Sexually Transmitted Diseases

Vaccines, Prevention, and Control

Second Edition

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Foreword

While there have been continued advances in the screening, treatment, and prevention of sexually transmitted diseases (STDs) since the publication of the first acclaimed edition of *Sexually Transmitted Diseases* in 2000, sexually transmitted infections (STIs) continue to pose a serious challenge to public health.

In the USA, for example, even as reported rates of gonorrhea fell to an historic low in 2010, surveillance data demonstrating that N. gonorrhoeae is becoming resistant to standard currently effective antibiotic treatment indicates the threat of treatment failure is a looming public health concern. Additionally, while overall syphilis rates fell for the first time in a decade in the USA per 2010 data, there was a dramatic increase among young black men, particularly black men who have sex with men, reflective of the disparity in STD rates that leave select populations disproportionately affected. The challenges faced in the USA are but a fraction of the global burden; according to the World Health Organization, nearly 448 million new curable STIs occur globally each year, and STIs rank in the top five disease categories for which adults seek healthcare.

In the face of the continued global challenge of STD prevention and control, this new edition will no doubt prove a timely and comprehensive resource for health professionals, researchers, and others invested in this complex public health issue. The book provides a comprehensive review of the global epidemiology of STDs, with insight into the myriad factors that contribute to the global epidemic, including anatomical and physiological factors that affect transmission. The global overview also provides a basis for comparison of STD epidemiology among various countries and regions and the relevant factors that contribute to the spread of disease. Individual STD pathogens, both viral and bacterial, are discussed in depth, with detailed information on epidemiology, clinical disease, and prevention strategies.

Indeed, a welcome update in this new edition is an expanded focus on prevention strategies in the second section. Several chapters highlight advances in our understanding of STD prevention and control, from the role of male circumcision in the prevention of STDs to STD vaccine acceptance. Also addressed is the effectiveness of particular prevention approaches for adolescents. Both in the USA and globally, teens and young adults represent a disproportionate number of new STD cases each year, and thus insight into prevention strategies directed at this population is essential. The new edition also offers enhanced information on topical microbicides and their potential clinical role in future STD prevention efforts.

For almost 100 years, since 1914, the American Social Health Association (ASHA) has educated the public about STDs. More recently, we've expanded

our scope to encompass sexual health with an emphasis on STDs. We have always felt that scientifically accurate information was the most basic step in educating people about such a complex subject.

The scope and breadth of this concise and comprehensive book, written and compiled by internationally recognized experts in the field, makes this new edition an essential resource for clinicians, researchers, students, and public health and medical professionals.

Lynn B. Barclay
President and CEO
American Social Health Association

Chapter 1

Global Epidemiology of Sexually Transmitted Diseases

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Chapter Outline

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INTRODUCTION

Many infections are sexually transmitted although some, including HIV and hepatitis B and C, are also transmitted by blood or blood products; others, like human papillomavirus (HPV) and herpes simplex virus (HSV) can also be transmitted by close bodily contact.

In 2005, the World Health Organization (WHO) estimated there were 448 million cases of the four major curable sexually transmitted infections (STIs) (trichomoniasis, chlamydia, gonorrhea and syphilis) among people aged 15–49 worldwide (Schmid et al., 2009). The viral STIs are also extremely common, with an estimated 33 million people infected with HIV in the world, 24 million new HSV type 2 infections annually and 10% of women in the world harbouring genital HPV at any time (70% of cervical cancers are attributable to HPV types 16 and 18). The vast majority of cases occur in developing countries (Gerbase, Rowley, Heymann, Berkley & Piot, 1998). One of the major reasons why STIs are more common in developing nations is that a large proportion of these populations is aged 18–35 years, the age group considered to be at greatest risk for STI acquisition. Gender inequalities, limited services and poor education opportunities in many of these communities also contribute to the ongoing spread of these infections.

STIs are a major cause of morbidity and mortality, with HIV causing over one million deaths per year worldwide. In addition, chlamydia and gonorrhea are the leading causes of tubal infertility; oncogenic HPV infections are associated with cervical, anal, and other genital tract tumours; many of the STIs (including HIV, syphilis, hepatitis B, gonorrhea, chlamydia, and HSV) can be transmitted from mother to baby, resulting in neonatal death, severe disability, or chronic infection. STIs may enhance HIV transmission and acquisition, and this appears to be particularly important in parts of the world where STIs are very common, including parts of sub-Saharan Africa and South East Asia.

The rate of STI spread within a community depends on several factors, including the size of the susceptible population, exposure to an infected individual, efficiency of transmission, and duration of infectiousness. Epidemiological patterns of individual infections depend on the interplay between these factors and the social, economic, and political environment. At an individual level, risk factors for STI acquisition include early coitarche, multiple sexual partners, partners from high-risk groups, poor condom usage, and drug use. A major limitation to any STI control initiative is that most individuals with an STI do not have symptoms or, even if they do, they may not recognize these to be due to an infection. This means that, unless sexual contacts are found and treated and that screening for asymptomatic infections occurs on a regular basis in ‘at-risk’ populations, the majority of people with STIs will remain undetected and untreated.

Societal factors may also have a profound effect on STI transmission. An example of the effect of social, economic, and political changes on STIs is

the epidemic growth of these infections in the former USSR. Profound social and economic changes, and a partial collapse of the health system, have been contributory. The epidemic has been fuelled by growth in the commercial sex industry, unsafe intravenous drug use (IDU), and exchange of sex for drugs.

In addition to the personal health consequences, many STIs have important social, economic, and public health consequences, including family disharmony and breakdown, maternal and child ill-health, loss of income and productivity, and an enormous burden on social and health services. The global importance of STIs was acknowledged in 2000 when the United Nations drew up the Millennium Development Goals (MDG), aimed at reducing the global burden of disease and extreme poverty. One of the eight goals, MDG 6, 'combat HIV/AIDS, malaria and other diseases', relates directly to the most important STI worldwide. In addition, STIs are important in relation to several other MDGs, including MDG 3 'promoting gender equality and empowering women', MDG 4 'reduce child mortality' and MDG 5 'improving maternal health' (United Nations, 2000).

