 cell count. A host immune response then develops, partially controlling viral replication, but is unable to clear HIV from the body. A substantial proportion of patients (proportions in recent reports range from 50–92%) suffer a mononucleosis-like seroconversion illness characterised by fever, pharyngitis, lymphadenopathy, rash, splenomegaly and aseptic meningitis. Other HIV-infected patients are asymptomatic or suffer a more non-specific illness. These acute-phase effects then resolve as the immune system mounts an antiviral response that causes the viral load to decrease markedly. Simultaneously, there is a rebound increase in CD4 cell count to near baseline levels and the patient enters a period of clinical latency, although very high levels of viral replication continue, especially in the lymphoid compartment. The plasma HIV RNA plateaus to a constant level of viraemia known as the virological set point. If left untreated, the patient experiences a gradual decline in CD4 cell count, with a median loss of 80 cells per year. Progression to AIDS (the development of opportunistic infections or specific malignancies) occurs a median of 10 years after initial infection with HIV. At this time the CD4 cell count has usually fallen below 200 cells/μl and the patient is severely immunocompromised (Figure 1.1).<sup>2,27</sup>



**FIGURE 1.1** The various stages of HIV infection depicting the development of different opportunistic infections with advanced immunodeficiency and the impact of antiretroviral therapy on CD4 cell count recovery.



**FIGURE 1.2** Demonstrates the three phases of infection in a person from an endemic area.

\* Cirrhosis may develop during the period of attempted immune clearance.  
 \*\* Antiviral therapy increases the likelihood of HBeAg to anti-HBe seroconversion.  
 Active disease may occur despite loss of HBeAg.

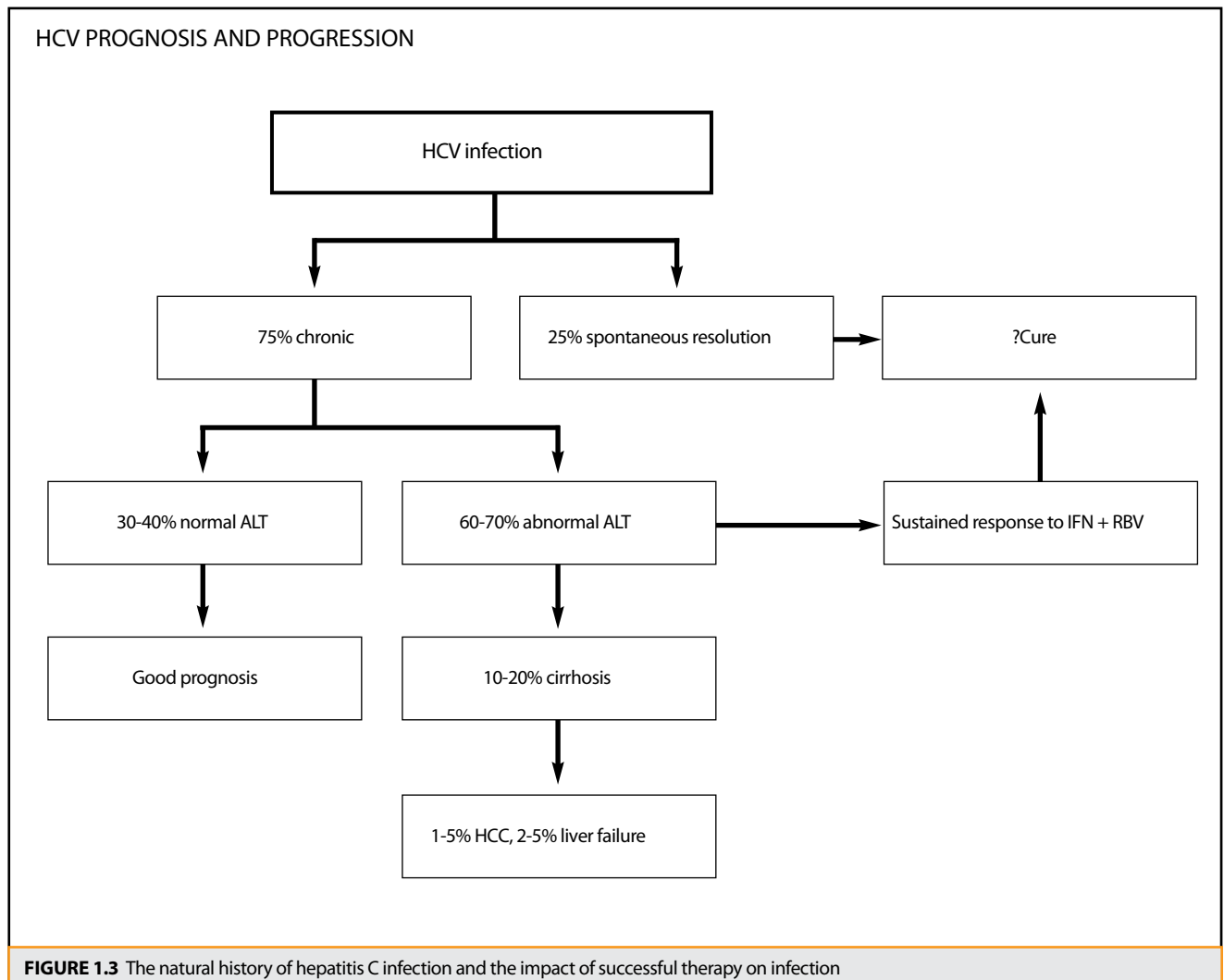
## HBV

HBV, by contrast, is almost exclusively an immune-mediated disease. The outcome of infection is largely determined by the age at which infection is acquired, which relates to the maturity of the immune response. In endemic countries where infection occurs during birth (perinatal infection) or in early childhood (early horizontal infection), over 90% of HBV transmissions will become chronic (as defined by a persistence of HBsAg for more than six months), and clinical acute hepatitis rarely occurs. If, however, an individual is infected as an adult, chronic infection will occur in less than 5% of people, although almost half will manifest clinical features of acute hepatitis.

