PREVENTION PREVALENCE AND TREATMENT OF HIV / AIDS

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Prevention, Prevalence and Treatment of HIV AIDS

ANCC Accredited NCPD Hours – 5 Hrs

Target Audience: RN/APRN

Need Assessment

In 2016, there were approximately 12769 people living with HIV in Washington. In 2017, 439 people were newly diagnosed with HIV. 13,810 People are living with HIV in 2018 in Washington and in 2018, King County experienced its largest one-year increase in the number of new HIV diagnoses since 2002. The increase was driven by the number of new HIV diagnoses among persons who inject drugs and the number of new diagnoses in persons with other risks, including men who have sex with men (MSM) who do not inject drugs, remained stable. Washington State is in an exciting position to build on the strong foundation of public and private investment to keep people living with HIV healthy and prevent new HIV infections. It is the responsibility of a Nurse practicing in the state to have a comprehensive knowledge on these standards.

Objectives

- Discuss the epidemiology of HIV/AIDS.
- Describe the modes of transmission of HIV.
  Describe the pathogenesis and classification of HIV.
- Identify the risky population and screening modalities of HIV
- Explain the diagnostic tests for HIV
- Analyse the Preventive strategies for HIV
- Adapt to the Reporting, Prevention and Treatment guidelines followed in the State of Washington.
- Describe the Antiretroviral therapy and its challenges.
- Analyse the adverse outcomes associated with HIV and its management

Goals

The goal of this article is to provide a practical review and update of information with reference to HIV/AIDS, addressing the crucial concerns that impact clinical and public health practice

Introduction

Since its first detection three decades ago, the HIV/AIDS pandemic has been profoundly shaped by criminal justice systems. Surveillance studies have commonly observed significantly higher prevalence of HIV infection among incarcerated populations as compared to analogous non-incarcerated groups. ***The elevated seroprevalences among individuals held in correctional facilities are, for the most part, a result of the political and criminal justice structures that penalize groups who already face multiple HIV/AIDS-related vulnerabilities, including individuals addicted to illicit drugs, sex workers, and sexual/gender minorities.*** However, evidence from a variety of studies, including molecular contact-tracing investigations and entry/exit antibody testing, have also identified within-prison transmission, facilitated by the dearth of evidence-based HIV prevention tools. In addition, ***exposure to correctional facilities has been strongly associated with elevated levels of co-morbidities like hepatitis C, tuberculosis, untreated mental illness including unmanaged substance use disorders and social/ structural factors (stigma, discrimination, political disempowerment, socio-economic marginalization and exclusion from non-correctional healthcare systems) linked to increased risk of HIV transmission and pathogenesis. [1, Rank 4]***

Epidemiology of HIV/AIDS

Coincident with the emergence and spread of the HIV/AIDS pandemic has been the growth in the global population of individuals held in penal facilities. ***According to the most recent estimates, approximately 10.1 million people were held in penal institutions, including police cells, pre-trial detention, so-called mandatory treatment facilities, jails, prisons and penitentiaries*** in 2011, equal to a rate of incarceration of 146 per 100,000 individuals. Driven in many settings by increased numbers of criminalized drug users, global correctional populations have nearly doubled since 2005. While unequalled in size or scope, the United States' correctional systems exemplify these trends. In the 1980s, the United States enacted harshly punitive laws against illicit drug users, including mandatory minimum sentencing requirements, as a reaction to the emergence of crack cocaine, especially among the country's population. As a result the number of individuals incarcerated in state and federal prisons increased, by almost 500% in a generation. More likely than the

general population to be non-white, poor, not engaged in regular medical care, and suffering from untreated substance abuse, prisoners in the United States exhibit an HIV prevalence of 1.5%, and approximately 15% of all people living with HIV/AIDS are in contact with the criminal justice system each year.

Recent advances in our understanding of HIV/AIDS transmission dynamics, in particular the central role played by HIV-1 RNA viral loads (VL) have revealed the substantial impact of effective HIV treatment on the incidence of new infections. In the wake of the HPTN-052 multicenter randomized controlled trial that demonstrated a >95% decrease in the likelihood of HIV transmission as a result of earlier highly-active antiretroviral treatment (HAART), as well as other evidence from observational studies and mathematical models, renewed HIV/AIDS prevention campaigns with HIV treatment as a cornerstone have been launched. These seek to reduce the incidence of new infections by lowering the community-level HIV RNA viral load. Some key aspects of Treatment-as-Prevention (TasP) efforts are identifying undiagnosed individuals and engaging and retaining them in medical care including HAART, with the goal of achieving non-detectable plasma HIV-1 RNA viral loads (VL).

Given the high proportion of individuals living with HIV/AIDS held in correctional facilities, optimism has been expressed that criminal justice systems could be an ideal focus of HIV testing and treatment efforts. However, studies of people living with HIV/AIDS in community settings have consistently observed that incarceration is a substantial barrier to consistent engagement in HIV treatment and care, including antiretroviral therapy. Thus, the criminal justice-based approach to individuals at high risk for HIV infection, especially people who use illicit drugs (PWID) and sex workers, and the high rates of incarceration borne by these groups, might compromise the impact of TasP-based campaigns. In order to contribute to efforts to optimize TasP-efforts as well as reduce HIV/AIDS morbidity and mortality among incarcerated individuals, we performed this review of incarceration among people living with HIV/AIDS, focusing on HIV prevalence and transmission, HIV testing, and HIV treatment among incarcerated populations. [2, Rank 3]

Facts about Epidemiology of HIV in United States

It is difficult to identify accurate denominators for the numbers of individuals and encounters in which exposure hasoccurred; moreover, transmission of the

virus depends on factors other than the mode of exposure. [92, Rank 4]

Both Washington State and King County have made mixed progress toward reducing disparities in HIV outcomes across groups defined by race/ethnicity. On the one hand, rates of new HIV diagnoses in Washington State in 2018 were higher among US born Black persons than other racial groups; in King County rates were higher for both US born Black and US born Latinx persons.

Epidemiological facts of HIV in USA

In 2018, there was a sharp increase in the number of new HIV cases among people who inject drugs (PWID), including clusters of linked cases. Public Health, community-based organizations, King County jails, and local healthcare organizations, increased HIV testing, the distribution of condoms, and the provision of syringe services in response to the outbreak.

As part of the National End the HIV Epidemic initiative, Washington is planning to expand the availability of comprehensive medical, preventive and social services to PWID and persons living homeless in the state.

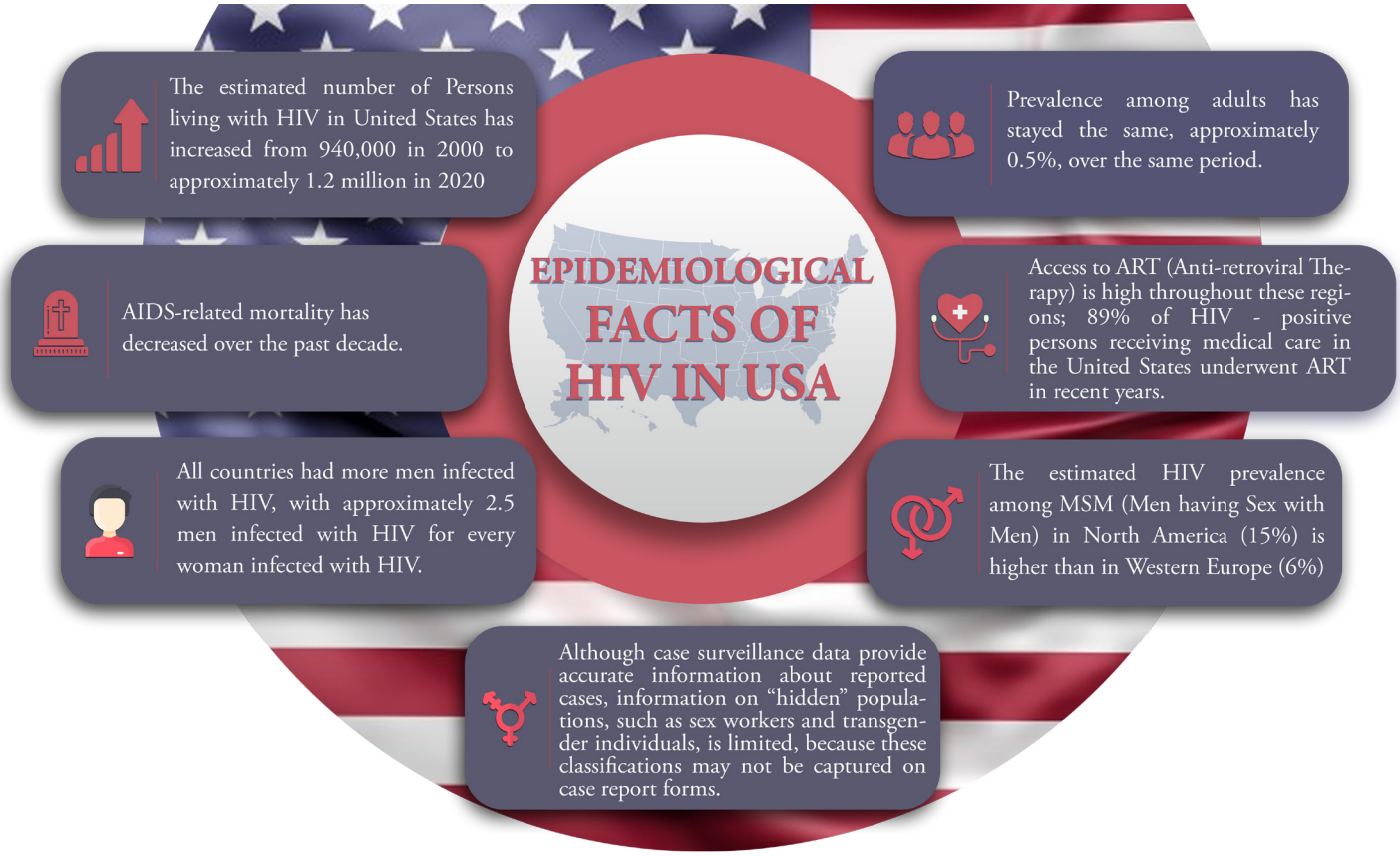


Table 1: Epidemiological facts of HIV in USA

HIV and its Mode of Transmission

More than 34 million people worldwide are infected with human immunodeficiency virus (HIV). ***There are two types- HIV-1 and HIV-2.*** It has long been understood that the HIV-1 of the donor often exhibits a reduced viral diversity following transmission to a new host. More recently, about ten years ago, it became clear that this narrowing is usually very sharp, with only one or a very few viruses establishing a disseminated infection in the newly infected individual despite the high diversity of HIV-1 populations in most donors. ***HIV-1 infection typically results from the transmission of a single viral variant, the transmitted/founder (T/F) virus. This phenomenon has become termed the transmission bottleneck of HIV-1*** and is incompletely understood.

The genetic bottleneck stems from physical and immunological conditions that prevent most variants within the incoming viral populations from establishing infection in a new host and is reflected by the low efficiency of HIV-1 transmission from a single sexual exposure. Thus successful infections in a new host frequently results from the dissemination of only a single variant after sexual transmission, in approximately 80% of heterosexual transmissions, approximately 75% of transmissions in men who have sex with men (MSM), approximately 70% of transmissions in mother-to-child and 40–80% of transmissions in intravenous drug users (IVDU). [93, Rank 3]

The transmission of parasites and pathogens is often referred to in the literature and public health information sites as having various 'modes' and 'routes'; however, these two terms are used interchangeably, which confuses two concepts important for evaluating the process whereby transmission evolves. In common usage, a 'mode' of transport (e.g. train, bus, car and bicycle) is easily distinguishable from a 'route' taken to get to a destination (e.g. via which city, or via which specific international departure and arrival point). Similarly, in reference to transmission, 'mode' should refer to the method that a pathogen uses to get from starting point to destination, whereas the 'route' is the path taken using the chosen mode and includes a starting point (site of pathogen presentation, or portal of exit), a specific pathway used, and a destination (where the pathogen enters). This distinction is important because the mode defines certain epidemiological characteristics of the pathogen and the disease, and hence expectations for its possible evolution (for example, sexual versus non-

sexual transmission). The routes for one mode may be several, or many, and dictate specifically how the pathogen will leave one body and infect another, e.g. faecal–oral, hand–oral, fomite–lung, etc. Until we know both the mode and route, the transmission is not fully defined. For example, a pathogen transmitted by the lung-to-lung route may be droplet-borne or airborne, and a pathogen transmitted by the vertical mode may take the transplacental or vaginal-skin route.

However, once we know both mode and route, the evolutionary trajectory may be hypothesized and control measures can be implemented. Knowledge of routes associated with a given mode might also indicate how restricted a particular pathogen might be in its transmission, which in turn may suggest more precise or wide-ranging methods of control. For example, airborne pathogens mainly spread from one respiratory tract to another, whereas vector-borne pathogens can be transmitted from vector to skin, from the vectors' faeces to lung, or from a vector bite to the blood stream.

The actual hierarchical order of the divisions and sub-divisions is debatable but these are the commonly used dichotomies. Within the evolutionary literature on disease, the major distinction made among transmission modes is between vertical and

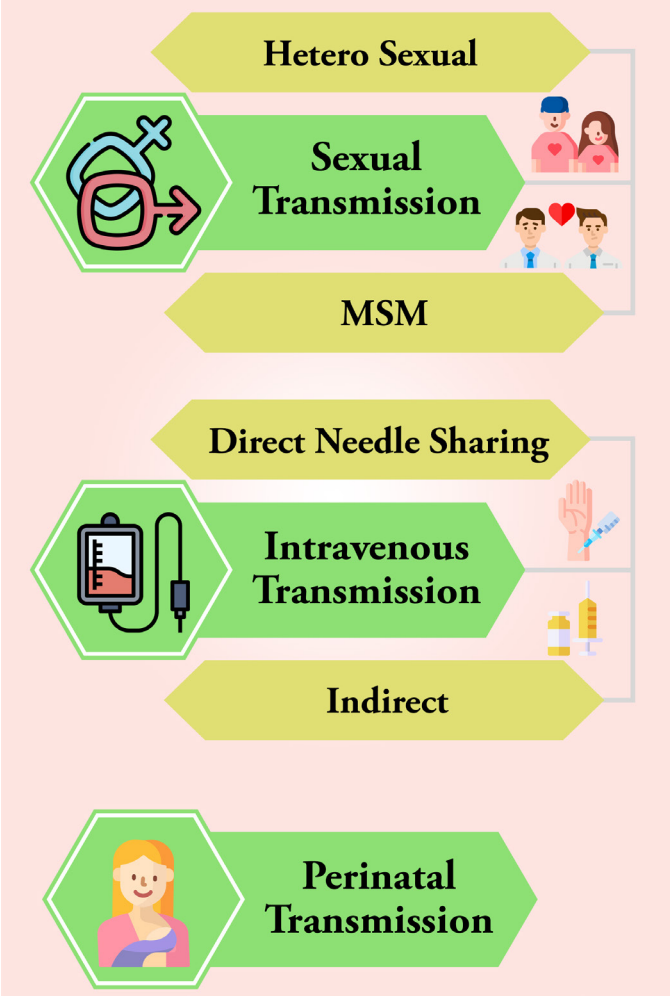


Figure 2: HIV transmission

horizontal transmission, with horizontal transmission commonly subdivided into sexual versus non-sexual. Most health and government organizations classify infectious diseases as being transmitted 'directly' (e.g. sexual, vertical, skin-to-skin contact) and 'indirectly' (e.g. airborne, vector-borne, vehicle-borne, water- and food-borne). As directly transmissible diseases are by definition spread by direct contact between individuals, this distinction may be more useful to warn medical workers that they may be at risk of infection by directly transmitted pathogens from their patients. Another

distinction is sometimes made based on the form of the transmission function in relation to density of infected individuals, namely frequency-dependent versus density-dependent transmission. [30, Rank 4]

Quantifying the contribution of different modes and routes to overall transmission of a pathogen is a major challenge, and the general lack of data on transmission for most pathogens is one of the greatest obstacles to studying its evolution. For example, understanding evolutionary pathways in transmission is more limited by reliable knowledge of the transmission mode than by the phylogenies of the pathogens involved. ***Generally, three approaches have been taken to establish and measure transmission mode: genetic studies involving markers, observation of contact processes and experimental studies.*** The presence of congruent host and pathogen phylogenies has also been used to infer that in the past pathogen transmission has been predominantly vertical. However, this interpretation has been questioned because congruent phylogenies may also result from the greater likelihood of host shifts between related taxa by horizontal transmission. Moreover, a high level of observed vertical transmission does not preclude a horizontal transmission route as the latter may be essential to maintain a high disease prevalence, in turn resulting in high effective vertical transmission.

Most infectious diseases have the potential to be transmitted by multiple modes, so a major issue is determining which modes are the most important in a particular host–pathogen system. Even modes that appear 'incidental' or unimportant, may, if they have a genetic basis, be the target of selection in novel circumstances. A classic example is the protozoan Toxoplasma gondii. While the one definitive host, a species of Felidae, sheds oocysts in the stool, these can infect most warm-blooded organisms when they consume contaminated vegetation or raw meat. ***Species such as sheep, humans, mice and rats can maintain infection through congenital or neonate transmission, and several cases of sexual transmission have also been documented in experimental studies.***

Transmission mode can obviously be determined by many methods. Contact tracing and inferring transmission modes based on behaviours among contacts is a method commonly used in humans. Age specificity of infection, location of the pathogen, site of the lesions and the biology of the transmission stages are all pointers to the transmission mode. While these methods are important in identifying modes and in directing control measures in human and

agricultural diseases, quantifying the level of transmission by the different modes remains a challenge. [34, Rank 4]

Sexual Transmission

Sexual intercourse was implicated as a primary mode of transmission of the virus even before the etiologic agent (HIV) had been identified. However, the sexual transmission of the virus is not highly efficient, and the risk of acquiring the infection as a result of a single sexual exposure is relatively low. Sexual transmission depends on the type and frequency of sexual encounters, as well as the prevalence of other risk factors. With respect to heterosexual transmission, as with other sexually transmitted diseases, women are at higher risk than. Transmission rates may also vary depending on the risk group of the originally infected partner. The risk of transmission has been shown to be lower for female partners of hemophiliacs and bisexual men and for partners of transfusion-infected persons than it is for female or male partners of injection drug users

Delineation of the precise biological mechanisms involved in the heterosexual transmission of HIV has been complicated by the difficulty of identifying a potential series of sexual encounters in which exposure to HIV is known to have occurred each time. We know that cell-free virus is infectious for blood product recipients and that cell-associated virus can infect cell lines in vitro. We simply do not know the relative contributions of cell-free and cell-associated HIV transmission in various at-risk sexual contact. Furthermore, viral factors that may influence the efficiency of transmission are so far poorly understood, it is not yet known whether specific viral genotypic or phenotypic attributes influence the efficiency of viral transmission.

Transmission is known to be facilitated by a compromise of the integrity of mucosal surfaces and the presence of other sexually transmitted diseases, such as syphilis and chancroid. By increasing circulating lymphocytes and macrophages that may harbor HIV at the site of local infection, the presence of sexually transmitted diseases may potentially increase infectiousness as well. As a result, the prevalence of sexually transmitted diseases in a population of individuals at risk for HIV infection can significantly alter the efficiency of virus spread.

If a virus-transmitting donor has advanced HIV disease, the recipient may also be more likely to become infected. Furthermore, infection by an advanced-stage donor is associated with a higher incidence of acute viral syndrome may be due to increased viral load in the transmitter or to

increased virulence of the transmitted strains of HIV.

Originally, it was thought that the virions and infected cells found in semen are directly imported from the blood. However various studies have now shown that the ***genital tract constitutes a distinct viral compartment that locally produces viral particles and infected cells presumably under a different selective milieu than in the general circulation. As a result, the viral quasispecies in the genital compartment are related to, yet distinct from that in blood.*** Therefore, during a transmission event, the viruses to which the recipient is initially exposed may already differ from the viruses found in the blood of the donor. Most data compare viral populations in semen to those in the blood circulation; however, limited data exist to suggest the possibility of a similar effect in the female genital tract compared to the blood circulation of the same donor.

Although the viruses in the genital compartment are thought to move back and forth between the blood and the genital compartment, generally this movement appears limited and doesn't seem to negate the reduced genetic diversity observed in the genital tract. Individual infected CD4+ cells or virions from the blood may infiltrate into pockets of uninfected target cells in the genital tract to generate local foci of infection or even sustained, autonomous virus replication which would lead to clonal amplification or full compartmentalization of virus in the genital tract. Studies of the male genital tract in macaques and humans indeed demonstrated that SIV and HIV-1 can replicate in leukocytes within the testes, epididymis, prostate and seminal vesicles during all stages of infection.

These leukocytes, mainly T lymphocytes and to a lesser extent macrophages, are localized in the stroma and secretory epithelium of these organs. Infection of these cells could lead to the release of free viral particles and infected cells in the lumen and thus in the seminal plasma during ejaculation. Prostate and seminal vesicles are likely the main source of cell-free HIV-1 in semen, as they display higher levels of infection than the epididymis and the testes. This is supported by the fact that vasectomy has little or no effect on seminal viral loads.

The genital fluid includes semen in males and cervical vaginal fluid in females. Genital fluids are known to contain proteins that can enhance or reduce the viral infectivity. In semen for example, a well-known enhancer of viral infectivity is the semen-derived enhancer of virus infectivity (SEVI). SEVI is made up of peptides found in semen that aggregate into amyloid

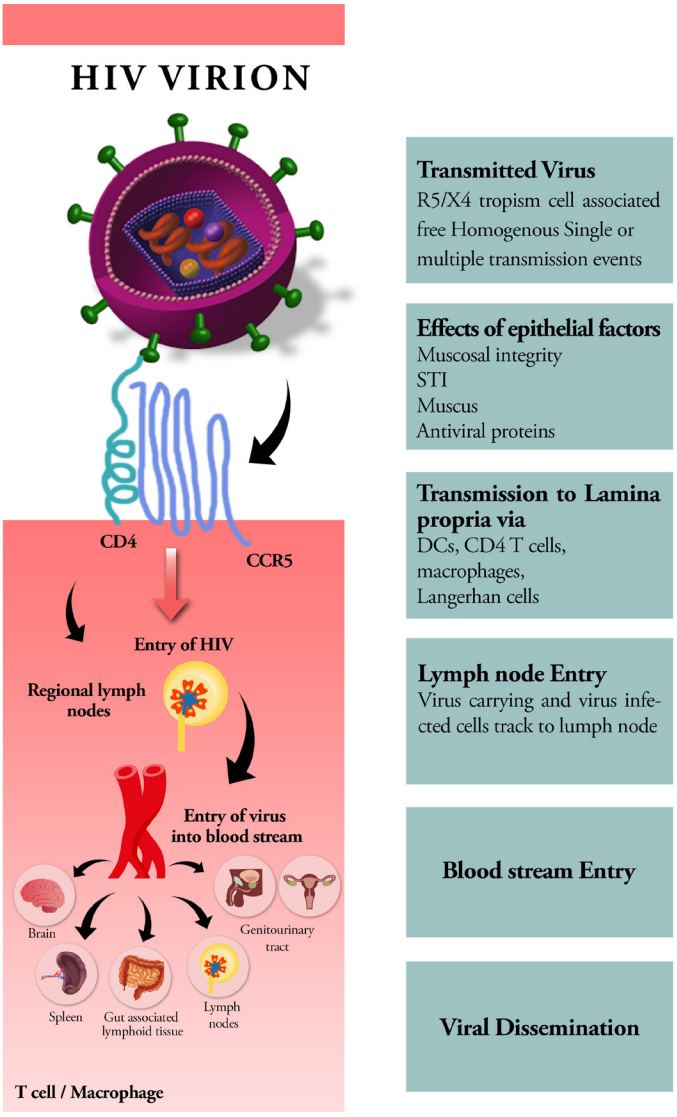


Figure 3: Sexual transmission of HIV

fibrils and are capable of enhancing virus attachment to target cells and increase infectivity by up to 400,000-fold using a mechanism that involves cationic charges of the fibrils.

Looking at pre-infection in women, inflammatory cytokines have been shown to enhance HIV-1 acquisition. Furthermore, it has also recently been shown that high levels of inflammation may select for transmission of viruses that are less infectious. These effects likely reflect an impact of inflammatory cytokines upon the transmission bottleneck.

