

9.13

Acquired immunodeficiency syndrome

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Abstract

In the 25 years since the first reported cases of acquired immunodeficiency syndrome (AIDS), more than 70 million people have been infected with the human immunodeficiency virus (HIV). HIV is a retrovirus that is spread from mother to child, through blood contamination and through sex. Antiretroviral drugs administered to HIV-infected pregnant women and the newborn child, together with exclusive or no breastfeeding, have drastically reduced mother to child transmission. Screening of blood supplies, universal safety precautions in medical settings and needle exchange programmes for intravenous drug users are effective in avoiding blood borne spread. Reduction in sexual transmission is achievable through sexual abstinence, monogamy, condoms, treatment of concurrent sexually transmitted infections, male circumcision and HIV counselling and testing.

When spread, HIV specifically infects and replicates in CD4+ cells, leading to the systematic destruction of CD4+ cells over a period of years. The drop in CD4+ T-cell numbers to low levels leads to individuals developing symptoms including weight loss, low-grade fevers, night sweats, frequent fungal infections and eventually various opportunistic infections and malignancies, which signal the onset of AIDS. Until then, individuals who have been asymptomatic with HIV infection over several years have been infectious, thereby creating the conditions for the efficient spread of this virus. HIV infection is readily diagnosed by assays detecting antibodies, viral components and the viral genome. More than 25 antiretroviral drugs are known to be effective against HIV. Combinations of these drugs, referred to as highly active antiretroviral therapy, are effective in treating HIV infection.

Globally, it has proven to be a substantial challenge to extend HIV prevention programmes and provide treatment to those who most need it, as a disproportionately large burden of this disease is in poor countries. This pandemic has created many ethical, social, human rights and political challenges. The estimated 25 million people that have already died from AIDS far exceeds the total killed in all the major wars of the twentieth century. AIDS is the world's most devastating epidemic and the deadliest in the history of humankind.

History of AIDS

First reported cases of AIDS

AIDS was first reported in 1981 by a young physician from the University of California Los Angeles School of Medicine who described the occurrence, without identifiable cause, of *pneumocystis carinii* pneumonia (PCP) in four gay men in Los Angeles (Gottlieb *et al.* 1981). This new disease was also reported to and published by the US Centers for Disease Control and Prevention (CDC) in June 1981 and marked the beginning of awareness of the epidemic potential of AIDS in the USA. In 1982, the disease was given the name 'acquired immunodeficiency syndrome (AIDS)'. At this time very little was known about the epidemiology and transmission of AIDS, and initially it was thought that only homosexuals and injecting drug users were affected but reports soon emerged that the disease was also occurring in haemophiliacs and Haitian immigrants in the United States.

A greater understanding of the mode of transmission of AIDS was gained following the reported death from infections related to AIDS, of a young child who had previously received multiple blood transfusions, causing worldwide concerns about the safety of the blood supply, and the first cases of possible mother-to-child transmission of AIDS. By the time reports emerged that the disease was also transmitted heterosexually, it was apparent that the world was facing a disease of epidemic proportions.

Discovery of HIV as the cause of AIDS

The discovery that HIV caused AIDS was not a simple or direct path and required a substantial collaboration among different groups of scientists and clinicians. Only after the discovery of the Human T leukaemia virus types 1 and 2 (HTLV-1 and HTLV-2) in the 1980s, did the scientific community accept that it was possible for retroviruses to infect humans. The marked decline in CD4 cells and possible mode of transmission led scientists to believe that AIDS was possibly caused by a retrovirus. In 1983, a virus was isolated from a patient with lymphadenopathy, which was later named lymphadenopathy-associated virus (LAV). In the same year two distinct

viruses were isolated from an AIDS patient in Haiti, one which cross-reacted with antibodies to HTLV, while the other virus killed target T cells. It proved to be challenging to make the link between the virus and the clinical disease, AIDS, because the clinical signs of disease develop several years after the infection. However, through persistent isolation of the virus from patients with AIDS, the linkage was made possible (Gallo 2002; Gallo and Montagnier 2003). A series of important papers describing isolates of the new retrovirus, methods for its continuous production, and analyses of its proteins were published in *Science* and *Lancet* in 1984 and provided the scientific evidence that HIV is the cause of AIDS.

Viral structure and genetic diversity

Viral structure and replication

HIV belongs to the family Retroviridae and the genus *Lentivirus*: Lenti meaning slow due to the long time from infection to disease. HIV, being a retrovirus, encodes the enzyme, reverse-transcriptase, which makes DNA from viral RNA. HIV genetic material, as proviral DNA in the nucleus of infected cells, is able to persist in long-lived reservoirs such as resting T cells, thwarting efforts to clear HIV from the body.

Viral particles are spherical, about 100 nm in diameter. HIV has two major structural components—the core and the envelope. The core comprises the Gag (group-associated antigens) proteins, including: the matrix protein (p17), which lies just beneath the envelope, and the capsid protein (p24) which encloses the viral RNA. The envelope, a lipid membrane, consists of two ‘Env’ glycoproteins, gp120 and gp41. These proteins exist as trimers on the viral surface facilitating binding and entry to the host cell. Besides reverse transcriptase, two other enzymes, integrase and protease, collectively known as polymerases, are carried inside the viral particle and are encoded by the ‘Pol’ gene of HIV. In addition to the major structural proteins, a number of regulatory and accessory proteins are also produced, including: Tat and Rev, which enhance levels of gene expression, and Vif, Vpr, Vpu and Nef, which function to increase viral production and infectivity. Regulatory and accessory proteins are usually only produced once the virus infects cells and are not present inside the viral particles (Morris and Cilliers 2005).

HIV can attach to any cell that has a CD4+ receptor. Although these receptors are found primarily on the CD4+ lymphocytes,

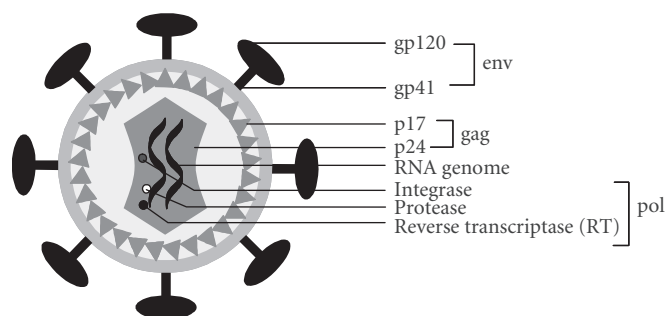


Fig. 9.13.1 Schematic diagram of HIV showing the constituent proteins and enzymes.

Source: Adapted from Morris and Cilliers (2005) with permission from Cambridge University Press.

they are also found on a range of mononuclear cells including macrophages, B cells, mature CD8+ cells and cells in the central nervous system. The process of HIV replication begins when gp120 binds to surface CD4+ and a co-receptor molecule, either CCR5 or CXCR4 (Moore and Doms 2003). Once HIV has successfully attached to the cell, a conformational change occurs allowing gp41 to insert itself into the host cell membrane. The capsid is then intruded into the cytoplasm of the cell where the viral RNA is reverse-transcribed to DNA and transported to the nucleus where, with the aid of the viral enzyme integrase, it is incorporated into human DNA. The transcription process, however, is imperfect and mutations are common occurrences during replication. The ‘errors’ in this step are a major reason why HIV is able to escape the immune system and persist (Weiss 2001).

After the viral DNA has been incorporated into the host DNA it is indistinguishable from the host DNA and is referred to as the ‘provirus’. Each time the cell divides, the viral DNA will be passed on to the progeny cells. Proviral DNA can remain quiescent for extended periods of time or become transcriptionally active, particularly in cases where there is inflammation (Simon and Ho 2003).

The virus makes use of the host cell machinery to replicate itself. Messenger RNA directs the production of viral proteins. After cleavage by viral proteases to generate individual proteins, structural proteins aggregate just beneath the plasma membrane surface for inclusion into the new virions. Envelope glycoproteins insert themselves into the cell membrane and mature viral particles are formed when the virus buds through the membrane. Full-length unspliced genomic RNA is transported to the plasma membrane to be incorporated into the viral progeny. As the new HIV is extruded from the host cell, lipid from the cell wall is incorporated onto the virus and forms the envelope of the progeny virus. A single CD4+ cell is capable of producing hundreds of new HIV progeny.

Genetic diversity

There are two HIV types, HIV-1 and HIV-2. HIV-2 is less pathogenic than HIV-1 and largely restricted to West Africa, with limited spread to other countries and is genetically more closely related to SIV than to HIV-1. Numerous HIV-1 subtypes and circulating recombinant forms (CRF) make up the complex mosaic of the global HIV-1 pandemic (McCutchan 2006). Specifically, HIV has been classified into three groups, M, N and O. The Major Group (Group M) comprises the viruses that are currently dominating the global AIDS epidemic. The Outlier Group (Group O) and the non-M non-O group (Group N) are much less common. Based on their phylogenetic relatedness, the Group M viruses have been further subdivided into nine subtypes or clades; A, B, C, D, E, G, H, J and K. Two of these, subtypes A and F have been further subdivided into sub-subtypes (referred to as A1, A2 and F1, F2, respectively).

An analysis of 23 874 HIV samples from 70 countries shows that in terms of viral diversity, subtype C viruses dominate and account for half of all HIV-1 infections worldwide while subtypes A, B, D and G account for 12%, 10%, 3% and 6%, respectively. Circulating recombinant forms were responsible for 18% of infections worldwide. Subtype C is dominant in Africa and Asia while subtype B is the commonest subtype in Europe and the Americas (Hemelaar *et al.* 2006).

HIV diversity is generated either through mutations introduced into viral genomes during replication or during the recombination of viral genomes. Mutations are introduced into the viral genome

primarily due to the error-prone nature of the viral replication enzyme, reverse transcriptase. HIV has an average mutation rate of 5×10^{-6} mutations per nucleotide per cycle of virus replication (Smith et al. 2005). As a consequence, no two viruses are identical within an infected individual, allowing for rapid adaptation to fluctuating selection pressures such as immune responses and antiretroviral drugs.

Natural history of HIV infection

Following the introduction of HIV into the human body, there is replication in local CD4+ cells before spread to the gut-associated lymphoid tissue, where there is high level HIV replication leading to virus levels in blood which can exceed ten million viral particles per ml. During viral replication in the gut-associated lymphoid tissue, there is a rapid decline in the numbers of CD4+ T lymphocytes, with the CD4+ cell count dropping by up to 50% within weeks post-infection.

Within a few weeks of the onset of HIV infection, the host immune response curtails viral replication resulting in a decline in the viral load and a slow increase in CD4+ T-cell numbers for a few months before starting its slow progressive decline (Fig. 9.13.2). At the time of the immune response, many infected individuals experience influenza-like symptoms characterised by chills, malaise, and weakness for a few weeks.

Within 6–12 months following the onset of HIV, viral replication reaches a level which is referred to as the ‘set point’. The level of the set point correlates with the rate of disease progression. Most individuals remain clinically well (asymptomatic) for an average of 8–9 years although the asymptomatic interval may vary widely. For reasons that are not fully understood, some individuals never develop control over viral replication and progress to AIDS within 1–2 years of infection (rapid progressors) while others have remained disease-free for up to 20 years, often with undetectable viral loads (long-term non-progressors).