The natural history of chronic HBV infection has been defined by stages of immune response. Initially patients have no immune response to the virus and are said to be in the immunotolerant phase. At this time, they have normal liver function despite high levels of HBV DNA and detectable HBeAg, indicating active viral replication.

Later in life, usually in the second to fourth decades, the immune system is triggered to attack the virus-infected hepatocyte and a period of immune clearance ensues, whereby patients demonstrate flares of elevated serum aminotransferase levels with histological evidence of active hepatitis.

If these flares persist for too long or are substantial, the patient may ultimately develop cirrhosis and liver failure. About 25–40% of people with long-term infection will die of cirrhosis or hepatocellular carcinoma (HCC) (Figure 1.2). However, if these immune-based clearances are successful, the patient will demonstrate an HBeAg seroconversion to anti-HBe, have undetectable HBV DNA by hybridisation assay and show normalisation of serum aminotransferase levels with associated improvement of liver histology. The person with HBV infection then enters into the latent phase with an improved long-term prognosis (Figure 1.2).



Occasionally, under the pressure of immune-mediated flares, HBV mutants are selected. These so-called precore (or HBeAg-negative) mutants fail to secrete HBeAg protein but still replicate, as evidenced by detectable HBV DNA in serum and elevated serum aminotransferase levels. HBeAg-negative infection is particularly prevalent in certain geographical areas, such as around the Mediterranean basin and in South East and northern Asia. In Australia, migrants from these regions are frequently infected with such variants.<sup>3</sup>

## HCV

Unlike HBV, the immune response generated in adults newly infected with hepatitis C is usually inadequate to effectively control viral replication. As a consequence, the majority of acute infections progress to chronic infection, defined as a positive HCV RNA in serum six months after the estimated date of infection. The proportion of people estimated to clear acute hepatitis C varies between 25% and 40%, and clearance occurs more frequently in patients who are symptomatic or who become jaundiced. Understanding of the natural history of chronic hepatitis C infection has improved in recent years with the realisation that fewer people progress to cirrhosis than was originally estimated (Figure 1.3). Models based on large longitudinal community-based cohorts estimate the risk of progression to cirrhosis to be 7% at 20 years and 20% at 40 years of infection.<sup>27</sup> Estimates of hepatitis C-related mortality are 1% at 20 years and 4% at 40 years.<sup>28</sup> Despite this, an increasing burden of advanced liver disease is anticipated within Australia in future years, with between 15,000 and 20,000 cases of cirrhosis by the year 2010.

Factors associated with an accelerated risk of progression include older age at infection, male gender, heavy alcohol intake, co-infection with HBV and HIV and possibly obesity, linked to the presence of steatosis (fatty liver) on biopsy. The risk of liver failure in people with compensated cirrhosis is around 4–5% per year and the risk of hepatoma around 1–3% per year in Australia.

People who have chronic hepatitis C and normal liver function tests generally have very low rates of fibrosis progression. At present the majority of these patients are not routinely offered HCV therapy and are treated only in the context of clinical trials.

## Co-infection with HIV, HBV or HCV

Multiple blood-borne viral infections in the same individual can markedly alter the natural history of disease. For example, HBV has no adverse effect on HIV or the development of AIDS, but HIV does influence HBV and can be associated with accelerated development of cirrhosis and liver failure. The exact mechanism(s) of the pathogenesis of this co-infection are presently unknown but are probably due to virological (higher HBV viral load in co-infection) and host immunological (dysregulated immune responses) factors.

Individuals with HIV and HCV co-infection have higher HCV viral loads and a more rapid course to end-stage liver disease. This has been demonstrated by the correlation between declining CD4 cell counts and the increasing percentage of HCV-related hospital admissions and deaths among people with HIV and HCV co-infection.<sup>29</sup>

## Chlamydia trachomatis

The natural history of genital chlamydia infection varies depending on whether infection is caused by the D to K serovars, or the L1 to L3 serovars.

### D to K serovars

Primary sites of genital infection with D to K serovars of *C. trachomatis* in adults are mucosal surfaces lined by columnar epithelium, hence urethritis, endocervicitis, proctitis and pharyngitis can result, depending on the type of sexual activity. Most of these infections are mild and it is more likely that infected people remain asymptomatic for a considerable time rather than developing obvious symptoms and signs. In infants following mother-to-child transmission, primary sites of infection are the naso-pharynx, the conjunctivae and, more rarely, the vagina or urethra.

Genital D to K chlamydia infections can spread from their site of original infection. In women, cervical infection tends to spread upwards through the endometrium causing a mild endometritis with onward spread to the mucosal lining of the fallopian tubes with resulting salpingitis.

Infection can spread from the surface of the fallopian tubes into the surrounding peritoneum and supporting ligaments resulting in pelvic inflammatory disease (PID). Sometimes transcoelomic spread can result in perihepatitis (the Fitz-Hugh Curtis syndrome). In men, ascending infection can result in epididymo-orchitis. In adults, both PID and epididymo-orchitis caused by *C. trachomatis* tend to be milder than similar gonococcal disease, but the potential for long-term damage in women (pelvic sepsis, tubo-ovarian abscess, infertility and increased risk of ectopic pregnancy) is equivalent in both infections: chlamydia PID is a more silent and insidious infection than the gonococcal variety. In infants, naso-pharyngeal infection is often a precursor to the development of pneumonitis.<sup>22</sup>

### L1–L3 serovars (LGV)

Until quite recently lymphogranuloma venereum (LGV) remained an uncommon infection mostly seen in tropical and sub-tropical resource-poor countries. It was exceedingly rare in Australia, New Zealand and other Western countries. Tropical LGV has three stages:

- A primary ulcer on the genitals, usually of short term duration
- A secondary stage characterised by systemic symptoms, inguinal lymphadenitis and sometimes a moderately severe proctitis

- A third stage with chronic sequelae: bubo formation often with rupture and discharging inguinal sinuses, lymphatic obstruction with genital elephantiasis and rectal stricture and fistula formation

In 2003 and 2004 the first cases of rectal infection with an L2 serovar in MSM were identified in the Netherlands and subsequently more cases have been detected in most other Western countries with significant populations of homosexually active men, including in major Australian cities.