In HIV-infected men, transmission fluid contains both cell-free virus from the seminal plasma and cell-associated virus from seminal cells. The latter are usually the most abundant HIV-susceptible host cell in semen as seminal CD4+ T lymphocytes are often depleted during chronic infection. The relative contribution of cell-associated vs cell-free seminal virus towards transmission is yet to be resolved. One study supports the transmission of cell-free virus as opposed to cell-associated virus, although this interpretation has been questioned. Interestingly, viral variants isolated from seminal leukocytes are sometimes phylogenetically distinct from cell-free virions found in the seminal plasma indicating that they may differ phenotypically and in their transmission potential. A discrepancy is often observed between the number of infected leukocytes and the cell-free viral load in semen. It appears therefore that the HIV-infected cells in semen are not the primary source of cell-free virus in seminal plasma and that probably distinct sources contribute to either cell-free or cell-associated HIV-1 shedding in semen.

Ordinarily, it is expected that cell-associated virus would represent older partially archived, more stable viral populations

while the cell-free viruses in plasma would represent recently produced viruses, based upon the very short half-life of cell-free virus in blood or transmission fluids.

One would expect then that if the majority of transmitted viruses originated from infected seminal cells, that these would resemble earlier viruses in the donor. While this has been reported in a study, the inferred donor ancestral virus identified in the recipient was shown to originate from blood but there was no analysis of virus from the genital compartments to trace as best as possible the steps from blood to transmission. [94, Rank 4]

Intravenous Drug Users Transmission

The disseminated infection seemed to be derived from a single variant in 40–80% of the transmissions of new infections that were analyzed. In an analysis that combined data from 5 different studies, only one transmitted/founder virus was detectable in 21 of 32 (66%) recent intravenous drug use-associated HIV-1 infections. In aggregate, this is not different from the rate of infections traced to a single transmitted/-founder virus following sexual transmission. This strongly suggests that a substantial bottleneck at or near transmission exists during IVDU-associated transmission, in which there is no mucosal barrier to transmission.

The data used in this 5-study analysis almost exclusively come from two research groups working in different settings. In a North American cohort, 4/10 (40%) of the IVDU infections studied were traced to a single transmitted/founder. Although this is significantly lower than the rate of single founder infections identified following sexual transmission, this study nonetheless suggests that there remains a substantial bottleneck in Intravenous Drug Users transmission despite the absence of a physical barrier to transmission. In a Russian Intravenous Drug Users cohort, 9/13 (69%) infections studied were traced to a single transmitted/founder. If this latter study is combined with unpublished analysis of 7 further infections from the same research group, then 16/20 (80%) of the Intravenous Drug Use infections studied were traced to a single transmitted/founder virus from this Russian cohort.

A substantial limitation to interpretation of these studies is that the size of the initial inoculum in Intravenous Drug Users cases is very difficult to estimate because, in part, it depends upon the volume of blood transferred during the use of shared needles and/or syringes, upon the infectiousness of the transferred virus and upon the donor's viral load. The volume of blood drawn into the syringe to confirm that the needle is in

a vein, will be highly variable (perhaps 100 µl) and subsequently diluted by a variable volume of drugs in the syringe.***A related practice of direct needle sharing has been termed booting Practices such as booting - drawing blood into the syringe a second time and re-injecting it to rinse residual drug solution out of the dead-space as well as flushing the needles with water before sharing,*** will all affect the final volume of donor blood that is transmitted to the recipient. In simulations, high dead space syringes transfer approximately 84 µl without rinsing and 1 µl of donor blood with rinsing, and low dead space syringes transfer ~2 µl without rinsing and much smaller volumes (<0.001 µl) with rinsing. There is thus a wide range of possible transferred volumes, even under relatively controlled laboratory conditions.

A second factor that needs to be considered will be the infectiousness of the HIV-1 in the retained donor blood. This will be affected by practices such as drug heating, the time between needle sharing, etc. Third, the size of the virus inoculum will be determined by the viral load of the donor. Viral loads of recently infected Intravenous Drug Users and individuals infected by heterosexual transmission are very often over 100,000 cp/ml, (100 cp/µl), in almost half of the study participants tested. Recently infected individuals may account for a disproportionately large fraction of HIV-1 transmission under many conditions. In any event, a log mean viral load of 16,000 cp/ml was calculated for North America and Europe (where these IVDU studies were conducted) using a large dataset derived mostly from chronically infected individuals. These viral loads, particularly those of recently infected individuals, are high enough that the presence of multiple variants in submicroliter volumes of blood is probably common. Despite this, new HIV-1 infections in Intravenous Drug Users are very frequently traceable to a single founder virus, similar to what is observed for sexual transmission.

Another limitation to these studies is that it is not possible to rule out that some of the transmissions presumed to occur via the Intravenous Drug Users route could also have been actually transmitted sexually. In the case of the 20 transmissions analyzed from Russian Intravenous Drug Users, the transmission would almost certainly need to have been from another drug user (even if sexually transmitted), as the Intravenous Drug Users epidemic in the region is predominantly subtype A and the sexually transmitted epidemic is predominantly subtype B. Finally, it is also not possible to rule out transmission of more than one very

closely related virus. This may be more likely when the donor has an acute infection that has not fully diversified.

A separate category of drug injection practices can be termed indirect needle sharing because they do not directly involve passing a contaminated needle and syringe between individuals

Despite these limitations, when aggregating all available data, the overall rate of new infections traced to a single variant in presumed Intravenous Drug Users transmission appears to be much higher than what can be expected from the estimated viral inoculum, and statistically indistinguishable from the rate in sexual transmission. That there is a drastic drop in viral diversity from intravenous inoculum to new HIV-1 infection is supported by a study in rhesus macaques. Five macaques were challenged with an intravenous dose of 2 × 105 viruses of one of two viral isolates with diversity typical of early chronic HIV-1 infection, plausibly a larger dose than is normally experienced during Intravenous Drug Users transmission. In three of the five macaques, the resulting infection was traced to between 1 and 4 distinct variants. Thus, even under these controlled conditions, the diversity of the HIV-1 infection from intravenous exposure is drastically reduced compared to the diversity found in the inoculum.

"The primary category of intravenous transmission is direct needle sharing, which involves the reuse of needles and syringes that have been contaminated through prior use by an infected individual. Penetration of the needle through the skin is sufficient for contamination and subsequent transmission of HIV infection, as has been demonstrated in cases of needle stick injuries among health care workers"

To the extent that these data are explained by selection following Intravenous Drug Users inoculation, we must conclude that the mucosa of the genital tract is not absolutely required to produce a transmission bottleneck. We suggest that there may be substantial selection and/or stochastic narrowing at the level of establishment of systemic infection.

Thought must be applied to the role of the genital tract mucosa as a physical barrier to HIV-1 infection in sexual transmission. Analysis of an aggregate of currently available data suggests that the rate of new infections traceable to a single variant is not different between Intravenous Drug Users and sexual transmission. However, there are substantial uncertainties associated with concluding that the mucosal barrier is not meaningful to HIV-1

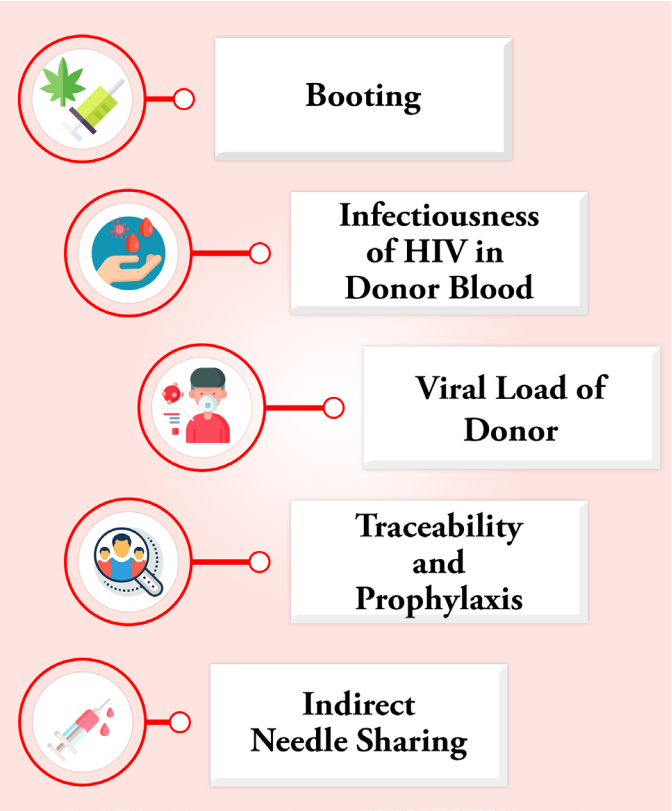


Figure 4: Factors affecting HIV infection in intravenous drug users

transmission.. In particular, there are studies that suggest that genital mucosal surfaces do provide a substantial barrier to HIV-1 viral particles that is likely to be meaningful to sexual transmission, although not essential for the transmission bottleneck. Nonetheless, in light of the substantial bottleneck associated with IVDU transmission, it is challenging to understand why sexual transmission to recipients with a range of STIs (such as syphilis and other ulcerating infections, gonorrhea and chlamydia) leads to an increased risk of HIV-1 infection, and possibly an increased risk of infection by multiple HIV-1 variants. Perhaps the effects of the STIs that actively promote the establishment of HIV-1 infection are the key, important effects rather than effects associated with compromise of the mucosal barrier. [95, Rank 3]

Perinatal Transmission

Female injection drug users or partners of male injection drug users represent the largest number of HIV-infected women of childbearing age, constituting a sizable threat for perinatal transmission of HIV. ***The transmission of HIV from an infected mother to her offspring may occur in utero, during the birth process (intrapartum), or at some time following birth (postpartum) by breast-feeding.*** Approximately 25 to 30 percent of neonates born to HIV-seropositive mothers become infected.

For infants born to HIV-seropositive mothers, the transplacental transfer of maternal anti-HIV antibodies complicates the accurate estimate of the number of infants infected in utero versus those infected during or after birth. Many HIV-infected pregnant women are unaware of their infection, the opportunity for the early diagnosis and treatment of their infected infants frequently may be missed. Interventions to prevent postpartum transmission, such as avoidance of breast-feeding, are not available to women who do not know that they are infected with HIV. In perinatal transmission, a variety of factors, usually

associated with latter-stage disease, including the presence of maternal p24 antigenemia and low maternal CD4+ lymphocyte counts at the time of conception, correlate with the likelihood of infection of a neonate. Additional risk factors in perinatal transmission include high maternal CD8+ T-lymphocyte counts, placental membrane inflammation, and maternal fever. It is likely that many HIV infections in infants are acquired at birth through contact with contaminated blood or secretions. Among twins born to HIV-infected mothers, a higher risk of HIV infection is seen in the firstborn, even for twins delivered by cesarean section, suggesting that factors related to the delivery process affect the risk of infection.

The fact that both the virus donor and the recipient are known in the case of perinatal HIV infection provides potential opportunities for interventions to decrease the risk of viral transmission. Recent studies have shown that antiviral treatment of an HIV-infected mother with zidovudine (AZT) can significantly decrease the likelihood of HIV infection in her offspring.

Understanding patterns of HIV Transmission

A focused and strategic approach to the HIV response should be based on a clear understanding of the spatial and temporal variation of HIV transmission patterns and associated risk behaviours.

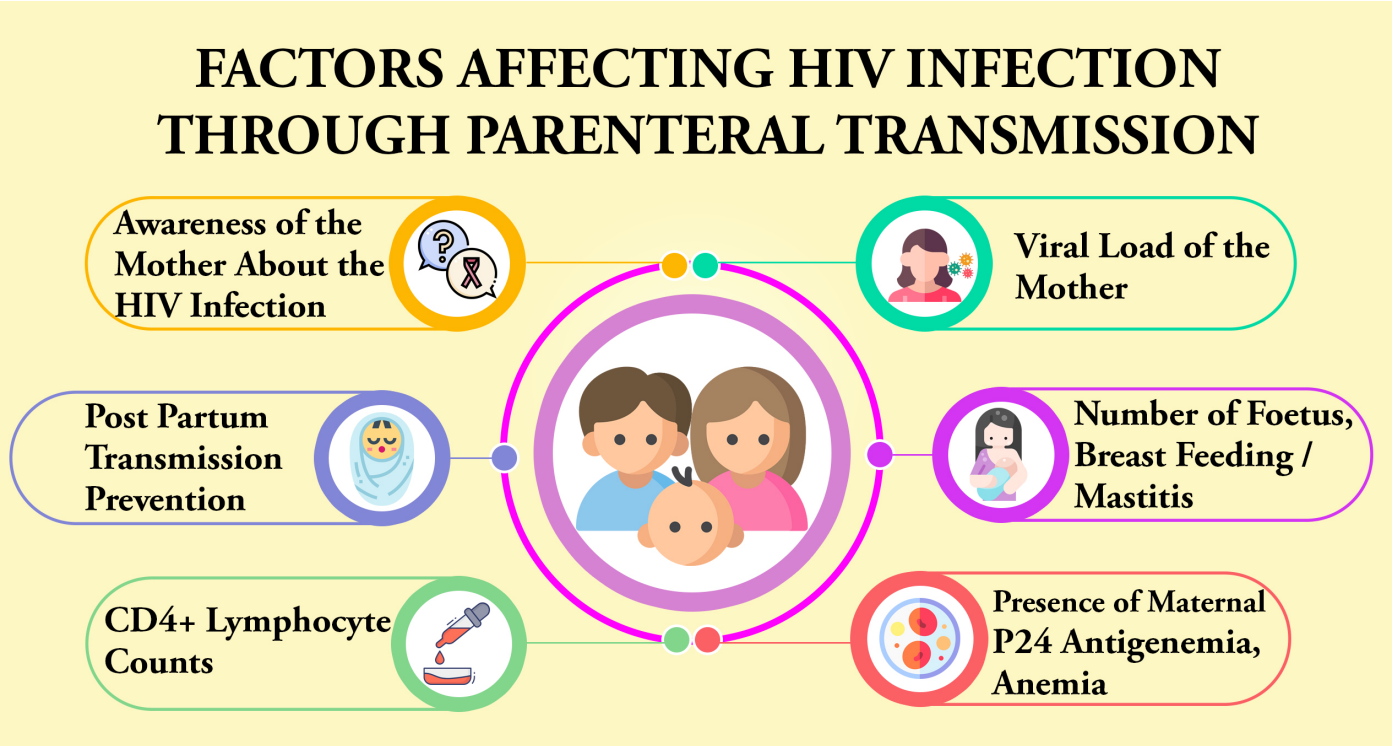


Figure 5: Factors affecting HIV infection through parenteral transmission

The 'Know your Epidemic/Know your Response' efforts are intended to help countries become more systematic in their prevention approaches by using strategic information to inform programme planning and decisions regarding resource allocation. The proposed process includes a comprehensive review of available epidemiological data, analysis to determine the distribution of new infections by modes of transmission, and a comparison of current prevention responses and resource allocation with the modelled HIV incidence estimates. The modes of transmission analysis have constituted a vehicle through which this approach has been considered, developed and implemented.

To date, modes of transmission analyses have been conducted or are underway in more than 30 countries worldwide. Results for those countries that have successfully completed modes of transmission exercises show wide variation between and within regions. Application of the modes of transmission model has shown that the majority of new infections are likely to occur in the general population among stable, discordant couples and those individuals who have multiple sex partners.

Priority should therefore be given to those interventions and combinations of interventions, specific to the local context, which may have the biggest impact on the epidemic including the promotion of medical male circumcision in high HIV prevalence countries, expanding HIV testing and counselling services and expanding access to antiretroviral therapy for treatment and prevention. It should also continue to promote safe sexual behaviour including the reduction of multiple sexual partners and high levels of condom use, and strengthen comprehensive HIV programmes for sex workers.

In Latin America, prevention efforts should continue to focus on reducing risky behaviour among Men having sex with men, while efforts in Morocco, North Africa, should focus greatly on commercial sex networks. These programmes should include targeted communication, education and condom programming, as well as community mobilisation. In eastern Europe and the Middle East, reducing new infections among IV drug users should be essential, by providing sterile drug injecting equipment and drug substitution therapy. ***Access to antiretroviral therapy should be promoted in all key populations to ensure good health outcomes and to reduce HIV transmission, while it is essential that programme activities for key populations be complemented by increased support for the protection of human rights, outreach to marginalised populations and for the***

reduction of stigma.

The modes of transmission results in Asia confirm the continuing focused nature of the epidemics in the region, with new infections concentrated in key populations and their immediate sexual partners. However, ***there is wide variation in the contribution of the different groups to the HIV epidemics in the region and the situation can change rapidly over a short time, as was illustrated in the Philippines. This diversity can be explained by variations in the size of key populations, behavioural factors, biological factors, timing of the introduction of HIV and the level and effectiveness of responses in key populations.*** As a consequence, the focus of effective prevention responses can vary greatly and careful local assessments are needed to guide those responses.

While HIV remains concentrated in key populations in most countries in Asia, the contribution of transmission to spouses of those currently or formerly at higher risk has increased in several countries in recent years.

Data on key populations are often limited and difficult to obtain and studies conducted among these populations, particularly in countries where such populations are stigmatised or marginalised, are most often not representative of the entire population. In some countries the size of the stable heterosexual population is assumed as the 'left-over' after all the other population group sizes have been estimated and the incidence contribution could be inflated if unknown risk groups or behaviours are not accounted for. Furthermore, the reliability of self-reported data on risk behaviour can be questionable and the extent of under-reporting or over-reporting is often not known. Some research studies have shown that responses to household survey questions about visiting sex workers or having multiple partners under-report the true behaviours. To the extent that models rely on this data they may underestimate the proportion of new infections occurring among these populations. Because of limited data at subnational or provincial level, the model is usually conducted at the national level and hence subnational variation in transmission patterns is not captured.

UNAIDS has developed a new tool to help countries assess the availability and quality of epidemiological and behavioural data and to help users better judge the reliability of results. ***One of the advantages of the modes of transmission analysis is that it usually forms part of a country-owned, multistage process which includes a comprehensive review of data and, where possible, a comparison with response data.***

Importantly, ***it helps to build capacity in countries and it brings together experts and stakeholders to critically review available data, to identify limitations or biases in the data and to identify and fill key gaps in their understanding of the epidemic and the contribution of specific risk populations. This process is central to any attempt to estimate the modes of HIV transmission.*** In this regard ***the indirect benefits of the Modes of Transmission analysis and the process in several countries have exceeded their direct technical value in mapping the HIV transmission by mode of exposure.***

The majority of countries that have conducted modes of transmission analysis have considered them useful. An outcome evaluation concluded that the modes of transmission studies achieved their main purpose of reinvigorating thinking about epidemic dynamics, HIV prevention and improving the HIV response. In most instances the process was well constructed and involved extensive incountry and international consultation with close involvement or coordination from the National AIDS Councils, among other governmental or non-governmental organisations and academic institutions. ***Both the epidemiological reviews as well as the modelling processes involved high level expertise and experience in countries***

The results of the modes of transmission studies have been considered in national planning efforts and grant applications in several countries. [25, Rank 3]

Determining Transmission Modes and Routes

Epidemiological tracing using genetic markers might seem a particularly useful approach to studying transmission mode, but while markers can identify the source and target of a transmission event, they cannot per se pinpoint the transmission mode unless combined with other approaches. A classic example is the tracing of HIV infections to particular healthcare workers. However, only by assessing associated risk factors (e.g. sexual activity of the health care workers and patients) was it established that many of these HIV infections were likely to have been blood-borne rather than sexually transmitted.

Genetic markers are perhaps most useful in determining transmission routes in multi-host systems. For example, microsatellite markers have been used to identify possible hosts of Schistosoma japonicum . DNA sequencing analysis of mosquito blood meals was used to establish which bird species were potentially important for West Nile virus transmission to humans.

Studies of co-inheritance of genetic markers in parasites and both cytoplasmic and nuclear genetic markers in their hosts can also provide information on the degree to which transmission is vertical or horizontal. Under perfect maternal transmission, there is complete linkage disequilibrium between host mtDNA and pathogen alleles, and degrees of departure from this can be used to back-infer the amount of horizontal transfer.

The comparison of patterns in pathogen phylogenetic distance is a related and promising approach to infer transmission mode. This approach can provide evidence for multiple transmission modes in a system, as different lineages may show different relationships. For example, if pathogen genetic distance between related hosts is less than expected by chance in some strains, it is likely that vertical transmission plays some role in their transmission mode, as has been demonstrated for feline immunodeficiency virus in lions. Conversely, if there is a strong spatial pattern in pathogen genetic distance but little effect of host relatedness, it is possible that horizontal transmission is the dominant mode.

Experimental infections also provide estimates of the relative importance of different transmission routes. For example, in avian influenza, experimental infections have estimated persistence of virus in the environment, and thus the relative importance of airborne versus environmental (faecal–oral) routes.

Similarly, experimental studies on Foot and mouth disease virus have used calves either directly exposed to other infected individuals or housed in buildings that had previously held infected individuals to study direct versus environmental transmission. As another example, to determine whether vertical (congenital) transmission alone was sufficient to maintain transmission of Toxoplasma gondii in brown rats, Rattus norvegicus, rats were trapped from local farms and released into a large naturalistic outdoor enclosure in the absence of oocysts from the feline definitive host. Over the subsequent three years, the rat population expanded but the seroprevalence remained approximately constant, showing feline hosts were not essential to maintain transmission. Although entomo-pathogenic Rickettsia is generally assumed to be vertically transmitted, experimental studies showed a phytophagous Rickettsia could be horizontally transmitted via the phloem; uninfected whiteflies (Bimesa tabaci) physically separated from infected whiteflies could acquire the infection by feeding on the same leaf.

Experimental studies exposing potential arthropod vectors to pathogens by

allowing them to feed on infected hosts are relatively commonplace. ***The detection of the pathogens (often viral RNA) can be in the saliva or head of the insect or in the whole insect.*** However, most such studies implicitly assume that the demonstration of pathogen replication in a vector following artificial exposure to a pathogen is adequate to infer vector-borne transmission in the field. Unfortunately, studying actual transmission under field conditions is expensive, time-consuming and rarely done.

Classification of HIV Infection

The identification and enumeration of HIV 1 or transmitted/founder viruses in acutely infected heterosexuals, men who have sex with men, Intravenous Drug Users and infants born to infected mothers provided an opportunity to explore such viruses for genetic signatures and phenotypic properties that might distinguish them from other viruses. Such studies had been undertaken previously with early but not transmitted/founder viruses, and they yielded intriguing findings, but the molecular identification of transmitted/founder viruses allowed for the first time such studies to be undertaken with far greater precision. From earlier studies, it was well established that the transmission of HIV-1 in humans selected for CCR5 (CC Chemokine receptor 5) tropic viruses, and that R5 viruses could be distinguished from CXCR4(CC chemokine receptor 4)tropic viruses (X4 viruses) genotypically by amino acid signatures primarily in the V3 region of Env. But the important question now raised was if there were additional genetic signatures and corresponding phenotypic properties that distinguish transmitted R5 from others. Put differently, is HIV-1 transmission essentially a stochastic process in which any reasonably fit R5 virus can be transmitted, or are there critical properties of viruses that are transmitted that distinguish them from the innumerable variants that circulate in every chronically infected individual? If such signatures and phenotypes could be identified, they could conceivably represent targets of rational vaccine or drug design.

The HIV-1 genome encodes two glycoproteins (as shown in Figure 6) - the surface subunit gp120 facilitates interactions with receptor molecules, while the transmembrane subunit gp41 anchors the Env (envelope) complex in the viral membrane and mediates fusion with the host cell membrane. HIV-1 gp120 contains five "hypervariable" domains that tolerate sequence heterogeneity.