As expected from the diverse cultures and sexual mores throughout the world, the epidemiology of sexually transmitted diseases (STDs) is highly variable in distribution and changing in different ways in different regions. The factors that influence these differences in prevalence and incidence are the nature of the STD itself, whether curable or incurable by antimicrobials, or preventable or non-preventable by vaccines. The availability of the highly developed healthcare network in western industrialized countries in contrast to developing countries influences the epidemiology, through ease of transmission, availability of diagnostic facilities and drugs, transmissibility of behavior modification messages, and levels of education allowing receptiveness to these messages. New diagnostic tests allow the definition of large reservoirs of asymptomatic infection, leading to marked changes in our understanding of the epidemiology of these infections. However, within the western industrialized countries there are also marked differences according to race, socioeconomic status, sexual preference, and the influence of drugs and prostitution. The data available to measure the epidemiology of STIs is limited, even in many western industrialized countries, and is often only available in developing countries through infrequent sampling studies. The importance of global comparisons of epidemiology is that it allows cross-comparison of the factors influencing spread and of optimal strategies for control, allowing adaption of the latter to the unique cultural characteristics and healthcare system of individual countries.

HUMAN IMMUNODEFICIENCY VIRUSES

Infection with the human immunodeficiency virus type 1 (HIV) and development of the acquired immunodeficiency syndrome (AIDS) was one of the major epidemics of the latter part of the twentieth century. The epidemic has spread to over 150 countries on the six populated continents with significant differences in

the epidemiology both between and within countries. The first clinical description of AIDS was made in the USA in 1981, with the recognition of unusual clusters of Kaposi's sarcoma and *Pneumocystis carinii* pneumonia, found in homosexual men. However, the deaths of a family in Norway (1976) were attributed retrospectively to HIV infection, and the isolation of HIV from a plasma sample collected in 1959 confirms the presence of HIV in the human population long before the 1980s (Jonassen, et al., 1997; Zhu, et al., 1998).

Following this initial observation in homosexual men in the USA, AIDS was reported in other populations, including IDUs, hemophiliacs, blood transfusion recipients, heterosexual adults from Central Africa, and infants born to mothers with HIV, showing that HIV was transmitted by homosexual and heterosexual sex, contaminated blood, and vertically from mother to baby. HIV has now reached virtually all demographic groups globally, irrespective of age, race, and income level.

Virology of HIV

HIV was first isolated at the Institut Pasteur Paris in 1983 (Barre-Sinoussi, et al., 1983) from the lymph node of a patient with lymphadenopathy. Further analysis by electron microscopy and DNA sequencing confirmed the virus to be a member of the lentivirus genus of the Retroviridae family.

The lentivirus genus is further divided into five groups, based on the vertebrate hosts they infect: bovine, equine, feline, ovine, and primate. The primate lentivirus group is divided into 14 separate lineages based on phylogenetic analysis of pol sequences. This group contains HIV-1, HIV-2 and 12 primate species-specific simian immunodeficiency viruses (SIVs), which do not infect humans. Lentiviruses are primarily characterized by long incubation periods before the onset of disease and cause a persistent, lifelong infection. Additionally, lentiviruses have the ability to infect lineages of hemopoietic cells, in particular non-dividing cells such as CD4+ lymphocytes and differentiated macrophages. Consequently, disease manifests as an immunodeficiency.

Transmission of HIV

HIV is transmitted in three major ways: through sexual contact, in blood, and from mother to child. The majority of HIV-1 infections are acquired through heterosexual contact, which accounts for approximately 85% of all infections globally; however, increasing numbers of infections are being reported in other 'at risk' groups such as men having sex with men (MSM), IDUs, and sex workers. At the start of the HIV epidemic, homosexual or bisexual male-to-male (sometimes combined with IDU) transmission was the main risk behavior identified in developed countries, and this remains one of the main modes of transmission in these countries. In contrast, heterosexual spread in the general population is the main mode of transmission in sub-Saharan Africa, which remains the most

heavily affected region, with 68% of the global burden. Currently, HIV affects both men and women worldwide in approximately equal numbers, although more women than men are living with HIV in sub-Saharan Africa. The presence of other diseases, in particular STIs such as genital herpes, chancroid (ulcerative diseases), gonorrhea, and chlamydia (non-ulcerative), enhances the risk of sexual transmission of HIV.

Mother-to-child transmission (MTCT) of HIV can occur *in utero*, during labor, and *postpartum* via breastfeeding. The risk of transmission from mother to child *in utero* and during labor is increased if the maternal CD4+ T lymphocyte count is low, the maternal plasma HIV viral load is high, there are concurrent STIs, maternal tuberculosis, prolonged rupture of membranes, and if the baby is delivered vaginally. Breastfeeding transmission is dependent on duration of breastfeeding, high breastmilk viral HIV RNA levels, and maternal mastitis (Mepham, Bland, & Newell, 2011). Globally, the number of children born with HIV has decreased from 500 000 (320 000–680 000) in 2001 to 370 000 (230 000–510 000) in 2009 (UNAIDS, 2010). However, MTCT rates differ greatly between resource-rich and -poor settings, with the majority of cases of MTCT cases occurring in low- to middle-income countries. In Papua New Guinea, 10% of newly infected cases of HIV are due to MTCT via perinatal exposure. The introduction of antiretroviral prophylaxis in sub-Saharan African countries has been instrumental in reducing MTCT, in keeping with the UNAIDS goal of eliminating MTCT by 2015 (UNAIDS, 2010). In resource-rich settings such as North America and Europe, MTCT has virtually been eliminated (<2%) by the adoption of interventions, including antenatal use of highly active antiretroviral therapy (HAART), targeted elective Cesarean section births, and avoidance of breastfeeding (Mepham, Bland, & Newell, 2011).