The vast majority of these cases have been characterised by moderately severe to severe rectal proctitis with systemic symptoms (fever and malaise) and little or (more often) no involvement of inguinal lymph nodes.<sup>30</sup>

### Herpes simplex virus – types 1 and 2 (HSV-1 and HSV-2)

Both HSV-1 and HSV-2 can cause genital herpetic infection. The most common scenario for genital infection with either of the herpes simplex viruses is for a person, during a sexual contact, to acquire the virus on a genital mucous membrane or cutaneous surface with either extremely mild symptoms or no symptoms at all marking the event. In the case of a person with no previous exposure to HSV-1 or HSV-2, and where a large dose of virus is acquired, within a few days of acquisition painful vesicles or blisters develop which rapidly break down to form shallow tender ulcerations. At the same time, draining lymph nodes become enlarged and tender and there may be systemic symptoms of fever and malaise. This is called primary genital herpes infection. It is distressing and uncomfortable in both men and women and may last up to three weeks before spontaneously remitting. There is a third group of people whose first contact with genital HSV (the initial attack) lies somewhere between the extremes of the severe primary outbreak and the entirely asymptomatic group.

The virus establishes latent infection in sensory nerve ganglia in the vicinity of the spinal cord and periodically reactivates with migration down the nerve fibres and intermittent release of infectious virions onto the surface—this is called 'viral shedding' and is the cause of most onward transmission of HSV. All people infected with genital HSV undergo the same pattern of recurrent reactivation of latent virus and intermittent reappearance of infectious virions at a surface site. For some people, recognisable symptoms of blistering and ulceration accompany this reactivation; for others asymptomatic reactivation is the rule. Genital infection with HSV-2 is more likely to result in symptomatic recurrences than genital infection with HSV-1.

Neonatal HSV infection can manifest as lesions localised to the skin, eyes or mouth; an encephalitis; or a severe disseminated life-threatening infection.<sup>5</sup>

### Human papillomavirus

There are still substantial gaps in knowledge about the natural history of genital HPV infection. Most infections are acquired in adolescence and early adult life and HPV infection shares characteristics with other STIs, namely: it is more common in those who commence sexual activity early; those who have frequent partner changes or multiple partners; and those whose partner has or has had frequent partner changes. However, few sexually active people avoid acquiring one or more of the genital HPV types during their lifetime. The outcomes of anogenital infection with HPV include:

- 'Invisible infection' where the only indication that infection has occurred is the presence of HPV DNA in epithelial cells, as detected by an appropriate test
- Cytological signs of infection as seen in a cytological smear or in material taken by biopsy (e.g. at colposcopy). Such cytological changes are in the form of low-grade or high-grade squamous intraepithelial lesions (LSIL or HSIL)
- Typical exophytic warts

In general, HPV infections tend to resolve over time in immunocompetent people presumably reflecting increasing immune control over the virus, although local immune mechanisms in epithelium are still poorly understood. Genital HPV infection may persist for many years despite apparent complete clinical resolution and it is not uncommon for people who become immunosuppressed later in life to develop recurrences of anogenital warts which had troubled them in their early adult life. In time many exophytic warts disappear even without treatment and most low-grade and even high-grade squamous intraepithelial lesions regress. However, a small percentage of squamous intraepithelial lesions do develop into anogenital cancers. This is much more likely to occur if the HPV types causing the lesions are high-risk types, the most common being types 16 and 18. On the other hand, exophytic warts caused by HPV types 6 or 11 appear to have virtually no potential to develop into cancer.<sup>6</sup>

### Neisseria gonorrhoeae

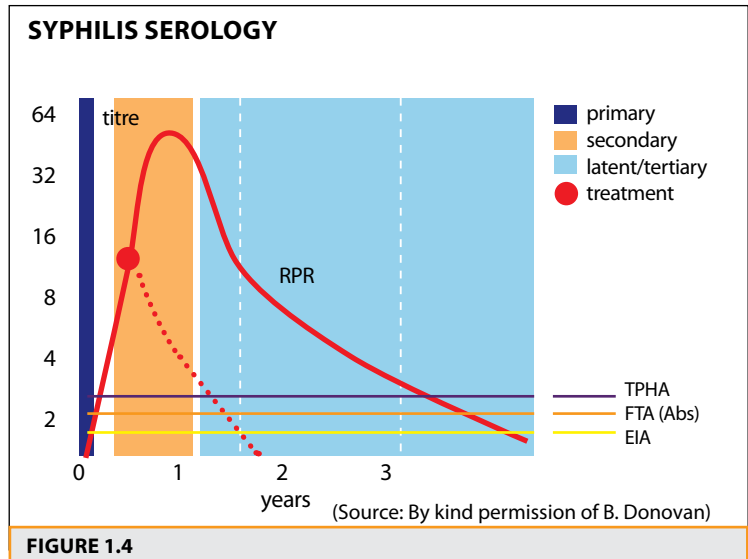
*Neisseria gonorrhoeae* targets exactly the same columnar cells in the mucous membrane of urethra, endocervix, rectum, pharynx and conjunctiva as does *Chlamydia trachomatis*. Within a few days the infection elicits a vigorous local immune response with the production of cytokines and the influx of large numbers of polymorphonuclear lymphocytes. Thus, most strains of gonorrhoea tend to produce visible signs of inflammation, i.e. meatitis, urethritis, and cervicitis, although it is only the infection in the male urethra which usually results in early detectable symptoms of dysuria and purulent discharge. Infection at other sites is much less likely to cause readily recognisable symptoms, at least in the first few weeks. A small percentage of men seems to acquire urethral gonorrhoea asymptotically, probably