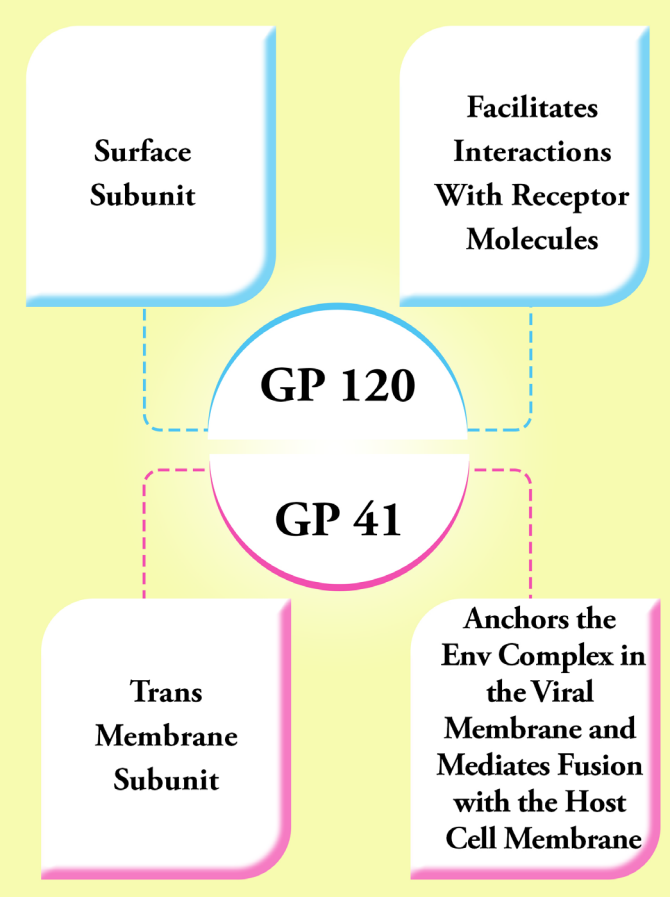


Figure 6: HIV 1 Genome

The gag gene encodes viral core proteins, the pol gene encodes a set of enzymes required for viral replication, and the env gene encodes the viral surface glycoprotein gp160. (as shown in Figure 8)

Compared with HIV-1 infection, HIV-2 infection is characterized by a much longer asymptomatic stage, lower plasma viral load, slower CD4 cell count decline, lower AIDS-related mortality rate.

HIV-1 transmission might select for traits other than coreceptor usage came from a genetic comparison of the viral env sequences from eight subtype C HIV-1 transmission pairs. Studies were conducted prior to reports describing single genome amplification (SGA) and thus carries the caveat that molecular clones of env could have contained in vitro generated artifacts from Taq polymerase mis- incorporation or recombination. It was found out that in each subject pair, regardless of whether virus was transmitted MTF (male to female) or FTM (female to male), the newly transmitted viruses encoded statistically shorter and less glycosylated V1–V4 regions than did envs from the chronically infected partner.

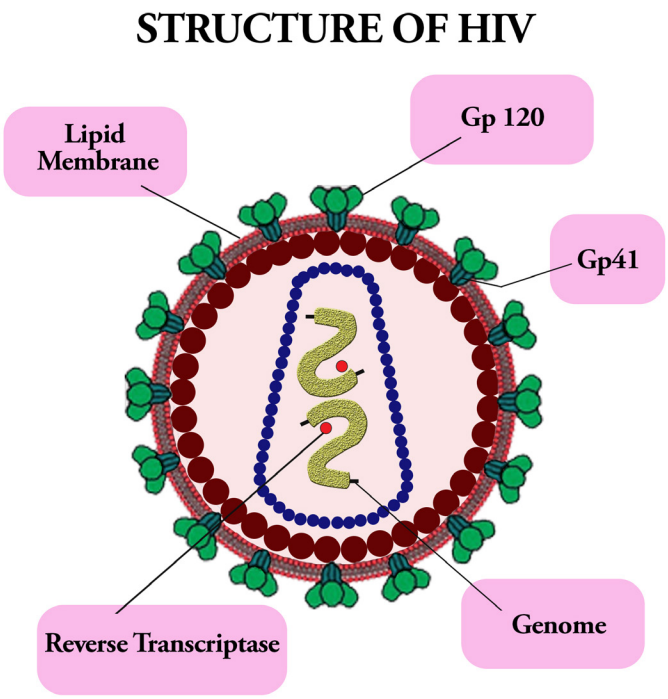


Figure 7: Structure of HIV

More ***compact Env glycoproteins might interact more efficiently with relevant target cells in the genital mucosa.*** This observation was subsequently confirmed using SGA (Single Genome Analysis) methods in an independent cohort of

10 subtype C transmission pairs. With non-Single Genome Analysis methods, it is found out comparing Envs from subtype A HIV-1 acutely infected sex workers to a database of matched chronic virus sequences and 13 subtype D and A transmission pairs. Interestingly, such differences in acute versus chronic Envs were not seen in studies of recently transmitted subtype B HIV-1 heterosexual or men having sex with men infections, suggesting that subtype differences in the virus or maturity of the epidemics may influence the contribution of such a phenotype to HIV-1 transmission.

Most recently, researchers compared over 7000 SGA-derived env gp160 sequences from 275 acutely or chronically infected subtype B subjects and observed statistically robust signatures comprising single amino acids, glycosylation motifs, and multisite patterns of clustered amino acids. These included signatures near the CCR5 (CC chemokine coreceptor) binding surface, near the CD4-binding site, in the cytoplasmic domain of gp41, and in the signal peptide. The motif with ***highest statistical significance was at amino acid position 12 in the signal peptide, which may affect Env expression and incorporation of Env into virions.*** The second most significant signature was at amino acid position 413–415, which affected a glycan involved in escape from antibody neutralization. How these changes might affect HIV-1 transmission is currently unknown.

Transmitted HIV-1 genomes were also analysed for distinguishing properties by phenotypic characterization. It has been difficult to link sequence differences observed between chronic and acute Envs, even within transmission pairs, to a distinct phenotypic property that might influence transmission other than CCR5 tropism. In an analysis of Zambian subtype C transmission pairs, it was found that ***Envs from the newly transmitted viruses retained sensitivity to neutralization by the partner's antibodies and in fact were more sensitive on average than Env variants derived from the transmitting partner.*** This characteristic coupled with shorter variable loops in early viruses led to the hypothesis that transmissibility was linked to loss of Env modifications required for neutralization resistance in the chronically infected host but dispensable in the immunologically naïve partner.

Despite this, the acute Envs were not generally more sensitive to neutralization by either pooled HIV-1–positive sera or to a majority of broadly neutralizing antibodies. Moreover, the acute and chronic Envs had similar requirements for high CD4 and CCR5(CC Chemokine receptor 5) levels on target cells and they showed comparable utilization of CCR5 chimeric proteins

> "The HIV genome contains three major genes including gag, pol, and env, encoding major structural proteins as well as essential enzymes. In addition to these three major proteins, HIV also encodes proteins with certain regulatory and auxiliary functions containing Tat and Rev, which activate viral transcription and control the splicing and nuclear exports of viral transcripts, respectively. Four other genes encode accessory proteins Vif, Vpr, Vpu and Nef, which are not essential for replication in certain tissues. The viral genome is flanked by LTRs (long terminal repeats) that are required for viral transcription, reverse transcription and integration. The genome dimerization and packaging signal is located between the 5'-LTR and the gag gene"

and alternative coreceptors. Also, following up on genetic signatures of virus transmission identified characterized the phenotypic effects of the position 12 polymorphism in the Env leader sequence, which was found to be an enriched motif in transmitted/-founder viruses. Experiments showed an association between a positive amino acid (histidine) at position 12 and higher Env expression, higher virion Env incorporation, and higher virion infectivity compared with control viruses.

The first biological analysis of complete HIV-1 subtype B transmitted/founder env genes, and of subtype B and C transmitted/founder full-length viral genomes, showed these viruses to be uniformly CD4 (cluster of differentiation 4) dependent and CCR5 (chemokine receptor type 5) or CCR5/ C X CR4 (chemokine receptor type 4) dual tropic. These findings thus revealed that ***CCR5 (chemokine receptor type 5) tropism is a property of the transmitted virus itself and not a phenotype that evolves in the initial days and weeks of infection.*** Similarly, transmitted/founder viruses were found to show neutralization sensitivity patterns typical of tier 2 or 3 primary virus strains with V3 and coreceptor binding surface regions well protected from binding by neutralizing monoclonal or polyclonal HIV-1 antibodies.

Again, these were properties of the transmitted/ founder virus at or near the moment of virus transmission and were not properties that evolved in early infection. Subtype B and C transmitted/founder genomes encoded viruses that replicated efficiently in primary human CD4+ T cells but much less well in monocyte-derived macrophages, consistent with results obtained with Env pseudotyped viruses. These observations were extended to

subtype A transmitted/founder viruses, which replicated efficiently in primary human CD4+ T cells but very poorly in monocyte-derived macrophages. Interestingly, a substantial proportion of subtype D transmitted/founder viruses replicated efficiently in both CD4+ T cells and macrophages, which may correlate with enhanced neuropathogenesis of subtype D viruses more generally. Again, these findings described features of transmitted/-founder viruses at or near the moment of transmission and not virus properties that evolved in the newly infected host. Thus, these findings have particular relevance to rational vaccine design efforts and studies of virus transmission in general. With respect to animal models and human tissue explant studies of HIV-1 transmission, the results suggest that tissue macrophages may not play a significant role in HIV-1 transmission and that prototypic macrophage-tropic HIV-1 strains such as BaL, ADA, and YU2 may not be best suited as challenge viruses.

Researchers recently examined the genetic and biological basis of the HIV-1 population bottleneck in mother-infant HIV-1 transmission in subtype C infections. They used SGA techniques to characterize 19 transmission pairs, of which 10 involved intrauterine transmission and nine intrapartum transmission. There was a stringent transmission bottleneck in each case. Thirteen of 19 transmissions were estimated to be from a single virus. Intrapartum (but not intrauterine) transmissions were characterized by transmitted/founder Envs that were shorter and had fewer potential amino-linked glycans in V1–V5. Mother and infant viruses were similar, however, in their sensitivity to soluble CD4, a panel of neutralizing monoclonal antibodies, and to autologous and heterologous polyclonal antibody neutralization. Thus, ***a distinguishing transmission phenotype was not evident.***

The most comprehensive and systematic assessment thus far of the biology of transmitted/founder Envs compared with chronic HIV-1 Envs has been conducted. These investigators compared the biological activity of 24 clade B transmitted/founder Envs with that of 17 chronic controls. To increase the likelihood of an intact mucosal barrier in the acutely infected recipients and thus the likelihood of identifying phenotypic properties associated with mucosal transmission, only transmitted/founder Envs from individuals productively infected by a single virus were enrolled in the acute infection arm of the study. Env pseudotyping was used to assess envelope function in single-round infectivity assays to compare coreceptor tropism, CCR5 (chemokine receptor type 5) utilization, primary CD4+ T-cell subset tropism, dendritic cell

trans-infection, Env fusion kinetics, and neutralization sensitivity between acute and chronic Envs. ***Transmitted/founder and chronic Envs were phenotypically equivalent in most assays, although transmitted/founder Envs were slightly more sensitive to neutralization by the CD4-binding-site antibodies b12 and VRC01 and by pooled human HIV hyperimmune immunoglobulin (HIVIG).*** These findings were independently validated using a panel of 14 additional chronic HIV-1 Env controls.

With a relatively large number of transmitted/founder and acute Envs now having been examined across a number of different studies and by different investigative groups, it seems that no single major genetic or phenotypic signature is required for transmission beyond the use of CCR5. Current data suggest that an array of genetic traits, including but not limited to shorter variable loops and reduced numbers of amino-linked glycosylation sites is associated with enhanced virus transmission at least for subtypes A, C, and possibly B. The structural implications of these signatures and of the modestly enhanced neutralization sensitivity of subtype B viruses are not yet understood.

However, the possibility exists that relatively subtle alterations of Env structure and function in the context of the native Env trimer could provide sufficient selective advantage during the eclipse phase of HIV-1 transmission to result in preferential transmission of such viruses.

The recent finding that HIV-1 gp120 binds to the CD4+ T-cell gut homing integrin α4β7 has raised the possibility that this capacity is important to an infecting virus by targeting cells capable of trafficking to the gut-associated lymphoid tissue. It has been reported that α4β7 highly expressing CD4+ T cells are more susceptible to productive infection by HIV-1 than those expressing low levels of the integrin, in part because this subset is enriched for activated CD4+ cells, and in part because α4β7hi cells express high levels of CCR5 and low levels of CXCR4. Interestingly, a small sample of acute subtype A and C virus Envs bound α4β7 with high affinity, and in some cases, later virus strains showed significantly reduced binding, consistent with an early requirement for infection of α4β7-expressing cells that is dispensable once infection in the gut mucosa has been established. Given that HIV-1 transmission is inherently inefficient and likely represents the most vulnerable point in the natural history of HIV-1 infection, identifying unique properties and potential vulnerabilities of transmitted/founder viruses remains an important objective. [96, Rank 4]

While it would be obviously advanta

geous for a pathogen to use all possible transmission routes, as in any evolutionary process involving a complex phenotype, there are likely to be direct trade-offs between these routes themselves or these routes may have other indirect fitness effects. In an evolutionary context, trade-offs are quantified by measuring the genetic correlations between different traits: a negative genetic correlation between alternative transmission modes suggests that increasing one transmission mode would decrease the other.

It has been commonplace in theoretical and general discussion to expect trade-offs in transmission mode. This is most obvious in the conflict between vertical and horizontal transmission. Activities of a host or parasite that increase the rate of horizontal transmission (e.g. greater production of infectious particles) may increase mortality or decrease reproduction, and this will correspondingly reduce vertical transmission of the parasite via the offspring, necessarily leading to an evolutionary trade-off. Correspondingly, theory predicts that there should be a trade-off between pathogen virulence and transmission mode. If the pathogen kills the host quickly there is a cost in terms of a reduced number of infectious particles, which decreases horizontal transmission. At low host densities, contact rates between host and pathogen may drop below the threshold necessary for persistence, so that persistence is more likely if the pathogen can be vertically transmitted and has a low virulence so the host survives till reproduction.

These concepts seem intuitive when considering, for example, the insect baculoviruses, which are invariably lethal when horizontally transmitted but are largely asymptomatic when vertically transmitted. Natural populations of insects are often characterized by large seasonal variation in abundance, including a complete absence of stages that transmit horizontally; hence, such populations harbour covert baculovirus infections that are vertically transmitted. Another example is the protozoan parasite Ophryocystis elektroscirrha of monarch butterflies, Danaus plexippus, which is transmitted horizontally when adult butterflies ingest spores on host plant leaves, and vertically when spores are transmitted on the outside of the eggs.

As expected, strains of the parasite that produce more spores are transmitted more effectively horizontally (to other adults via the leaves). However, their vertical transmission is actually reduced because larger numbers of spores on the eggs cause more severe infections that lead to premature death of the larvae and pupae. However, these strains are efficiently horizontally transmitted because they leave more spores

on the leaves. Similar trade-offs are seen in a wide range of host–pathogen systems, from malaria to microsporidia, myxozoans and bacteriophage.

The shape of the trade-off is likely to be important in determining whether evolutionary changes lead predominantly to one mixed mode, or to the maintenance of both modes as genetic variants with alternative pathways. This is because the trade-off shape is critical in determining the outcome of evolutionary predictions. The measurement of the shape of the trade-off also presents particular challenges, because estimates of genetic correlations per se cannot incorporate nonlinearities (other than by transformation) and so we lack the statistical tools for estimating nonlinear genetic trade-offs. The shape of the trade-off curve is also critical in determining the outcomes of coevolution between hosts and pathogens with regard to resistance and infectivity.

The dependency of trade-offs on environmental conditions also needs to be considered. Intriguingly, research on microsporidians in mosquitoes has shown that the factors influencing selection on vertical versus horizontal transmission include food availability and whether the parasites are embedded in co-infections. Long-term environmental changes in SO2 levels, by affecting the likelihood of infection via leaves, has been posited as the cause of shifts between leaf-to-leaf (horizontal) and seed (vertical) transmission of the fungal pathogen of wheat, Phaeosphaeria nodorum. [37, Rank 4]

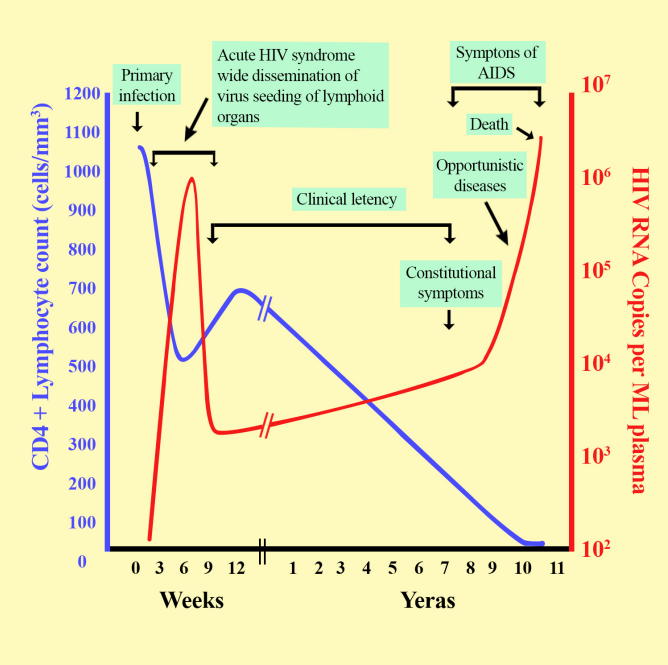
Pathogenesis of HIV/ AIDS

Without treatment with HIV medicines, HIV infection advances in stages, getting worse over time. ***The three stages of HIV infection are***

(1) Acute HIV infection or syndrome

(2) Chronic HIV infection and

(3) Acquired Immunodeficiency Syndrome (AIDS). (as shown in Graph 1)



Graph 1: HIV Course of Infection

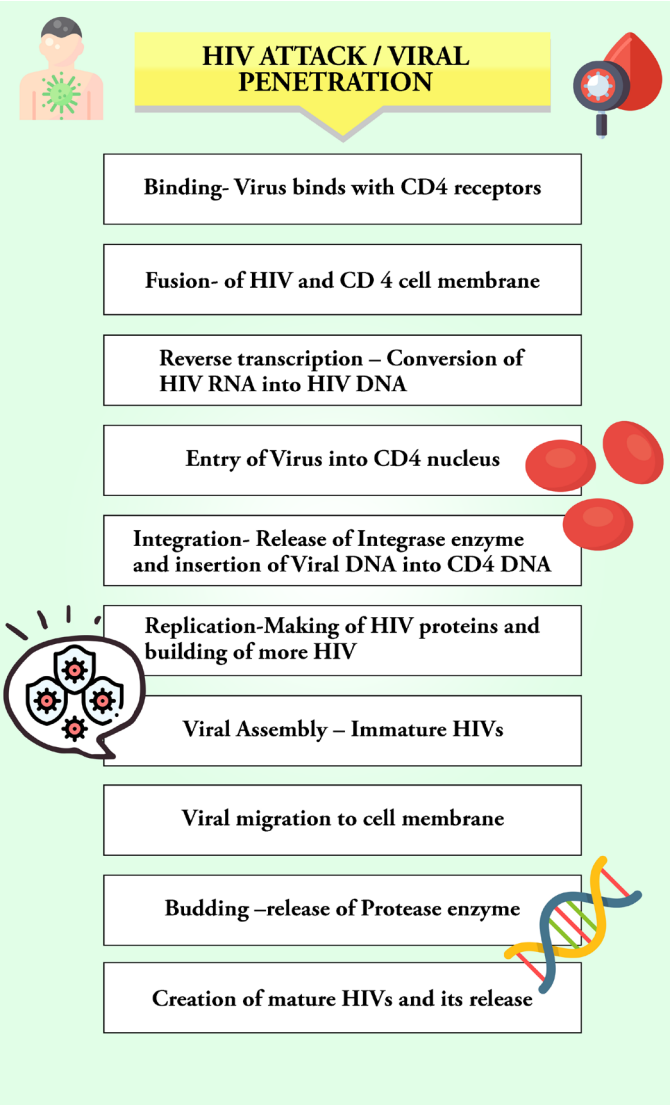


Figure 9: Pathogenesis of HIV

One of the first observations made in the evaluation of various HIV isolates was the viral heterogeneity involved with the ability to infect and replicate in primary CD4+ T-lymphocytes and macrophages.

Moreover, whereas all viruses could grow in most primary CD4+ T-cells, differences were appreciated when HIV isolates were added to primary macrophages or to established CD4+ T-cell lines. Some grew well in macrophages and others in the T-cell lines. Those growing in macrophages generally did not induce cytopathology or multinucleated syncytial cell formation; those growing in T-cell lines were syncytium-inducing (SI) viruses.

After binding to CD4, uses secondary cellular receptors for attachment to and subsequent entry into cells. These virus co-receptors are important binding sites for chemokines that recruit immune cells to the location of their secretion. In high concentration, these chemokines can compete for virus attachment to the chemokine receptor. The NSI (Non-syncytium-inducing) viruses primarily use the CCR5 receptor and are known as R5 (M-tropic) viruses; the T-cell line viruses use the CXCR4 receptors and are known as X4 (T-tropic) (X4) or viruses. Some HIV isolates can use both receptors and are called dual/tropic or R5/X4 viruses. Generally, during acute virus infection, an R5 virus emerges as the dominant type and over time, in many cases, becomes dual/-tropic. Later, in about half of the cases, an X4 or more cytopathic strain emerges. The X4 viruses are associated with a more rapid progression to AIDS.

Recognition of the co-receptors for binding sites of HIV has led to various approaches to block this interaction through specific drugs. Maraviroc prevents HIV infection via CCR5 (chemokine

receptor type 5); other drugs in development target CXCR4 (chemokine receptor type 4). The therapies directed at CCR5 were not considered to be detrimental to the immune system, because about 1% of the human population lack CCR 5 expression (CCR 5) and have no obvious immune abnormalities. These individuals are much less likely to be infected by HIV unless they encounter an X4 virus. However, these CCR5-negative people have been shown to have a greater chance to develop severe disease from West Nile virus. It is less certain what a drug against CXCR4 would do to compromise the immune system. Conceivably, it could lead to the emergence of HIV strains that use other co-receptors. ***Currently, there are at least 9 chemokine co-receptors that can be used by HIV for attachment to various cells of the body.***

This heterogeneity of HIV, which is evident biologically, can also be appreciated genetically. ***The 2 types of HIV, HIV-1 and HIV-2, exist and differ by about 40%.*** In addition, based on genetic variations, 3 groups of HIV-1, differing by about 30% (M, N, and O) have been identified, and 8 groups of HIV-2 have been recognized (A-H), for which A and B are the most common HIV-2 groups in circulation.

This viral heterogeneity can also be appreciated in the change in HIV properties over time in the same individual. Early viruses, as noted above, are usually the R5 type, which grow slowly to low titer in CD4+ T-cell cultures. Then, ***when the individual develops symptoms or AIDS, a related X4 virus emerges, which replicates rapidly to high titer in culture and is cytopathic.*** This virus can then lead to AIDS much more quickly than R5 viruses, although R5 viruses have also been associated with 50% of AIDS cases. [5, Rank 3]

Another noteworthy finding is that ***when viruses are isolated from different tissues of the same individual, variations in their biological property can be found.*** For example, a virus coming from the blood may have the ability to infect peripheral blood mononuclear cells (PBMC) and to down-modulate CD4 expression, whereas those from the brain can be quite infectious for macrophages and not affect CD4 expression. This observation indicates that the same virus transmitted to an individual can, through multiple replicative cycles, become selected in various tissues as a virus related to the transmitted virus but having different biologic properties. It may be responsible for the pathology observed in the infected tissue.

Importantly, ***when more than one virus infects the same cell (perhaps at the same time, when the CD4 receptor has not yet been down-modulated), interactions between the 2 RNA strands of each virus***

can take place. Recombination can then occur. These recombinant viruses contain genetic information from 2 or 3 different viruses. Some may have genetic regions from up to 7 different subtypes. This observation has suggested that, over time, recombinant viruses will become more common and may take on different biologic properties, including resistance to anti-viral drugs or ability to infect many cell types. For this reason, recombination among HIV strains represents a newly emerging challenge in HIV pathogenesis.

Indicators of HIV/AIDS

The very diverse transmission modes that occur in closely related pathogen species suggests that the evolution of new transmission modes is ongoing and likely commonplace in nature. For example, many closely related strains of sexually transmitted diseases have both sexual and non-sexual transmission. However, it is often not clear if transitions to a given transmission mode are simply the product of the host ecology and unrelated to genetic change. [40, Rank 3]

Within 2 days after transmission, the HIV isolate, often a single strain, enters the bloodstream and can infect a variety of different tissues depending on its different biologic properties. The number of cell types reported to be susceptible to infection is quite large and includes cells of the brain, the GI tract, and the kidney, and as well as oral keratinocytes and epithelial cells.

This infection of different cells occurs not only with the free virus, but importantly also with virus-infected cells. The latter results during the replicative cycle when HIV integrates its proviral DNA into the chromosome of the cell. These cells, present in blood and genital fluids, can be a major source of transmission by interacting with cells of the immune system and mucosal tissues in the body.