It was identified early in the epidemic that HIV was transmitted through blood and blood products, and recipients of these products were a significant source of HIV infections in developed countries. The first HIV antibody screening test, an anti-HIV antibody test, was licensed by the FDA and made available to blood banks in 1985; along with donor deferral, this dramatically reduced the number of HIV infections. Progressive improvement in HIV testing, in particular the introduction of nucleic acid testing in 1999, has reduced the detection of the infectious window period (seroconversion) to less than a week, and a current estimate for the risk of acquiring HIV via blood transfusion or blood products in the USA is 1 in 2 million (Perkins & Busch, 2010). The risk of acquiring HIV through blood transfusion or blood products in low- to middle-income countries is unknown, but is certainly higher than in developed countries owing to the high prevalence of HIV, the frequent use of paid donors, and poor screening programs (Jayaraman, Chalabi, Perel, Guerriero, & Roberts, 2010).

HIV transmission from sharing contaminated drug injecting equipment remains a major global problem and accounts for an increasing proportion of new HIV infections in eastern Europe, South America, and East and South East Asia, where the prevalence of HIV in some IDU populations has been estimated

at 40% (Mathers, et al., 2008). In regions where the HIV epidemic is rapidly expanding (such as central Asia), HIV prevalence in IDU in some cities is 25–30% (Thorne, Ferencic, Malyuta, Mimica, & Niemiec, 2010). Lack of available sterile injecting equipment, failure to adopt a harm reduction philosophy, and an aggressive antidrug law enforcement approach has marginalized some IDU communities and is driving the epidemic in some central Asian countries.

Aside from blood transfusion and IDU-associated transmission, HIV can also be transmitted within healthcare settings. The main sources of HIV infection in the healthcare setting include the use of non-sterile needles, syringes, and improperly sterilized medical equipment (Chant, et al., 1993). Large outbreaks have occurred in Romania, Russia, and Libya, affecting children, from the use of shared syringes and improperly sterilized needles (Ganczak & Barss, 2008). HIV can also be transmitted from healthcare workers to patients and from patients to healthcare workers via exposure to HIV-infected blood or other body fluids, primarily through needlestick injuries. Plasma donations for money are also a source of transmission in the healthcare setting and it was reported that, in 2006, commercial plasma and blood donations were responsible for 69 000 cases of HIV in China (Ganczak & Barss, 2008). Occasional cases of HIV transmission through artificial insemination (prior to semen screening), allograft and organ transplantation, and from non-parental bloodborne exposure have been described. Outside of the healthcare setting, HIV has occasionally been transmitted from tattooing, biting, and exposure to contaminated needles (Ganczak & Barss, 2008).

Societal and environmental factors acting at the local, regional, and national levels that affect the spread of HIV include population migrations (labour, refugees, resettlement, commuting, etc.), urbanization, social disruption due to war, poor medical services, poverty, and the low social status of women (Perrin, Kaiser, & Yerly, 2003).

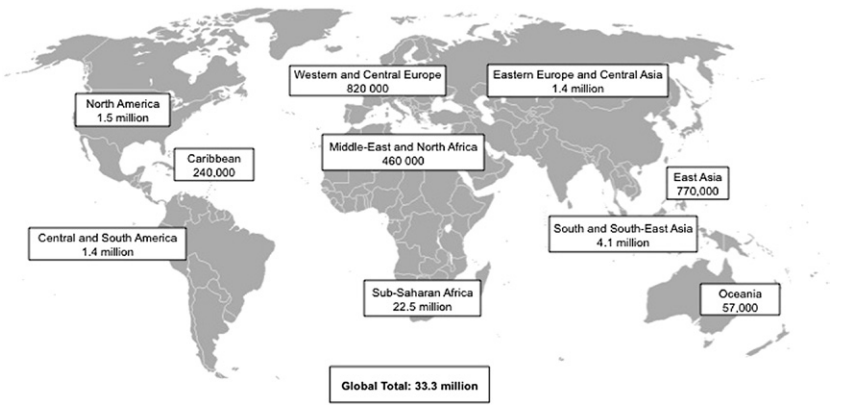

FIGURE 1.1 World map showing by region the estimated number of adults and children (global total 33.3 million [31.4–35.3 million]) living with HIV as of the end of 2009 (from UNAIDS Report on the Global AIDS Epidemic, 2010).

HIV Epidemics

The World Health Organization UNAIDS Global Epidemic Update reported at the end of 2009 that 33.3 million (31.4–35.3 million) adults and children were living with HIV/AIDS (see Figure 1.1). The global distribution of HIV/AIDS cases is not uniform, and regions such as sub-Saharan Africa and Asia still carry the highest burden with respect to HIV-infected individuals.

Globally, the number of newly infected individuals is declining, and in 2009 an estimated 2.6 million (2.3–2.8 million) new infections were reported, a 19% reduction from 1999. This amounts to approximately 7100 new infections per day. The incidence of HIV has decreased by more than 25% in 33 countries, of which 66% are in sub-Saharan Africa, which carries the greatest HIV burden. In contrast, the incidence of new infections has increased by more than 25% in countries in Central Asia, Bangladesh, and the Philippines since 2001. The epidemic has stabilized in Western, Central and Eastern Europe, and in North America, with no increase in new HIV infections. However, there are expanding epidemics in high-risk groups such as MSM and IDU and their sexual partners in some high-income countries, and in Eastern Europe and Central Asia.

The number of AIDS-related deaths has decreased since 2001; in 2009, 1.8 million deaths were reported. This decrease can be attributed to the increased availability of antiretroviral treatment, particularly in low- and middle-income countries. In high-income regions such as North America and Western and Central Europe, AIDS deaths decreased dramatically soon after the introduction of antiretroviral treatment. However, it is only now that a decrease is being observed in lower income regions such as sub-Saharan Africa and the Caribbean, as antiretroviral treatment reaches these regions. The number of deaths has stabilized in Central and South America and Asia but increased in Eastern Europe and Central Asia. The number of children born with HIV has decreased overall and in particular in low- and middle-income countries.