reflecting infection with less virulent strains or strains less well equipped to elicit a mucosal immune response; some of these strains are more likely to cause epididymo-orchitis than clinically obvious mucosal infection. Untreated, *N. gonorrhoeae* invades the submucosa sometimes causing submucosal abscesses, spreads into adjoining glandular structures such as Bartholin's, Skene's and Littre's glands with the potential for further abscess formation. A mild lymphadenitis in draining lymph nodes often accompanies acute infection. Gonorrhoea initiates an inexorable ascending infection to the fallopian tubes, surrounding ligaments and adjoining organs in women, causing an acute pelvic inflammatory disease. Less commonly, infection spreads to the epididymis and testis in men, causing an acute epididymo-orchitis. The infection eventually resolves, but, in the absence of early treatment, healing occurs with damaging scar tissue formation and fibrosis. In the urethra and the fallopian tubes such scarring can permanently interfere with normal function. A small number of gonococcal strains has the potential to invade the blood stream causing bacteraemia with systemic symptoms and disseminated skin and joint manifestations (disseminated gonococcal infection).

In the neonate, infected by its mother at birth, gonorrhoea characteristically produces an acute sight-threatening conjunctivitis which is recognised two or three days after birth.<sup>31</sup>

### Treponema pallidum

The natural history of syphilis in an adult is divided into three stages—primary, secondary and tertiary.



Someone without clinical signs or symptoms of syphilis, but having positive syphilis serology and no history of having been treated for syphilis, is said to have latent syphilis. By convention in Australia and the UK, primary and secondary syphilis and the first two years of latent infection are called 'early' syphilis (i.e. the period during which syphilis is infectious by sexual contact), while tertiary, cardiovascular, neurosyphilis and latent infection beyond two years is called 'late' syphilis. In the USA 'early' syphilis refers only to the first twelve months of infection. Table 1.2 and Figure 1.4 describe the stages of syphilis in adults with a guide to accompanying serology results.

TABLE 1.2 Stages of syphilis in Adults					
INFECTIOUS			NON-INFECTIOUS except vertically		
<b>EARLY (&lt;2 years)</b> Early latent (asymptomatic)	<b>RPR</b> 1:8 or greater	<b>SPECIFIC TEST</b> Reactive	<b>LATE (&gt;2 YEARS)</b> LATE LATENT (asymptomatic)	<b>RPR</b> Very variable, usually 1:4 or less – sometimes becomes non-reactive eventually	<b>SPECIFIC TEST</b> Reactive
Primary (chancres)	May be non-reactive, but then increasing titre with time	Reactive (except very early in infection)	Tertiary (skin lesions, gummata)	Usually less than 1:16	Reactive
Secondary (rash, mucous membrane lesions, alopecia, lymphadenopathy)	1:8 or greater (i.e. 1:16, 1:32, 1:64)	Reactive	Cardiovascular (aortitis)	Usually less than 1:16	Reactive
Specific test = TPPA or TPHA, FTA ABS, EIA			Neurosyphilis (may be asymptomatic – only abnormal CSF being demonstrated)	1:8 or greater	Reactive

Primary syphilis (the chancre) is a self-limiting condition, with ulceration healing within a few weeks in untreated patients. Secondary syphilis is also self-limiting with clinical manifestations resolving over several weeks, although, in at least 25% of untreated people, relapses of secondary syphilis continue to occur over the first two years after infection. Tertiary syphilis, cardiovascular and neurosyphilis occur at a variable period of time after infection, from as short as one year through to forty years later. Historical studies done on untreated patients indicate that only about 30% of those with syphilis develop these late manifestations of disease. In the other 70%, immune responses manage to control the infection. Co-infection with HIV may alter the natural history of syphilis.<sup>26</sup>

### Trichomonas vaginalis

Trichomonal infection occurs in vaginal epithelium and the lining of the urethra of men and women. It can also infect the cervix; acute trichomonal inflammation at this site causes the clinical appearance called 'strawberry cervix'. Sometimes infection spreads to associated glands (e.g. Bartholin's and Skene's). The organism has been isolated from the prostate gland and from epididymal aspirates, but its role in prostatitis and epididymitis is uncertain; if it does occur it is rare. Trichomonal infection in pregnancy has been associated with an increased risk of pre-term delivery, preterm rupture of membranes and maternal puerperal infection.<sup>12</sup>

### Bacterial vaginosis

The natural history of bacterial vaginosis remains largely a mystery. There is an association with pelvic inflammatory disease but the significance of this is uncertain. The presence of bacterial vaginosis in pregnancy (both symptomatic and asymptomatic) may lead to low birth-weight in babies, premature delivery and post-partum endometritis but the results of studies of therapeutic interventions against bacterial vaginosis in early pregnancy have been surprisingly variable. There is no clear consensus on how best to manage bacterial vaginosis in pregnancy as yet, but some experts recommend screening and treatment of high-risk mothers (especially those with a previous history of premature delivery).<sup>13</sup>

### HIV and STIs—co-infection and the cofactor effect

There is a complex interaction between HIV and STIs. Very early in the HIV epidemic, studies in sub-Saharan Africa showed that STIs causing ano-genital ulcerative disease (GUD) substantially increased the risk of people acquiring HIV.<sup>32</sup> This finding was not surprising, as any breach in genital skin or mucous membrane was likely to increase ease of entry for HIV. Subsequently, studies showed it was possible to recover HIV from genital ulcers (including herpetic ulcers) in HIV-positive people. In other words, the presence of GUD made it more likely that HIV-positive people could transmit the infection to a sexual

partner. Successfully treating the STI responsible for GUD stopped the shedding of HIV and decreased the risk of HIV transmission. The synergy between HIV and genital HSV-2 infection is especially worrying because HSV-2 is the most common cause of genital ulceration around the world and both symptomatic and asymptomatic shedding of HSV-2 occur relatively frequently in patients with the infection. Studies have shown that HSV-2 sero-positivity itself is a risk factor in both the acquisition and transmission of HIV.<sup>33</sup> While suppressive therapy with antiviral drugs (e.g. acyclovir, valaciclovir, famciclovir) may decrease the risk of transmission of HSV-2 and so decrease the risk of transmission of HIV in patients with co-infection, routine use of these drugs in every HSV-2 sero-positive person is not a realistic option globally.