Kinetic studies have shown that during the asymptomatic period up to a billion HIV particles and two billion CD4+ T cells are destroyed and produced each day. Thus while individuals may be clinically well,

the virus continues to replicate, particularly in the lymph nodes, causing a gradual decline in CD4+ T-cell numbers. The drop in CD4+ T-cell numbers to low levels leads to individuals developing AIDS symptoms including weight loss, low-grade fevers, night sweats, and frequent fungal infections and eventually various opportunistic infections and malignancies, which signals the onset of AIDS. With the deterioration of immune function, the viral load increases and, in the absence of treatment, death usually occurs within 6 months to 2 years after an AIDS diagnosis (Burger and Poles 2003). Treatment with Highly Active Antiretroviral Therapy (HAART) significantly extends the time period between AIDS diagnosis and death. There is accumulating evidence that the onset of AIDS may be about 1–2 years shorter following onset of HIV infection, in Africa compared to the developed world (Jaffar et al. 2004).

Laboratory assays

The isolation of HIV in 1984 and the establishment of its causal relationship with AIDS led to the development the first commercially available HIV serological tests by 1985. Subsequently there has been a rapid evolution in HIV diagnostic technology that has matched the rapidly evolving understanding of the natural history of HIV disease. Currently, a wide range of assays are available for adult and paediatric diagnosis, monitoring disease progression and therapeutic success, as well as for research and surveillance. These assays can be performed on a range of biological tissues such as serum, plasma, saliva, whole blood, urine, seminal fluid and cervico-vaginal specimens.

Antibody detection

Detection of antibodies using serological tests such as a standard enzyme immunoassay (EIA) is most often used for screening or diagnosis of HIV infection. A major advance has been the availability of rapid HIV antibody tests. The two limitations of these serological tests are, firstly, detection of infection during primary infection when antibody levels are low or absent and secondly, determination of whether a reactive EIA or positive rapid HIV test in newborns is

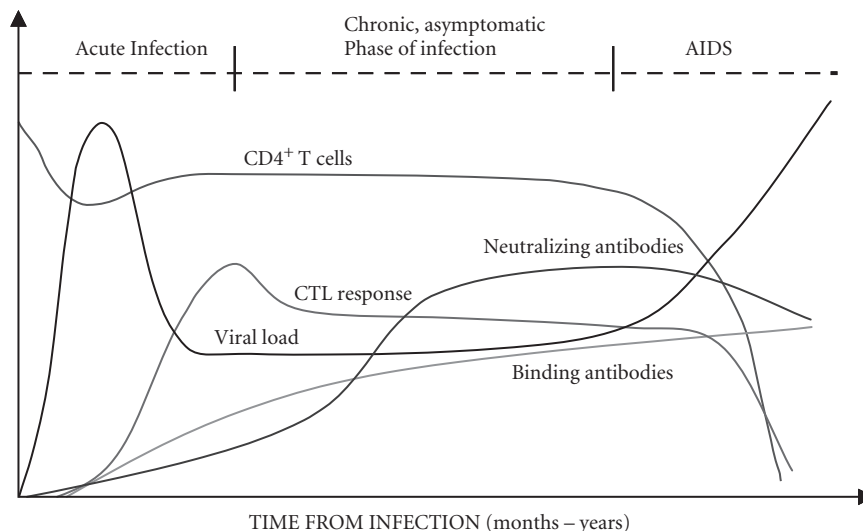


Fig. 9.13.2 Schematic diagram showing the natural history of HIV infection. Source: Adapted from Morris and Cilliers (2005) with permission from Cambridge University Press.

due to infection in the baby or due to passively transferred maternal antibodies. In these instances, the use of polymerase chain reaction technology for detection of viral RNA is helpful.

Antigen detection

Standard EIA tests are available for p24 antigen, which is often the earliest antigen that can be detected in acute HIV infection before the presence of antibodies is detectable. It is therefore used to identify the presence of HIV infection during the window period, the period between onset of HIV infection and the detection of HIV antibodies.

Nucleic acid detection

Plasma viral load is a marker of viral replication and is used to monitor therapeutic success in patients on antiretroviral treatment. A number of commercially available tests provide sensitive quantification as low as 50 copies of HIV RNA copies per ml (Berger *et al.* 2005). There are also tests for cell-associated HIV which measure branched DNA levels.

CD4+ cell counts

The number of CD4+ T-cells reveals the degree of immunodeficiency and is therefore a key criterion for initiating antiretroviral treatment. At present, flow cytometry analysis is the standard method for quantification of CD4+ cells. Where CD4+ quantification is not readily available, total white cell counts are sometimes used as a proxy marker (Spacek *et al.* 2006).

T-cell immune response detection

Various assays have been developed to assess the presence of a cellular immune response to HIV antigens. The earlier approaches like the Chromium release assay and the tetramer assay have now largely been superseded by the Elispot assay and the Intracellular cytokine stain assay. The latter two assays depend on the release of certain cytokines, such as interferon-gamma, when T-cells from the patient recognize HIV antigens used in the test. These assays are very sensitive and can sometimes be positive in the absence of any other markers of HIV infection—suggesting that the patient has previously encountered and can recognize HIV antigens, perhaps through a previous HIV exposure or aborted HIV infection. The hypotheses of aborted HIV infection and clearance of established HIV infection have not been confirmed empirically.

Assays to identify recent HIV infection

For research and surveillance purposes, differentiating between established/prevalent infection and new/incident HIV infections is critical for monitoring trends in the epidemic or efficacy of new interventions under trial. A number of tests have been developed for this purpose; most are based on differences between antibody responses in early versus established HIV infection. The three most commonly used serologic assays for estimating incidence from prevalent studies are the 'detuned' or STARHS (Serologic Testing Algorithm for Recent HIV Seroconversion) assay, Immunoglobulin G Capture BED-enzyme immunoassay (BED-CEIA) and the Avidity Index (AI) (Dobbs *et al.* 2004, Parekh and McDougal 2005; Janssen *et al.* 1998). All of these assays have substantial limitations and tend to over-estimate the incidence of infection due to their high false-positive rates.

STARHS consists of a less sensitive, first-generation ELISA followed by a later-generation ELISA with increased sensitivity. Recent infection (within the last 129 days, depending on viral sub-type) is indicated if the first-generation ELISA is negative and the second-generation ELISA is positive.

The BED-CEIA attempts to identify recent HIV infection by measuring increasing levels of anti-IgG as a proportion of overall IgG. Recent infection (within the last 153 days) is indicated by a ratio of HIV-specific IgG/total IgG less than 0.8.

The AI attempts to identify the weak antibody-antigen interaction present early in HIV infection compared to later stages where this interaction is stronger and more difficult to disrupt. Recent infection (within 120 days) is indicated by an Avidity Index less than 80%.

Other assays in development are the Affinity assay, IgG3 isotype assay and anti-HIV p31 assay.

Global epidemiology of HIV

Since the first reported cases of AIDS in 1982, an estimated 70 million HIV infections and about 25 million AIDS-related deaths have occurred globally (UNAIDS 2006). In 2007, UNAIDS estimated that globally there were 33.2 million (upper and lower bound of estimate: 30.6–36.1 million) adults and children living with HIV infection. Furthermore, globally a total of 2.5 million (1.8–4.1 million) new infections occurred and 2.1 million (1.9–2.4 million) people died from AIDS in 2007 (UNAIDS 2007).

Differences in the time of introduction of HIV and rates of HIV transmission in specific countries and populations have resulted in a complex mosaic of epidemics (Abdool Karim *et al.* 2007). In most countries HIV continues to spread and in countries with limited access to antiretroviral treatment, morbidity and mortality rates are on the rise.

A distinctive feature of the pandemic in the 21st century is its increasing burden in women. Women now comprise about 42% of those infected globally, over 70% of whom live in sub-Saharan Africa. Of significance is that a quarter of all new HIV infections occur in young adults under 25 years of age (UNAIDS 2003). Notably, where HIV transmission is predominantly sexual, HIV infection rates are 3–6-fold higher in adolescent girls compared to boys in the same age group (Pettifor *et al.* 2005; UNAIDS 2006).

The HIV epidemic varies substantially from one geographical area to another. For the purpose of epidemiological surveillance at a country level, UNAIDS and WHO have categorized the HIV epidemics broadly as 'low level', 'concentrated', or 'generalized'. The typology is based on the extent to which HIV infection is present and spreading in the general population compared to spread of HIV in sub-populations that are most at risk. An additional scenario 'hyperendemic' has been recently included to describe countries with generalized HIV epidemics where the HIV prevalence in the general population is in excess of 15% and HIV continues to spread. In reality most countries have a mix of epidemic scenarios. Of importance is keeping up to date on the sources of new infections, as it is dynamic and is key to shaping an effective country level response to the epidemic (Abdool Karim *et al.* 2007).

In 2007, about 5% of the adult population living in sub-Saharan Africa were infected with HIV in contrast to less than 0.4% in East Asia, North Africa and the Middle East, West and Central Europe and Oceania (UNAIDS 2006). Sub-Saharan Africa is severely affected by

HIV and accounts for 67.8% [22.5 million (20.9 million–24.3 million)] of global infections (Fig. 9.13.3) (UNAIDS 2007). It is estimated that 1.7 million (1.4 million–2.4 million) people in this region became newly infected in 2007, while 1.6 million (1.5–2.0 million) died from AIDS in this period. The majority of infections in sub-Saharan Africa occur through heterosexual contact, where women have about 2–3 times more HIV infection compared to men (Abdool Karim and Abdool Karim 1999).

Southern Africa epitomises a ‘hyper-endemic’ scenario and remains at the epicentre of the pandemic (Abdool Karim 2006a). HIV prevalence is >15% in the general adult population fuelled by extensive heterosexual spread, widespread concurrent sexual partnerships, and transmission in discordant stable couples.

Several countries in sub-Saharan Africa have shown a decline in HIV prevalence in recent years, including Kenya, urban areas in Rwanda, Zimbabwe and urban areas in Burkino Faso (Hallett *et al.* 2006; Kayirangwa *et al.* 2006; UNAIDS 2005, 2006). In contrast, while Uganda has for years been an excellent role-model for successfully impacting the HIV epidemic, more recent data demonstrate an increase in HIV infection in young women (Shafer *et al.* 2006).

HIV prevalence in the Middle East and North Africa is low and the national HIV prevalence has not exceeded 0.3%, with the exception of Sudan, where national prevalence in 2005 was estimated at 1.6%. A total of 380 000 (270 000–500 000) people were living with HIV in this region in 2007. The main modes of transmission in this region are unprotected sexual contact (including commercial sex and sex between men) and injecting drugs using contaminated equipment. In some countries in North Africa and the Middle East, a significant number of infections still result from contaminated blood products, blood transfusions or lack of infection control measures in health care settings although the extent of this has decreased significantly over the last decade.