The number of people living with HIV in sub-Saharan Africa accounts for 68% of the global burden of HIV, where the epidemic continues to be spread by heterosexual contact. Southern Africa is most severely affected, with 10 countries accounting for 34% of the global total of people living with the infection. Although incidence in a number of countries has declined, prevalence rates still remain high in some countries (such as Swaziland), where prevalence in the adult population is estimated at 25.9%.

In Asia, most national epidemics have stabilized, with prevalence rates decreasing in a number of countries: for example, the prevalence rate in Cambodia has decreased from 1.2% in 2001 to 0.5% in 2009. Epidemics in this region are generally restricted to specific at-risk populations such as IDU, sex workers and their clients, and MSM, although epidemic patterns vary from country to country. A dramatic increase in the number of people living with HIV from 760 000 in 2001 to 1.4 million in 2009 was observed in Eastern Europe

and Central Asia, where the epidemic is primarily driven by IDU and sex workers and their clients (UNAIDS, 2010).

One-third of all people living with HIV in Central and South America reside in Brazil. In this region, HIV is primarily spread by MSM, although in countries with established epidemics such as Argentina and Peru, heterosexual transmission is increasing. Transmission by IDU is a growing problem in this region, particularly amongst incarcerated individuals (Coelho, Perdona, Neves, & Passos, 2007).

In high-income regions with mature epidemics (such as North America and Western and Central Europe), the epidemic has stabilized, although new infections are increasingly reported in specific populations (especially MSM). From the early 1990s to 2006 the number of new infections acquired through unprotected sex between men in the USA has increased by over 50% (Hall, et al., 2008). Similar trends have been observed in Europe (Sullivan, et al., 2009). Infections amongst injecting IDU in North America and Europe are generally declining; however, regions of high incidence, such as Estonia and the Mexico–USA border, have been identified (Brouwer, et al., 2006; Mathers, et al., 2008). In these regions an additional source of new infections is immigrants from HIV-endemic areas (Lattimore, et al., 2008; van de Laar & Likatavicius, 2009).

The epidemic in Oceania is well established and, although relatively small compared to other regions, the number of individuals living with HIV has almost doubled, from 28 000 in 2001 to 57 000 in 2009 (UNAIDS, 2010). In the key countries in this region, namely Australia and New Zealand, the main mode of transmission remains unprotected sex between men, whereas heterosexual contact accounts for the majority of HIV infections in Papua New Guinea (Coghlan, 2008).

HIV-2

HIV-2 originated from cross-species transmission from sooty mangabey monkeys to humans in West Africa and was first described in Senegal in 1985. HIV-2 is predominantly found in West African countries (Guinea-Bissau, Gambia, Senegal, Cape Verde, the Côte d'Ivoire, Mali, Sierra Leone, and Nigeria), where there are an estimated 1–2 million people infected with HIV-2. Infections have also been reported in countries with socioeconomic ties to West Africa (Portugal, Angola, Mozambique, Brazil, and parts of India) and other regions, including Europe, USA, and Asia (Korea and Japan) in immigrants and their partners. Dual infection with HIV-1 can occur, and it is estimated that 0.3–1% of HIV-infected individuals in West Africa are coinfected with HIV-1 (Campbell-Yesufu & Gandhi, 2011).

HIV-2 can be classified into eight genetic groups, A–H, with only groups A and B circulating widely (Takebe, Uenishi, & Li, 2008). Group A viruses have been found in western Africa, including Guinea-Bissau, Senegal, Gambia, and Mali, whereas group B viruses are present in Côte d'Ivoire, Ghana, and Nigeria (Takebe, et al., 2008). A recombinant HIV-2 virus (HIV-2 CRF_01AB) has been identified

in West Africa and in Japan (Ibe, et al., 2010). The modes of transmission of HIV-2 are similar to those of HIV-1; however, transmission efficiency is lower. Individuals infected with HIV-2 have higher CD4+ lymphocyte counts, lower plasma viral loads, and a longer asymptomatic period with slower disease progression.

Molecular Epidemiology of HIV

Following the publication of the first full-length HIV sequences from Europe, Africa, and the USA, and SIV sequences from non-human primates, it was realized that there was significant diversity in HIV viruses at the nucleotide and amino acid level (McCutchan, 2000).

Three major mechanisms contribute to HIV genetic variability: i) the error prone nature of reverse transcriptase (RT), leading to the introduction of point mutations at an average of one substitution per genome per cycle of replication; ii) the high viral turnover at all stages of disease; it is estimated that 10^{10} virions are produced in an infected individual daily (Ho, 1997); and iii) recombination, a major source of diversity of the global epidemic, where a coinfected cell can produce a viral genome containing more than a single HIV subtype (Robertson, Sharp, McCutchan, & Hahn, 1995).

HIV-1 viruses can be divided into three genetically divergent groups: the M (main) group, containing the majority of pandemic HIV-1 viruses and accounting for over 30 million infections; the O (outlier) group, which contains viruses from central African countries; and the N (non-M, non-O) group, which has only been identified in a few individuals in Cameroon. A P group has been described but, like the N group, viruses have only been found in a small number of Cameroonians (Robertson, et al., 2000; Tebit & Arts, 2011).

The M group can be further divided based on sequence analysis of complete genomes into nine subtypes, designated A–D, F–H, J and K, two sub-subtypes (A1 and A2, F1 and F2), 48 circulating recombinant forms (CRFs), and a growing number of unique recombinant forms (URFs) (Robertson, et al., 2000). CRFs arise though recombination between different HIV subtypes and are classified as new if complete genome sequences are available from three or more epidemiologically unlinked individuals and they have become endemic in populations. Examples include CRF02_AG and CRF01_AE, which are endemic in West Africa and South East Asia. URFs, on the other hand, are recombinant viruses that have been identified only in a single individual, have a unique structure and subtype composition but do not as yet meet the criteria to be classified as a CRF.