HIV shedding also substantially increases from genital sites during infection with other STIs. Gonococcal urethritis and cervicitis in men and women with HIV infection lead to substantially higher HIV viral loads in genital secretions than when people do not have gonorrhoea. Appropriate treatment for gonorrhoea causes a precipitate fall in such high HIV viral loads.<sup>34</sup> Any STI associated with local inflammation increases the risk of acquiring HIV for a person without infection and enhances the risk of passing on HIV from a person with the infection to sexual partners.<sup>35</sup> Even in bacterial vaginosis, a condition not characterised by local inflammation, but where the vaginal alkalinity is raised, there is an enhanced risk of a woman acquiring HIV infection, perhaps because the usual protective acid environment of the vagina is lost.

In addition, HIV alters the natural history of many STIs (especially syphilis and genital herpes, but also HPV) and some STIs appear to have an influence on the natural history of HIV (again syphilis and herpes). In summary, the interaction of STIs with HIV is a synergistic one which considerably enhances the transmission of HIV in populations and cumulatively increases the burden of morbidity and mortality of all STIs around the world.<sup>36</sup>

## Therapy

### HIV

The course of HIV has been drastically altered by the introduction of highly active antiretroviral therapy (HAART or combination antiretroviral therapy). This therapy usually consists of a combination of at least three drugs from two or three of the different classes of antiretroviral drugs: the nucleoside analogue reverse transcriptase inhibitors (NRTIs), the non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs). A combination of three agents, usually two NRTIs combined with either an NNRTI or PI, is administered when the CD4 cell count falls below a certain threshold. Although the optimal time to commence therapy has not been established, Australian and international guidelines recommend that treatment should be considered when the CD4

cell count falls below 350 cells/mm<sup>3</sup>, with some suggesting intervention around 350 cells/mm<sup>3</sup>, or when the HIV viral load is above 55,000 copies/mL. Individualised decisions should take into account the patient's readiness to start therapy, the baseline CD4 cell count and HIV RNA level and the potential risks and benefits of treatment. Combination antiretroviral therapy is very potent in reducing viral load and delaying drug resistance, and has resulted in a dramatic reduction in mortality and increased life expectancy in people with HIV infection. This success has meant that HIV infection is becoming a chronic manageable disease for many people in many industrialised countries. Immune-based therapies, such as interleukin-2 and therapeutic vaccination, are also under investigation.

The aim of therapy for HIV infection is to sustain an undetectable viral load, which is achievable in approximately 50–60% of patients, and to produce immune reconstitution. Immunological benefit may be modest (CD4 cell counts frequently remain below normal levels) but may still occur in those who fail to achieve full virological suppression.

At present we do not know the long-term durability of the response in those who achieve virological control or whether drug resistance and loss of efficacy will ultimately emerge. Many of the antiretroviral drugs have significant side effects and some have complex dosing schedules, making adherence (a major determinant of the development of resistance) an issue for concern. However, fixed dose combination drugs are now available and most of the newer antiretroviral agents are administered once or twice daily, making adherence to combination regimens easier. Long-term survival of these people also has unmasked chronic drug toxicities, particularly metabolic problems such as lipodystrophy and lipoatrophy, hyperlipidaemia, insulin resistance and hepatic mitochondrial toxicity.<sup>37</sup>

## HBV

The goal of HBV treatment is to prevent the development of hepatocellular failure and hepatocellular carcinoma (HCC). This is achieved through suppression of viral replication with resolution of hepatic inflammation, as viral eradication with loss of HBsAg is rare. Treatment is usually initiated in people with elevated HBV DNA >10<sup>4</sup>–5 IU/mL and/or evidence of hepatitis with raised alanine aminotransferase (ALT) or fibrosis or inflammation on liver biopsy. Response to treatment can be assessed biochemically (ALT), virologically (HBV serology and DNA) or histologically (liver fibrosis). Currently, a number of different agents are available, including immunomodulators (interferon- $\alpha$  and pegylated (PEG) interferon- $\alpha$ ) and antiviral nucleos(t)ide analogues (lamivudine, adefovir and entecavir). In HBeAg-positive people, the aim of treatment is HBeAg seroconversion which is associated with a durable suppression of HBV DNA off treatment in 50–90% of people. Treatment with interferon- $\alpha$  is

a four to six months finite course associated with HBeAg seroconversion rates of around 20%, with higher rates (30%) using the longer acting pegylated interferon- $\alpha$ . As interferon is an immunomodulator, it is not associated with viral resistance. It does have significant systemic side effects, however, which often means that patients prefer the oral nucleos(t)ide analogues.