The HIV epidemics in Latin America and the Caribbean are associated mainly with unsafe sex (both heterosexual and men who

have sex with men) and use of contaminated drug injecting equipment, especially among the poor and unemployed. In Latin America, an estimated 1.6 million (1.4–1.9 million) people were living with HIV in 2007. In most Latin American countries, HIV prevalence is highest among men who have sex with men.

In North America, Western and Central Europe, HIV prevalence has remained below 1% and AIDS mortality has been low because of the widespread availability of antiretroviral therapy. A total of 2.1 million people infected with HIV live in these regions (Fig. 9.13.3), of whom about 1.3 million live in the United States. A total of 77 000 people were newly infected in these regions in 2007 (UNAIDS 2007). Unsafe sexual practices between men and the use of contaminated drug injecting equipment are the most important routes of transmission of HIV in these regions. However, in recent years there has been an increase in heterosexual transmission and more women and members of minority ethnic groups have become infected through unsafe sex.

Epidemic patterns have also been changing in Eastern Europe and Central Asia in recent years, where an increasing number of women are being infected, many of whom acquire HIV infection from their male partners who became infected through injecting drugs using shared, contaminated injecting equipment. The epidemics in this region are continuing to grow. The total number of people living with HIV increased by about 36% from 2003 to 2005 (UNAIDS 2006). UNAIDS estimates that, of the 1.6 million (1.2–2.1 million) people living with HIV in this region, 150 000 (70 000–290 000) were newly infected with the virus in 2007. The Russian Federation and Ukraine account for the majority of infections in this region; most are infected through injecting drugs using contaminated equipment.

In South and South-East Asia, it is estimated that there were 4.0 million (3.3 million–5.1 million) people living with HIV at the end of 2007; 340 000 (180 000–740 000) became newly infected with HIV; and 270 000 (230 000–380 000) died from AIDS during 2007 (UNAIDS 2007). About 69% of all people infected with HIV in this



Fig. 9.13.3 Global distribution of people (adults and children) living with HIV in 2005 (33.2 million (30.6–36.1 million)). Major modes of HIV transmission are abbreviated as follows: MSM = men who have sex with men, HSex = Heterosexual, and IDU = injection drug use (Adapted from: UNAIDS (UNAIDS 2007)).

region live in India. However, with a total population of over 1 billion people, the adult prevalence in India is still below 1% (NACO 2006). In India, HIV transmission is primarily heterosexual, with female sex workers and their clients being the main drivers of HIV transmission (Mawar *et al.* 2005).

In East Asia (including China, Japan, Mongolia, Republic of Korea and Democratic People's Republic of Korea) adult prevalence remains low and has not yet reached 0.1%. In most of the rest of the countries in Asia, HIV prevalence remains low; only Cambodia, Thailand and Myanmar had adult HIV prevalence rates above 1% (1.6%, 1.4% and 1.3%, respectively) in 2005 (UNAIDS 2006).

Thailand provides an example of the dynamic nature of the evolving epidemic at a country level. The main routes of transmission in the late 1980s and early 1990s were through the use of non-sterile equipment in injecting drug users and through unsafe sexual behaviours. While the 100% condom use policy in brothels made a major impact on preventing sexual spread of HIV to the general population, its more conservative policy on needle exchange and methadone treatment has enabled HIV to spread rapidly to injecting drug users, who are potentially an important bridge to the general population. In 2005, it was estimated that about 43% of all new infections in Thailand occurred in the low risk heterosexual population, while 21% of new infections occurred among men who have sex with men (Gouws *et al.* 2006).

Of 75 000 (53 000–120 000) people infected with HIV in Oceania, it is estimated that over 70% are living in Papua New Guinea, where the epidemic started recently, but is growing rapidly. The number of cases of HIV in Papua New Guinea has increased by about 30% per year since 1997 (UNAIDS 2006), reaching an adult prevalence of 2.4% in 2007, with the main mode of transmission being unsafe sex. HIV prevalence in other countries in this region (including Australia, New Zealand, and Fiji) has remained low at about 0.1% (UNAIDS 2006) and is mainly concentrated in men who have sex with men and intravenous drug users.

Transmission of HIV

HIV spreads sexually, vertically from HIV infected mothers to their unborn infants, and through contaminated blood and blood products. It is estimated that sexual transmission (heterosexual and sex between men) accounts for about 84%, injecting drug use for about 7%, mother to child transmission for about 6% and unsafe health care practices for about 2.5–5% of the global HIV burden in 2006. While the attributable fraction of HIV transmission globally through injecting drug use is relatively small, it accounts for more than 80% of all HIV infections in Eastern Europe and Asia and is an important bridge to the general population.

HIV transmission is sometimes viewed purely from a biomedical perspective of underlying biology and within an epidemiological paradigm of risk groups and risk factors. However, such an approach is inadequate to understand the complexity of HIV transmission. It is important to recognise that social, economic, human rights and political perspectives are as important 'drivers' of HIV transmission that render some groups or populations more vulnerable to HIV acquisition.

Sexual transmission

While the probability of HIV transmission through a single coital act is very low, this risk increases with repeated exposure, co-infection

with sexually transmitted infection(s) especially genital ulcers, genital immaturity, receptive anal sex, circumcision status of male sexual partner, higher viral load in the HIV infected person and the susceptibility of the exposed individual (Vernazza *et al.* 1999). The risk of HIV infection is 3 per 10 000 contacts for the male partner compared to 20 per 10 000 contacts for the female partner in peno-vaginal sex. Hence, on average, women are seven times more likely to become infected. This ratio rises in peno-anal sex, where the risk ratio for the receptive compared to insertive partner exceeds 20:1, highlighting the importance of receptive anal sex as an important factor not only for men but for women as well.

The underlying biological mechanisms of sexual transmission of HIV are poorly understood. Studies have shown that both semen and vaginal secretions have both cell-free virus and T cells and macrophages which contain HIV. CD4+ positive cells are present both in the male urethra and female vagina—but it remains unclear whether CD4+ cells in the lumen or in the mucosa are involved in the infectious process.

High viral load is associated with more efficient transmission of HIV (Quinn *et al.* 2000). Viral load varies according to the stage of HIV infection, and is elevated during early infection, as well as during advancing HIV disease and progression to AIDS as immunity diminishes. Viral load is also higher during periods where there are other co-infections including herpes simplex virus type 2, malaria, tuberculosis and intestinal parasites. Ulcerative and non-ulcerative sexually transmitted infections contribute to higher HIV transmission and acquisition risk.

The various biological factors that influence the risk of HIV acquisition and transmission occur in a milieu of social, behavioural and cultural situations which also impact on the spread of HIV. These include poverty, gender-based economic and power differentials, gender-based violence, migrant labour, sex work and alcohol abuse.

Transmission through blood

Transmission through blood and blood products includes the sharing of needles and syringes during illicit drug use, inadequately screened or unscreened transfusion of blood and blood products, contaminated needles and/or equipment in health care settings or through traditional healing practices.

The risk of HIV transmission via infected donor blood and blood products was recognised early in the HIV epidemic. The implementation of widespread screening of the blood supply has reduced this mode of transmission drastically. However, some national blood screening efforts are impeded by inadequate resources for HIV testing, poor quality assurance of HIV testing procedures, inadequacy of staff training and the quality and choice of laboratory procedures (UNAIDS 2006). A particular challenge for the provision of safe transfusion products is the 'window period', when HIV antibody tests are negative but infectious HIV is present in the blood.

In healthcare settings HIV can be transmitted between patients and health care workers in both directions via blood on sharp instruments, and may also be transmitted between patients through re-use of contaminated instruments. This risk can be reduced through universal precaution practices including use of gloves, standard infection control measures, rigid containers for needles and single use syringes.

The sharing of needles and syringes among injecting drug users is a high risk practice for HIV transmission. Sterile needle exchange programmes are effective in reducing HIV transmission among injecting

drug users. The illicit nature of injection drug use and associated social stigma have compromised efforts to reduce HIV transmission in injecting drug users resulting in continuing high rates of transmission in these populations with bridging transmission to the general population in some instances.

Mother-to-child transmission

HIV is transmitted *in utero* (pre-partum), during the process of childbirth (intra-partum) and post-partum through breastfeeding. In the absence of any intervention, the mother-to-child transmission rate is between 20% and 40%. Most transmission from mother-to-child occurs during childbirth where mother's infected blood in the birth canal infects the baby, resulting in 10–20% of babies becoming infected. About 5% of babies become infected in utero. Breastfeeding accounts for 5–20% of babies becoming infected, depending on length and type of breastfeeding. The risk of perinatal HIV transmission is influenced by the severity of HIV disease in the mother (high RNA viral load and low CD4+ count), the route of delivery (caesarean section versus vaginal delivery), and the type of breastfeeding practices (exclusive breastfeeding or mixed feeding) and duration of breastfeeding. Notable advances have been made in reducing mother-to-child transmission of HIV to very low levels through the use of antiretroviral drugs, obstetric practices including caesarean delivery, and management of breastfeeding.

As availability of antiretroviral therapy to reduce mother-to-child transmission during childbirth increases, breastfeeding is assuming a proportionately greater role as a source of HIV spread to newborn babies in settings where formula-feeding is not an affordable option.

Breastfeeding, particularly in poor countries, can account for one-third to one-half of all mother-to-child transmissions. This risk is reduced substantially if the mother exclusively breastfeeds her baby since mixed feeding (breastmilk plus formula milk or any other feeds, including water) increases the risk of HIV transmission to the baby. Duration of breastfeeding affects the rate of transmission. A meta-analysis (Coutsoudis *et al.* 2004) of breastfeeding studies from sub-Saharan Africa estimated the cumulative probability of acquiring HIV infection to be 3% at 3 months, 5% at 6 months, 9% at 12 months, and 15% at 18 months.

Obstetric practices, such as vaginal delivery (compared to caesarean section) and prolonged rupture of membranes (>4 h), increase mother-to-child HIV transmission. Invasive procedures during labour and delivery, such as foetal scalp monitoring, amniocentesis, foetal scalp electrodes, episiotomy, and instrumental delivery, may also increase the risk of transmission. Circulating HIV variants in the mother are selected through immune pressure which is HLA dependent. Where the father has a substantially different HLA profile, the risk of transmission and/or the viral load in the baby is higher.

HIV prevention strategies

HIV prevention focuses, on the one hand, on reducing the likelihood of and vulnerability to infection in those who are currently uninfected and, on the other hand, on reducing the risk of transmission from those who are currently infected with HIV. The latter is an important new opportunity for enhancing prevention efforts through integration of prevention programmes into the health services which are scaling up AIDS treatment and the prevention of mother-to-child transmission. Knowledge of HIV status is an important gateway for targeted prevention and care efforts. It creates an

opportunity to address prevention efforts along a continuum that includes those uninfected who are at high risk of getting infected, those recently infected, those with established infection but asymptomatic and those who have advancing HIV disease and those on antiretroviral treatment. Within this context, groups that are particularly vulnerable can be targeted and their particular needs addressed. Proven interventions are available for preventing HIV through any of its transmission modalities (Table 9.13.1).