When infected cells interact with mucosal cells, HIV can be transferred readily to the individual. Such virus-infected cells can be found at levels of 50,000 cells in some genital fluids, and the efficiency for infected cells to transmit the virus is often better than that of the free virus. Moreover, *by time-lapse photography, virus-infected cells have been shown to transfer HIV to many different cultured cervical or rectal epithelial cells. These same cells are often resistant to direct infection by HIV. Infection most likely occurs by cell-to-cell contact.*

HIV transmission via the oral cavity occurs rarely. The amount of infectious virus in the saliva is quite low, and

virus-infected cells are not commonly found. This lack of infection can also be reflected by the large number of anti-viral substances found in saliva. They can block virus infection by both cells and free virus. [15, Rank 3]

With this heterogeneity of HIV isolates and the ability of the virus to be transmitted readily through the mucosae and the blood, the existence of individuals who have survived a long time with the infection (> 10 yrs) without showing signs of the disease and without therapy is noteworthy. Among these long-term survivors (LTS) or long-term non-progressors, a subgroup, now termed 'elite controllers', has been identified. These people, for at least 2 and some for over 10 yrs, have not shown the presence of any virus in the plasma, although they remain infected. These individuals reflect optimal control of HIV among long-term survivors and probably possess the same processes of immune resistance as LTS, but their responses are more effective.

The anti-HIV immune activity of infected individuals is mediated by the innate or natural immune system and the adaptive or acquired immune system. Up until recently, the adaptive immune system was given most of the attention by the HIV scientific community. The role of the innate immune system, however, has now received a greater appreciation. ***Cells of the innate immune system include NK cells, NKT cells, plasmacytoid dendritic cells (PDC), and γδ T-cells.*** Circulating soluble factors are part of this system and include complement and mannose-binding lectin that can attach to HIV directly and inactivate it. The B- and T-lymphocytes are the most active components of the adaptive immunity. ***In both the innate and adaptive immune systems, dendritic cells and macrophages, as antigen-presenting cells, can play an important role.*** In a comparison of both immune systems, a key difference is that the innate immune system has a rapid immune response (from minutes to days), whereas the adaptive immune system takes days to weeks. Innate immunity does not need to be antigen-specific, but responds more to conformational structures. It can therefore interact quickly against viruses and bacteria as pathogens without recognizing a specific component of a virus or bacterium. The adaptive immune system is much more antigen-specific. Both immune systems have been conserved through evolution. Evidence suggests that the adaptive immune system evolved from the innate immune system, probably about 450 million years ago, when the shark developed a mandible. At that time, a transposon appears to have entered a primitive immunocyte and established the process of gene

re-arrangement, leading to the variations in T-cell receptors and B-cell antibodies.

In brief, when the innate immune system encounters a pathogen, it rapidly secretes cytokines that can have direct anti-microbial activities (e.g., interferons) or play a role in increasing both NK (an innate immune cell) and adaptive T-cell responses. The latter activity involves increasing MHC expression and enhancing T-lymphocyte functions. [77, Rank 5]

Understanding patterns of HIV Transmission

Autologous neutralizing antibodies are usually detectable only after the first few months of HIV-1 infection. Nonetheless, there is evidence that antibody-based selection sometimes exerts selective effects soon after transmission and before the neutralizing antibodies was detectable by pseudovirus-based assays. The selective pressure of antibody persists for years in the chronic phase of HIV-1 infection. Escape and production of new antibodies, from which the virus escapes again, occurs in iterative cycles. These cycles are also observed in experimental macaque models of HIV-1 infection.

Evidence from B cell depleted macaques suggests that the constant antibody pressure gives some protection to the host, including reduced viral load and protection from disease progression. A third study showed no protection; however, the sham-depleted controls did not develop detectable neutralizing response against the challenge virus or these responses were severely delayed. In all cases, interpretation was complicated by the fact that complete depletions seem to be rarely achieved in macaques. In any event, it seems clear that any protective effect of antibody is dwarfed by a substantial protective effect of CD8+ T cell responses. Depletion of B cells in African green monkeys had no effect upon drops in CD4+T cells or (generally rare) progression to disease. However, even CD8+ T cell depletion has little effect, despite overwhelming evidence for their importance in human HIV-1 infection. This, along with the rarity of progression to disease and different dynamics of infection in SIV-infected African green monkeys calls into question to what extent they are a useful model for HIV-1 infection in humans. Interestingly, in human HIV-1 infection, B cell depletion of an individual resulted in the temporary appearance of a neutralization-sensitive variant associated with a higher viral load set point, suggesting a role for antibody in protection of humans.

Nonetheless, it is clear that presumably higher antibody pressure from more broadly neutralizing antibody responses

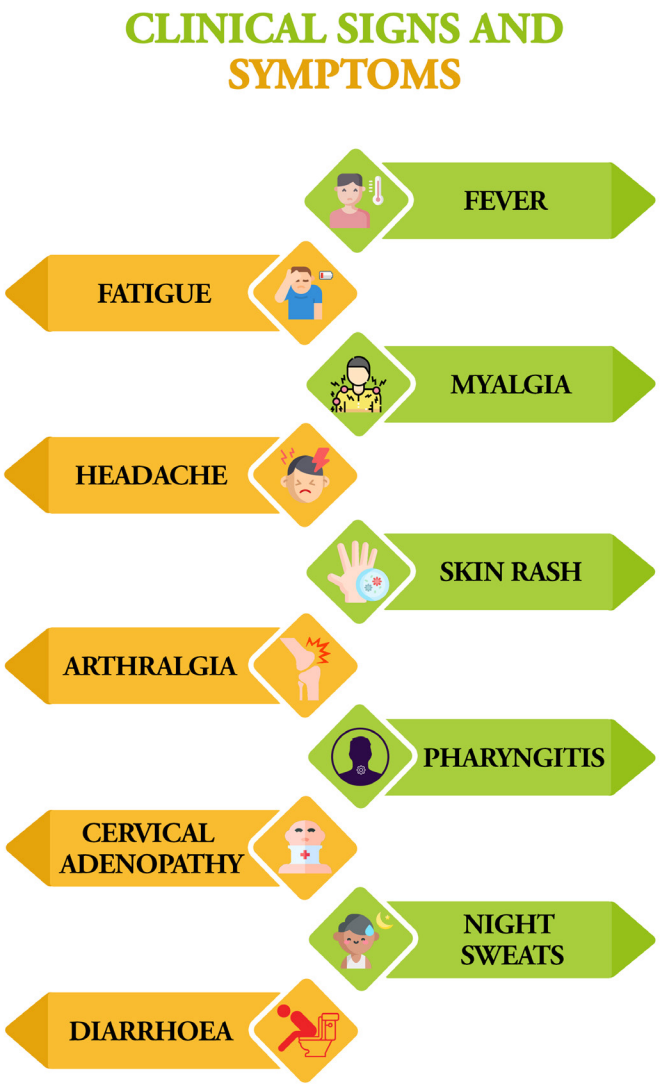


Figure 10: Signs and symptoms of acute HIV infection

does not result in protection from HIV-1 disease. Time to disease progression was no longer in individuals with more broadly neutralizing antibody responses. Clearly, the levels and breadth of neutralizing antibodies achieved in human populations was not sufficient to force selection of HIV-1 variants that were less fit or otherwise less able to induce disease. There is some evidence that such breadth and potency is experimentally achievable, although presumably higher than normally achieved during natural infection.

Population at Risk for HIV/AIDS

As a result of the ethical and logistical challenges often faced by researchers working with incarcerated populations, the majority of scientific investigations into HIV/AIDS-related transmission and pathogenesis risks among prisoners have been cross-sectional serosurveys of infection with HIV or related conditions, including tuberculosis often anonymized and rarely longitudinal (i.e., before, during and after incarceration) or linked to external data sources. These surveys have consistently identified elevated prevalence of infection compared to non-incarcerated populations. Meanwhile, ***observational studies conducted in non-correctional settings among groups at higher risk of infection with HIV, including injection drug users, sex workers, and members of sexual/gender minorities, have commonly associated incarceration with elevated risk of HIV infection in both crude and adjusted analyses.***

Recent analyses of the prevalence of HIV and related infections in correctional populations have confirmed this pattern. Among 2323 individuals entering, residing in or exiting the facility during the study

period, 27.4% were living with HIV/AIDS, approximately twice the national level, and the prevalence of bacteriologically-confirmed TB, at 3900 per 100,000, was 4.5 times the national average. The first published survey of HIV and TB in an African prison, the results suggest important linkages between HIV and TB infection in the prison and, through prison workers, prisoners and ex-prisoners, the local community. Similarly, a representative nationwide survey of 402 soon-to-be-released prisoners found high seroprevalences of both infectious disease, including HIV (19%) and untreated substance use disorders, with over half screened positive for alcohol use disorders and over one-third reporting use of opioids in the 30 days prior to arrest.

Many studies among injection drug users in varied settings have identified a heightened risk of HIV infection associated with incarceration, possibly a result of higher rates of used syringe sharing within correctional facilities. A number of recent studies explored the effect of incarceration on sexual risk among African-Americans, who have not only borne among the heaviest burden of the HIV/AIDS epidemic in the United States, but make up approximately 40% of those currently incarcerated in the United States. Among 1553 black men who have sex with men in six US cities, 60% reported a lifetime history of incarceration.

Certain behaviours and conditions put individuals at greater risk of contracting HIV include (as shown in Figure 11) [97, Rank 5]

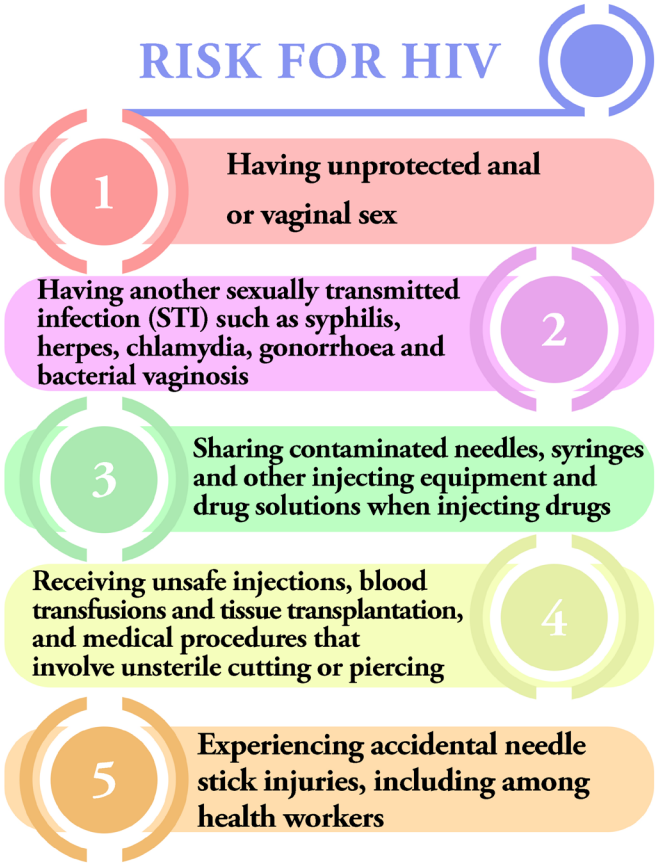


Figure 11: Population at risk for HIV

Screening for HIV/AIDS

Voluntary counseling and testing (VCT) for HIV infections have long been recognized as an important component of HIV prevention and treatment programmes. High levels of testing are prioritized in order to seek out undiagnosed individuals and link them to care. Since ***large proportions of HIV-positive individuals are unaware of their status, even in developed settings with advanced***

HIV/AIDS treatment and care systems where HIV tests are mandated to be a regular part of medical care, there is a clear need to increase testing rates, especially among populations with a high prevalence of HIV infection, such as incarcerated individuals.

Due to the special conditions imposed by incarceration, in particular that they are coercive environments that constrain the freedom and privacy of individuals, there have long been concerns around the legal and ethical implications of HIV testing within penal settings. As ***respect for patient autonomy, confidentiality and voluntary consent are fundamental aspects of healthcare and human rights,*** many national and international organizations oppose mandatory or compulsory testing of individuals in correctional settings, including the World Health Organization and UNAIDS. ***In many correctional systems, early policies of compulsory HIV testing among all prisoners have been abandoned following legal challenges, the cost of providing HIV/AIDS care, and the finding that they were ineffective.*** However, mandatory or compulsory testing continues in many state prison systems in the United States, Russia and some countries in Asia and the Pacific.

In the United States, despite the wide variety of correctional settings and laws governing their operation, the United States Centers for Disease Control and Prevention recommends universal voluntary opt-out HIV testing for all adults in health-care settings, including correctional systems, unless prevalence of undiagnosed infection has been documented to be less than 0.1%. Unfortunately, ***data on HIV testing within correctional systems globally is unavailable, and the distribution of different testing regimes — including mandatory, opt-in, opt-out, testing on demand, and none at all — is not known.*** Further, only limited data exists on the actual practice of HIV testing within correctional settings, almost all from federal, state and local prison systems in the United States.

New findings from a multi-centre observational study conducted in jails in the United States offered some evidence of the possible results of jail-based voluntary testing and linkage to care initiatives. Based on the recognition that 9 million individuals are admitted to a jail each year in the United States, the initiative collected client and program-level data on patterns of HIV testing and linkage to care at 20 jails in 10 communities. For HIV testing, the initiative's objective was to demonstrate its feasibility within jail settings and identify new and previously-detected infections. From 2007 to 2011, more than 877,000 admissions to the twenty institutions resulted in 212,464 (24.2%) individuals accepting an

HIV test. . In total, 822 newly-diagnosed individuals were detected. In a study of a subset of these HIV-positive individuals, newly-diagnosed individuals were younger (34 years versus 41 years), exhibited far higher levels of HIV risk behaviours and were much less likely to report possessing healthcare benefits than previously-diagnosed individuals. Newly-diagnosed individuals had a median CD4+ cell count of 432 cell/ml and less than one-quarter initiated ART prior to release from custody.

These findings add to evidence that jail-based opt-in or opt-out screening can identify previously-undiagnosed individuals, often earlier in their disease course. For example, an evaluation of a programme of rapid HIV testing in three urban jails in settings with high HIV prevalence, reported that of more than 129,000 admissions over the study period, 41,612 (32%) completed voluntary rapid testing, resulting in 142 newly-identified infections.

Most notably, a study using blood sera collected during a compulsory screening programme for syphilis infection at intake into the state prison system in North Carolina found that the HIV prevalence among incarcerated individuals was approximately 1.45%. However, only 20 of 22,134 tests, or 0.09%, were HIV positive and previously undiagnosed, although the authors reported they did not have access to each individual's entire testing history. Thus, although voluntary HIV testing may be feasible even in busy correctional environments with high rates of inmate turnover, and detection of HIV among previously undiagnosed individuals is of obvious medical benefit to them, this evidence suggests expansion of jail- and prison-based HIV testing might not substantially reduce the number of individuals unaware of being HIV-positive. [4, Rank 4]

Recommendations for HIV Screening

While HIV awareness is improving, many communities and individuals still face barriers to HIV testing and viral load suppression. A systematic review studied a complex intervention with its critical components designed to improve

Rapid voluntary counselling and testing (VCT) was studied in health facility and community based interventions and in diverse settings where there is a high risk for HIV exposure; such as bathhouses, STD clinics, inner city ED, tuberculosis (TB) programmes and antenatal programmes in endemic regions.

Until recently, some organisations have argued that HIV testing should continue using the conventional clinic or hospital testing approach. This is changing

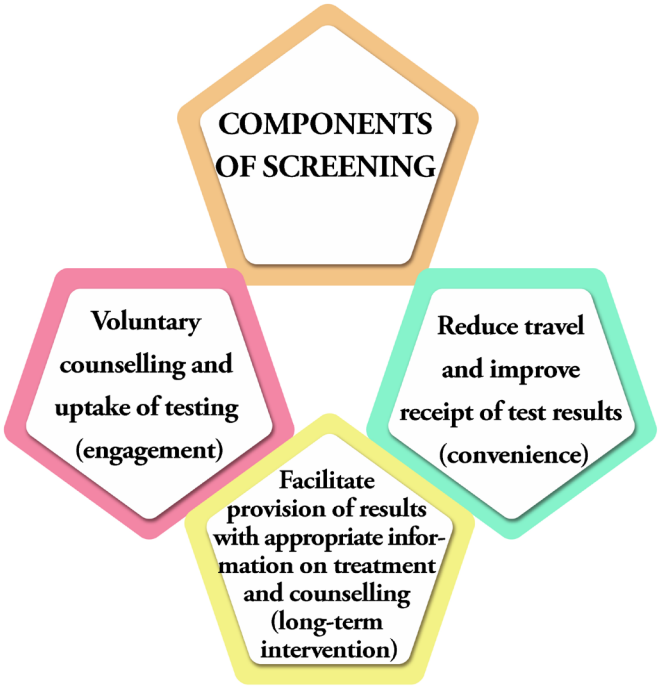


Figure 12: Components of HIV screening

and findings clearly suggest high-risk populations benefit from rapid Viral entered Therapy compared with conventional testing, especially in terms of uptake and receipt of results. Community based counselling and testing, which also uses a facilitated rapid approach with community engagement, has received considerable WHO and research attention.

Evidence from a study showed consistency of effect across settings, evidence for improved uptake in men, no uptake difference with low education status. These findings were corroborated by the evidence from prospective observational studies. The results from study are applicable across a variety of settings; for example, among at-risk youth, women and hard to reach men, repeat testing rates were comparable with those found in facilitated testing in high-risk men who have sex with men population in the USA. Men used rapid-testing approaches but that this usage was slightly less than women. This is an important finding because men are usually harder to reach for HIV testing and treatment programmes.

Rapid Viral entered Therapy has emerged as a complex intervention that can be used in community settings and health facilities in low-income and high-income countries. Previous systematic reviews have not included rapid voluntary counselling and testing studies conducted in health facilities, thus leaving rapid Viral entered Therapy approach primarily directed at Community based5 initiatives; for example, the WHO HIV guidelines highlights community-based voluntary counselling and testing sites, but not rapid voluntary counselling and testing for health facilities.

The study highlights the importance of three key components within a counselling and testing strategy. Complex interventions include components with varying degrees of interaction. ***Researchers suggest ongoing research is needed to improve HIV testing and viral load suppression: and this should include recognition of interacting components within the intervention, the number and difficulty of***

behaviours required by those delivering or receiving the intervention, the number of organisational levels targeted by the intervention, the number and variability of outcomes, and the degree of flexibility or tailoring of the intervention [10, Rank 3]

Policies and Practice for Screeening

HIV testing is an important step of the HIV care continuum and a critical component of prevention programs throughout the United States (US). Nationally, an estimated 18% of infected persons remain undiagnosed. ***Awareness of HIV infection decreases risk-taking behaviors, with earlier initiation of care resulting in decreased HIV-associated morbidity and mortality.*** In 2006, the US Centers for Disease Control and Prevention (CDC) released revised recommendations for routine, opt-out HIV screening in healthcare settings. Specifically, the revised recommendations include screening patients for HIV using an opt-out approach, the elimination of a separate written consent for HIV testing, and optional pre-testing prevention counselling.

Research has shown the benefit of rapid voluntary counselling and testing on uptake of HIV testing and receipt of results. This testing approach was effective in health facilities as well as community settings. Community based voluntary counselling and testing has received explicit attention in the recent WHO- HIV testing and treatment guidelines and WHO consolidated guidelines for key populations. This work supports Community based voluntary counselling and testing, but also finds that persons at high risk of exposure to HIV who use health facilities benefit from rapid voluntary counselling and testing. This finding is not yet reflected in the WHO Consolidated Guidelines for key populations.

Implementing rapid voluntary counselling and testing, with testing components tailored for high-risk communities, could improve health equity through earlier HIV diagnosis with possible retention in viral suppression programmes, reduced transmission and longer lifespans. In high-income countries, our results have particular importance for Aboriginal population, persons who inject drugs, prison populations, and certain migrant and minority populations. Additionally, routine use of rapid voluntary counselling and testing may avoid human rights violations among marginalised populations where testing may occur without informed consent and were existing stigma may create barriers to testing and treatment. Given the significant heterogeneity

in the trials, we suggest more research to study the components of the rapid voluntary counselling and testing and identify what works, for whom and in what settings. [15, Rank 5]

Importance of Consent to HIV Testing

While several jurisdictions reported a high level of provider education on HIV testing, many organizations in both cities reported opt-in consent approaches and pre-test counseling, suggesting the 2006 CDC recommendations are not being followed consistently.

The cause of inconsistency merits further research since statutes do not pose a substantial barrier in either jurisdiction. Previous implementation research has shown that this inconsistency may be due to

1) A lack of awareness or misunderstanding of the recommendations,

2) Disagreement with the recommendations, and/or

3) Organizational barriers that impede application of the recommendations.

Both cities may benefit from further research into why organizations continue to use both pre- and post-test counseling and do not use opt-out testing.

The two jurisdictions have taken different approaches to support and fund the expansion of routine testing. Approach has involved considerable funding for the distribution of free rapid test kits to local implementation sites including clinics, hospitals and community centres. This is in contrast to the approach which has encouraged performing venipuncture tests as part of routine visits and funding large volumes of HIV testing in hospitals and clinics with rapid results of standard testing. This divergence of approaches is reflected in the greater total number of rapid tests being utilized in disease control and much greater total number of venipuncture tests being performed in Houston.

Funding sources for testing also varied between the two jurisdictions which could have implications for the long term sustainability and scalability of these testing programs. Houston testing organizations reported much more third party billing and reimbursement from Medicaid, Medicare, and private insurance as a primary means to support their testing programs. Because of this, Houston organizations may be better positioned to more quickly adapt and benefit from expanded coverage through the Affordable Care Act (ACA), especially now that routine testing is rated a recommended service for coverage by the US Public Health Services Task Force (USPHSTF). However, this strong reliance on third party

reimbursement does leave these organizations more vulnerable to reimbursement challenges and inadequate reimbursement rates that may not cover the total cost of testing provision. The monitoring of HIV testing post-ACA and US Public Health Services Task Force implementation will allow for further exploration of the impact of these policies on testing programs.

Overall, few barriers to testing implementation were reported by organizations in both jurisdictions however, among those reported, lack of funding and organizational capacity to conduct testing were key barriers. Capacity barriers, such as staff size and time were moderate barriers for the surveyed organizations and may have been related to lack of funding to support these efforts at the organizational level, particularly among organizations in disease control. Although multiple methods of routine HIV testing have been promoted in DC, there is more reliance on rapid testing, which can be more time and labor-intensive than venipuncture testing. Time-related barriers and competing priorities have been extensively reported in literature, but research has found that providers cite consent and counseling requirements as time-intensive even when statutes have removed these barriers in a jurisdiction.

Interestingly, despite the generalized epidemic and high HIV prevalence, a commonly reported barrier included the perception that HIV was not a problem among the patient population. This perception may depend on the age of the population being served as a previous survey found that almost 40% of providers did not perceive HIV to be a problem among those 50 years of age and older.Patient discomfort or refusal for testing was a barrier in both cities and has been reported by providers elsewhere with clients often refusing due to low-perceived risk for HIV, recent testing elsewhere, fear of loss, fatalism, confidentiality concerns, and structural barriers.

In 2010, New York State enacted a statute requiring primary care settings to offer HIV testing to all patients between the ages of 13 to 64. Since this law was enacted, one study found that only 65% of emergency departments implemented HIV testing as required by the law. While changes to policy guidance at the jurisdictional level may increase testing, law alone is not the solution. ***Further increases in testing uptake may be realized with policy change and implementation at the organizational level, especially in jurisdictions with low uptake. Organizational leadership to drive local policy formulation, revision, and implementation is critical. Other facilitators include organizational buy-in from both providers and administration, written procedures for HIV***

testing, provider trainings, and dedicated staff and funding.

The self-reported responses were limited to the organizational knowledge, perceptions and/or experiences of the person completing the survey, thus the responses may not accurately reflect the practices or opinions of all providers or staff members. The differing routes of survey administration may have also led to variances in social desirability or comprehension of the survey questions. In addition, social desirability may have biased the results, especially in reporting of testing barriers. Furthermore, ability to statistically analyse barrier data was limited as many of the barriers received low rankings. Finally, generalizability of these findings may be limited, particularly in jurisdictions that have statutes in conflict with the 2006 CDC recommendations. Results presented herein may be useful to such jurisdictions after their statutes transition.

The range of approaches was appropriate given the distinct context of the epidemic in each jurisdiction. Reported implementation practices, such as types of tests used and the funding mechanisms most often used to pay for HIV testing, highlight this variation. Regardless of different implementation approaches, results suggest many organizations in at least two high burden jurisdictions have not aligned with all aspects of national testing recommendations.