Lamivudine was the first nucleoside analogue found to effectively reduce HBV DNA, with HBeAg seroconversion rates of 17–32%, usually in those with raised ALT. However, at four years, over 60% develop viral resistance to lamivudine. Recently, entecavir was licensed for first-line HBV treatment. This agent appears to be more effective than lamivudine, with 67% undetectable HBV DNA and 21% HBeAg seroconversion at 48 weeks.<sup>38,39</sup> HBV resistance has been estimated to be approximately 3% by three years, but is significantly higher in those with previous lamivudine resistance. As a second-line agent, adefovir is a nucleotide analogue that effectively suppresses HBV DNA but is also associated with resistance rates of 15% at four years. There is also the risk of nephrotoxicity and hypophosphataemia, which requires monitoring. The treatment of HBeAg-negative infection is problematic and therapy is probably needed lifelong to achieve viral suppression. Newer agents such as tenofovir and telbivudine will become available in the near future. Combination therapy may offer a future strategy for some patients if studies demonstrate this to be effective.<sup>29,37,40</sup> Finally, development of end-stage liver disease may mandate liver transplantation, the outcomes of which have been significantly improved with the use of these antiviral therapies and HBV immunoglobulin to prevent graft re-infection.<sup>41,42</sup>

## HCV

Similar to HBV, HCV is treated to prevent the development of cirrhosis, which is associated with hepatocellular failure and hepatocellular cancer. However, unlike HBV, the aim of treatment is viral eradication. The combination of pegylated interferon- $\alpha$  and ribavirin is now the standard of care for chronic HCV. Pegylated interferon is produced through the attachment of a polyethylene glycol (PEG) molecule to standard interferon. This improves the pharmacokinetic properties of interferon and allows for once-weekly administration. Not only is this new formulation more convenient to administer but response rates are enhanced. Sustained virological remission (SVR) is defined as the absence of HCV RNA from serum six months after completion of therapy and is influenced by both HCV genotype and HCV viral load. SVRs with standard interferon and ribavirin combination therapy were in the region of 35% for genotype 1 and 80% for genotype 2 and 3.

With pegylated interferon there is a significant improvement in genotype 1 response rates by approximately 10% to between 42% and 52%.<sup>35–45</sup> The anticipated SVR rate for genotype 2 and 3 patients

remains very high at around 80%. The duration of therapy required is also genotype dependent, with genotype 2 and 3 patients requiring only six months of therapy compared to 12 months for genotype 1 patients. Response rates in cirrhotic patients are also markedly improved with pegylated interferon therapy compared to standard interferon therapy (SVR 43% versus 33%). Once SVR has been achieved it is highly durable, with almost all patients (more than 95%) remaining clear of the virus with extended follow-up.

End-stage liver disease due to HCV is now the most common indication for liver transplantation in Australia. Graft re-infection is almost universal, although disease progression is still relatively slow in most cases.<sup>14,46</sup>

Until recently, access to treatment was dependent upon the demonstration of liver fibrosis on biopsy. However, with the improvement in treatment outcomes and a better understanding of the pathogenesis of HCV, treatment is now accessible for most patients with chronic HCV without biopsy. Furthermore, there has been significant progress in the development of the non-invasive assessment of liver fibrosis (eg fibroscan and fibrotest) which will become available in the future.

## STIs

The general principles of therapy for STIs are three, namely:

- To cure patients of their infection, if possible; if not, to relieve symptoms and to stop progression of disease
- To render individuals non-infectious as soon as possible to prevent ongoing transmission in the community
- To treat all sexual partners

Sexual health and public health physicians favour simple, single-dose treatments, capable of being taken immediately.<sup>47</sup> These are obviously ideal principles rarely met in practice, but they need to be kept at the forefront of the minds of all practitioners treating patients with STIs. Except for the viral STIs, simple, single-dose treatments now exist for almost all the common uncomplicated STIs. The development of azithromycin in the mid-1990s truly revolutionised therapy for genital chlamydia infection—prior to that time, treatment for chlamydia depended on doxycycline which had to be given for a minimum of seven days. Many patients failed to complete the course, failed to be cured and so remained potentially infectious.

Antiviral therapies are readily available in Australasia for genital herpes and, although not curative, they will relieve the symptoms of troublesome outbreaks (especially primary attacks) and substantially reduce viral shedding, thus reducing the risk of further transmission. Ongoing clinical trials are currently

assessing the public health effectiveness and practical utility of this chemotherapeutic intervention in high-risk groups (e.g. people with HIV infection and MSM with herpes).<sup>48</sup>

There is no antiviral therapy for HPV infection and none in development, clearance of clinical manifestations of this virus being mediated by the immune response in immunocompetent people.

Public health objectives inevitably link closely with treatment goals in STI management. Where effective treatment is available, the aim is to treat all sexual partners of patients diagnosed with an STI and, where there is no effective treatment, the lesser aim is to provide information, education and counselling for sexual partners. Contact tracing (partner notification) meets these aims. Because of the complex and synergistic interactions between STIs and HIV, especially in communities at high risk for both types of infection, clinicians must make a new commitment to contact tracing. ASHM's manual on contact tracing discusses this important aspect of STI management and is a great resource for busy practitioners.<sup>49</sup>

## Prevention

There is an effective and safe vaccine for HBV which is provided universally for babies and adolescents in Australia through the National Immunisation Program. It is important to offer vaccination to high-risk patients who have not been previously immunised. Unfortunately, technical difficulties associated with vaccine development suggest that effective vaccines for HIV and HCV are at least five to 10 years away.

There is also an effective and safe vaccine for hepatitis A virus. To prevent infection through sexual transmission of this virus, clinicians should encourage vaccination in all individuals who engage in sexual activities where any degree of faecal contamination of fingers or mouth could occur. This includes all MSM.