Reducing sexual transmission

Globally, the incidence rate of new HIV infections continues to exceed AIDS mortality rates. Reducing sexual transmission, especially heterosexual transmission, of HIV is critical to altering the current epidemic trajectory in many parts of the world. Prevention of sexual transmission can be achieved through reduction in the number of discordant sexual acts and/or reduction of the probability of HIV transmission in discordant sexual acts (Fig. 9.13.4).

There is no risk of HIV infection among those who practice sexual abstinence or lifelong mutual monogamy. Serial monogamy, where there are multiple sequential individual short-lived monogamous partnerships, is associated with an increased risk of HIV, but not to the same extent as the substantial increase in risk of transmission emanating from multiple concurrent sexual partnerships (Morris and Kretzschmar 1997). Reduction in the number of concurrent sexual partnerships and the use of condoms are key components of HIV prevention messages, widely promoted as part of 'ABC' campaigns promoting Abstinence, Be faithful and Condomise.

Male condoms

Condoms are a pivotal part of the fight against HIV/AIDS. They are inexpensive and relatively easy to use and provide protection against acquisition and transmission of HIV, a wide range of other sexually transmitted infections as well as pregnancy. When used correctly and consistently, the latex male condom is highly effective in preventing the sexual transmission of HIV. The strongest evidence for the role of condoms in preventing the transmission of HIV comes from sero-discordant couple studies, which uniformly show that increased condom use is associated with a substantially reduced risk of HIV transmission. However, there are still important questions regarding whether inconsistent condom use (that is, condom use in less than 100% of sexual contacts) is protective. While some studies have suggested that inconsistent condom use may offer more protection than no condom use whatsoever, others have demonstrated that the transmission of HIV among irregular condom users is similar to that of individuals who do not use condoms (Ahmed *et al.* 2001).

To be effective as a prevention option to impact on the growth of the epidemic, access to condoms needs to be drastically scaled up. In 2001, it was reported, that the overall provision of condoms to sub-Saharan Africa was 4.6 per man per year. An estimated 1.9 billion additional condoms would be needed to raise all countries to the average procurement level (about 17 condoms per man per year) of the six African countries that use the most condoms (Shelton and Johnson 2001). It would cost an estimated \$47.5 million a year to fill the 1.9 billion condom gap excluding service delivery costs and production. However, based on data on condoms procured in public sector health facilities across South Africa, the estimated unmet need for condoms is probably closer to 13 billion (Myer *et al.* 2001).

Table 9.13.1 Biomedical technologies for prevention for each modes of HIV transmission

Mode	Technology	Intervention
Blood and blood products	<ul style="list-style-type: none"> ◆ HIV screening for both virus and antibodies 	<ul style="list-style-type: none"> ◆ Selection of donors based on lower HIV risk profile ◆ Screening of all blood supplies with best available technology for viral detection during the window period of infection
Occupational exposure in health care settings	<ul style="list-style-type: none"> ◆ Barrier nursing - gloves, goggles, gowns as appropriate ◆ Universal Infection control practices ◆ Proper sharps and other biohazards disposal systems ◆ Post-exposure prophylaxis 	<ul style="list-style-type: none"> ◆ Guidelines for universal precautions ◆ Trained health care workers ◆ Availability of post-exposure prophylaxis ◆ Availability of barrier nursing paraphernalia ◆ Availability of disposal systems for sharps and other biohazardous materials
Exposure to infected blood through traditional skin cutting and blood letting practices	<ul style="list-style-type: none"> ◆ Infection control practices ◆ Barrier nursing 	<ul style="list-style-type: none"> ◆ Guidelines for universal precautions ◆ Adequate training of traditional healers ◆ Information to public raising awareness of HIV risk through traditional practices
Injecting drug use	<ul style="list-style-type: none"> ◆ Detoxification centres ◆ Sterile needles and syringes ◆ Maintenance therapy eg buponorphine 	<ul style="list-style-type: none"> ◆ Treatment/rehabilitation centres ◆ Free needle exchange programmes
Mother-to-child transmission	<ul style="list-style-type: none"> ◆ Determine mother and/or father's HIV status ◆ Antiretroviral drugs ◆ Alternative baby feeding options ◆ Non-invasive intra-partum procedures ◆ Caesarian section 	<ul style="list-style-type: none"> ◆ Implementation of a comprehensive prevention of mother-to-child transmission (PMTCT) programme
Sexual transmission		<ul style="list-style-type: none"> ◆ Abstinence ◆ Delay age of sexual debut ◆ Mutually faithful monogamous relationship between concordant couples ◆ 'Zero-grazing', i.e. no concurrent multiple partnerships
Consensual sex	<ul style="list-style-type: none"> ◆ Male condoms ◆ Female condoms ◆ HIV testing ◆ Sexually transmitted infection treatment ◆ Male medical circumcision 	<ul style="list-style-type: none"> ◆ Implementation of services for condom distribution, HIV education, and counselling, HIV testing, sexually transmitted infection treatment and circumcision services
Non-consensual/ coerced sex	<ul style="list-style-type: none"> ◆ Post-exposure prophylaxis ◆ Emergency contraception ◆ Sexually transmitted infection treatment 	<ul style="list-style-type: none"> ◆ Availability of health services for post-exposure prophylaxis, sexually transmitted infection treatment and emergency contraception
Experimental prevention tools to reduce sexual transmission (unproven)	<ul style="list-style-type: none"> ◆ Antiretroviral drugs as pre-exposure prophylaxis ◆ Acyclovir for herpes simplex virus type 2 treatment ◆ Microbicides ◆ Vaccines 	

Notwithstanding the challenges to condom access, a wide range of factors have been implicated as barriers to condom use; the most common being the widespread perception that condoms reduce sexual pleasure and that suggesting the use of condoms represents self-acknowledgement of HIV infection or a lack of trust in the partner. In the context of a marital relationship or stable partner-

ship where pregnancy is desired, or where subordination of women limits their ability to negotiate safer sex practices, attempts to introduce or promote condom use have had limited success.

Several studies have demonstrated that alcohol consumption is associated with inconsistent condom use; this phenomenon is particularly problematic because many individuals meet high-risk sexual

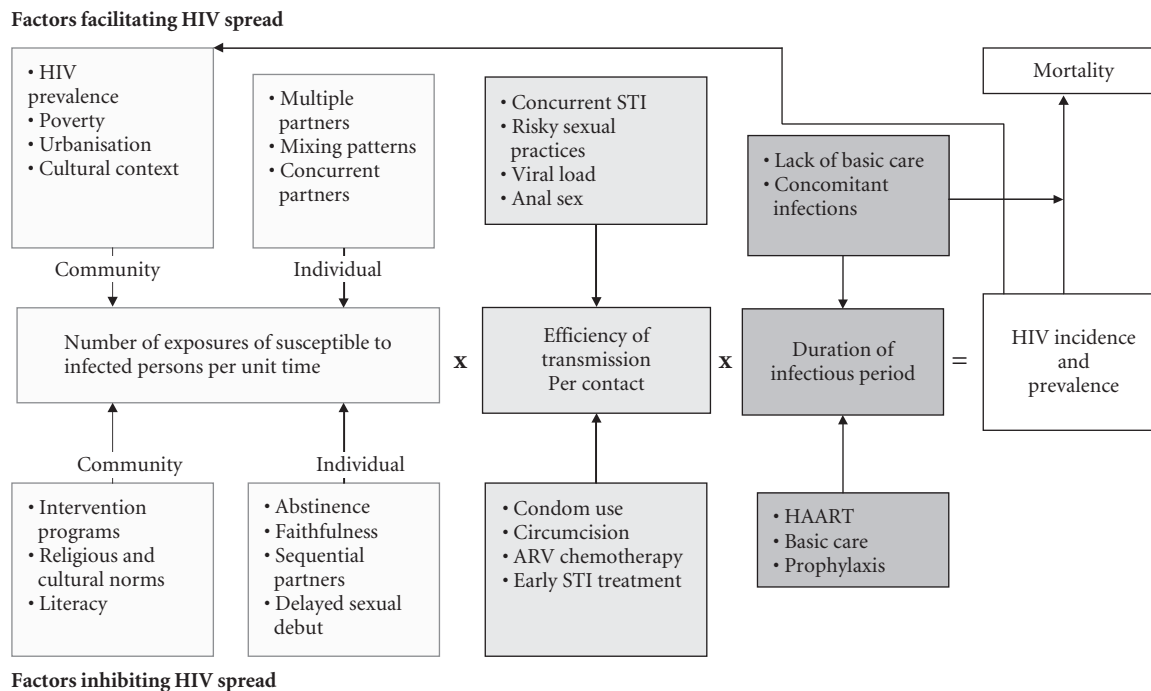


Fig. 9.13.4 Interplay between factors influencing sexual transmission of HIV Infection. Source: Department of Health, South Africa (2007).

partners in social settings where alcohol is available. Condoms use is lower in partnerships where an effective form of contraception is being used. This points to the need for interventions that promote dual method use (the simultaneous use of condoms with another form of contraception) among high-risk women. An important predictor of condom use is previous experience using condoms; individuals who have used condoms previously are more likely to use them in the future.

Female condoms

It is generally accepted that the efficacy of the female condom, when used correctly, is at least comparable to that of male condoms. While there are less data on the efficacy of the female condom, it protects essentially the same mucosal surface area as the male condom, and the polyurethane used in the construction of the female condom is stronger and less permeable than the latex used in most male condoms. Furthermore, female condoms do not degrade appreciably after several washings and, if they are cleaned appropriately, can be reused (unlike the male condom) though this practice is not widely recommended.

Sexually transmitted infections

HIV transmission and acquisition during heterosexual intercourse is enhanced in the presence of sexually transmitted infections, particularly ulcerative infections such as syphilis, chancroid and herpes simplex type 2 virus infection. Genital ulceration or inflammation caused by sexually transmitted infections increase the infectiousness of HIV-positive individuals and the susceptibility of HIV negative individuals.

The incidence of curable sexually transmitted infections is highest in sub-Saharan Africa, with 69 million new cases per year in a population of 269 million adults aged 15–49 (WHO 2001). This is an important factor in accelerating the spread of HIV in this region.

In rural South Africa, nearly 9% of adults have syphilis and almost one in 20 has gonorrhoea (Colvin *et al.* 1998). The prevalence of HIV infection in sexually transmitted disease clinic patients has exceeded 70% in Zimbabwe (WHO 2001) and exceeded 50% in Swaziland (UNAIDS 2002). It is estimated that only 14% of those in Africa in need of sexually transmitted disease services are able to access them.

Male circumcision

In 2006/7, three randomized control trials conducted in Africa consistently demonstrated that medical male circumcision reduces the risk of female to male transmission of HIV by 50–60% (Avert *et al.* 2005; Bailey *et al.* 2007; Gray *et al.* 2007). There may be an increased risk of HIV infection in men who engage in sex before complete healing of the circumcision wound. It is unclear as to whether male circumcision has any impact on the risk of male to female HIV transmission or on male to male HIV transmission. Mathematical modelling of the introduction of male circumcision suggests that 2–3 million HIV infections could be averted in sub-Saharan Africa. If integrated into a comprehensive package of male sexual and reproductive health services it could mark a critical milestone in increasing male involvement in HIV prevention.