The global distribution of HIV-1 subtypes and CRFs is far from uniform (see Figure 1.2) and varies significantly from region to region (Hemelaar, Gouws, Ghys, & Osmanov, 2011; McCutchan, 2006).

Temporal changes in subtype prevalence have been observed in some regions since the pandemic began and this is often driven by the population being infected. For example, in Oceania the epidemic was initially spread

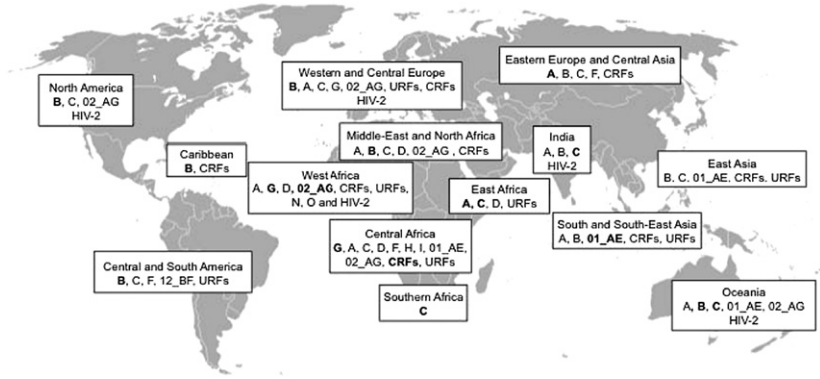

FIGURE 1.2 Distribution of HIV-1 M group, subtypes, CRFs, URFs, O group viruses, N group viruses, and HIV-2 throughout the world. Bold type indicates the predominant subtype(s). Common CRFs CRF01_AE and CRF_02AG are indicated as 01_AE and 02_AG, respectively. The designations CRFs and URFs indicate the presence of multiple other CRFs and/or URFs. Distribution of HIV-2 subtypes are not displayed.

through MSM and subtype B predominated. However, the epidemic, in addition to persisting in MSM, is now primarily driven by heterosexual transmission, and a shift from subtype B to subtype C as the predominant subtype has been observed (Hemelaar, et al., 2011). An increase in the proportion of CRFs causing infections globally has also been observed; however, this may reflect the change of classification of some subtypes to CRFs.

Subtype C, which is the commonest subtype in India, Southern and Eastern Africa, is the dominant subtype globally, accounting for nearly 50% of all infections (UNAIDS, 2010). The number and distribution of subtype B infections has remained relatively stable (2000–7) and accounts for 11% of infections worldwide. Subtype B predominates in North America, the Caribbean, Western and Central Europe, Latin America, Middle East and North Africa, and Oceania. However, in these regions, other subtypes cocirculate; for example, in Latin America subtypes C, F, and CRF12_BF and various URFs are present. Notably, few subtype B infections are found in sub-Saharan Africa (Hemelaar, et al., 2011; McCutchan, 2006; UNAIDS, 2010). Subtype A, including the two sub-subtypes A1 and A2, is highly prevalent in East and West Africa, Eastern Europe, and Central Asia. Subtype E, reclassified as a CRF (CRF01_AE), was the most prevalent subtype in Thailand and surrounding countries in South East Asia early in the regional epidemic.

Africa has by far the most diverse range of circulating subtypes and, in particular regions, such as the Congo River basin (Democratic Republic of Congo) in central Africa, where it has been suggested that the initial zoonotic jump from primates occurred, all subtypes (except subtype B) and many CRFs and URFs are present. Overall, subtype C is the predominant subtype on the African continent. In West Africa the predominant subtype is CRF02_AG and subtype G; however, all subtypes have been found in this region.

The subtypes F, G, H, J, and K have a very low global prevalence, as do the majority of CRFs, excluding CRF01_AE, CRF02_AG. The prevalence of URFs is generally low, although they have been found worldwide. URFs are predominantly present in regions where multiple subtypes circulate; for example, in South East Asia a URF containing CRF01_AE/B has been found (McCutchan, 2006).

Since its initial zoonotic jump from primates to humans, HIV has diversified into an extensive array of genetic variants evidenced by the rise in the number of CRFs being identified. This viral heterogeneity has significant implications for diagnosis, prevention, and treatment of HIV. Some key questions for each HIV subtype, CRF, and URF, regarding their infectivity and pathogenicity, remain largely unanswered. Additionally, the diversity and dynamic distribution of HIV subtypes, CRFs, and URFs makes vaccine development problematic and the development of regionally specific vaccines, diagnostics, and/or prevention strategies may be advocated in the future.

HTLV

The human T cell leukemia virus (HTLV) was first identified in humans in the 1980s (HTLV-1) (Poiesz, et al., 1980; Yoshida, Miyoshi, & Hinuma, 1982). Four HTLV viruses have been described (HTLV-1 to -4) with only HTLV-1 and -2 being associated with human disease. Infection with HTLV-3 or -4 is rare and has only been reported in primate hunters and communities from regions in central Africa and therefore infections are not well characterized (Bagossi, Bander, Bozoki, & Tozser, 2009; Calattini, et al., 2005; Mahieux & Gessain, 2009; Wolfe, et al., 2005; Zheng, et al., 2010). There are seven HTLV-1 subtypes and four HTLV-2 subtypes, mostly with high homology with their simian (STLV) counterparts (Casoli, Pilotti, & Bertazzoni, 2007). Accordingly, the spread of HTLV in humans is most certainly the consequence of cross-species transmission from non-human primates. HTLV proliferates by clonal expansion of infected lymphocytes and therefore, in contrast to HIV, genetic variation is limited. HTLV can therefore be transmitted via cell-associated virus in infected lymphocytes vertically, by breastfeeding, by exposure to infected blood or blood products (transfusion or IDU), and through sexual contact. HTLV-1 is the most prevalent HTLV virus infection in humans and is the causative agent of adult T cell leukemia and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) and uveitis (Poiesz, et al., 1980; Proietti, Carneiro-Proietti, Catalan-Soares, & Murphy, 2005; Verdonck, et al., 2007).