There are now two effective and safe vaccines against HPV licensed for use in Australia. There are several differences between them. Gardasil provides protection against HPV types 6, 11, 16 and 18 and is recommended for use in young women aged between nine and 26. There is a funded vaccination program for school girls and a two year catch up program for young women. Based on immunogenicity studies, Gardasil is also licensed in Australia for use in boys aged between nine and 15, but there are no data as yet on its effectiveness in preventing infection and disease in males. Cervarix, the other HPV vaccine is designed to protect against infection with HPV types 16 and 18, but also has activity against types 31 and 45. It is licensed for women and girls aged between 10 and 45 in Australia. Health practitioners should be offering HPV vaccine to all young women, preferably before they commence sexual activity. If Gardasil is used, it should protect women from the common genital wart viruses and the most common high-risk types of HPV. It should not be a substitute for regular

**Papanicolaou smears as other high-risk HPV types exist and circulate in the community.**

**Prevention strategies for the blood-borne viruses based on public health behaviour modification and harm minimisation approaches have been effective in Australia and elsewhere and remain the foundation of prevention for individuals at risk of these viral infections. All people should be given clear messages about the risks of STIs, the asymptomatic nature of most early STIs in men and women, the enhancing effects of STIs on the risk of acquiring HIV, the need for regular sexual health check-ups for those with multiple sexual partners or frequent changes of partner, and the reliability of male (or if preferred, female) condoms in substantially reducing the risk of transmitting and acquiring almost all the STIs.**

## References

- 1 Danta M, Brown D, Bhagani S, et al. Recent epidemic of acute hepatitis C virus in HIV-positive men who have sex with men linked to high-risk sexual behaviours. *AIDS* 2007;21(8):983–91.
- 2 Stewart G, (ed). *Managing HIV*. North Sydney: Australasian Medical Publishing Company Ltd; 1997.
- 3 Lee WM. Hepatitis B infection. *N Engl J Med* 1997;337:1733–45.
- 4 Schacter J. Biology of Chlamydia trachomatis. In: Holmes KK, Sparling PF, Mardh P-A, Lemon SM, Stamm WE, Piot P, Wasserheit JN editors. *Sexually Transmitted Diseases*. 3rd ed. New York: McGraw-Hill; 1999: 391–406.
- 5 Corey L, Wald A. Genital herpes. In Holmes KK, Sparling PF, Mardh P-A, Lemon SM, Stamm WE, Piot P, Wasserheit JN editors. *Sexually Transmitted Diseases*. 3rd ed. New York: McGraw-Hill, 1999: 285–312.
- 6 Koutsky LA, Kiviat NB. Genital human papillomaviruses. In Holmes KK, Sparling PF, Mardh P-A, Lemon SM, Stamm WE, Piot P, Wasserheit JN, editors. *Sexually Transmitted Diseases*. 3rd ed. New York: McGraw-Hill, 1999: 347–60.
- 7 Manhart LE, Holmes KK, Koutsky LA, Wood TR, Kenney DL, Feng Q, Kiviat NB. Human papillomavirus infection among sexually active young women in the United States: implications for developing a vaccination strategy. *Sex Transm Dis* 2006; 33: 502–8.
- 8 Dunne EF, Unger ER, Sternberg M, McQuillan G, Swan DC, Patel SS et al. Prevalence of HPV Infection amongst females in the United States. *J Am Med Assoc* 2007; 297: 813–9.
- 9 Bauer HM, Ault K. Human papillomavirus: current prevalence and future protection. [editorial]. *Sex Transm Dis* 2006; 33: 509–11.
- 10 Sparling FP. Biology of Neisseria gonorrhoeae. In Holmes KK, Sparling PF, Mardh P-A, Lemon SM, Stamm WE, Piot P, Wasserheit JN editors. *Sexually Transmitted Diseases*. 3rd ed. New York: McGraw-Hill; 1999: 433–50.
- 11 Stamm LV. Biology of Treponema pallidum. In Holmes KK, Sparling PF, Mardh P-A, Lemon SM, Stamm WE, Piot P, Wasserheit JN editors. *Sexually Transmitted Diseases*. 3rd ed. New York: McGraw-Hill; 1999: 467–72.
- 12 Krieger JN, Alderete JF. Trichomonas vaginalis and trichomoniasis. In Holmes KK, Sparling PF, Mardh P-A, Lemon SM, Stamm WE, Piot P, Wasserheit JN editors. *Sexually Transmitted Diseases*. 3rd ed. New York: McGraw-Hill; 1999: 587–604.
- 13 O'Brien RF. Bacterial vaginosis: many questions—any answers? *Curr Opin Pediatr* 2005; 17: 473–8.
- 14 The National Institutes of Health. Consensus Development Conference: Management of hepatitis C. *Hepatology* (supplement 1) 1997.
- 15 Gibb DM, Tess BH. Interventions to reduce mother to child transmission of HIV infection: new developments and current controversies. *AIDS* 1999;13(suppl A):S93–S102.
- 16 National Centre in HIV Epidemiology and Clinical Research. HIV/AIDS, viral hepatitis and sexually transmissible infections in Australia, Australian HIV Surveillance Report. 2006; 22: 4.
- 17 O'Sullivan BG, Gidding HF, Law M, Kaldor JM, Gilbert GL, Dore GJ. Estimates of chronic hepatitis B virus infection in Australia. *Australian & New Zealand Journal of Public Health* 2000; 28:212–6.
- 18 Law MG, Dore GJ, Bath N, Thompson S, Crofts N, Dolan K, et al. Modelling hepatitis C virus incidence, prevalence and long-term sequelae in Australia, 2001. *Int J Epidemiol* 2003; 32:717–724.
- 19 Serpaggi J, Chaix M-L, Batisse D, Dupont C, Vallet-Pichard A, Fontaine H et al. Sexually transmitted acute infection with a clustered genotype 4 hepatitis C virus in HIV-1-infected men and inefficacy of early antiviral therapy. *AIDS* 2006; 20: 233–40.
- 20 MacDonald M, Crofts N, Kaldor J. Transmission of hepatitis C virus: rates, routes, and cofactors. *Epidemiol Rev* 1996;18:137–46.
- 21 Crofts N, Jolley D, Kaldor J, van Beek I, Wodak A. Epidemiology of hepatitis C virus infection among injecting drug users in Australia. *J Epidemiol Community Health* 1997;51:692–7.
- 22 Stamm WE. Chlamydia trachomatis infections in the adult. In Holmes KK, Sparling PF, Mardh P-A, Lemon SM, Stamm WE, Piot P, Wasserheit JN editors. *Sexually Transmitted Diseases*. 3rd ed. New York: McGraw-Hill; 1999: 407–22.
- 23 King A, Nicol C, Rodin P. Herpes Genitalis and Hepatitis B Infections. In *Venereal Diseases*. 4th ed. London: Balliere Tindall 1980: 325–6.
- 24 Corey L, Adams HG, Brown ZA, Holmes KK. Genital herpes simplex virus infections: clinical manifestations, course, and complications. *Ann Intern Med* 1983; 98: 958–72.
- 25 Kim HN, Meier A, Huang M-L, Kuntz S, Selke S, Celum C et al. Oral herpes simplex virus type 2 reactivation in HIV-positive and –negative men. *J Infect Dis* 2006; 194: 420–7.