Reducing transmission through blood

Transmission of HIV through exposure to infected blood can occur through transfusion of blood and blood products, through sharing of needles and syringes among injecting drug users and through inadvertent nosocomial transmission (e.g. through needlestick injuries) in health care settings.

Injection drug use

Of the estimated 13.2 million injecting drug users worldwide, 78% of them reside in low- and middle-income countries, especially in

Eastern Europe, Central, South and South-East Asia. An estimated 10% of the world's HIV infections are attributed to injection drug use, which is the main mode of transmission in certain Asian and European countries. HIV epidemics among injecting drug users are characterized by significant regional inter-country and intra-country variations, and prevalence of HIV infection among injecting drug users has been shown to exceed 50% and in some cases reach even up to 90% of injecting drug users in a very short time-frame (UNAIDS 2004). Ukraine exemplifies how quickly the virus can spread through an injecting population: with the number of diagnosed HIV infections increasing from virtually zero in 1995 to 20 000 a year since 1996; 80% of these new infections are occurring in injecting drug users.

The sharing and reuse of injecting equipment, particularly needles and syringes, is responsible for the transmission of HIV and other blood-borne diseases and is widespread among injecting drug users. Needle sharing is often a consequence of a lack of perceived risk for HIV infection, group norms and rituals, inaccessibility of clean injecting equipment due to scarcity or relative cost of equipment, and/or the inability to carry injecting equipment due to potential negative social or legal consequences (UNAIDS 2004). Although injection drug use is distinct from sexual intercourse as a mode of transmission, the two routes are frequently linked epidemiologically. Injection drug users are often young and sexually active, potentially exposing their sexual partners, children and foetuses to the virus. In addition, injection drug use is common in the commercial sex industry.

Over the past 20 years, research among injecting drug users and the experience from numerous programmes and projects indicate that the HIV epidemics among injecting drug users can be prevented, stabilized and even reversed. Effective programmes typically include; drug dependence treatment, including substitution treatment (e.g. methadone programmes), outreach to injecting drug users to promote safer sex and injecting practices, clean needles and syringes, condoms, voluntary counselling and HIV testing, treatment of sexually transmitted infections, and interventions for special populations-at-risk such as prisoners and sex workers who inject drugs (UNAIDS 2004).

'Needle exchange' or 'syringe exchange' programmes, when part of a comprehensive harm-reduction approach, have been shown to reduce the risk of transmission without contributing to an increase in drug use (Des Jarlais *et al.* 1996; Vlahov and Junge 1998). Early implementation of needle exchange, community outreach, and access to sterile injection equipment have been critical factors in helping several cities avoid a serious HIV outbreak among injecting drug users (Des Jarlais *et al.* 1995). An analysis of 81 cities around the world showed that HIV prevalence decreased 5.8% in 29 cities with needle exchange projects compared to a 5.9% increase in HIV prevalence in 52 cities without such programmes (Hurley *et al.* 1997).

Blood transfusions

The transfusion of HIV-infected blood or blood products is probably responsible for 5–10% of cumulative infections worldwide (UNAIDS 2006), translating to an estimated 160 000 cases of HIV being transmitted every year (WHO 2005a).

In the 1980s and early 1990s the majority of HIV infections through blood and blood products were in haemophiliacs. In the past 15 years great strides have been made to build up the safety of

the blood supply, particularly in low- and middle-income countries. The creation of nationally coordinated blood transfusion services and introduction of a range of policies and procedures, with a particular focus on HIV screening of donated blood to detect antibodies to HIV, the reduction of unnecessary transfusions as well as development of improved donor screening and deferral techniques have helped to virtually eliminate the risk that HIV would be transmitted through donated blood in high-income countries. The ongoing concern is the risk of transmission when blood donors are in the window period where they are infectious but have no detectable HIV antibodies. The use of the newer generation p24 antigen assays, polymerase chain reaction to detect viral RNA and quarantine of first blood donations until subsequent donations prove to be uninfected are some of the strategies used to reduce the risk of transfusing infected blood (Heyns and Swanevelder 2005). Almost all countries have routine screening of blood donations for HIV antibodies (UNAIDS 2006), but some continue to experience problems due to poor organization of blood supply systems, inadequate quality assurance mechanisms, poor staff training and suboptimal laboratory procedures.

Nosocomial transmission and universal precautions

Health care workers exposed to blood and body fluids have a low but measurable risk of occupational infection with HIV. In a review of transmission probability estimates, infectivity following a needlestick exposure was estimated to range from 0.00% to 2.38% (weighted mean = 0.23%) (Baggaley *et al.* 2006). While international guidelines recommend the use of relatively inexpensive auto-disable syringes as the 'equipment of choice' to help prevent HIV transmission in health care settings, only 62% of low- and middle-income countries were using such syringes in their national vaccine programmes in 2004 (WHO 2005b). Risk of exposure to blood or other body fluids can be significantly lowered through workers' adherence to 'universal precautions,' which involves the routine use of gloves and other protective gear to prevent occupational exposures, safe disposal of sharps, and timely administration of a four-week prophylactic course of antiretroviral prophylaxis if a worker does get exposed.

Preventing mother-to-child transmission

Over 4 million HIV-infected children under the age of 15 were born to HIV-infected mothers; in 2005 alone, an estimated 700 000 children became newly infected. With few exceptions most children acquire their HIV infection from their mothers. Mother-to-child-transmission (MTCT) of HIV occurs in the intrauterine period, during labour and delivery, and postnatally through breastfeeding. Africa bears 70% of the global burden of HIV in all age groups, but has at least 90% of all the HIV-infected children in the world resulting in a reversal of decades of steady progress in child survival.

Substantial progress has been made in preventing MTCT. Before medical interventions became available, approximately one-third of babies of HIV positive mothers became infected with HIV. With a combination of antiretroviral drugs, changes in obstetric practices and alternatives to breastfeeding, MTCT rates below 1% can be attained and MTCT has been virtually eliminated in high-income countries.

The first research breakthrough in MTCT occurred in 1994 when the Paediatric AIDS Clinical Trials Group 076 trial showed that HIV

transmission from mother-to-child can be reduced from 25.5% to 8.3% using AZT. This efficacious regimen of AZT from about 12 weeks gestation and through labour and delivery in the infected mother and for a week post-birth to the infant has been widely implemented in industrialised countries. For resource-constrained settings, cheaper interventions using AZT or nevirapine are available. The Thai short course AZT regimen administered to mothers from 36 weeks gestation through the intra-partum period and the HIVNET 012-single dose nevirapine regimen (a dose to the mother at onset of labour and a dose to the infant within 72 h of birth) are preferred in resource-constrained settings. The main advantage of single-dose nevirapine is the ease of administration and low cost; the chief drawback is concern about drug resistance in the mother. Concerns about drug resistant viral strains have led to several trials using combination treatments to reduce transmission during the intra-partum period.

Breastfeeding is not recommended for HIV-positive mothers since this is associated with an increased risk of HIV transmission. However, lack of access to clean running water in resource-constrained settings has precluded the use of formula feeding. While exclusive breast feeding with abrupt weaning is one proven option of reducing breastfeeding risk in these settings, other options are under investigation (Coovadia *et al.* 2007), including studies of whether antiretrovirals given to baby (and mother) during breastfeeding may reduce MTCT.

Despite single-dose nevirapine being a readily implementable effective HIV prevention strategy to reduce MTCT in almost any country, only 9% of pregnant women in low- and middle-income countries were offered services to prevent transmission to their newborns in 2005 (Global HIV Prevention Working Group 2006). A lot more still needs to be done to expand interventions to reduce MTCT.

Voluntary counselling and testing

Knowledge of HIV status is not only a vital entrée to treatment, it is also essential for prevention of MTCT, prevention of transmission through blood transfusions and reducing sexual transmission of HIV infection. Voluntary counselling and testing (VCT) has been shown to be both efficacious in reducing risky sexual behaviours (The VCT efficacy study group 2000) and cost-effective as a prevention intervention. In a large multi-centre study ($n = 4293$), both men and women randomised to receive VCT significantly reduced unprotected intercourse with their primary partners than those receiving only health information (The VCT efficacy study group 2000). In this VCT trial, the centres in Kenya and Tanzania averted an estimated 1104 and 895 HIV infections and this translated into a cost-saving of US \$249 and \$346 per HIV infection averted in Kenya and Tanzania, respectively (Sweat *et al.* 2000).

Large numbers of HIV infected people, particularly in low- and middle-income countries, do not know their HIV status and are diagnosed too late (Shisana *et al.* 2005). While the aim is to put all those eligible for antiretroviral therapy (often defined as CD4 <200 cells/ml) on treatment, it is primarily those who are symptomatic and seeking care who are learning their HIV status and accessing care. VCT has traditionally been offered as an out-patient or ambulatory service based at primary care providers or specialized VCT centres. However, stigma, which is a common experience of those infected and affected by HIV, is a major obstacle to HIV testing and acknowledgement of individual risk of infection.

The traditional form of VCT was developed in the pre-ART era in response to human rights and ethical concerns about HIV testing that centred on the need to ensure autonomy and minimize harms for the client (Fylkesnes 1999). At that stage, VCT was mainly for prevention purposes. Unfortunately, this form of VCT has become a major obstacle to care due to the lack of capacity of health services to provide this time-consuming approach to VCT.

In an attempt to overcome this limitation, a number of different models to promote HIV testing have started to emerge, each designed to meet different goals, including:

- i. individual pre- and post-test counselling, which is the classic model that is client initiated and is typical of most free-standing VCT sites;
- ii. group information opt-in individual pre- and post-test counselling, which is widely used in high prevalence settings;
- iii. group information opt-out individual testing with individual post-test counselling for sero-positives, which is widely used during routine medical screening, e.g. antenatal clinics;
- iv. group information opt-in couple/family pre-test counselling with individual post-test counseling; and
- v. no specific pre-test information and testing is an opt-out option with individual post-test counselling, e.g. antenatal and sexually transmitted disease clinics.

Routine opt-out testing, with a right to decline, was pioneered in Botswana in 2004. A population-based study on attitudes, practices, and human rights concerns showed that of 1268 adults interviewed, 81–93% were in favour of opt-out HIV testing as it enhanced access to treatment. Barriers to testing included fear of learning one's status (49%), lack of perceived HIV risk (43%), and fear of having to change sexual practices with a positive HIV test (33%) (Weiser *et al.* 2006). In the USA, routine opt-out testing in health care settings has been recommended since 2006.

While alternate models of VCT have engendered some concern about coercion of clients to participate in HIV testing, most of these concerns are readily remedied. Some have argued for a move away from the 'HIV exceptionalism' approach to a 'HIV normalization' approach wherein HIV is treated as an infectious disease. In this context VCT is essential for both HIV prevention and early diagnosis for timely access to treatment (De Cock and Johnson 1998).

Community interventions for HIV prevention

Community intervention strategies can be categorized according to three approaches: mass media (e.g. television, radio, newspapers/magazines, posters); community mobilization, through which the community becomes a participant in the design of the intervention; and interpersonal communication involving direct, face-to-face approaches such as counselling.