An estimated 15–20 million individuals are said to be infected with HTLV worldwide (de The & Bomford, 1993), (see Figure 1.3) although by and large the lack of quality global data does not permit a reliable estimate of worldwide prevalence (Hlela, Shepperd, Khumalo, & Taylor, 2009). The estimate of infected individuals may be higher as: i) seroprevalence studies in the general population are limited; ii) data from Africa and Asia (excluding Japan) was limited; iii) the global population has increased by approximately 17% since this prediction; and

FIGURE 1.3 Global distribution of HTLV-1 and -2, including regions where HTLV-1 is present (open circles) and regions of high HTLV-1 endemicity (filled circles), locations of ethnic groups where HTLV-2 is endemic (filled triangles), and locations of HTLV-2 associated with intravenous drug use (open triangles). Adapted from Slattery et al. 2011.

iv) diagnosis of HTLV has improved (Hlela, et al., 2009). HTLV-1 is distributed worldwide; however, prevalence rates vary between geographical regions (Hlela, et al., 2009; Proietti, et al., 2005; Slattery, Franchini, & Gessain, 1999).

Regions of high endemicity include south-western Japan (specifically the islands of Okinawa and Tsushima), intertropical Africa (sub-Saharan countries, Guinea-Bissau, Cameroon, and Benin, up to 5%), the Caribbean, some areas within South America, Melanesia (e.g. Papua New Guinea), and the Middle East, specifically Iran. Ethnic clustering of HTLV in indigenous populations in South America has also been reported (Slattery, et al., 1999; Sonoda, Li, & Tajima, 2011). However, the calculated seroprevalence in the general population versus specific populations varies in each of these regions (Hlela, et al., 2009). In North America and Europe, HTLV-1 seroprevalence rates are low in blood donor populations: Norway, 0.002%; Greece, 0.00556%; and North America/Canada 0.01–0.3% (Proietti, et al., 2005), and infection is generally restricted to select groups such as immigrants from endemic areas, their offspring and sexual contacts, IDU and sex workers; although in IDU populations in North America and Europe, the prevalence of HTLV-2 infection is higher than that for HTLV-1.

Subtype A, the cosmopolitan subtype of the six HTLV-1 subtypes, is distributed globally in HTLV-endemic areas. There is geographic restriction of the remaining subtypes with subtypes B, D, and F being found predominantly in central Africa, subtype E in south and central Africa, and subtype C in Melanesia (Proietti, et al., 2005).

HTLV-2 was originally thought to have a more constricted geographical distribution in comparison to HTLV-1, being localized to indigenous tribes in South America. However, HTLV-2 has been identified in ethnic groups in the Democratic Republic of Congo, Cameroon, the Central African Republic, and

Gabon, contradicting this theory. HTLV-2 has also spread to Europe and North America through IDU (Slattery, et al., 1999).

GENITAL HERPES

Herpes simplex virus type 2 (HSV-2) usually affects the genital or adjacent areas, with transmission being sexual. The proportion of people infected with HSV-2 varies markedly between countries, within the two genders, and the different populations within those countries (Smith & Robinson, 2002).

Herpes simplex virus type 1 (HSV-1) usually causes oropharyngeal infection, with transmission being by direct contact. However, both viruses can cause oropharyngeal or genital infections. HSV-1 is becoming an increasingly common cause of primary genital infection in most western countries, especially in adolescents, but is much less commonly a cause of recurrent infection (Haddow, et al., 2006). HSV-2 is still the major cause of initial genital herpes in adults and the pronounced cause of recurrent genital herpes (90–98% of cases).

After initial infection of the skin or mucosa, the virus is transmitted by sensory nerves to the dorsal root ganglia or to trigeminal ganglia, for HSV-2 and HSV-1, respectively, where it becomes latent. Reactivation of both viruses in the oral and genital areas is frequent and is much more often asymptomatic than symptomatic (Wald, et al., 1997). Only approximately 20% of patients infected with HSV-2 recognize genital lesions. Another 60% can be taught to recognize typical or atypical lesions, leaving 20% with true asymptomatic shedding (Koutsky, et al., 1992). Patients shed frequently, e.g. 20.1% of all days in subjects with symptomatic genital herpes and 10.2% of all days in individuals with asymptomatic genital HSV-2 infection (Tronstein, et al., 2011). Shedding occurs from vulva, cervix, urethral and perianal skin in women, and from penile and urethral skin in men, intermittently from different regions and often for very short periods (<12 hours) (Wald, et al., 1997). Furthermore, it is now known that most transmission of HSV-2 occurs via asymptomatic shedding, although the greatest risk of transmission at any one time is during primary infection. The annual rate of transmission between partners discordant for genital herpes appears to vary from 4% to 30% depending upon whether this is male–female, female–male, and whether the recipient has had previous HSV infection or not (Mertz, Benedetti, Ashley, Selke, & Corey, 1992). Both HSV-1 and HSV-2 infections are associated with significant complications, such as neonatal infection and death (increasingly caused by HSV-1), meningitis or encephalitis, recurrent rashes, and eye disease.

Infection with either HSV-1 or HSV-2 is usually associated with an antibody response, which reflects the presence of latent virus within the body and of subsequent asymptomatic or symptomatic shedding from oral or genital mucosae. The age-specific acquisition of herpes simplex virus has therefore been studied by serologic means. However, it was initially difficult to differentiate infection by HSV-2 and HSV-1, because of the antigenic similarity between most of the proteins shared

by these two closely related viruses. One of the most divergent proteins between the two viruses is glycoprotein G, consisting of approximately 238 amino acids in HSV-1 and 699 amino acids in HSV-2. Furthermore, patients infected with HSV-2 have type-specific antibodies to the immunodominant epitopes of gG2 which are not present in gG1 and can be measured by ELISA or Western blot (Ho, Field, Irving, Packham, & Cunningham, 1993; Ho, Field, Sjogren-Jansson, Jeansson, & Cunningham, 1992). ELISAs based on glycoprotein G2 are now widely used to estimate the incidence and prevalence of HSV-2 infection in various populations, as this is more accurate than estimates based on clinical cases. In addition, as the majority of HSV-1 and HSV-2 infections are asymptomatic, these ELISAs are often used for diagnostic purposes. The sensitivity and specificity of HSV-2 tests varies geographically, hence evaluation of test performance in a given setting is important in determining which test is most appropriate for use in a particular setting (Biraro, Mayaud, Morrow, Grosskurth, & Weiss, 2011).