Research has shown that neither awareness of CDC guidelines nor jurisdictional policy change alone fully scales up testing to the levels recommended in the 2006 guidelines. It is likely that a multi-faceted approach is needed that includes awareness campaigns, policy change, and reduction of jurisdictional and organizational-specific barriers. Few multi-faceted approaches have been rigorously evaluated to determine if they can widely span multiple jurisdictions with diverse epidemics, policy, and resources. Further implementation research and dissemination of implementation research findings is critical to the expansion of routine HIV testing and early diagnosis of HIV infection. [22, Rank 4]

Diagnostic Evaluation of HIV

Diagnosis could be affected by certain pathophysiological factors and development of antibodies. (as shown in Figure 13)

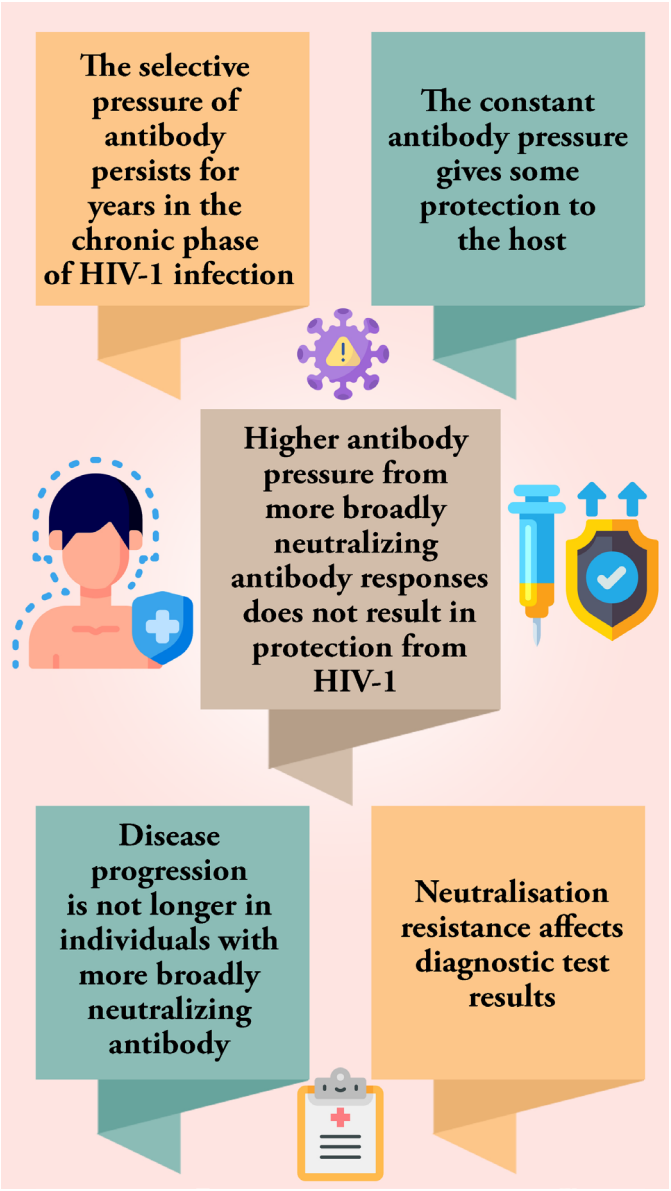


Figure 13: Physiological factors affecting Diagnosis of HIV

Serological Tests

Several types of serological assays have recently been developed and new bio-markers continue to be found. These assays can differentiate between recently acquired and long-term infections based on certain markers (as shown in Figure 14)

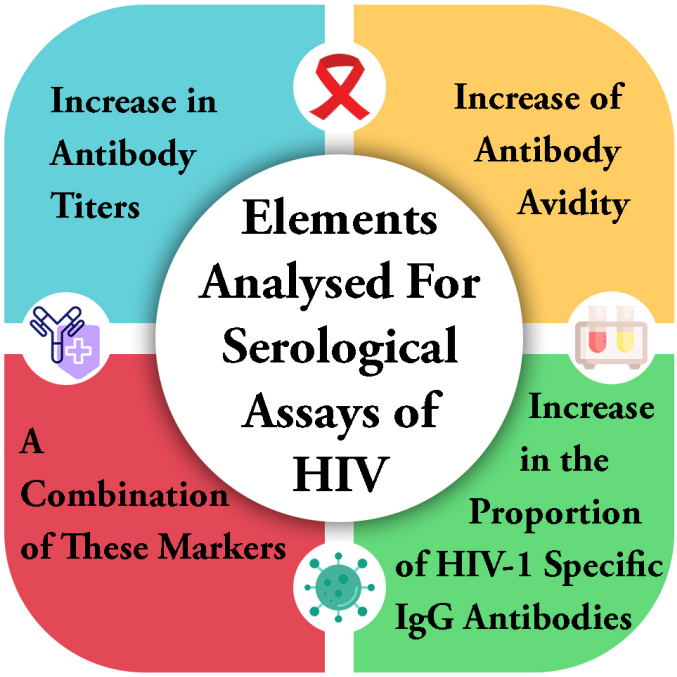


Figure 14: Elements analysed in Serological tests for HIV

Infected individuals are classified as either recently or long-term infected if they fall above or below a well-defined threshold. Serological assays have been reviewed extensively. [10, Rank 5]

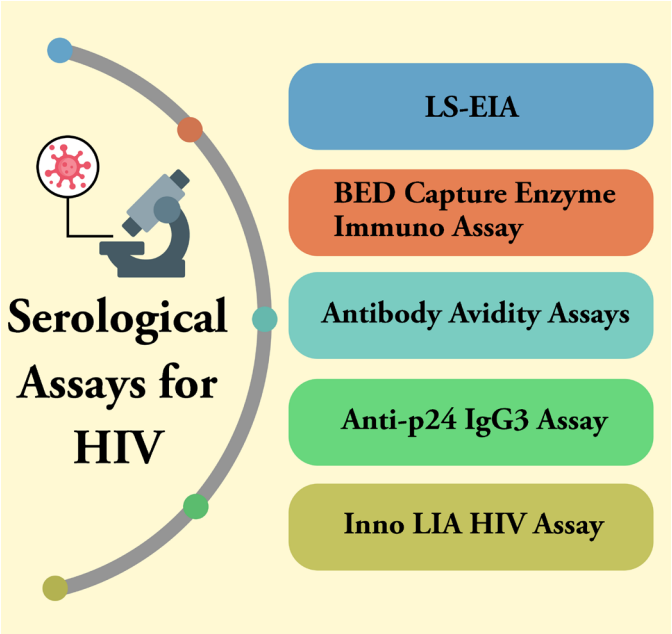


Figure 15: Serological assays for HIV

LS-EIA (Less Sensitive Enzyme Immunoassays)

The Less Sensitive Enzyme Immuno-assays ***(LS-EIA), also known as the detuned assay,*** was one of the first serological assays to identify HIV infection recency. ***This assay is based on the gradual increase in HIV-1 antibodies over time after sero-conversion.*** The underlying assumption is that recently infected individuals will have lower levels of HIV-1 antibodies compared to those with established infections. In this approach, specimens are serially tested with an enzyme immune-assay (EIA) that is diluted. A recent infection is identified when a specimen tests positive with a less diluted EIA but negative with a less sensitive enzyme immune-assay.

Commercial assays include the Abbott HAVAB (3A11 ELISA) and Avioq HIV-1 microelisa. The 3A11 ELISA is no longer available commercially. These assays have been produced with antigens from subtype B, which is the most common HIV strain circulating in the USA and Europe. A number of studies have tried to evaluate these assays in the field with non-subtype B viruses. However, non-B subtypes produced antibodies with reduced binding affinities, leading to an increase in the false-recency rate. The LS-EIA assays are a potentially cost-effective and quick method to implement. However, they have to be adapted to different subtypes and evaluated on a larger scale across various geographical regions.

BED Assay

Another frequently used serological assay is the BED capture enzyme immuno-assay. The ***BED assay estimates the proportion of HIV-1 specific IgG to the total IgG.*** Recent HIV infection is identified when the HIV specific IgG is lower than the total IgG. The assay uses peptides from immunodominant regions of gp41 glycoprotein of three different HIV-1 strains (as shown in Figure 16). CRF is Circulating recombinant forms.

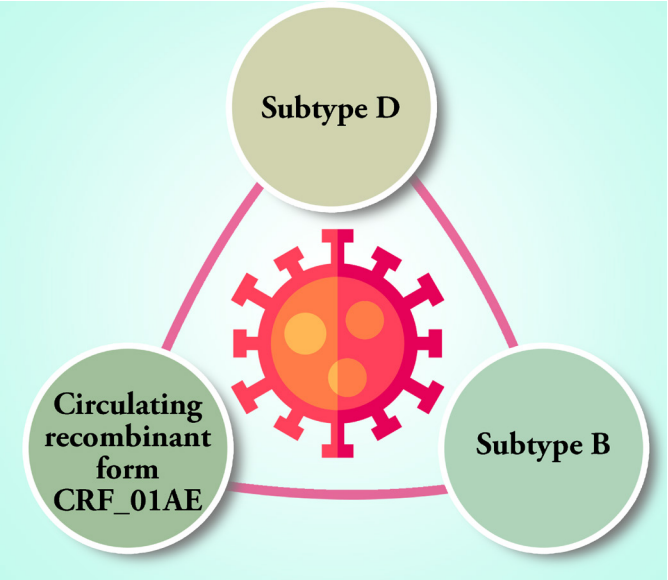


Figure 16: HIV strains for BED Assay

The use of three different strains allows the detection of recently infected individuals with different HIV-1 subtypes.

False-recent HIV infections are more likely to be identified in chronically infected individuals (i.e., individuals in the late stage of HIV infection, elite controllers or individuals on ART). The performance of the BED assay can be improved by adding covariate information from clinical data or by adjusting for the false-recency rate. Its accuracy has also been found to vary by geography and HIV-1 subtypes. [12, Rank 2]

Antibody Avidity Assays

Another approach for identifying recent HIV infections ***is to investigate the quality of the antibody response. This can be done by measuring its avidity or strength of antibody-antigen binding. The Limiting Avidity assay (LAg) was the first assay to become commercially available to measure avidity.*** LAg measures the antibody binding to low concentrations of a multi-subtype peptides derived from an immunodominant region of gp41. In this assay, specimens are incubated with and without a chaotropic agent that disrupts antibody-antigen interactions. Antibodies normally become resistant to disruption over the course of the HIV infection. Those with low ratio avidity are indicative of recent HIV infection.

Avidity assays are normally more sensitive than the BED or detuned assays.

> **"The largest number of HIV infections has occurred with group M HIV-1 strains, which can be further subdivided into 9 subtypes or clades differing by at least 15%. Clade B is the most common virus in the United States. It is also found in China, but has emerged as well as a recombinant between clades B and C viruses"**

Nevertheless, some studies have shown that this assay can be affected by other pathogens, such as Mycobacterium Tuberculosis(TB). In addition, the assay misclassifies samples from individuals on antiretroviral therapy with low viral load, and in people infected with HIV-1 subtypes D.

Anti-p24 IgG3

IgG3 is one of the second predominant subclasses in the antibody response towards HIV. ***IgG3 isotypes to p24 antigen are present in early infection and then decline.*** This makes IgG3 an attractive biomarker for the identification of recent HIV infections, since high IgG3 levels are associated with a high HIV-1 viral load. ***The HIV-1 Bio-Plex assay is one method that specifically measures the p24-specific IgG3 responses.*** Although IgG3 has been observed to decline over time, about

one-third of individuals exhibit relatively high IgG3 levels in the late stage of HIV-1 infection. [15, Rank 5]

Inno LIA HIV Assay

The Inno-LIA HIV-1/2 assay measures the increase in antibody-antigen reactivity following the seroconversion event. The assay was first designed for the confirmation of an HIV diagnosis, and is similar to a western blot test. The emergence of antibodies to various HIV-1 proteins at different time points after seroconversion is used to characterise the recency of infection. ***The Inno-LIA assay detects antibodies to recombinant peptides of HIV-1 (p17, p24, p31, gp41 and gp120) and HIV-2 (gp36 and gp105).*** The intensity of the antibody-antigen bands is scored and used to determine the recency of infection.

The Inno-LIA assay is advantageous because it can be used to confirm both an HIV diagnoses and a recent HIV infection. This assay can therefore significantly reduce costs. However, it can only detect a recent HIV infection within 36 to 67 days of the seroconversion date. The assay has not been evaluated in elite controllers, individuals receiving antiretroviral therapy and in individuals with a late stage of disease or AIDS

Molecular Tests for Recent HIV Infection

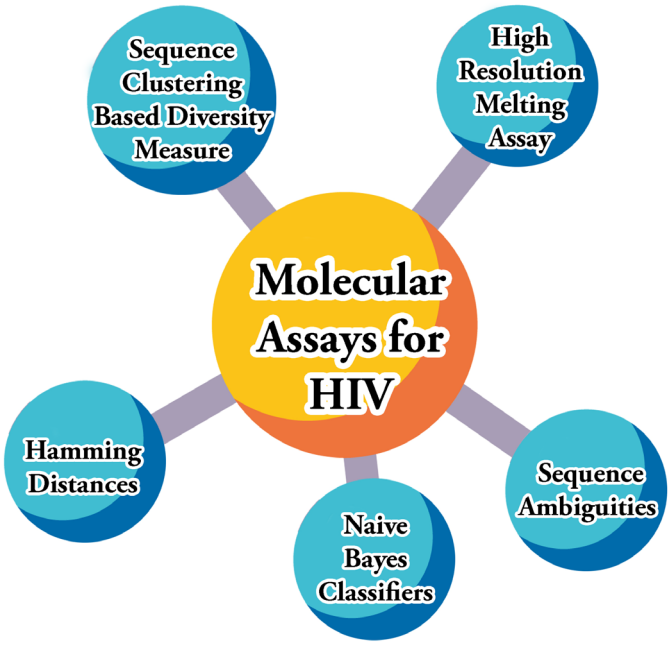


Figure 17: Molecular tests for HIV

Most HIV infections are caused by a single transmission (i.e., founder) virus, which results in an initial homogenous viral population that will diversify over time. Upon transmission, the virus is able to diversify rapidly within the host due to immune response and the fact that HIV-1 Reverse Transcriptase enzyme is error prone. Virus genetic diversity increases in an approximately linear fashion for several years after infection, reaches a plateau, and declines in the late stage of infection. Virus diversification in early HIV infection provides a strong rationale for identifying recent HIV infection. Some methods, such as the high resolution melting assay

(HMA), are able to estimate HIV recency without the use of a viral genotype. However, the majority of molecular methods utilize viral sequences. Molecular methods that use sequences were developed for population and single-genome or clonal sequencing.

High Resolution Melting Assay

The high resolution-melting (HMA) assay is one of the simplest molecular methods. The assay uses the melting temperature of the DNA duplexes from amplicons. Multiple regions across the HIV-1 genome including gag, pol and env can be used without the need to sequence them. HMA provides a single numeric score that reflects the level of diversity in the amplified region, which increases linearly over the course of the HIV infection. There is concordance between the a High Resolution Melting Assay score and viral diversity. This was obtained by next generation sequencing (NGS) and Shannon entropy analysis.

This assay is a relatively inexpensive technology that can be implemented in resource-limited settings that do not have access to sequencing infrastructure. For example, High Resolution Melting Assay has been successfully used in clinical trials. However, it has been shown to have limitations. For example, the ***assay is sensitive to insertions and deletions, which are common features of the HIV genome.*** Another limitation is its inability to distinguish between infections caused by single and multiple HIV strains. ***This assay can be adapted to many HIV strains*** and could complement serological assays in resource-limited settings.

Sequence Ambiguities as a Marker of Recent HIV Infection

This approach is based on counting ambiguous nucleotide positions produced during population Sanger sequencing. Multiple nucleotides at the same position indicate that polymerised chain reaction amplification was performed from multiple templates and that the patient harbors heterogeneous viruses. The number of ambiguous positions increases as the viral population diversity grows over time. For example, a linear increase in viral diversity within HIV-1 pol is associated with an increase of 0.2% ambiguous nucleotides per year. A significant difference in the frequency of ambiguous sites has been observed among individuals with recent and established HIV infections in both HIV-1 subtype B and non-subtype B infections.

A number of different threshold values for the ambiguity index have been suggested. A threshold of 0.47% performed

the best in discriminating recent (≤1 year) from established HIV infections. In that manuscript, the threshold of 0.47% returned a sensitivity of 74.5% and specificity of 87.2%. Researchers compared BED classification (≤6 months) with the ambiguity index using a threshold of 0.45%, which provided a sensitivity and specificity of 82.7% and 78.8%, respectively. They also found that varying the base-calling thresholds had little effect on the sensitivity and specificity. However, the two previously mentioned studies used different base calling strategies, PCR and sequencing methodologies, which makes it difficult to compare their results. One further limitation is that the BED assay was used as the gold standard to identify recent HIV infections. This assay has been shown to have a high false-recency rate.

A limitation of this method is that it normally underestimates the number of ambiguous positions during Sanger sequencing. Another limitation is the non-homogenous selective pressure of the immune system on HIV genetic regions, which makes it difficult to choose one unique threshold. Other limitations include the unknown impact of ART, the effect of low HIV-1 RNA in viremic/elite controllers and the reduced number of ambiguous positions in the late stage of HIV infection. Lastly, HIV infection with multiple viruses can attenuate accuracy.

Naive Bayes Classifiers

The naive Bayes classifier is based on the observation that viral diversity increases in an approximately linear fashion over the course of HIV infection. This method makes use of available clinical markers such as CD4+ cell counts over the course of HIV infection and any concurrent AIDS associated diagnosis. Individuals are classified into one of four different stages of HIV infection. The first stage limits HIV infection to within one year, with two intermediate stages that include chronically infected individuals, and a fourth stage which corresponds to AIDS (as defined by a CD4+ < 200 copies/mL). ***A standard Bayesian model can be fitted to estimate the probability of an individual being in one of the four stages conditional on the frequency of ambiguous sites in the HIV-1 pol gene, the CD4+ cell count and a concurrent AIDS diagnosis.*** The naïve Bayes classifier was designed to have a high positive predictive value for identifying true recent HIV infections.

This method was successfully used to estimate the proportion of individuals at different stages of HIV infection in a large sequence cohort of HIV-1 subtype B infected men who have sex with men in the Detroit metropolitan area. The study utilized HIV-1 sequences available through a

routine drug resistance-screening program coupled with available clinical data to estimate prevalence, incidence and timing of HIV transmission. The authors found that individuals were eight times as infectious during the first year of HIV infection as compared with individuals who had established infections. They also found that 42% to 46% of the HIV transmissions came from individuals who were recently infected. This method has a great potential to understand how HIV recent infection can drive different HIV epidemics. However, it needs to be applied and evaluated in different geographic regions and with different HIV-1 strains.

Hamming Distances

In relation to HIV diversity, HD can be used to measure the number of nucleotide differences between pairs of sequences. When applied to viral quasispecies, Hamming distance can be used to estimate the stage of HIV infection. The Hamming distance of recent HIV infections, caused by a single founder virus, does not overlap with the Hamming distance from established HIV infections. However, HDs of infections resulting from multiple founder viruses can overlap, resulting in a misclassification as an established infection.

Researchers devised a binary classification (recent vs. established infection) based on the tail characteristics of the Hamming distance distribution of HIV-1 env sequences. A Hamming distance value that divides the lower 10% (Q10) of the HD frequency distribution from the upper 90% was shown to be able to distinguish a recent from an established HIV infection. The Q10 statistic was lower in recent HIV infections compared to chronic infections, and was shown to distinguish whether infections originated from a single or multiple founder strains. The authors also demonstrated a high sensitivity (97%) and specificity (100%) when applying the Q10 statistic.

This approach has recently been applied to high throughput pyrosequencing data and has the potential to be cost-effective for routine surveillance. ***The test is yet to be validated in long-term non-progressors, rapid progressors and among ART-experienced patients.*** A further limitation is the potential impact of indels and recombination, particularly when using variable regions across the HIV-1 genome, such as env. The Hamming distance approach also does not take into account the nature of the evolutionary events. The assay relies on availability of viral quasispecies and might not be widely used in resource-limited settings without routine HIV genotyping infrastructure.

> "The Hamming distance (HD) is a number that denotes the difference between two binary strings of equal length, i.e., the number of positions at which the corresponding symbols are different"

Sequence Clustering Based Diversity Measure

A sequence clustering based measure (SCBD) of HIV diversity has been proposed. ***This method determines HIV infection recency by using two principles. (as shown in Figure 18) The first principle*** involves intra-patient clustering, which is defined as the closeness of viral quasispecies within an individual's sample. An increase in intra-patient HIV diversity is correlated with the time since infection. The second principle uses inter-patient HIV diversity, which is a measure of the presence of multiple founder viruses within an individual.

The algorithm of the Sequence Clustering Based Diversity Measure method first classifies an infection as recent if there is a low intra-patient diversity. If there is high inter-patient diversity, then the SCBD method will classify the sample as originating from a long-term infected individual. The purpose of the method is to reduce the misclassification of recent infections by using the inter-patient clustering measure.

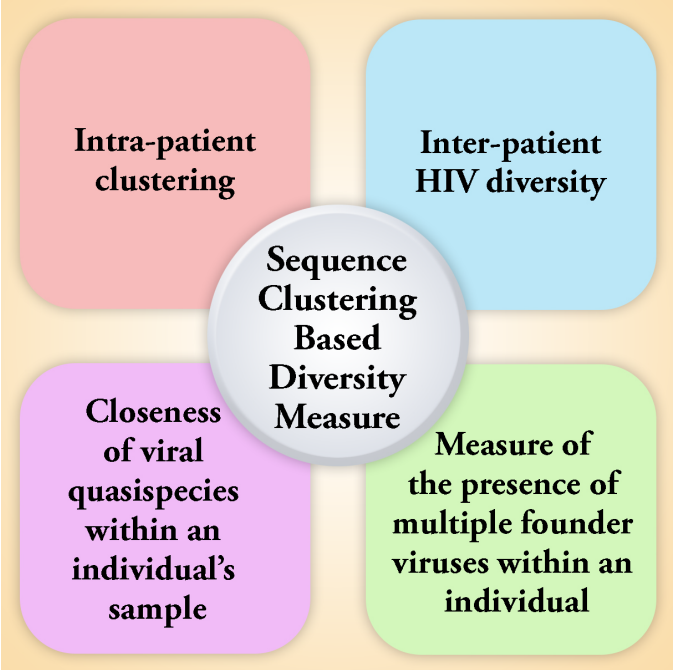


Figure 18: Principles of Sequence Clustering Based Diversity Measure

In order to minimize the impact of indels on calculated diversity, the authors used a pairwise dot matrix alignment, which accounts for the nature of evolutionary events when calculating pairwise diversity. Researchers proposed Sequence Clustering Based Diversity Measure cut-off of 1.0% based on the known evolutionary rate of the env gene. The assay was tested on a dataset containing 398 incident and 163 chronic infection cases. It achieved an overall accuracy of 99.3%, with a sensitivity and specificity of 99.5% and 98.8%, respectively. The method overcomes the limitations of using only intra-patient diversity, since these do not account for the impact of indels and recombination on calculated diversity measures. The application of this method could be limited as the generation

Prevention and Management of HIV

Prevention of sexual HIV transmission has been a priority since the beginning of the epidemic. To control the epidemic many interventions are necessary as no isolated prevention intervention is effective enough on its own.

The most potent intervention to reduce sexual transmission of HIV is Antiretroviral therapy. Findings of the landmark HIV Prevention Trials Network (HPTN) 052 trial, revealed that immediate ART treatment in serodiscordant couples reduced HIV transmission in the uninfected partner by 96% due to universal viral suppression. In a thorough analysis of the evolution of vertical versus horizontal transmission, researchers examined the consequences of different forms of the trade-off between vertical and horizontal transmission. They also showed that polymorphism in transmission mode was possible if the trade-off was convex but if the trade-off was concave, then mixed-mode transmission of one genotype was favoured. E.g. In a situation where increased horizontal transmission that increases mortality continues to decrease vertical transmission. Their model included competition among the symbionts for resources within the host, and this complicates the outcomes, depending on the interaction within the host.

A strong theoretical framework for the study of the evolution of vector transmission for prevention was developed in the context of epidemiological and genetic dynamics of two host systems. Using this framework, they identified the forces leading to a second host acting as an effective vector, and showed that there was a positive feedback between evolution of vector transmission and evolution of virulence. The evolution of transmission mode in relation to virulence is important from an applied perspective. Thus, if highly virulent strains can coexist with non-virulent ones, very serious health consequences of disease in a subset of the population may be due to virulent pathogen variants. This may be less desirable than the presence of only one strain of intermediate virulence. Researchers investigated this in diseases that had both environmental and direct host-to-host transmission, the worry being that environmentally transmitted genotypes might show higher virulence, as their persistence would be less compromised by a shortened host lifespan.