A common theoretical model used in developing behavioural interventions (Bertrand *et al.* 2006) requires the direct impact of the intervention to increase knowledge, change attitudes, and enhance self-efficacy, leading to a reduction in risk behaviours, greater utilization of health services and, ultimately, a reduction in HIV prevalence. An overall approach to the way interventions are designed and implemented suggests that for an intervention to be successful, it needs to be based on behavioural theory, designed to

change specific risk behaviours, delivered by health professionals, delivered in an intensive manner, delivered to individuals, delivered as part of routine health services; and should incorporate skill-building (Crepaz *et al.* 2006).

The mass media approach targets the general population, regardless of level of HIV risk. Thus, the message that is delivered through the mass media must carefully consider the impact of the content and approach of their messages. In the early 1980s in the USA, mass media messages tended to emphasize the severity of the disease and the fatal outcome. The unexpected outcome of that approach was to induce fear and cause many people to shun individuals in high-risk groups and persons with AIDS, resulting in stigmatization. Stigmatization is now one of the major barriers to effective control of the epidemic, and has compromised efforts to promote HIV testing.

A systematic review (Bertrand *et al.* 2006) of interventions using the mass media in low- and middle-countries found that only two of the desired outcomes were achieved in 50% or more of the trials: knowledge of HIV transmission and reduction of high-risk activities (multiple partners, visiting sex workers, etc.). Few of the mass media intervention studies resulted in an increase in reported use of condoms.

A review (Eke *et al.* 2006) of community-based programs, suggested that success was dependent on the interventions being tailored to respond to the unique contexts in which risk behaviours occur (e.g. in Thailand and Cambodia, a high proportion of sexual risk behaviour occurs in brothels, which then become a logical target for intervention), addressing contextual variables and practices such as sociocultural norms (e.g. acceptance that extra-marital sex is to be expected), and the provision of adequate resources with which to implement the intervention.

A successful example of a community mobilization strategy (Wu *et al.* 2002), aimed at new drug users in southern Yunnan Province in China, produced a two-thirds reduction in HIV incidence within one year. Another successful example of an intervention targeting a specific community is the Sonagachi Project, which organized commercial sex workers in Kolkata, India to promote safer sex, better working conditions, better health-seeking behaviours and better access to health care (Jana *et al.* 2004).

Community intervention strategies, like the successful examples above, can prevent HIV infection, but they must be carefully designed, and should mobilize the target population to participate in the intervention design and implementation.

Post-exposure prophylaxis

HIV infection is initially established within the dendritic cells of the skin and mucosa before spreading through lymphatic vessels and developing into a systemic infection. Thus, there is a 'window of opportunity' following exposure for the use of antiretroviral therapy to prevent systemic infection.

There are several groups who could benefit from post-exposure prophylaxis (PEP). These include health workers, laboratory personnel, and individuals with likely exposure to HIV through sexual contact (including rape) or breast milk. The success of PEP in preventing established infection depends on a number of factors, including route and dose of exposure, efficacy of drug(s) used, interval between exposure and initiation of drug(s), and level of adherence to the drug. The dose of exposure depends primarily on the route of infection and the stage of infection of the source. Thus, receptive

anal intercourse and deep accidental needle sticks carry the highest risk of exposure and the greatest challenge for effective PEP. People who are in the acute or terminal stages of HIV disease will also have the highest levels of HIV, and thus present the highest risk to those exposed to them.

It is unlikely that placebo-controlled double-blinded clinical trials of PEP will ever be conducted for logistical and ethical reasons. A case-control study of PEP following occupational exposures (Cardo *et al.* 1997) showed 81% protection against HIV infection. A study of PEP following sexual exposure, primarily through anal intercourse, also showed a protective effect (Roland *et al.* 2005).

An important issue in implementing PEP is whether it will lead to behavioural disinhibition, i.e. individuals believing, because of PEP, they can safely engage in high-risk activities. Thus, counselling on the need for reduction of risk exposures should be an integral part of any PEP programme.

The US Centers for Disease Control and Prevention has issued guidelines for management of occupational, sexual and other exposures to HIV (Panlilio *et al.* 2005). The current consensus is that combination antiretroviral therapy should be initiated as soon as possible after exposure, and continued for at least 4 weeks.

Scaling up prevention interventions

Despite substantial increases in knowledge of what works in preventing HIV infection, and resources for their implementation, the virus continues to spread. The inability to curb the epidemic in many settings is due to the inability to implement proven HIV prevention strategies at the necessary scale and magnitude to those who need it most, and not recognising the link between HIV prevention and broader development needs especially in resource-constrained settings.

In 2006, the gap between HIV prevention needs and provision of prevention programmes was substantial. A significant constraint to prevention efforts has been the inability to integrate HIV prevention: (i) within a comprehensive AIDS strategy, including prevention integrated with AIDS treatment; (ii) within other national development programmes; (iii) into poverty reduction strategies; (iv) into education programmes; (v) into health services, especially sexual and reproductive health services; (vi) into programmes aimed at reducing gender inequalities; and (vii) into initiatives to enhance economic and political opportunities for women and girls.

Prevention efforts have generally targeted whole communities or those who are HIV negative. There is a steady shift in prevention efforts from a narrow focus on HIV uninfected persons to a more effective continuum of prevention that includes those who are uninfected, recently infected, infected but asymptomatic as well as those with advancing HIV disease and on antiretroviral therapy.

To improve the impact of known effective HIV prevention interventions, implementation needs to be done to scale, targeting the key populations in the epidemic with integrated approaches that recognize that prevention planning and implementation needs to take the context into account.

New HIV prevention technologies under investigation

Several trials of new HIV prevention technologies are currently underway. Antiretroviral prophylaxis, microbicides and vaccines are being tested and may have great potential in the future.

Pre-exposure prophylaxis

Certain groups are repeatedly exposed to possible infection by HIV. These include health workers, laboratory personnel, sex workers, injection drug users, and both homosexual and heterosexual individuals who have multiple partners and are unwilling to take precautions (as well as their spouses and/or regular partners). The concept of pre-exposure prophylaxis is not new, but has now gained considerable popularity as a possible strategy for reducing the risk of infection among high-risk groups.

However, there are many issues inherent in long-term prophylaxis with any drug. These include the need for inexpensive drugs, the potential for serious toxic side effects, development of viral resistance to the drug with repeated use, the potential impact on behavioural disinhibition (i.e. increasing risky behaviour and decreasing condom use), the possible need for multiple drug combinations, and assuring an acceptable cost:benefit ratio.

Several studies of the antiretroviral drug, tenofovir, were initiated to assess its effectiveness as pre-exposure prophylaxis (Liu *et al.* 2006). Results from one pre-exposure trial conducted in Ghana, Cameroon, and Nigeria (Peterson *et al.* 2007) showed no increased risk of drug-associated toxicity from oral tenofovir, and did not observe any increase in high-risk behaviour.

Whether pre-exposure prophylaxis becomes a widely implemented, acceptable prevention strategy will depend on the results of these trials evaluating efficacy/effectiveness, toxicity and behavioural disinhibition. If pre-exposure prophylaxis is shown to be safe and effective, implementation programmes of this potential prevention strategy will need to emphasize the concomitant use of other prevention strategies such as condoms.

Microbicides

Topical microbicides, products designed to prevent the sexual transmission of HIV and other sexually transmitted pathogens, are one of the most promising prevention tools currently under development that women can use to protect themselves from HIV (Stone 2002). Potentially, they can be applied vaginally to prevent both male-to-female and female-to-male transmission.

Currently in the research pipeline are over 60 substances that are being studied as possible microbicides. Some 50 of these substances are in pre-clinical development, and 11 have entered various stages of human clinical testing.

Microbicides in human trials have one of four mechanisms of action:

- i. Surfactants, e.g. nonoxynol-9 and C31G (Savvy), which act by disrupting cell membranes.
- ii. Vaginal defence enhancers, which boost the body's natural defences against infection by maintaining the naturally acidic environment of the vagina by increasing lactobacilli or by rapidly acidifying alkaline ejaculate, e.g. BufferGel.
- iii. Attachment and fusion inhibitors, which bind to pathogens or to receptors on healthy human cells thereby preventing attachment, e.g. Carraguard, PRO2000 and Cellulose Sulphate.
- iv. Replication inhibitors, or antiretroviral agents, which act locally in the reproductive tract mucosa at various steps in the HIV replication cycle and therefore have a narrow spectrum of activity, e.g. Tenofovir gel, Dipavirine and UC781.

Early studies of the spermicide, nonoxynol-9, showed this product, which acts by disrupting cell membranes, to be harmful as it caused lesions in the genital tract and increased the risk of HIV infection. Subsequent studies of Savvy, another product in the same class, were halted due to low HIV incidence rates in the trial sites. Trials of Cellulose Sulphate, were stopped in 2007 due to safety concerns. Gel formulations of inhibitors of the chemokine receptor, CCR5 have shown promise in animal models and are currently being developed for early human studies.

There are significant challenges in conducting microbicide effectiveness trials, including the ethical need to promote condoms thereby undermining the ability to show the effect of the microbicide, low HIV incidence rates in some trial populations, poor adherence to study products and high rates of pregnancy as study products are discontinued during pregnancy.

Vaccines

A safe, protective and inexpensive vaccine would be the most efficient, effective and possibly the only way to control the HIV pandemic. Despite intensive research, development of such a candidate vaccine remains elusive. Safety concerns prohibit the use of whole killed HIV or live attenuated virus as immunogens (Sheppard 2005). Many different approaches using recombinant technologies have been pursued over the past two decades. Initially, efforts were focused on generating neutralizing antibodies using recombinant monomeric envelope gp120 (AIDSVAX) as immunogen. This vaccine did not induce neutralizing antibodies and the phase III trials failed to show protection against HIV acquisition. Antibody-mediated HIV neutralization is complicated by the high genetic diversity of the variable Env regions, epitopes masked by a carbohydrate shield (glycosylation) and conformational rearrangements (Garber *et al.* 2004).

Since CD8+ T-cell responses have been shown to control viral replication *in vivo*, recent vaccine development has focused on eliciting cellular immune responses. Unfortunately, safety and immunogenicity studies of adenovirus vector-based T cell vaccine have failed to show a protective effect and may be associated with an increased risk of HIV infection.

Vaccine development is severely hampered by the lack of any immune correlate which has been shown to prevent viral infection or clear initial viral infection. The human immune system generally fails to spontaneously clear HIV infection and so there is no natural immune process for the vaccine candidates to mimic. It is, however, believed that approaches aimed at eliciting both humoral and cell mediated immunity are most promising to prevent or at least control retroviral infection (Ho and Huang 2002).

Most of the efforts to produce a vaccine have concentrated on looking at components of the virus that may stimulate protective immunity and substrates that may enhance the immune response. While natural immunity has not been observed in HIV/AIDS, several researchers (Clerici *et al.* 1992; Detels *et al.* 1994; Detels *et al.* 1996) have identified groups of men who have sex with men and female sex workers who have been repeatedly exposed to HIV and have not become infected. Some of these individuals were shown to lack the CCR-5 receptor on CD4+ cells to which the HIV attaches (Dean *et al.* 1996). However, these individuals comprise only a subset of 'resistant' individuals. If the factors that allow these individuals to resist infection can be identified it might be possible to confer the 'resistance factor' on individuals lacking it, thus artificially providing

them some measure of protection against HIV infection. This approach would represent an alternative approach to the traditional strategies of vaccine development and might overcome the apparent lack of natural immunity to HIV.