- 26 Sparling PF. Natural history of syphilis. In Holmes KK, Sparling PF, Mardh P-A, Lemon SM, Stamm WE, Piot P, Wasserheit JN editors. *Sexually Transmitted Diseases*. 3rd ed. New York:McGraw-Hill; 1999: 473–8.
- 27 Chakraborty R and Rowland-Jones S. The pathogenesis of HIV disease. *J HIV Ther* 1999;4:2–8.
- 28 Dore GJ, Freeman AJ, Law M, Kaldor JM Is severe liver disease a common outcome for people with chronic hepatitis C? *Journal of Gastroenterology and Hepatology* 2002;17, 423–30.
- 29 Dieterich D. Hepatitis C virus and human immunodeficiency virus: clinical issues in co-infection. *Am J Med* 1999;107:79S–84S.
- 30 Simms I, Ward H, Martin I, Sarah A, Ison C. Lymphogranuloma venereum in Australia. *Sex Health* 2006;3: 131–3.
- 31 Hook EW III, Hunter Handsfield H. Gonococcal infections in the adult. In Holmes KK, Sparling PF, Mardh P-A, Lemon SM, Stamm WE, Piot P, Wasserheit JN, editors. *Sexually Transmitted Diseases*. 3rd ed. New York: McGraw-Hill; 1999: 451–466.
- 32 Cameron DW, Simonsen JN, D'Costa LJ, Ronald AR, Maitha GM, Gakinya MN et al. Female to male transmission of human immunodeficiency virus type 1: risk factors for seroconversion in men. *Lancet* 1989;2(8660):403–7.
- 33 Wald A, Link K. Risk of human immunodeficiency virus infection in herpes simplex virus type 2-seropositive persons: a meta-analysis. *J Infect Dis* 2002; 185:45–52.
- 34 Cohen MS, Hoffman IF, Royce RA, Kazembe P, Dyer JR, Costello DC et al. Reduction in concentration of HIV-1 in semen after treatment of urethritis: implications for prevention of sexual transmission of HIV-1. *Lancet* 1997; 349: 1868–73.
- 35 Laga M, Manoka A, Kivuvu M, Malele B, Tuliza M, Nizilla N et al. Non-ulcerative sexually transmitted diseases as risk factors for HIV-1 transmission in women: results from a cohort study. *AIDS* 1993; 7: 95–102.
- 36 Robinson NJ, Mulder DW, Auvert B, Hayes RJ. Proportion of HIV infections attributable to other sexually transmitted diseases in a rural Ugandan population: simulation model estimates. *Intl J Epidemiol* 1997; 26: 180–189.
- 37 International AIDS Society-USA Panel. Antiretroviral therapy in adults: Updated recommendations of the International AIDS Society-USA Panel. *J Am Med Assoc* 2000;283:381–90.
- 38 Chang TT, Gish RG, de Man R, Gadano A, Sollano J, Chao YC, et al for the BEHoLD A1463022 Study Group. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. *N Engl J Med* 2006;354(10):1001–10.
- 39 Lai CL, Shouval D, Lok AS, Chang TT, Cheinquer H, Goodman Z, et al for the BEHoLD A1463027 Study Group. Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. *N Engl J Med* 2006;354(10):1011–20.
- 40 Hoofnagle JH and Di Bisceglie AM. The treatment of chronic viral hepatitis. *N Engl J Med* 1997;336:347–356.
- 41 Torresi J and Locarnini S. Antiviral chemotherapy for the treatment of hepatitis B virus infection. *Gastroenterol* 2000;118 (suppl):S83–S103.
- 42 Shaw T and Locarnini S. Combination chemotherapy for hepatitis B virus: the final solution? *Hepatology* 2000;32:430–2.
- 43 Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomized trial. *Lancet* 2001, 358: 958–65
- 44 Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncales FL, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002, 347: 975–82
- 45 Hadziyannis SJ, Sette H, Morgan TR, Balan V, Diago M, Marcellin P, et al for the PEGASYS International Study Group. Peginterferon-alfa 2a and ribavirin combination therapy in chronic hepatitis C. A randomized study of treatment duration and ribavirin dose. *Annals of Internal Medicine*, 2004;140: 346–55
- 46 Pianko S and McHutchison JG. Treatment of hepatitis C with interferon and ribavirin. *J Gastroenterol Hepatol* 2000;15:581–6.
- 47 Hunter Handsfield H. Principles of treatment of sexually transmitted diseases. In Holmes KK, Sparling PF, Mardh P-A, Lemon SM, Stamm WE, Piot P, Wasserheit JN editors. *Sexually Transmitted Diseases*. 3rd ed. New York:McGraw-Hill; 1999: 711–21.
- 48 Russell DB. Herpes and HIV infection-has the time come to act? *Sex Health* 2006; 3: 67–71.
- 49 Australasian Society for HIV Medicine (ASHM). Australasian contact tracing manual. 3rd edn. Sydney: ASHM; 2003.