It should be noted that most studies have assumed that ***transmission is under 'pathogen control',*** that it is genetic variation in thepathogen rather than in the host that is driving the evolution of transmission mode, even though the frameworks for

doing otherwise are well established in theory. It remains to be seen whether more complex 'transmission-genetics' makes other coevolutionary scenarios possible, in a way analogous to what is seen with genetics of resistance and infectivity.

Different strategies for human immunodeficiency virus (HIV) prevention including earlier HIV diagnosis and the use of antiretroviral therapy (ART) to prevent transmission of HIV (treatment as prevention [TasP] and pre- and post-exposure prophylaxis [PrEP and PEP]) are of considerable interest. The Joint United Nations Programme on HIV and AIDS (UNAIDS) declaration on HIV and AIDS in 2011 confirms that HIV prevention must remain the cornerstone of the HIV response.

PEP (Post Exposure Prophylaxis) is the use of short-term ART to reduce the risk of acquisition of HIV infection following exposure. It is widely available following occupational exposure to HIV and has become increasingly available for nonoccupational exposure to HIV.

Prevention interventions that can significantly decrease risk of viral infection include are as follows. (as shown in Figure 19)

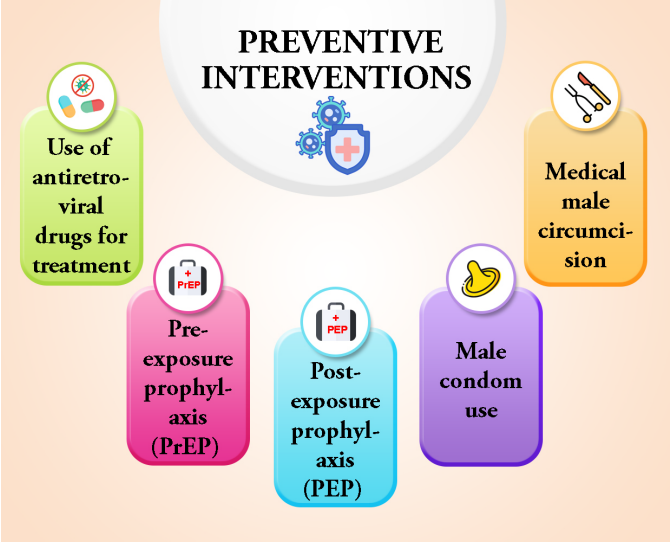


Figure 19: Preventive interventions of HIV

The number of people with newly acquired HIV infection continues to rise, with 2.3 million new infections worldwide in 2012. There is a resurgence of the HIV epidemic among men who have sex with men (MSM) in North America and Western Europe. Between 2000 and 2006 there was an 86% rise in the annual number of new HIV diagnoses in this risk group. It is essential for HIV prevention efforts to maintain their intensity and that novel ways of preventing HIV infection are incorporated into existing strategies in order to reduce the incidence of HIV infection. [48, Rank 5]

Post Exposure Prophylaxis (PEP)

It may take up to 72 hours for HIV to be detected in regional lymph nodes, up to 5 days to be detected in blood, and about 8 days to be detected in the cerebrospinal fluid. This offers a window of opportunity

> "A recent macaque study of intermittent Pre-exposure prophylaxis and Post-Exposure Prophylaxis with oral combined tenofovir and emtricitabine following rectal inocula demonstrated that a post-exposure dose was essential to prevent infection."

to prevent acquisition of HIV infection following exposure by inhibiting viral replication or preventing dissemination of infection, if ART is started early.

Evidence for PEP

Much of the data for PEP efficacy comes from animal models. Data from retrospective analyses of PEP for occupational exposure as well as vertical (mother-to-child) transmission studies add to the evidence base for HIV PEP. Based on this data, PEPSE (Post-Exposure Prophylaxis following Sexual Exposure) is likely to be effective.

Animal models

Most animal models have shown benefit of Post-Exposure Prophylaxis in terms of preventing HIV acquisition. However, comparisons between these studies are difficult as they use different retroviruses,inocula volumes, and modes of transmission. The greatest protection was achieved with the first Truvada dose between 22 hours and 7 days pre-exposure, with the second dose 2 hours post-exposure.

Other studies have shown that 28 days subcutaneous tenofovir administered to macaques after intravenous or intravaginal exposure prevented 100% of infections if given within 24 or 36 hours, respectively. The proportion of macaques infected increased with:

1) Longer intervals to tenofovir administration (no protection if administered 72 hours post-exposure); or

2) Decreased duration of treatment. One study showed no protection from triple PEP after intravenous inoculation which may have been due to the inoculum size or route of administration.

> "Recent evidence in pregnant women who had not received antiretroviral therapy suggests that dual or triple antiretroviral therapy for the neonate is more effective than monotherapy in preventing mother-to-child transmission."

Vertical transmission

Studies illustrating a reduction in vertical transmission of HIV with antiretroviral treatment of pregnant women also support the efficacy of Post Exposure Prophylaxis. In AIDS Clinical Trials Group (ACTG) 076, reduced incidence of HIV was observed in neonates given 6 weeks of zidovudine within 48 hours of delivery to women who had not received any antiretroviral therapy prior to delivery.

Occupational exposure to HIV

There are no prospective randomized controlled trials of Post Exposure Prophylaxis efficacy due to the ethics of withholding a potentially efficacious treatment and the difficulty in recruiting the high number of participants that would be required for such a study.

Much of the rationale for Post Exposure Prophylaxis use in humans is derived from a case-control study of health care workers occupationally exposed to HIV, which demonstrated that a 28-day course of zidovudine was protective. This study has limitations, including a small number of cases; also, cases and controls were derived from different countries and data on exposure characteristics were collected retrospectively. To date, there are at least 24 cases of PEP failure following occupational exposure, mostly after the use of zidovudine monotherapy.

PEPSE (Post-Exposure Prophylaxis following Sexual Exposure)

There is a paucity of data regarding the efficacy of PEPSE and no randomized controlled trials. An observational Post-Exposure Prophylaxis following Sexual Exposure study undertaken in Brazil among MSM (men having sex with men) provided with Post-Exposure Prophylaxis for use after a high-risk exposure demonstrated fewer HIV seroconversions among individuals taking PEPSE compared to those who did not; however, the study also found that people did not estimate their own risk well. When they took Post-Exposure Prophylaxis, it was effective but the overall HIV incidence remained unchanged compared with historical rates because they did not access Post-Exposure Prophylaxis after other high-risk episodes. A recent systematic review of PEPSE concluded that it was not possible to determine its effectiveness due to the lack of evidence, although it may be cost-effective in certain circumstances. [52, Rank 2]

> "Risk of HIV transmission = risk that source is HIV-positive × risk of exposure* (*including cofactors such as sexually transmitted infections (STIs), high viral load, and bleeding)."

Assessment of Risk of HIV Transmission

The decision to initiate Post Exposure Prophylaxis should be based upon a risk/benefit analysis weighing up the risk of an individual acquiring HIV and the potential for harm due to Post Exposure Prophylaxis. Risk of HIV transmission is greatest for blood transfusions, followed by vertical exposure, sexual exposures, and other parenteral exposures.

Sexual exposure accounts for the majority of HIV infections, with much variability in the risk of acquiring HIV depending on the specific sexual act. The risks from sexual exposure ranged from low for oral sex to 138 infections per 10,000 exposures for receptive anal intercourse. Unprotected receptive anal intercourse (UPRAI) and sharing needles have the highest risk of acquiring HIV per exposure. Insertive anal intercourse (IAI) and vaginal intercourse (receptive and insertive) and oral sex are described as having lower per-act risks.

FACTORS DETERMINING RISK FOR HIV INFECTION AFTER AN UNPROTECTED SEXUAL CONTACT

- Type of intercourse
- HIV status of individual
- High plasma viral load in the source
- Presence of sexually transmitting infections
- Breaches in the mucosal barrier
- Exposure to blood
- Ejaculation
- Circumscision

Figure 20: Factors predicting HIV infection

Anal intercourse

An Australian cohort study estimated that the per-contact probability of HIV transmission in men having sex with men through unprotected receptive anal intercourse was 1.43% with ejaculation and 0.65% without ejaculation. The risk through insertive anal intercourse was 0.62% in uncircumcised men and 0.11% in circumcised men. A meta-analysis demonstrated a per-act risk of unprotected

receptive anal intercourse of 1.4%, with no significant difference between heterosexuals and men having sex with men. They also showed that there was much variability in the risks of anal intercourse, and that it may increase the risk of transmission even when the partner is on antiretroviral therapy.

Vaginal intercourse

A European study estimated the risk of receptive vaginal intercourse to be 0.08%, and insertive vaginal intercourse to be 0.04%.This risk is reduced when the partner is on effective antiretroviral therapy. Caution should be used in using these estimates as heterosexual infectivity is variable and thought to be underestimated, and cofactors such as genital ulcer disease have a significant impact on transmission risks.

Oral intercourse

There has been some observational data that HIV can be transmitted through oral intercourse, but the risks are difficult to estimate, due to the likelihood of other concurrent sexual risk exposures, and are thought to be very low. ***A study estimated a per-act risk of receptive oral intercourse with ejaculation at 0.06% with an HIV-positive partner or partner of unknown status, with no increased risk with insertive oral intercourse.*** Where the HIV status of the source is unknown, it is important to consider the local HIV prevalence within the relevant risk groups. [56, Rank 3]

Vaginal intercourse

The HIV status of the source individual is key to determining the risk of HIV acquisition for the person exposed, and thereby, whether Post exposure prophylaxis is indicated. It is important that active attempts are made to determine the HIV status and treatment history of the source individual. This is often not possible, particularly in the cases of sexual assault or when casual partners are untraceable. If it is not possible to determine the HIV status of the source, assumptions about their HIV risk must be made based on demographic characteristics, which will vary from region to region.

The risk of HIV transmission is highest in those people who have had blood or mucosal exposure to someone who is HIV-positive and with a detectable viral load. Unprotected receptive anal intercourse remains the highest sexual risk exposure for HIV acquisition. The previously listed cofactors may influence the risk of HIV transmission and should be taken into account when determining whether an

individual should receive Post-Exposure Prophylaxis following Sexual Exposure.

Other factors

High plasma viral load in the source:

This may be particularly relevant during primary HIV infection, which accounts for a significant proportion of new infections. US guidelines now recommend that the risk of HIV transmission and the protection conferred by effective ART should be discussed with HIV-positive patients – this is highlighted also as a reason to consider starting HIV treatment during primary HIV infection. Low or undetectable plasma viral loads reduce the risk, but transmission may still be possible. Viral loads in the genital tract usually correlate with plasma viral loads, but there can be exceptions and viral suppression in the genital compartment may lag behind plasma. The HIV Prevention Trials Network (HPTN) study demonstrated that early initiation of antiretroviral therapy results in a 96% relative risk reduction of HIV transmission in serodiscordant couples. Results of the PARTNERS study presented at the Conference on Retroviruses and Opportunistic Infections (CROI), showed no HIV transmissions to date between serodifferent MSM and heterosexual couples where the-HIV-positive partner had an undetectable HIV viral load.

Sexually transmitting infections (STIs):

There is evidence that STIs enhance HIV transmission and increase HIV shedding from the genital tract. This may not be the case in individuals receiving effective antiretroviral therapy.

Breaches in the mucosal barrier:

This includes mouth or genital ulcer disease and trauma.

Exposure to blood:

Menstruation or other bleeding may also facilitate transmission.

Ejaculation:

The risk of HIV transmission is likely to be greater if ejaculation occurs. Among a community cohort of men having sex with men, the risk of HIV acquisition per episode of unprotected receptive anal intercourse with and without ejaculation was estimated to be 1.43% and 0.65%, respectively.

Circumcision:

Circumcision significantly reduces HIV acquisition among heterosexual men in high prevalence countries. A meta-analysis of observational studies among male-to-male sex suggests circumcision may have little impact upon HIV acquisition, as receptive anal intercourse is the key driver of transmission. However, there may be benefit for men having sex with men who exclusively or almost exclusively practice IAI (insertive anal intercourse). An

Australian cohort showed a reduction in per-act risk of HIV transmission from 0.62% in uncircumcised male-to-male sex to 0.11% in circumcised male-to-male sex. Data from observational studies suggest a 73% relative risk reduction for men who are circumcised and practice mainly insertive anal intercourse. [63, Rank 4]

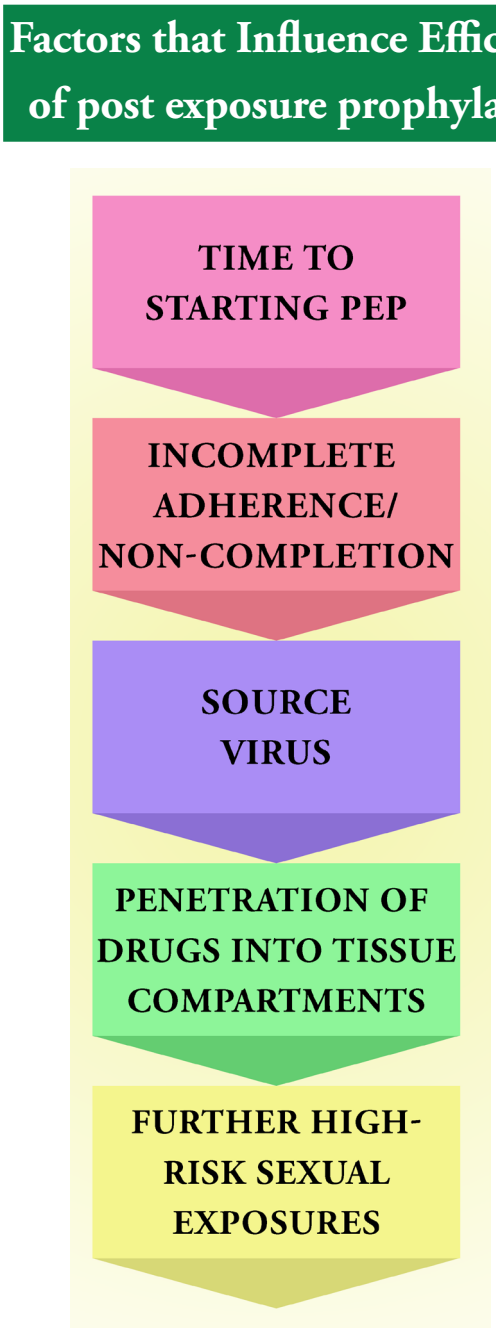


Figure 21: Factors influencing PEP effectiveness

Individuals have acquired HIV following both occupational and sexual exposures, despite the use of insertive anal intercourse. Therefore, PEP is not 100% effective. Various factors that influence PEP effectiveness (as shown in Figure 21)

Time to starting post exposure prophylaxis(PEP)

PEP is likely to be ineffective if initiated more than 72 hours after exposure; the majority of international guidelines do not recommend post exposure prophylaxis provision after this time, and other guidelines recommend even shorter window periods. New York State guidelines recommend nonoccupational post exposure prophylaxis is given no more than 36 hours after exposure. This discrepancy exists as there has have been no prospective trials in humans to assess the optimal time for commencement of post exposure prophylaxis after an exposure. However, the data from animal studies provide strong evidence of increasing rates of failure of post exposure prophylaxis by 48–72 hours after exposure.

Another study investigated 28 days of tenofovir started at different post-exposure intervals in vaginally exposed macaques; only one seroconversion in an animal started on post exposure prophylaxis 72 hours post-exposure was found compared to none in the 24- and 48-hour post-exposure

groups; this was a statistically significant finding.

Occupational guidelines recommend that PEP is commenced as soon as possible after the exposure. The time to initiating PEPSE is often longer than for occupational exposure. This may be as a consequence of both delays in patients seeking post exposure prophylaxis as well as the provision of post exposure prophylaxisby health care professionals.

Adherence to post exposure prophylaxis

Adherence and completion rates of 4 weeks of post exposure prophylaxis among health care workers and individuals exposed nonoccupationally are often poor, which may impact upon its efficacy. Pill burden and the side effects of treatment may influence completion rates. Other factors such as psychological distress and re-evaluation of risk may also impact post exposure prophylaxis completion.

A recent systematic review of post exposure prophylaxis use in victims of sexual assault showed poor adherence, with better completion rates in developing countries. Unmeasured factors such as stigma associated with sexual assault may play a role in this. However, in a recent meta-analysis of post exposure prophylaxis in non-forcible exposure to HIV, taking into account those that were lost to follow-up, found that 67% of people completed a 28-day course of post exposure prophylaxis. This was higher in groups that had counseling throughout the course of treatment. Psychological and social support is important adjuncts to effective post exposure prophylaxis services.

Drug resistance in the source

Post exposure prophylaxis efficacy may be compromised if the source has a virus that is resistant to one of the agents used. The prevalence of antiretroviral resistance among those with primary HIV infection and those chronically infected with HIV has plateaued at 8% in the UK and Europe, but this is not the case in low- and middle-income countries. A meta-analysis has demonstrated a significant increase in the prevalence of drug resistance over time since antiretroviral rollout in regions of Sub-Saharan Africa. If the source is known or suspected to have drug resistance, the post exposure prophylaxisregimen should be tailored accordingly.

There is evidence that, even with optimal viral suppression in the blood, HIV can be detected in other tissue compartments. As different antiretroviral agents penetrate these compartments to different degrees, the choice of drugs used in post

exposure prophylaxis could influence its efficacy. [67, Rank 4]

Risks of post exposure prophylaxis

Behavioral and psychological implications:

Despite concerns that Post-Exposure Prophylaxis following Sexual Exposure and

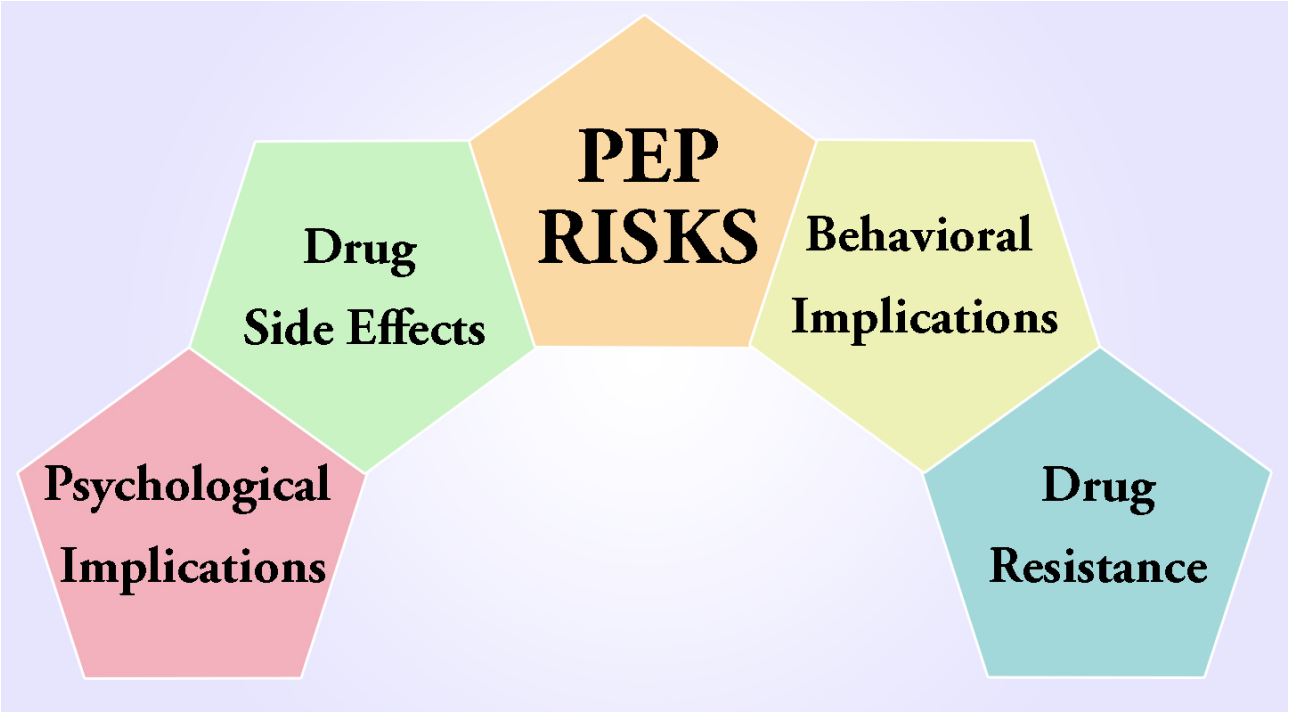


Figure 22: Risks Associated with PEP

There are risks of starting post exposure prophylaxis (as shown in Figure 22)

Drug side effects:

All ART can cause side effects, which should be considered carefully and discussed before starting post exposure prophylaxis. Symptoms, such as diarrhea, are one of the main reasons for nonadherence and discontinuation of PEP. Drug side effects are discussed further in the section describing the various antiretroviral options for post exposure prophylaxis

Pre Exposure prophylaxis availability will reduce individual commitment to other primary prevention strategies, such as condoms and behavioral interventions, there is little evidence of increased risk behavior among individuals with access to post exposure prophylaxis, and in a large randomized trial of Pre Exposure prophylaxis, there was a reduction in risky behavior. The impact of open-label PrEP (Pre Exposure prophylaxis) use upon risk compensation has yet to be determined. The availability of Post-Exposure

Prophylaxis following Sexual Exposure in clinics provides an opportunity to offer health education, health promotion, risk reduction strategies, and HIV prevention strategies such as Pre Exposure prophylaxis to high-risk individuals who may not access services otherwise.

Drug resistance:

There is a potential risk of drug resistance developing in those who fail to complete post exposure prophylaxis and acquire HIV. Poor adherence was a risk for subsequent seroconversion in a retrospective analysis of Post-Exposure Prophylaxis following Sexual Exposure failures. It is likely that adherence and treatment completion rates will be better with more tolerable post exposure prophylaxis regimens. [70, Rank 2]

Choice of ART(Antiretroviral Therapy)

The choice of drugs to be used for post exposure prophylaxis is based on those used to treat established HIV infection.

For HIV therapy, combination drug therapy with at least three drugs is more effective than single drug regimens. Most Post-Exposure Prophylaxis following Sexual Exposure guidelines recommend three drugs for PEPSE based upon the evidence for treating HIV-positive individuals and that late presentation for Post-Exposure Prophylaxis and the potential for drug resistance in the source make triple therapy likely to be more effective than mono- or dual-therapy Post-Exposure Prophylaxis.

A recent study has been the first to effectively demonstrate that a two or three drug regimen is more effective than monotherapy for non-occupational Post-Exposure Prophylaxis. This study also showed that dual therapy can be as effective as triple therapy, with no difference in efficacy seen. The cost benefit of adding in a third drug should be considered, but this is a decision that needs to be made in the context of the individual patient, their risks, and the risk of the source. Almost all guidelines advise a triple therapy regimen. Expert advice should be sought if the source is known or suspected to have viral resistance.

Nucleoside Reverse Transcriptase Inhibitors (NRTI)

Zidovudine (an NRTI) is the only drug to date for which there is evidence of reduced HIV transmission risk following occupational exposure. Combivir - a fixed dose combination of zidovudine and lamivudine (another NRTI) was frequently used for post exposure prophylaxis - PEP. Combivir is commonly associated with side effects, particularly gastrointestinal, which

may contribute to poor adherence. The routine use of abacavir is not recommended. A hypersensitivity reaction is reported in up to 8% of patients with established infection.

Truvada (a fixed dose combination of tenofovir disoproxil fumarate [TDF] and emtricitabine [FTC]) is better tolerated than Combivir with fewer side effects, so is often a first choice post exposure prophylaxis component. Both TDF and FTC penetrate the genital tract and rectal tissue well in animal models. Truvada has been shown to significantly reduce acquisition of HIV when used as PrEP (Pre Exposure Prophylaxis) in male to male sex although studies in heterosexuals are conflicting.

Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTIs)

Nevirapine has been associated with significant toxicity (particularly hepatic) as post exposure prophylaxis and is not recommended. Efavirenz has a lower incidence of hepatic and cutaneous toxicity, but as it may be associated with significant central nervous system disturbance, it is not an ideal choice for post exposure prophylaxis. Newer NNRTIs, etravirine and rilpivirine, are well-tolerated, although rash is common on etravirine and there have been case reports of severe rash in HIV-positive individuals. Rilpivirine causes rash less commonly and is currently being evaluated as post exposure prophylaxis

Protease inhibitors

It is likely that post exposure prophylaxis is aborting and inhibiting replication and dissemination rather than preventing infection and that part of this activity will be achieved by rendering new virions non-infective. Therefore, although boosted protease inhibitor (PI/r) act at a post-integrational stage of the HIV life cycle, they should still provide benefit as post exposure prophylaxis.

Nelfinavir, lopinavir/ ritonavir (LPV/r), atazanavir/ritonavir (ATV/r), and more recently darunavir/ritonavir have all been used or evaluated as PEP. PIs have been associated with metabolic abnormalities as well as gastrointestinal side effects. Kaletra, a fixed dose combination of lopinavir/ritonavir is the recommended Protease inhibitor for inclusion with post exposure prophylaxis regimens in the US, but commonly causes diarrhea.

Although newer Protease inhibitors have better gastrointestinal tolerability than lopinavir/ritonavir in treatment trials, a recent randomized comparison of atazanavir/ritonavir versus Kaletra-based post exposure prophylaxis, each with Combivir, revealed similar and high discontinuation rates (36% in each arm) and similar

discontinuation rates secondary to PI side effects (16% due to LPV/r and 17% due to ATV/r). An Australian study compared Protease inhibitors -based post exposure prophylaxis (Combivir plus nelfinavir – an unboosted Protease inhibitor no longer routinely used) with a triple NRTI combination (tenofovir disoproxil fumarate, lamivudine, and stavudine). Although the triple Nucleoside Reverse Transcriptase Inhibitors regimen was more frequently associated with peripheral neuropathy and transaminitis, discontinuations were significantly less frequent than on Protease inhibitor -based post exposure prophylaxis.

There is also an increased risk of drug–drug interactions with the use of Protease inhibitors. A recent post exposure prophylaxis study found that almost half of the participants were regularly taking at least one prescribed medication. These included corticosteroids, anticonvulsants, antidepressants, anti-lipids, and antihypertensives, which are known to hav post exposure prophylaxis e potential drug interactions with Protease inhibitor s. It is important to consider drug–drug interactions with prescribed and nonprescribed drugs, including recreational drugs when selecting the best post exposure prophylaxis regimen.

Other drug classes

Raltegravir (RAL), an integrase inhibitor, has a favorable tolerability, safety, and metabolic profile, and is well-tolerated as post exposure prophylaxis. It acts before viral integration and thus may be more effective at preventing HIV infection. It has fewer side effects and fewer drug–drug interactions than other classes of antiretroviral medications. The New York State Department of Health recently started using Raltegravir, emtricitabine, tenofovir disoproxil fumarate as its first-line occupational and nonoccupational post exposure prophylaxis regimen, and the Center for Disease Control (CDC) now recommends the use of Raltegravir for occupational post exposure prophylaxis. A recent interventional study assessed Raltegravir as part of a triple drug post exposure prophylaxis regimen, including emtricitabine and tenofovir disoproxil fumarate, in comparison to emtricitabine and tenofovir disoproxil fumarate. Researchers found the Raltegravir regimen had a high completion rate, was effective, and avoided potential drug–drug interactions. However, there was a small risk of acute muscle toxicity. Two other INIs, elvitegravir and dolutegravir, have been licensed recently. Elvitegravir is currently being evaluated as post exposure prophylaxis in a study in the US using Stribild;

however, cobicistat has similar drug–drug interactions as ritonavir.

Maraviroc (MVC), the only licensed CCR5 antagonist, also performs well from the perspectives of safety and tolerability. HIV can use one of two co-receptors, CCR5 (chemokine receptor type 5) or CXCR4 (chemokine receptor type 4), to enter host cells. Although Maraviroc only inhibits chemokine receptor type 5, there is evidence that the majority of transmitted HIV uses this co-receptor, indicating Maraviroc could be a useful post exposure prophylaxis option. Studies investigating Maraviroc as post exposure prophylaxis and Pre Exposure Prophylaxis options are ongoing. There is also evidence that both Raltegravir and Maraviroc penetrate the genital tract and rectal mucosa well; this may be an important consideration for PEP. More data is required as to their efficacy, although, consistent with national guidance, many centers use Raltegravir for post exposure prophylaxis cases where drug–drug interactions or tolerability problems preclude the use of lopinavir/ritonavir. Considerations include resistance and cost-effectiveness.

The US British Association for Sexual Health and HIV (BASHH) Post-Exposure Prophylaxis following Sexual Exposure guidelines recommend Truvada and Kaletra for 28 days but are currently being reviewed. The guidelines also make recommendations for alternative agents in the event of intolerance, drug–drug interactions, or resistance in the source. US guidelines for nonoccupational post exposure prophylaxis prefer tenofovir disoproxil fumarate, lamivudine, and Raltegravir; lopinavir/ritonavir; or EFV with 3/ emtricitabine, and list several regimens as alternatives. [72, Rank 2]

Evaluation of Patients Presenting for exposure prophylaxis

All patients who present for post exposure prophylaxis should have evaluation of the following:

Prophylaxis following Sexual Exposure provides one aspect of a larger HIV prevention strategy and should be provided in the context of other preventative measures, including promotion of condom use, counselling, and support around behavior modification in order to reduce future risk.

Awareness of post exposure prophylaxis and its availability for both clinicians and those who are eligible to receive it are crucial to ensure that post exposure prophylaxis is used to its full potential in any HIV prevention strategy. A recent study among an HIV-positive cohort in London showed that there was only 50% awareness of the availability of PEP overall, and 64% in those who had a detectable HIV viral load. Data from the CDC

EVALUATION OF PATIENTS PRESENTING FOR PEP
Determination of HIV status of person presenting for PEP before starting post exposure prophylaxis and 3 months after completion of post exposure prophylaxis
Timing and frequency of exposure
HIV status of source
Transmission risk from the exposure
Evaluation for sexually transmitted infections, hepatitis, and emergency contraception at initial presentation and during follow-up period
Advice regarding safer sex and risk reduction strategies
Follow-up to evaluate adherence and side effects of medication.

Table 1: Evaluation of Post exposure prophylaxis

assessing HIV providers' prescription of Post-Exposure Prophylaxis following Sexual Exposure in two US districts for their patients were poor, with 59.7% and 39.3% having ever prescribed PEPSE.

The decision to start post exposure prophylaxis should be made on a case-by-case basis, addressing the unique risks and benefits for each patient. This should consider the risk of transmission according to exposure and the likelihood of the source being HIV-positive as well as the potential for harm as a result of Post-Exposure Prophylaxis following Sexual Exposure.

The indications for provision of Post-Exposure Prophylaxis following Sexual Exposure will continue to be debated but there will be increasingly more discussion about the efficacy and availability of Pre-exposure Prophylaxis. This could potentially provide another tool in the strategy of HIV prevention, but further evidence is required and there are ongoing clinical trials to determine the safety and effectiveness of this strategy among different groups. In the meantime, Post-Exposure Prophylaxis following Sexual Exposure is a useful tool in ongoing efforts to reduce the incidence of HIV infection, particularly among risk groups. [75, Rank 5]

Pre Exposure Prophylaxis (Pre EP)

Pre-exposure Prophylaxis is another drug-based HIV prevention strategy that has been shown to decrease the risk of HIV acquisition in some trials but not others. iPrEx (Pre-exposure Prophylaxis Initiative), a trial of oral Truvada as Pre-exposure Prophylaxis in MSM, demonstrated a 44% reduction in HIV incidence in MSM who were taking Pre-exposure prophylaxis

compared to control subjects. The study demonstrated that those who were adherent, based on measured drug levels, had a greater risk reduction, and therefore greater efficacy of Pre-exposure Prophylaxis if used as it is prescribed. However, consideration to the cost, feasibility, and the potential for risk compensation behaviors needs to be given.

Treatment as Prevention (TasP) utilizes the fact that suppressed plasma viremia is strongly correlated with a significant reduction in HIV infectiousness. This has been shown to be highly effective at an individual level: the HPTN 052 trial demonstrated a significant (96%) reduction in linked HIV transmissions among the couples where the HIV-positive partner was randomized to immediate, as compared to deferred, ART. Data on whether effective HIV therapy and the consequent fall in "community viral load" reduces HIV incidence, have been conflicting. This is likely to result from the disproportionate number of new HIV infections arising from individuals with undiagnosed or primary HIV in some epidemics. It is likely that we will need to focus on several factors to reduce new HIV infections, including: reducing the burden of undiagnosed HIV infection, educating patients and clinicians to recognize the symptoms of primary HIV, and starting ART in those who wish to in order to reduce the risk of them transmitting to partners.

PrEP means Pre-Exposure Prophylaxis, and it's the use of anti-HIV medications to keep HIV negative people from becoming infected. PrEP is approved by the Food and Drug Administartion and has been shown to be safe and effective at preventing HIV infection. Even though Pre-exposure prophylaxis has been around in the U.S. since 2012, a lot of people still are looking to learn about it. And, even fewer people feel like they know enough about it to be able to make an informed decision about whether or not to use it. For people using Pre-exposure prophylaxis, can't really feel or see Pre-exposure prophylaxis working when use it. Pre-exposure prophylaxis (PrEP) is a new HIV prevention approach where HIV-negative individuals use anti-HIV medications to reduce their risk of becoming infected if they are exposed to the virus. It is an additional tool for people to consider in the HIV prevention toolbox. Pre-exposure prophylaxis trials have happened or are happening in Africa, Asia, South America, and North America. They include different people who may be exposed to HIV through unprotected anal and vaginal sex and sharing injection needles.

Combination Prevention Strategies for HIV

Increasingly, the place of exposure prophylaxis lies within a wider combination of prevention strategies, which include biomedical, structural, and behavioral interventions to prevent HIV infection and address the interacting causes of HIV risk and vulnerability. These should be tailored to the local needs of the population and include Post exposure prophylaxis, Pre-exposure Prophylaxis, TasP (treatment as prevention), and risk behavioral interventions such as condom use. HIV prevention and treatment strategies are interdependent. The failure to focus on those with the greatest risk, to focus resources on primary transmission of HIV, and a lack of structural interventions that focus on the causes of vulnerability has already led to rising rates of HIV infection and will likely continue to do so.

Falling rates of HIV infection have been linked to changes in behavioral and societal norms. However, there are still two new infections for every person who is started on HIV treatment. PEP is an important component of prevention strategies, and its role as a public health strategy will evolve as other prevention measures such as Pre-exposure Prophylaxis and Treatment as Prevention become more widely available. As long as individuals continue to be exposed to HIV, there will be a role for timely PEP. [72, Rank 4]

Worldwide, 33.4 million people are now living with human immunodeficiency virus (HIV). About 2.7 million people were newly infected with the virus in 2008. The total number of people living with HIV in 2008 was more than 20% higher than the number in 2000, and the prevalence was roughly threefold higher than in 1990. During the late 1990s, after the introduction of combination antiretroviral therapy, the numbers of new acquired immunodeficiency syndrome (AIDS) cases and deaths among adults and adolescents declined substantially. In the United States, the Centers for Disease Control and Prevention's (CDC's) HIV prevention activities during the past two decades have focused on helping uninfected people at higher risk of acquiring HIV to change and maintain behaviors to keep them uninfected. Despite the success of these efforts in reducing HIV incidence in the late 1980s and early 1990s, the number of new HIV infections was estimated to be 55,400 per year for 2003–2006.

A wide range of effective interventions is currently available to reduce transmission of HIV/AIDS. However, most of these HIV prevention interventions focus

on changing individual risk behaviors. Long-term, sustainable risk reduction may require taking into account factors that are external to the individual. HIV prevention programs need to address the contexts in which people live; that is, larger, external factors that may influence risk-taking behaviors. Very few of the available HIV prevention interventions address larger structural or environmental factors that either facilitate or impede behavior change. This article describes a process that was undertaken to identify a range of interventions that can be defined as structural, and to examine the feasibility of implementation and their perceived impact if implemented. It was proposed that such interventions could inform CDC policy development and potential program expansion.

Social and economic factors as well as laws and policies affect the transmission and differential distribution of HIV/AIDS. This perspective emphasizes social conditions as determinants of disease. Structural interventions promote health by altering the structural context within which health is produced. Structural interventions have been defined as HIV prevention interventions that include physical, social, cultural, organizational, community, economic, legal, and policy factors.

Research has highlighted the role of structural factors that either facilitate behavior change or act as barriers to risk reduction. These factors either directly or indirectly affect an individual's ability to reduce the risk of getting infected or assist in changing behaviors. For example, stable housing for HIV-positive individuals was associated with changes in risk behaviors. Changes in housing status significantly reduced the risks of drug use, needle use, needle sharing, and unprotected sex. Similarly, uninterrupted insurance coverage, as a structural intervention, had shown strong and positive effects on the use of ambulatory care and antiretroviral therapy.

In recent years, conditional cash transfer programs have focused on changing health behaviors such as smoking cessation, weight loss, and, more recently, promotion of HIV/AIDS prevention. Examination of social and environmental factors that influence risks suggests that modifying these social environmental factors may facilitate risk reduction by the individuals and also provide justification for developing intervention approaches tailored to specific determinants of risks. Successful structural and environmental public health interventions in other domains include taxation on cigarettes, aswell as helmet and seat belt laws. Public policy may play a role in shaping environmental outcomes to stem HIV transmission. [31, Rank 4]

AIDS Vaccine Trials

The total number of people living with HIV is estimated to be near 33.4 million, with 97% living in low- and mid-income countries and 48% being women. Preventing HIV infection and AIDS is a global priority, and a number of behavioral, barrier, antiretroviral drug-based and vaccine approaches have been the subject of intense research. While antiretroviral treatment (ART) in HIV-infected individuals slows progression to AIDS and death, its benefit at a population level is dependent on the availability of drugs and adherence to treatment regimens. A safe, effective, and durable vaccine is needed to stem the pandemic.

The development of an AIDS vaccine has faced many challenges over the past 25 years. Current AIDS vaccine candidates do not elicit broadly neutralizing antibodies capable of preventing infection by the vast diversity of HIV isolates. The first test-of-concept trial of a cell-mediated immunity (CMI)-based vaccine did not show efficacy and raised the concern that the vaccine might enhance the risk of infection for some vaccinees. Vaccine candidates in current trials are designed to induce HIV-specific cell-mediated immunity responses that could slow HIV replication, destroy HIV-infected cells, preserve immune memory, delay disease progression, and possibly prevent secondary transmission by reducing the quantity of virus in body fluids (viral load).

Other HIV prevention modalities have shown promise. Prompt postexposure prophylaxis reduces the risk of transmission due to occupational or sexual exposure. Treatment of mother and/or child before and after childbirth has reduced the risk of mother-to-child transmission. Very recently, the first successful demonstration of protection by tenofovir-containing vaginal gel has provided proof-of-concept for topical microbicide pre exposure prophylaxis (PrEP). Tenofovir gel reduced HIV acquisition by an estimated 39% overall, and by 54% in women with high adherence to the dosing regimen of before and after sexual exposure.

Furthermore, in some experiments, animals that became infected despite receiving TDF as PrEP or PEP showed delayed onset of viremia and delayed seroconversion, demonstrating that even in the case of incomplete protection against infection, PrEP or PEP may lead to attenuated acute infection (perhaps by allowing the immune system to gain some control of the virus). The demonstrated efficacy of tenofovir disoproxil fumarate in the treatment of HIV infection, the lack of reported serious safety problems associated with its use, its

> **"Animal studies have provided evidence that Pre Exposure Prophylaxis and postexposure prophylaxis (PEP) with tenofovir disoproxil fumarate (TDF), alone or in combination with emtricitabine (FTC), can protect against simian immunodeficiency virus (SIV) and chimeric simian HIV (SHIV) infection."**

long half-life, and its relatively high threshold to drug resistance make this antiretroviral agent an attractive candidate for systemic or topical prophylactic use.

Tenofovir and related drugs have high concentrations in genital tissues, so repeated exposure with locally aborted HIV infection is theoretically possible and, if it occurs, may lead to the development of HIV-specific cellular immune responses. Several clinical efficacy trials using tenofovir disoproxil fumarate alone or in combination for oral or topical prophylaxis are ongoing. Other drugs are also being considered for use in such regimens. However, more safety and efficacy data are needed, and there are significant practical barriers to widespread prophylactic use of antiretroviral therapy.

Antiretroviral therapy for HIV-infected individuals may prove useful in the prevention of secondary transmission. Viral load is the single greatest risk factor for all modes of transmission. Sexual transmission of HIV has been closely linked to viral load in the blood of the infected host, which probably serves as a surrogate, albeit imperfect, for HIV concentration in the genital tract. In addition to lowering plasma viral load to nearly undetectable levels, Antiretroviral therapy can decrease viral load in genital secretions, although patients having a detectable semen HIV load may have no detectable virus in their blood plasma, highlighting the residual risk of HIV-1 transmission during unprotected intercourse. Observational studies and recent modeling work have triggered considerable interest and concerns regarding the use of antiretroviral therapy in HIV-infected individuals to prevent secondary transmission.

In the coming years, ***systemic pre exposure prophylaxis or drug-based microbicides (which in this discussion is considered a topical form of pre exposure prophylaxis) may be proven to safely confer protection against HIV infection.*** In that instance, even though the implementation of a "background" intervention would require careful consideration by national governments, pre exposure prophylaxis might be proposed as a baseline intervention for AIDS vaccine trial participants. In effect, by allowing repeated

exposures to HIV that do not lead to established infection, pre exposure prophylaxis may allow exposure-induced immunity to alter vaccine-induced immunity; on the other hand, vaccination could influence susceptibility, thus altering the efficacy of pre exposure prophylaxis.

Similarly, antiretroviral therapy in HIV-infected individuals to prevent secondary transmission may gain momentum in populations with a high prevalence of HIV infection. Low-dose exposure, presumably more common when the donor is receiving antiretroviral therapy, which can reduce virus concentration in both blood and genital secretions, might therefore be countered more easily by pre-existing, vaccine-induced immunity in the recipient. These possibilities offer new opportunities for combination biomedical HIV prevention research and raise several questions about potential interactions and/or synergies between pre exposure prophylaxis, Antiretroviral therapy for prevention, and AIDS vaccines. Such potential interactions should be considered when designing intervention trials and when "translating" the results of randomized, controlled trials to predictions of how the interventions, when introduced into broad use, may influence public health. [27, Rank 5]

With the negative result of the STEP trial and the realization that even the most

> **"The recent RV144 Thai trial of a prime-boost vaccine regimen aiming at inducing both cell-mediated immunity and antibody responses showed in a modified intention-to-treat analysis a 31% reduction in the risk of infection."**

potent vaccines designed to elicit conventional CD8+ memory T cell responses were unlikely to confer elite controller status to the majority of infected vaccinees, the HIV/AIDS vaccine development field was left with no clear pathway to an effective vaccine only the hope that increasingly detailed and sophisticated structural analysis of the interaction between env and a growing panel of broadly neutralizing monoclonal antibodies isolated from HIV+ patients would lead to advances in env immunogen design, and eventually, a vaccine capable of eliciting high titer, broadly neutralizing antibodies.

However, recent data suggesting that mucosal infection might be prevented by more prosaic antibody-targeted vaccines that induce antibody responses capable of virus or infected cell binding, but not necessarily broadly neutralizing activity, or alternatively, by stringent control of infection through TEM-generating vaccines, offers a new approach to HIV/AIDS

vaccine development based on exploiting the immune vulnerabilities of the virus during the early stage of infection. Although neither of these vaccine strategies is sufficiently optimized for clinical use in their current form, it is not unreasonable to suggest that both empirical optimization and rational design can improve the efficacy of each approach, and that the combination of these disparate and independent approaches might result in additive or potentially synergistic increases in overall efficacy.

The RV144 vaccine approach might be empirically improved by optimization of priming vectors and their env inserts and the env protein immunogens used in the boost, as well as the use of more potent adjuvants with the protein boost. Obviously, novel immunogens derived from structure-function analysis of broadly neutralizing monoclonal antibodies could be incorporated into these antibody-targeted prime-boost designs as they are shown to be effective. This optimization might be accomplished using both NHP models and adaptive clinical trial. [25, Rank 2]

Given variability in the magnitude, quality and duration of vaccine-elicited immune responses in humans and both the immune evasion capabilities and diversity of HIV, it is unlikely that any single vaccine approach will be effective in all potential transmissions. And, of course, when infection occurs in the face of significant immunologic pressure that does not confer solid protection, it almost inevitably leads to immune escape, and potentially, generation of transmissible viruses that are no longer sensitive to the involved immunologic mechanism.

While strategies such as mosaic vaccine insert/ immunogen designs can broaden vaccine-elicited immune responses, and help overcome the sequence diversity of transmitted HIV strains, a more general solution to this issue may lie in the development of multimodal vaccines that target different immune vulnerabilities (much like the need for multiple, differentially-targeted anti-retroviral drugs in effective combination anti-retroviral chemotherapy regimens). This strategy is subtly different than the oft-repeated conventional wisdom mantra that an optimally effective AIDS vaccine should induce both humoral and cellular immunity, in the hope that one arm of the adaptive immune system can confront the fraction of virus not effectively dealt with by the other. [20, Rank 4]

Evidence based Intervention in preventing complications

An effective intervention should be available, and the distress and subsequent investigation caused by a positive test result must be outweighed by the benefit of early treatment.

Several issues should be considered with respect to screening for asymptomatic neurocognitive impairment. For a test to be clinically useful the disease must have a well-defined early stage that would progress to a more severe stage without intervention. Since no effective therapy for asymptomatic neuro-cognitive impairment other than antiretroviral therapy has been identified, the benefits of screening asymptomatic patients who have normal daily functioning and are already taking antiretroviral therapy are debatable, particularly because no single screening method seems to be adequately sensitive and specific enough to diagnose asymptomatic neurocognitive impairment in all clinical settings.

In many patients, asymptomatic neurocognitive impairment is not progressive; for instance, around half of individuals with any HIV-associated neurocognitive disorder fluctuate in cognitive functioning over time, with improvement from HIV-associated neurocognitive disorder to unimpaired cognitive function occurring as frequently as deterioration. This variability might be due to true fluctuations in pathological processes, perhaps reflecting varying degrees of HIV replication in the central nervous system, or might reflect limitations of the neuro-psychological tests. Importantly, whether or not the poor outcomes reported for those diagnosed with asymptomatic neurocognitive impairment are driven primarily by HIV, by comorbidities, or by both is unclear.

Identification of patients who have early-stage impaired cognitive function might have some merit, so that risk factors can be controlled, treatment adjusted, and disease progression monitored. Changes to antiretroviral drug regimens based on distribution into the nervous system, monocyte activation, or neurotoxicity have been posited in the treatment of asymptomatic neurocognitive impairment, but randomised clinical trials to support these or other interventions, such as exercise or cognitive rehabilitation, have not been done.

As a result there is no strong consensus on the best course of action for patients who are taking adequately suppressive antiretroviral therapy and are diagnosed with asymptomatic neurocognitive impairment, and there is no widely accepted therapeutic framework in which to change antiretroviral therapy on the basis of differences in the

estimated efficacy or toxicity of antiretroviral drugs in the central nervous system. A remaining important consideration is the impact of the screening process on patients; informing an asymptomatic individual that he or she has cognitive impairment could cause psychological distress. For these reasons, routine cognitive screening for asymptomatic neurocognitive impairment has not yet been widely adopted in the clinic. [15, Rank 4]

Compared to urban areas, there were relatively few factors associated with survival for rural areas. Of note, there were no significant racial/ethnic differences in survival in the rural areas, although there were in the urban areas, where non-Hispanic blacks and to a lesser extent Hispanics were disadvantaged relative to non-Hispanic whites. One possible explanation is that income inequalities among racial/ethnic groups may be smaller in rural areas than in urban areas, but these data were not available for analysis.

Older age at the time of diagnosis, on the other hand, was associated with lower survival in both areas, as has been reported in other studies. Not surprisingly, in both areas, diagnosis during earlier time periods was associated with lower survival, which is to be expected given the significant advances in HIV/AIDS treatment. Having an unknown transmission category was also associated with lower survival in both areas. This may be due to information not being collected because the person died rapidly or because people who deny risk may deny signs and symptoms and delay seeking medical care and subsequently diagnosis.