The spectrum of clinical manifestations of AIDS

Opportunistic infections, which seldom cause serious disease in immunocompetent people, are common in HIV-infected individuals. Indeed, most of the morbidity and mortality associated with HIV infection is almost always as a consequence of opportunistic diseases or malignancies that occur when immunity is impaired, usually corresponding with a CD4+ count below 200 cells/ml. Infections caused by more virulent pathogens, such as *Mycobacterium tuberculosis* or *Streptococcus pneumoniae*, often occur with lesser degrees of immune suppression. Over 100 opportunistic infections by viruses, bacteria, fungi and protozoa have been associated with AIDS. The spectrum of clinical manifestations includes:

Dermatological manifestations

Cutaneous abnormalities are common and some of the conditions are unique and virtually pathognomonic for HIV disease, e.g. Kaposi's sarcoma.

Neurological manifestations

Apart from dementia, HIV-infected patients are at risk for a wide range of neurologic diseases. Global cerebral disease can present with altered mental status or generalized seizures, whereas focal disease often produces hemiparesis, hemisensory loss, visual field cuts, or disturbances in language use. Fungal, viral and mycobacterial meningoencephalitis are the most common causes of global cerebral dysfunction, and progressive multifocal leukoencephalopathy (PML), primary CNS lymphoma and toxoplasmosis account for the majority of focal presentations.

Pulmonary manifestations

HIV-associated pulmonary conditions include both opportunistic infections and neoplasms. The opportunistic infections include bacterial, mycobacterial, fungal, viral and parasitic pathogens. Some of the more common respiratory infections associated with HIV patients include: pneumonia, tuberculosis and pulmonary Kaposi's sarcoma.

Endocrine manifestations

A number of endocrine abnormalities develop in patients with HIV infection; some due to infiltration of endocrine glands by tumour or infection.

HIV wasting

This condition was first recognised as an AIDS-defining illness by the US Centers for Disease Control and Prevention in 1987. The 'wasting syndrome' is defined as a weight loss of at least 10% in the presence of diarrhoea or chronic weakness and documented fever for at least 30 days that is not attributable to a concurrent condition other than HIV infection itself.

Haematologic manifestations

Clinically significant haematologic abnormalities are common in persons with HIV infection. Impaired haematopoiesis, immune-mediated cytopenias and altered coagulation mechanisms have all been described in HIV-infected individuals.

Renal manifestations

Renal disorders during HIV infection range from fluid and electrolyte imbalances commonly seen in hospitalized HIV-infected patients, to HIV-associated nephropathy, which can progress rapidly to end-stage renal disease.

Gastrointestinal manifestations

Common gastrointestinal disorders include diarrhoea, dysphagia and odynophagia, nausea, vomiting, weight loss, abdominal pain, anorectal disease, jaundice and hepatomegaly, gastrointestinal bleeding, interactions of HIV and hepatotropic viruses, and gastrointestinal tumours (Kaposi's sarcoma and non-Hodgkin's lymphoma).

Ophthalmic manifestations of HIV

Numerous ophthalmic manifestations of HIV infection may involve the eye including tumours of the periocular tissues, a variety of external infections, HIV-associated retinopathy, and a number of opportunistic infections of the retina and choroid.

Otolaryngologic manifestations

HIV disease is associated with a variety of problems in the head and neck region; as many as 70% of HIV-infected patients eventually develop such conditions.

Oral manifestations

Oral manifestations of HIV disease are common and include oral lesions and novel presentations of previously known opportunistic diseases. Some are caused by fungal infections, e.g. candidiasis; while others are due to viral infections, e.g. herpes simplex, herpes zoster, human papillomavirus, cytomegalovirus, hairy leukoplakia and Epstein-Barr virus. Other oral complications include periodontal disease, neoplastic lesions and lymphomas.

Rheumatologic and musculoskeletal manifestations

Musculoskeletal syndromes that occur in HIV-infected patients include manifestations of drug toxicity, reactive arthritis, Reiter's syndrome, infectious arthritis and myositis.

Tuberculosis and HIV

In resource-constrained settings, the most common presenting illness of AIDS is tuberculosis (TB). TB is a global public health problem that has been exacerbated by the HIV epidemic. In 2003 an estimated 8.8 million new cases of TB were diagnosed and 1.7 million people died from the disease. The most severely affected region has been sub-Saharan Africa, where TB notifications have, on average, trebled since the mid-1980s, and death rates on treatment have reached 20% compared with the 5% that can be achieved by good TB-control programmes without HIV (WHO 2005c).

AIDS has changed the profile of TB patients globally; from a disease of the malnourished, elderly and men to a disease of young people, predominantly women. Extra-pulmonary TB is common in

AIDS patients; together with other reasons for smear-negative TB, this has created a major diagnostic problem. The result is large numbers of patients being treated for TB without microbiological confirmation of infection. The rapid growth of the HIV epidemic has resulted in a rapidly growing TB epidemic. Rising TB incidence rates in those who are HIV infected has had a spillover effect of rising TB incidence rates even among those who do not have HIV infection.

In much of sub-Saharan Africa, the strain of growing TB and HIV epidemics has led to the emergence of extensively drug resistance TB. Global increases in multidrug-resistant (MDR-TB) and extensively drug-resistant (XDR-TB), are threatening both TB and HIV treatment programs worldwide. The former is defined as resistance to both isoniazid and rifampin, whereas the newly defined XDR-TB consists of MDR and resistance to a fluoroquinolone and at least one injectable second-line TB drug (kanamycin, amikacin or capreomycin). Together, they raise concerns of a global epidemic of untreatable TB and pose a huge threat to TB control. In high prevalence TB and HIV areas of the developing world, the current DOTS (Directly Observed Treatment, Short Course) strategy is proving ineffective because available resources are being outstripped by the large number of patients in need of treatment. As a consequence TB treatment and outcomes are sub-optimal and MDR and XDR TB are on the rise.

Treatment

Antiretroviral therapy (ART)

The ART era started in 1987 with the approval of AZT (also known as zidovudine), a thymidine nucleoside analogue that interrupts the transcription of viral RNA to viral DNA by blocking the action of the reverse transcriptase enzymes. During the late 1980s additional nucleoside reverse transcriptase inhibitors (NRTIs) were developed. As more antiretroviral drugs of different classes became available, triple combination therapy was shown to have greater and more durable benefits than either mono- or dual therapy. The big treatment breakthrough occurred in 1996 with the introduction of protease inhibitors (PIs) that are capable of blocking the assembly of the progeny HIV within the CD4+ cell, marking the beginning of the era of highly active antiretroviral therapy (HAART). A third class of antiretrovirals, the non-nucleoside reverse transcriptase inhibitors (NNRTIs) was developed soon after the first PIs became available.

Combinations of drugs from these three classes of antiretrovirals are widely used as the 'standard of care' (Wood 2005). The currently recommended regimens for adults that demonstrate the most potent virologic and immunologic efficacy are those composed of two NRTIs together with either a NNRTI or a PI (DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents 2006b). Although HAART is not a cure, it has dramatically improved rates of mortality and morbidity, improved quality of life, revitalized communities and transformed perceptions of AIDS from a plague to a manageable, chronic illness.

Several international HIV treatment guidelines exist to guide clinicians in the management of HIV-infected individuals and are based on a combination of evidence from randomised clinical trials, observational cohorts and expert opinion.

Since the advent of HAART in 1996, most guidelines have evolved to keep up with new evidence. For example, the United States Depart-

ment of Health and Human Services (US DHHS) guidelines initially advocated a more aggressive therapy but have subsequently moved towards a more conservative approach. The 2006 DHHS guidelines (DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents 2006b) recommend initiation of treatment in all asymptomatic patients with <200 CD4+ cells/ml and allowing clinical judgement to be exercised at earlier stages of disease.

The WHO recommendations for expanded access in low and middle-income countries (WHO 2004) take into account the lack of medical and laboratory infrastructure in many countries that have a high AIDS burden. The WHO guidelines emphasize treatment of patients with significant symptomatic disease and those with CD4+ cell count <200 cells/ml. A substitute for the CD4+ cell count criterion in resource-constrained settings where a CD4+ cell count is not available is a total lymphocyte count <1200 cell/ml. All of the guidelines emphasize initiation of ART for symptomatic patients with HIV-related symptoms (WHO stages 3 & 4), while the decision to initiate treatment of asymptomatic patients is more complex and is based on the patient's readiness to adhere to long-term therapy, together with an assessment of the level of existing immunodeficiency, the risk of disease progression and the risks and costs of therapy. In resource-constrained settings, the threshold for entry into an ART programmatic will also need to take cognizance of the resultant numbers to be treated, available financial and medical infrastructure and the resources necessary to identify treatment beneficiaries.

The dynamics of HIV in paediatric patients is distinct from that of adults. Most children infected with HIV have contracted the disease through vertical transmission from their mothers. The mean survival of vertically HIV infected children ranges from 75–90 months and only a fraction of the HIV-infected children survive to around 10 years of age without ART. In countries where it has been successfully introduced, ART has substantially changed the face of HIV infection in children, with many HIV-infected infants and children now surviving to adolescence and adulthood. Guidelines for treatment of HIV-infected children are also continually evolving. The decision to start therapy and what drugs to choose for children is complex (DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents 2006a). While HIV-infected children suffering from impaired growth and development may benefit from earlier initiation of HAART, the criteria for treatment initiation is based on CD4+ percentage, viral load and clinical condition.

Prophylaxis and treatment of co-morbidities

The best way to prevent opportunistic infections is to prevent exposure to the infectious agent. However, this is not possible for all opportunistic infections because several are thought to be caused by a reactivation of latent infection, e.g., tuberculosis, herpes simplex virus, cytomegalovirus and toxoplasmosis.

Improvement in immune function following the initiation of HAART can significantly lessen the morbidity of opportunistic infections. Furthermore, the incidence of a number of opportunistic infections and associated mortality can also be reduced through the use of prophylactic agents like cotrimoxazole.

Specifically targeted interventions like preventive therapy for tuberculosis in high risk patients, chemoprophylaxis for malaria for HIV infected pregnant women in malaria endemic areas, and vaccinations against pneumococcal infections and influenza in HIV

infected adults can be used to lessen the morbidity and mortality from opportunistic infections. Although not generally regarded as an opportunistic infection, vaccinations against hepatitis B should be considered in selected patients who are shown to be non-immune because of the effect that HIV has on the natural history of hepatitis B (Maartens 2005).