Worldwide, HSV-2 seroprevalence has been compared in antenatal populations and in STD clinic populations. Very few randomized population-based studies have been performed. However, in the USA, the National Health and Nutrition Examination Surveys (NHANES) since 1976 have allowed accurate age-specific seroprevalence to be estimated across the nation (Centers for Disease Control and Prevention, 2010a; Fleming, et al., 1997; Johnson, et al., 1989). In randomly sampled American populations between 14 and 49 years there was a 30% increase in HSV-2 seroprevalence from 16% to 21% from 1976–84 to 1988–94, which then decreased to 16–17% in 1999–2004 and 2005–8. Seroprevalence was greater in women (21%) than men and showed marked racial variation in non-Hispanic blacks at 39.2% as compared to whites. The former are also at greater risk of HIV infection. In Australia, a median of 12% of a random sample of the population was infected, including up to 16% of women, 8% of men, and up to 18% of the indigenous population (Cunningham, et al., 2006). Urban populations showed a higher seroprevalence than rural populations. European, national, and cross-sectional serologic surveys between 1989 and 2000 found HSV-2 seroprevalence ranged from 24% in Bulgaria to 14% in Germany, 13% in Finland, 11% in Belgium, 9% in the Netherlands, 6% in Czech Republic, and 4% in England and Wales. Women were significantly more likely to be HSV-2-seropositive (Pebody, et al., 2004). A population-based adult study in Japan estimated the HSV-2 seroprevalence rates to be 7.4% in men and 9.3% in women (Doi, et al., 2009).

The highest HSV-2 seroprevalence in the world has been recorded from sub-Saharan Africa. In randomly sampled rural and urban populations, HSV-2 seroprevalence often exceeds 50% in women and 25% in men, and may reach 75% and 60%, respectively after age 30 (Obasi, et al., 1999; Paz-Bailey, Ramaswamy, Hawkes, & Geretti, 2007; Smith & Robinson, 2002).

In various populations, including general surveys, pregnant women, college students, and attendees at blood banks at antenatal clinics and STD clinics, a consistent cluster of factors that influences the acquisition of HSV-2 has been

recognized. These include age, ethnic origin, socioeconomic group or educational level, gender, regional or geographic variables, and sexual exposure, including age of first exposure, total number of sexual partners, and obviously a partner with herpes (Eberhart-Phillips, et al., 1998; Johnson, et al., 1989). Prior HSV-1 exposure may delay and decrease the prevalence of HSV-2 infection.

The lifetime number of sexual partners is one of the most important risk factors for HSV-2 infection and therefore HSV-2 antibodies have often been used as a marker for STIs. However, HSV-2 antibody may not always be a good marker for frequency of exposure in age cohorts where there has been little circulation of HSV-2 (e.g. in the 21-year-old cohort in Christchurch, NZ) (Eberhart-Phillips, et al., 1998).

Surveys of antenatal clinical attendees provide a reasonable approximation for prevalence in the general population where such studies have not been done. Comparisons of seroprevalence studies in pregnant women showed that, in the southern USA, Italy, Spain, Sweden, France, Iceland, Japan, Taiwan, and Australia, the highest seroprevalence was in the USA (black African American antenatal patients in Atlanta), followed by Sweden, France, Australia, Italy, and Taiwan, and was lowest in Japan (Smith & Robinson, 2002). In the teen years there appear to be regional pockets of high seroprevalence in some countries, e.g. in the USA in 2005–8 overall HSV-2 seroprevalence was 1.4% (Centers for Disease Control and Prevention, 2010a); there are also regional pockets of low seroprevalence, e.g. in 16-year-old Swedes and 21-year-old New Zealanders (3–4%) (Eberhart-Phillips, et al., 1998; Perkins, Coughlan, Franklin, Reid, & Taylor, 1996; Rosenthal, et al., 1997). However, in Cincinnati seroprevalence was 12% in a 12–22-year-old age cohort (Eberhart-Phillips, et al., 1998; Perkins, et al., 1996; Rosenthal, et al., 1997).

Although they are usually asked to declare whether they have had past STDs, serosurveys of blood bank donors can be useful estimates of population seroprevalence, e.g. 5% in Poland, 8% in London, 8.7% in Croatia, and 13% in Sydney (Rode, Lepej, & Begovac, 2008; Görander et al. 2008; Field et al., unpublished observations). In attendees at STD clinics, seroprevalence is usually much higher, e.g. in Japan, Spain, UK, Sweden, and New Zealand it ranged from 21% to 26% and in the USA from 40% to 57%. In STD clinics in Sydney, Australia, HSV-2 seroprevalence was 40% in 1984–5 (Cunningham, et al., 1993). The HSV-2 seroprevalence amongst MSM is also proportional to the number of lifetime partners, is increased in HIV-positive men, and varies geographically within western countries. Fifty seven percent of all MSM in a Sydney STD clinic were positive, but this increased to 78% of HIV antibody-positive men, and 72% of commercial sex workers (CSWs) attending the same clinic were HSV-2-seropositive (Cunningham, Field and Ho, unpublished observations).

A recent global estimate of the world burden of HSV-2 infection amongst those aged 15–49 years was 536 million in 2003 (~16% of the world's population), and was higher in women (315 million) than in men (221 million). The regional estimates are shown in Figure 1.4.