Challenges in ART provision

Since 2000, the collective efforts of activists, researchers, service providers, pharmaceutical companies, policy makers and international agencies have generated real momentum in scaling up AIDS treatment and prevention across the globe, particularly in low- and middle-income countries. Coverage of ART in the developing world has more than doubled—increasing from 400 000 in 2003 to approximately 1 million by June 2005 (WHO 2006). While still short of the WHO goal of ‘3 by 5’, the momentum in expanding treatment access is a remarkable achievement despite the initial challenges in implementing AIDS treatment programmes, especially in Africa where the burden is largest. The scale of ART provision was guided by what WHO refers to as the ‘Public health approach to AIDS treatment’. This involved standardizing first and second line ART regimens, creating algorithms for determining who was eligible for ART and how to manage patients on ART. This standardization enabled health care workers who are not physicians to become involved in AIDS care. Indeed, in much of Africa, nurse practitioners or intermediate-level clinicians are the main providers of ART. However, many challenges with respect to the scale up and sustained provision of treatment remain. These include constraints in scaling up VCT, stigma and discrimination, challenges in achieving high levels of treatment adherence and side effects and toxicity such as hyperlipidaemia, insulin resistance, frank diabetes mellitus, acute life-threatening lactic acidosis, asymptomatic lactic acidemia, chronic myopathy, peripheral neuropathy and gastrointestinal intolerance.

While these challenges are being resolved, new challenges are emerging in scaling up the treatment and sustaining the ART provision in resource-constrained settings. While the various practical and political challenges in ART provision have changed since 2000, three over-arching challenges—under-developed, overburdened health care services, the persistence of stigma and the failure to integrate prevention into care—continue to hamper the effort to maximize the benefits of ART implementation (Abdool Karim 2006b).

Impact of AIDS

Impact of AIDS on mortality

Globally, AIDS has joined the leading causes of premature death among both women and men 15–59 years of age (Piot 2006). In the worst affected countries like South Africa, AIDS is the single largest contributor to premature loss of life and accounts for about half of the disability adjusted life years lost. In Africa, one important feature of AIDS related mortality is its age and gender frequency distribution. While the overall AIDS related mortality rates are highest in the 20–40-year age group, women experience higher mortality rates at younger ages in Africa.

The introduction of ART has helped slow the rising mortality due to AIDS. In high-income countries the introduction of HAART led to significant declines in AIDS mortality rates (Palella *et al.*

1998; Detels *et al.* 1998) (See <http://www.cdc.gov/hiv/topics/surveillance/resources/slides/trends/index.htm>). Unfortunately, this trend has not yet become evident in most poor countries, where mortality rates due to AIDS continue to climb. However, as ART becomes more widely available in poor countries, it is hoped that mortality will start to fall.

Impact of AIDS on society

The social impact of AIDS is more pronounced in generalized epidemics and in settings where heterosexual transmission is dominant. For example, the AIDS epidemic in sub-Saharan Africa has had widespread impact on many sectors of society, impacting beyond the individual, to the family structure and society at large. High death rates in the socially and economically most active sectors of society are impacting dramatically on economic activity, financial wellbeing and social progress. Indeed, AIDS has become the biggest threat to the continent’s development not only for the current generation of young adults as well as the next generation. UNAIDS estimates that AIDS is reducing the per capita growth rate by 0.5–1.2% annually in sub-Saharan Africa. Life expectancy has halved in some countries and millions of adults are dying in their economically productive years, thereby impacting on the economic dependency ratio. Many families are losing their income earners and the families of those who die have to find money to pay for their funerals.

As the epidemic progresses, social cohesion in already fragile communities is being further eroded. An increasing number of households are either grandmother or child-headed. Children who are orphaned struggle to survive without parental care and frequently cease attending school because they cannot afford school fees and uniforms or have to look after younger siblings (Johnson 2001). A decline in school enrolment is one of the most visible effects of the HIV/AIDS epidemic on education in Africa.

Private industry and companies of all types face higher costs of training, insurance, benefits, absenteeism and illness. A number of skilled personnel in important areas of public management and core social services are being lost to AIDS. Essential services are being depleted and scarce resources are put under greater strain. As the epidemic matures, the health sector suffers the additional pressures of caring for those with AIDS. Not only has health utilization increased, but other illnesses that deserve attention (such as diabetes, malaria, hypertension, etc.) are being crowded out by the increasing morbidity that AIDS brings.

The worst of the epidemic impact has yet to come. In the absence of massively expanded prevention, treatment and care efforts, the AIDS death toll on the continent of Africa is expected to continue rising before peaking around the end of this decade.

Ethical and human rights issues

Human rights challenges in AIDS treatment provision

The continued spread of HIV globally and the immense and growing burden of AIDS places a moral, scientific and ethical imperative on individuals and societies to mobilise political will and resources to respond to the pandemic. This imperative extends to the urgent need to conduct research to find new ways of preventing and treating AIDS. The immediacy of the challenge and need for solutions has redefined the way medical practitioners, governments, and health service providers, amongst others, respond to an infectious

disease and the way in which researchers conduct research and clinical trials.

During the early days of the epidemic, AIDS was identified with already socially and/or legally marginalised or stigmatised groups, such as men who have sex with men, injecting drug users, racial minorities and sex workers. The uncertainty of the cause of the new disease and how it is spread created conflict between human rights activists and public health practitioners. Classical infectious diseases approaches of 'isolate and contain', as practiced in the sanatoria of Cuba, the closure of bath-houses in San Francisco, and restrictions on entry of HIV infected persons to the USA were at odds with the ongoing campaigns in the gay community to secure their rights. As knowledge of natural history of infection grew, levels of social stigma and discrimination did not diminish but an uneasy balance was struck between respect of the right of the infected person and public good. A phrase coined by Bayer (Bayer and Fairchild 2006), 'HIV exceptionalism', captures the outcome of this balance between the rights of those infected with broader rights of society to be protected from an incurable infectious disease.

In the pre-HAART era, the manifestation of protection of the rights of the individual infected person was most apparent in HIV testing policies. All HIV testing had to be voluntary, client-initiated and done in the context of pre- and post-test counselling by a trained person. In contrast to management of other health conditions where the clinician made decisions about what diagnostic tests are undertaken, HIV set new standards of patient autonomy to make this decision in an informed manner. Furthermore, disclosure was the prerogative of the infected person. Several precedent-setting judgements in the courts of law reinforced this right in several countries (Jonsen 1990; Kirp 1989; Kirp and Bayer 1992). Prohibitions on pre-employment HIV testing in the workplace are another of the human rights achievements in response to workplace-based discriminatory policies against those with AIDS.

Research showing the substantial benefit of AZT in reducing mother-to-child transmission of HIV re-opened some of the early HIV testing debates in industrialised countries, focusing now on whether HIV testing should be compulsory for all pregnant women in light of potential benefit to the unborn baby. These debates were echoed in poor countries as single-dose nevirapine became available for prevention of mother-to-child transmission of HIV. Despite the high HIV prevalence in pre-natal settings many women choose not to test because of real or perceived fear of testing positive, fear emanating from the social consequences of having HIV infection. The status of women in these settings, as well as fear of violence and discrimination, impact a number of decisions infected mothers make—whether to have an HIV test, take their intra-partum dose of medication, ensure their babies receive nevirapine, or breast-feed their babies.

The introduction of HAART in industrialized countries in the late 1990s highlighted the economic disparities between north and south. Global activism, spurred on by social movements of people living with AIDS, community groups, professional organisations and advocacy groups, resulted in major reductions in drug prices. Importantly, it also led to the establishment of International Assistance Funds to help countries provide these life-saving drugs; the Global Fund against AIDS, Tuberculosis and Malaria and the US President's Emergency Plan for AIDS Relief (PEPFAR).

These initiatives have set important precedents for how the global community responds to public health crises. Other long-standing

public health challenges are benefiting, such as maternal and child health, reproductive health services, tuberculosis and malaria. Importantly, these funds are supporting efforts to increase access to ART, expand training of health care workers, strengthen health care services, and build new facilities including laboratory infrastructure and drug distribution systems in resource-constrained settings. While these efforts cannot undo the historical inequities between north and south, they demonstrate the importance of global commitment and joint action.

Ethical challenges in AIDS research

The disparities between north and south in the context of HIV prevention trials have led to substantial debate on research ethics. In the mid-1990s, a prominent medical journal questioned the ethics of conducting placebo-controlled trials for the prevention of MTCT in Africa and Thailand. The argument was that PACTG 076 regimen of AZT, which has been shown to be effective in reducing MTCT in the USA, should be the control intervention in all subsequent MTCT trials. The counter-arguments were that the ATCG 076 regimen of AZT was not implementable in resource-constrained settings and hence the need to assess the efficacy of short implementable courses of antiretrovirals against the existing standard of care in the countries hosting the trials. The centrepiece of these debates is whether placebo-controlled trials were justifiable when an intervention exists regardless of whether the intervention was not affordable or feasible in the host country, as was the case with the AZT regimen emanating from the PACTG 076 trial. A certain level of paternalism dominated these debates—issues of exploitation, duties of sponsors and questions about the voluntariness of the informed consent process in poor and low literate populations. This debate led to the revision of several international ethical guidelines to clarify when placebo controlled trials are ethically justifiable.

New standards in HIV prevention and treatment research have emerged that pay particular attention to community engagement and participation through formalised structures such as Community Advisory Boards; assessments of comprehension of the informed consent process prior to enrolling volunteers into trials; up-front provision for post-trial access and provision of ancillary care. In contrast to non-HIV research, additional responsibilities are placed on HIV researchers to provide therapies unrelated to the study interventions, e.g. provision of HAART for HIV vaccine trial participants who become infected. In some instances, the pendulum has swung too far across and researchers have become over-protectionist and risk averse in the conduct of HIV prevention research in these settings.

Conclusion

The last 25 years has seen the emergence of a completely new pathogen and its devastating consequences. The magnitude of the global HIV epidemic also spurred the scientific community to develop several interventions that are proven to prevent HIV infection and over 25 new drugs that are effective in treating AIDS. For each of the three main modes of HIV transmission, there are effective strategies to prevent HIV infection using existing technologies (like circumcision and male condoms) or new technologies like antiretrovirals to prevent MTCT, female condoms and new HIV tests to protect the blood supply. The challenge has been to implement

these interventions to scale given the historical under-development of public health systems in the countries worst affected by AIDS.

While medical research has made enormous strides in the prevention of MTCT and blood borne spread, changing sexual behaviour to reduce HIV risk has proved more challenging. However, there are notable exceptions. Thailand reversed its HIV epidemic through its 100% condom programme in brothels, and Uganda has been able to alter the course of its epidemic through political will for programmes that reduced high risk behaviours. Vaccines have been key to infectious disease control and, in some instances, eradication. Developing an HIV vaccine has proven to be elusive, due mainly to the absence of identifiable natural immunity against HIV infection in humans. The enormity of this vaccine development challenge led to the creation of the AIDS vaccine enterprise, which is a global collaboration amongst scientists to work towards the common goal of a safe and effective AIDS vaccine.

AIDS has redefined the way in which doctors relate to their patients, the way in which research is conducted and the way in which activism has forced redress in global inequities to life-saving medical care. The experiences of the AIDS epidemic over almost three decades has illustrated that AIDS is more than a medical problem; it is also a social and development problem with profound consequences on the very fabric of society. It is impacting on security, social cohesion, economic growth and is even reversing some of the health gains of the last century.

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