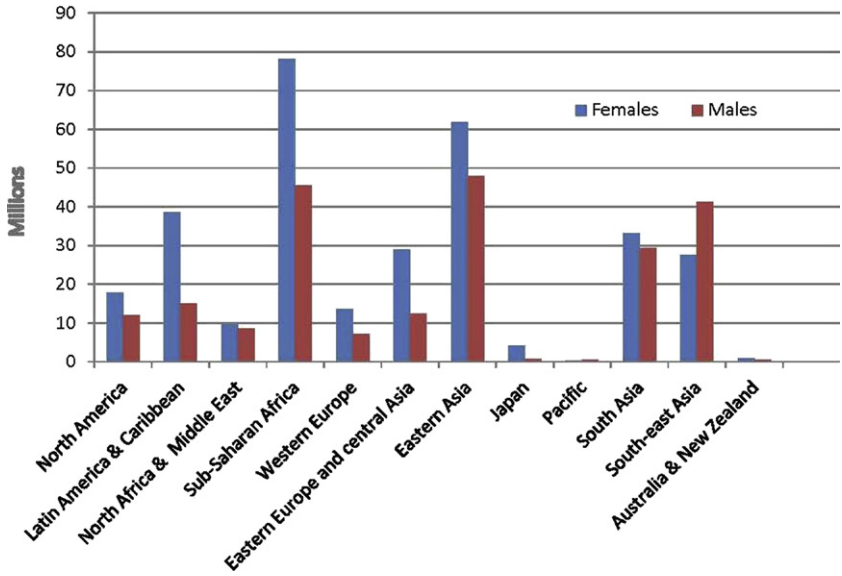

FIGURE 1.4 Regional estimates of HSV-2 prevalence in 2003. Adapted from Looker KJ, Garnett GP, Schmid GP. An estimate of the global prevalence and incidence of herpes simplex virus type 2 infection. *Bulletin of the World Health Organization*, October 2008, 86(10): 808–9. Please see color plate section at the back of the book.

Sub-Saharan Africa shows the highest seroprevalence, and this probably enhances HIV transmission (Looker, Garnett, & Schmid, 2008).

Serosurveys of various populations around the world at different times have shown marked changes in seroprevalence. As mentioned above, the NHANES studies provide the best data for the USA, showing a 30% increase between 1976–80 and 1988–94, mostly in young whites in their teens and twenties; but there is then a subsequent reduction back to 16% for 2005–8. Random consecutive serosurveys in pregnant women at similar times also showed increases: in Reykjavik, Iceland (4–23%, 1979–85); Lyon, France (11–17%, 1978–85), and Stockholm, Sweden (17–32%, 1969–89) (Smith & Robinson, 2002). However, an increase was not observed between slightly later surveys of similar populations in 1986 and 1996 in Sydney (14.5–11.4%), perhaps reflecting a greater awareness of sexual transmission of HIV during that decade. However, in many countries there has been a marked increase in genital herpes caused by HSV-1, which is attributed to increased orogenital contact, e.g. in Sydney, Australia the proportion of HSV-1 anogenital isolates rose from 30% to 41% between 1979 and 2003 (Haddow, et al., 2006). Unfortunately, it is not possible to measure the important national and global burden of sexual HSV-1 infection serologically as there are no tests to distinguish genital from orolabial infection.

The incidence of neonatal herpes varies markedly worldwide, from 1.65 to 60/100 000 live births, being high in parts of the USA (Seattle/Birmingham),

lower in Australia and Sweden, and apparently very low in the UK. HSV-2 seroconversion and genital shedding in late pregnancy is a major risk factor, but in the UK, and increasingly in Australia, HSV-1 infection is as common as HSV-2, reflecting the upsurge in genital herpes due to HSV-1 (Haddow et al., 2006; Corey & Wald, 2009; Jones, et al., unpublished). The HSV-2 seroconversion rate during pregnancy may also vary widely. In Seattle, USA, the seroconversion rate was 1.3% or 2% of susceptible women. HSV-2 shedding at term may occur in 8–15% of HSV-2-seropositive women by polymerase chain reaction (PCR) (Corey & Wald, 2009). In contrast, the seroconversion rate for HSV-2 in pregnancy in Sydney is <0.5%.

Regions with a high HSV-2 seroprevalence usually have a high prevalence of other STIs, such as chlamydia. HSV-2 antibody seropositivity also increases the chance of HIV acquisition by 3–5-fold via homosexual and heterosexual transmission in both high risk and general populations worldwide (Freeman, et al., 2006; Wald & Link, 2002). Recent HSV infection is associated with higher risk of HIV acquisition (Reynolds & Quinn, 2005), probably through increased transmissibility of HIV in the presence of genital ulceration and infiltrating T cells.

CYTOMEGALOVIRUS

After initial infection with cytomegalovirus (CMV), which is usually asymptomatic and mostly occurs in childhood, the virus remains latent within leukocytes of the marrow and blood (probably granulocyte-macrophage precursors) for life, reactivating relatively infrequently after immunosuppression or advancing AIDS. Chronic active infection and reinfection may occur in certain circumstances. Therefore the epidemiology of CMV is best measured by IgG antibody reflecting the prevalence and incidence of infection, and by viral shedding in saliva, genital secretions, urine, and blood as an indicator of active infection likely to result in transmission. The virus infects and reactivates in salivary glands and cervical mucosa, and can be transmitted via saliva, urine, semen, or cervical secretions (Boeckh & Geballe, 2011).

Infection with CMV is considered endemic and ubiquitous throughout the world, with the seroprevalence amongst young adults ranging from 40% to 100%, with the higher rates of seroprevalence occurring in developing countries (and in those of lower socioeconomic status in the developed industrialized countries). The virus is acquired at six stages during life: *in utero* via transplacental infection; at term via cervical shedding; during breastfeeding; during infancy (especially spread through saliva and urine in daycare centres); sexual transmission (both heterosexual and male homosexual); and infant to susceptible parent in adulthood, completing the cycle through infection of susceptible pregnant women and infection of the fetus *in utero*.

Sexual transmission of CMV has been shown by high rates of cervical shedding in women and higher seroprevalence amongst heterosexual women attending STD clinics, in CSWs, and MSM. However, in MSM, in STD clinic