The socioeconomic status of the area where the person was diagnosed was not associated with survival in rural areas. In urban areas, there was a clear association between decreased survival and low socioeconomic status, whether measured by the poverty index or the low affluence index. The association between decreased survival and individual- and area-level low socioeconomic status has been reported by others. It is likely that the rural area socioeconomic measures are less reflective of individual socioeconomic status than urban measures. Additionally, there may be some unmeasured cultural factors present only in rural areas in Florida that may lessen the impact of low socioeconomic status on AIDS disease progression. It would be beneficial for future studies to measure socioeconomic status in smaller geographic areas or at the individual level to further investigate the role of socioeconomic status in AIDS survival in rural areas. [67, Rank 3]

The Role of Education in Prevention of HIV/AIDS

Many adolescents living with AIDS do not receive adequate support and care – and many others are not aware of how to protect themselves from AIDS. School-based HIV/AIDS education is a common and well-proven intervention strategy for providing information on HIV/AIDS to young people. However, lack of skills among teachers for imparting sensitive information to students can lead to programme failure in terms of achieving goals.

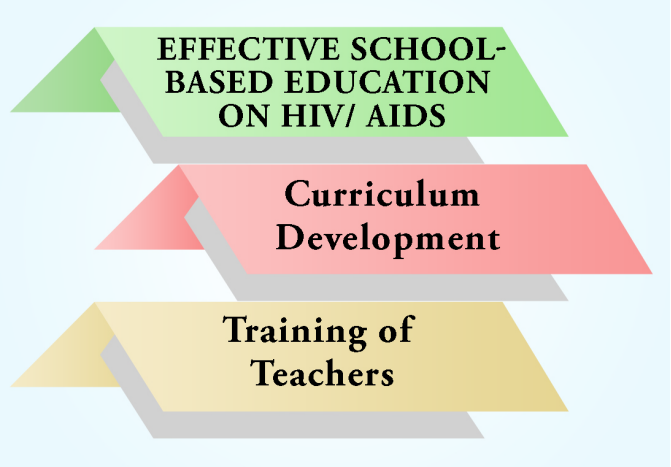


Figure 23: School based HIV education for prevention

Education is an effective tool to reduce the social and economic vulnerabilities that often make girls and women more prone to become infected with HIV/AIDS. Education promotes gender equality and women empowerment; what's more, it has added benefits such as delaying marriage for young girls and providing an avenue for family planning. These benefits will help to educate and provide better opportunities for young girls and have positive ripple effects within a community. In addition to helping with HIV prevention, education increases the tolerance and empathy of individuals who have contracted the disease. By addressing fears and changing attitudes, education reduces discrimination and stigmas – the leading causes for children and adolescents to drop out of school.

Strategies on HIV and AIDS in the State of Washington

Statewide, annual HIV case counts have been stable over the past decade. Between 550 and 600 people are newly diagnosed with HIV infection each year. About one in three cases is diagnosed late in the course of his or her HIV illness, or develops AIDS within 12 months of HIV diagnosis. HIV rates are highest among gay and bisexual men, as well as racial or ethnic minorities.

Screening for HIV/AIDS

In Washington, health care providers, health care facilities, clinical laboratories, veterinarians, and others have responsibilities for reporting suspected or confirmed cases of certain conditions under public health surveillance. Included are specific

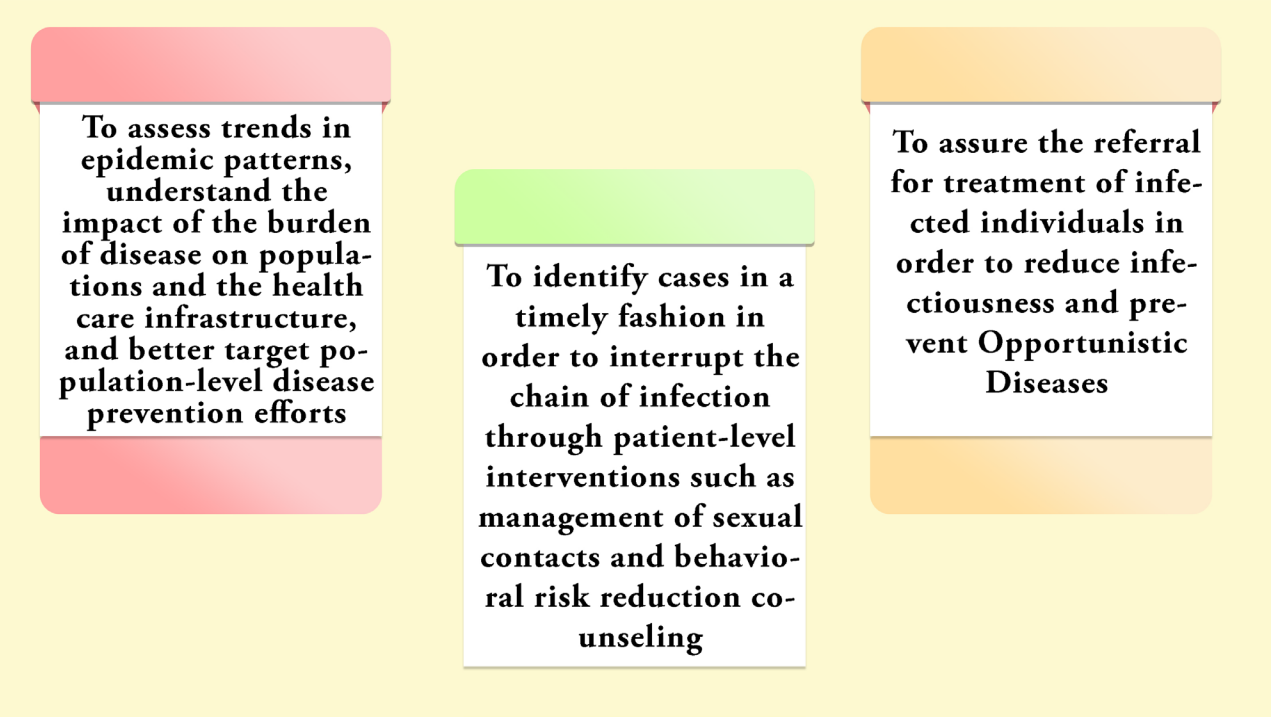


Figure 24: Purpose of Reporting and Surveillance

acute and chronic communicable diseases, occupational asthma, birth defects, blood lead levels, and pesticide poisoning. Most communicable notifiable conditions are reported to the local health jurisdiction. HIV infection and CD4 counts except King County and tuberculosis are reported to the Washington State Infectious Disease office.

Legal Reporting Requirements

Health care providers: AIDS and HIV infection notifiable to local health jurisdiction within 3 working days

Health care facilities: AIDS and HIV infection notifiable to local health jurisdiction within 3 working days

Laboratories:

For HIV, positive Western blot assays, p24 antigen or viral culture tests are notifiable within 2 workdays to Public Health-Seattle & King County (PHSKC) for labs in King County and the Washington State Department of Health (DOH) for labs outside of King County. All results, whether they are positive or not detectable, on HIV nucleic acid tests (RNA or DNA) are notifiable on a monthly basis. All CD4+ absolute counts and percentage of total lympocytes comprised by CD4+ lymphocytes are notifiable on a monthly basis.

Local health jurisdictions:

Notifiable to Washington Department of Health within 7 calendar days of case investigation completion or summary informa

tion required within 21 calendar days of notification

Notification

Notification means that individuals testing positive will be counselled about the importance of notifying spouses and partners and will be given the choice to notify, to allow the healthcare provider to notify, or to refer to the local health jurisdiction for assistance in notifying the spouse.

Confidentiality

All medical records are confidential and must be maintained in a manner that protects that confidentiality. Confidentiality of medical information means that a person's medical information (including HIV testing and HIV results) may not be disclosed to anyone unless the individual signs a release-of-information form. However, there are exceptions to this. Medical information can be disclosed under certain circumstances, including:

- When it is given from one healthcare provider to another healthcare provider for related ongoing medical care of the patient
- In a life or death emergency
- To a third-party payer or insurance provider
- In reporting notifiable conditions to the local health jurisdiction or the Department of Health (DOH)

HIV case reporting and partner notification

The intent of contacting persons reported with HIV infection is to assist infected persons in notifying spouses and sex and needle-sharing partners that they may be infected, and to provide referral for care and other services. Public health staff elicits partner information, then work with the infected person to determine which he/she will reach and which public health will contact. Exposed persons are then offered counseling and testing to learn of their status, hasten their entry into care if positive, and prevent further transmission to others. Public health officials will contact the principal health care provider to determine the best means of contacting the HIV-infected person to conduct partner notification. The health care provider, who recommends the health officer not meet with the HIV-infected individual, must inform the HIV-infected individual of the necessity to notify partners, assist in notifying partners, and inform health officials of the identity of certain partners.

Health officers shall use identifying information only for contacting the HIV-infected individual to provide post-test counseling, to assure health services are being accessed, to contact partners, or to investigate behaviors that endanger the public health.

Post Exposure Prophylaxis guidelines - Washington

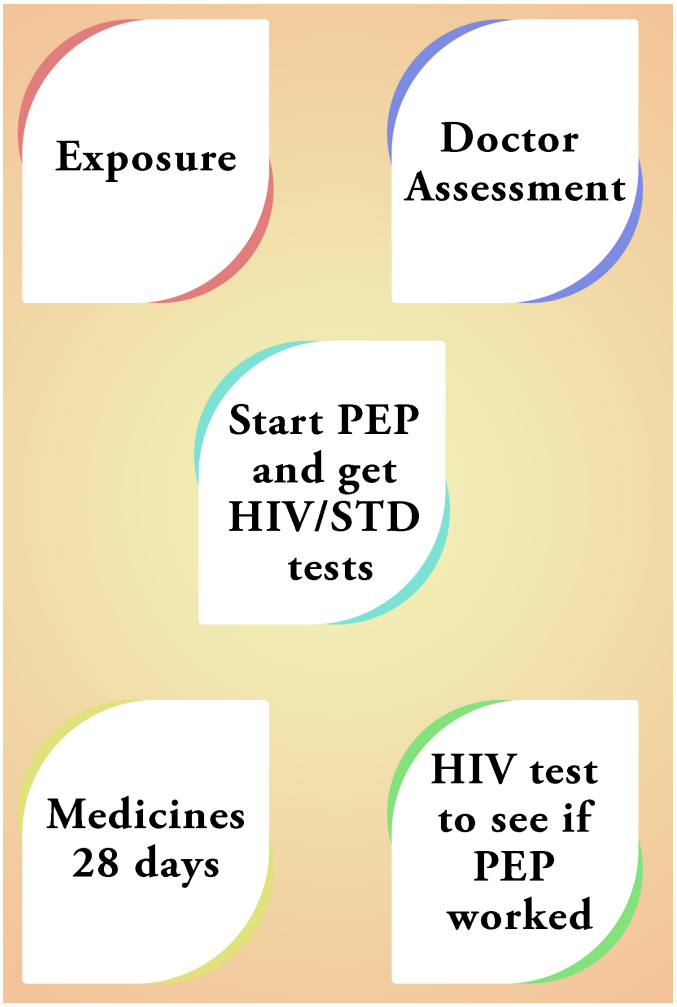


Figure 25 : Post exposure prophylaxis

Pre Exposure Prophylaxis Guidelines

PrEP without insurance can cost up to $14,000 a year, however very few people end up paying that amount. Health insurance, including Medicaid, covers PrEP. Drug companies also provide discounts to those who qualify.

Figure 26: Pre Exposure Prophylaxis

End AIDS Washington: A Plan for America

This new federal initiative seeks to reduce the number of new HIV infections in the United States by 75 percent within five years, and then by at least 90 percent within 10 years, for an estimated 250,000 total HIV infections averted.

Financial Assistance Program

Financial assistance programs are available for both HIV-positive and HIV-negative Washingtonians. There are also community programs available to help you look at different programs and apply for the ones that are right for you.

Early Intervention Program (EIP)

It is Washington States AIDS Drug Assistance Program. It is administered by the Washington State Department of Health in the HIV Client Services Office. Many services are available to assist enrollees with out of pocket costs for their HIV care, including medical/lab, mental health, dental medications.

The Washington HIV/STI Prevention Project (WHSPP)

It is an internet-based survey designed to monitor demand, uptake, and unmet need for HIV prevention interventions, with a focus on pre-exposure prophylaxis (PrEP). This report presents the results from a second round of the survey, conducted from November 2018 to January 2019. Comparisons with the 2017 (Round 1) data allow for monitoring progress towards End AIDS Washington goals.

Health Management Guidelines for HIV-Infected Persons

Component 1 Physical Examination	**Comprehensive history, physical, and review of systems**
Component 2 HIV Tests Serologic Test	**CD4+ cell counts and percentages every three to four months, Viral load every three to four months, Plasma HIV RNA levels, HIV resistance testing**
Component 3 Laboratory Tests	**Routine complete blood count and chemistry panel,Glucose-6-phosphate dehydrogenase, Fasting lipid panel, Urinalysis and creatinine clearance**
Component 4 Vaccine recommendations	**Pneumococcal infection,Influenza annually, Tetanus, diphtheria,pertussis with tetanus booster very 10 years,Varicella, Hepatitis A and B, Human papilloma virus (HPV) in both males and females, Meningococcal, Measles, mumps, rubella, Primary varicella Zoster**
Component 5 Coinfection and comorbidity screening	**Tuberculosis (follow-up chest X-ray if positive PPD) repeated periodically, Toxoplasma gondii, Viral hepatitis, Herpes viruses, Cytomegalovirus, Syphilis (RPR or VDRL), Other STIs, Cervical cancer, Anal human papillomavirus, Breast cancer**

Figure 27: Health Management in HIV patients-Washington State

Special Populations Affected with HIV Infection

Women

Globally, women account for nearly half of all people living with HIV and represent even a greater proportion of those affected in low- and middle-income countries. Gender inequalities and harmful gender norms that promote unsafe sex and limit access to health services, education, and economic opportunities continue to drive the HIV epidemic in many countries. As a consequence, the prevalence of HIV among girls and young women is more than double that of similarly aged males. Despite this, women are still largely underrepresented in HIV cure research. Most cure-related research and clinical trials take place in developed countries, where the HIV epidemic is predominantly driven by men who have sex with men. Therefore, differences in barriers to eradicating HIV between men and women have not been adequately considered.

The profile of the global HIV/AIDS epidemic has changed dramatically over the past three decades, from a disease that predominantly affected men to one that is affecting a growing number of women. Women now represent over 50% of the 33.3 million people living with HIV globally. In regions of sub-Saharan Africa, women constitute a disproportionate 60% of HIV cases. In Latin America and the Caribbean, the percentage is over 35 and 50%, respectively. In Asia, the proportion of women living with HIV (WLWH) has grown even more rapidly. In China, for example, the male-to-female sex ratio among HIV-positive people has narrowed from 9:1 in the 1990s to 3:1 in 2007. In North America, men who have sex with men continue to account for the majority of people living with HIV, but the proportion of women living with HIV has steadily increased over the past decade. In Canada, 26% of newly diagnosed HIV infections in 2009 were among females aged 15 years and above, more than double the proportion observed in 1999 (12%).

Differences in the biological and social realities of men and women are key drivers of the feminization of the HIV epidemic. In the context of heterosexual vaginal intercourse, the efficiency of male-to-female HIV transmission is two times greater than female-to-male transmission, owing to a more receptive contact surface of the vagina, a higher concentration of HIV in semen compared to vaginal fluid and cervical ectopy. Social factors can exacerbate this increased risk. For instance, women who are economically disadvantaged or

who have experienced gender-based violence are more likely to engage in unprotected sex, have multiple partners and resort to trading sex for money, drugs, food or housing. These women are also less likely to have the capacity to affirm one's self and to negotiate condom use, discuss fidelity with partners and leave risky relationships.

Access to and maintenance in treatment also varies by gender, both globally and in Canada. women living with HIV experience several barriers to care which are heavily shaped by gender, including stigma and discrimination, violence, mental health and addiction issues, a lack of financial resources, lack of social support and feelings of isolation, inflexibilities in clinic hours, negative experiences with health care providers, a lack of services focusing on women, long travel distances to services from rural or remote areas and competing responsibilities as mothers, partners, friends, homemakers, paid-workers and care-givers in which women prioritize the needs of others above their own.

Conflicting results have been published in terms of sex differences in outcomes after treatment initiation. While some authors have reported improved virological suppression in males, others have showed advantages in females. However, most evaluations have found no sex differences after adjustment for confounding variables. Nevertheless, women are more likely to be non-adherent, have treatment interruptions and experience more adverse drug reactions. Also, HIV infection increases the severity of menopause and menstrual disorders, osteoporosis, pelvic inflammatory disease and vulvo–vaginal and cervical diseases.

Women also have distinct reproductive health concerns, including contraception, fertility and pregnancy. Provision of the full range of contraceptive options and access to safe abortion services are critical components of care to prevent unplanned pregnancies and improve women's overall health. It is similarly critical to support women to safely achieve their future reproductive goals through pre-conception, pregnancy and post-partum services and support including access to fertility treatment services as required, as an increasing number of HIV-positive women express the intention to have biological children. In addition to reproductive concerns, sexual satisfaction, sexual functioning and sexual negotiation are increasingly important concerns to address as women living with HIV have been wrought with sexual stigma and a near absence of supportive services.

Women's experiences of HIV infection are unique and tailored services that respond to women's needs are critical for improving the overall health outcomes of

women living with HIV. In response, some regions have created women-specific HIV/AIDS programmes and services. For instance, in Canada, some of these include the Oak Tree Clinic, Positive Women's Network, the Maple Leaf Medical Clinic, Women's Health in Women's Hands Community Health Centre and the Centre for AIDS Services of Montreal Women; in the United States (US), the Johns Hopkins HIV Women's Health Program, the Women's Collective, Sister Love Inc. and US Positive Women's Network; and globally, Women Fighting AIDS in Kenya, Mama's Club in Uganda, Mujeres Positivas in Latin America and Women Organized to Respond to Life-threatening Diseases. Despite the emergence of this model of care, the concept of women-specific HIV/AIDS services remains largely undefined. These approaches are not well conceptualized and little is known about the key characteristics of women-specific HIV/AIDS services. [75, Rank 3]

Overall health should be optimized and health care coordinated with other providers to ensure attention to standard primary care and management of chronic diseases. A number of chronic medical illnesses occur not infrequently in individuals with HIV and certain conditions may be associated with HIV or its treatment. Many of these illnesses are associated with adverse maternal and/or fetal outcomes, and medications used to treat them may also be associated with potential harm. Furthermore, antiretroviral agents are associated with increased risk of certain chronic problems, such as glucose metabolic abnormalities.

> **"A drug classified as Food and Drug Administration category D indicates positive evidence of human fetal risk, but potential benefits to mother may make risk acceptable; FDA category X indicates evidence of human fetal risk, which clearly outweighs any possible benefit. If a woman is taking an FDA category D or X drug, then the feasibility of safely stopping or substituting a drug that may be safer in pregnancy should be determined."**

All current medications, including prescription, over-the-counter and complementary medications, should be reviewed and potential adverse effects associated with the drugs assessed.

For many drugs, in particular newer medications, experience in human pregnancy may be extremely limited and decisions should be made on a case by case

basis, based on individual medical needs and the availability of alternative medications with equal efficacy

Food and Drug Administration drug classification can give some guidance about what is known or not known about potential teratogenic risk with use during pregnancy, based on animal data and human experience. and better safety profile. In general, teratogenic risk is limited to the first trimester of pregnancy when major fetal structures form, but often before pregnancy is realized. It is also important to remember that there can be other potential adverse effects of medications on the mother, fetus or pregnancy course which should be considered as well when a woman is planning to conceive.

Women should be evaluated for the need for appropriate prophylaxis or treatment for opportunistic infections before attempting to conceive. Medications for such treatment or prophylaxis should be carefully chosen based on safety, tolerability, and potential toxicity considerations when used in pregnancy. Assessment prior to conception also allows the provider to implement appropriate management of anemia or other nutritional deficiencies. [76, Rank 3]

An assessment of the need to initiate or modify an antiretroviral regimen should be made for all women living with HIV prior to conception. antiretroviral therapy should be initiated in women who meet the criteria for HIV treatment according to the Department of Health and Human Services (DHHS) Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents and should be strongly considered when the male partner is not HIV-infected prior to attempting to conceive, with the primary treatment goal of achieving a stable, maximally suppressed maternal viral load prior to conception. ***The choice of ART regimen should take into account current adult treatment guidelines, what is known about the use of specific drugs in pregnancy and the risk of teratogenicity or other adverse effects.***

However, the potential adverse effects of antiretroviral therapy on certain pregnancy outcomes, readiness for life-long therapy, and risks versus benefits of stopping antiretroviral therapy postpartum should be part of the deliberations. If a current Antiretroviral regimen is not effective (i.e., suboptimal suppression of viral load), not well tolerated, or associated with significant adverse effects, then it should be modified prior to attempts at conception.

Nevertheless, in women who are initiating Antiretrovirals prior to attempts to conceive, Efavirenz should be avoided, if

possible. For women planning to conceive and already on an effective antiretroviral regimen including Efavirenz, regimen modification should be considered if there are available, acceptable, and effective alternatives.

Children

The virologic and immunologic benefits of highly active antiretroviral therapy (HAART) in children in resource-rich countries have been confirmed by trial data in low-income and middle-resource countries. Global treatment access for HIV-infected children is rapidly increasing; an estimated 356,400 children younger than 15 years received highly active antiretroviral therapy in 2009 in resource-limited countries, a 29% increase since 2008. The definition of who is in need of treatment is likewise expanding rapidly. Research has demonstrated that immediate highly active antiretroviral therapy significantly reduces mortality and morbidity in HIV-infected infants, and the World Health Organization has revised its guidelines to recommend highly active antiretroviral therapy initiation in all HIV-infected children younger than two years.

However, treatment in children is complicated by changing drug pharmacokinetics with age, caused by the continuing development and maturation of the organs involved in drug metabolism. Drug pharmacokinetics are further complicated by malnutrition and drugs required for treatment of coinfection with tuberculosis (TB) and malaria. ***Children initiate therapy during a period of rapid growth and development, and face a lifetime of drug exposure.*** Highly active antiretroviral therapy potential adverse effects on metabolism are central to managing pediatric HIV, but research has been limited in children. [80, Rank 3]

An estimated 3.2 million children currently live with human immunodeficiency virus (HIV). Children with perinatal HIV infection (PHIV+) in the era of highly active antiretroviral therapy (HAART) have significantly improved odds of survival compared to the pre- highly active antiretroviral therapy era and are living into adolescence and adulthood in unprecedented numbers. In the United States, mortality amongst HIV-infected children declined from 7.2 per 100 child-years in 1994 to 0.6 per 100 child-years in 2006, a more than 90% reduction. Similar achievements have been made in Europe. In these resource-rich settings, those with perinatal HIV infection live longer, and fewer die of opportunistic infections, but PHIV+ still face significantly

> "Efavirenz (EFV) is the only antiretroviral drug with evidence of teratogenic risk, based on preclinical primate data and retrospective case reports after first trimester human exposure; however, recent data suggest that the risk is likely to be quite low."

higher odds of morbidity and mortality compared to their uninfected peers.

Overall, ***it is estimated that HIV-infected children have mortality rates 30 times higher than uninfected children of similar age in the United States*** [10]. Although deaths from opportunistic infections have decreased significantly, deaths from end-stage, acquired immunodeficiency syndrome (AIDS), sepsis and renal failure are now more common [10]. And as HIV infection transforms from a terminal illness to a chronic disease, new comorbidities emerge, including metabolic disorders and cardiovascular and kidney diseases. [85, Rank 4]

The feasibility of initiating antiretroviral therapy within 24–48hrs of birth, the ability of antiretroviral therapy to make faster reductions in the size of the viral reservoir that continue for longer in infants compared with adults, and the ability of antiretroviral therapy to minimise the effect of factors in early life that would otherwise counteract the reduced immune activation resulting from a tolerogenic environment, all provide a rationale for the proposition that unique possibilities exist to facilitate eradication or remission of HIV in children. However, there are also specific obstacles that narrow both the window of opportunity and the range of immunotherapeutic interventions that can be used in children. In particular, the very poor levels of antiretroviral therapy adherence in adolescence, coupled with the normal onset of adolescence as early as 8 years and 9 years of age in females and males, respectively, effectively places a time limit on the age by which immunotherapeutic interventions need to be in place

HIV Associated Tuberculosis

HIV and tuberculosis (TB) have always been faithful comrades facilitating each other in spreading across the globe.

In the year 2014, an estimated 1.5 million had died due to TB with a quarter of them caused by HIV. Pulmonary TB is the commonest form of TB even in HIV even though it is more frequently associated with dissemination locally and systemically, when the two infections coexist. Therefore, early diagnosis and prevention of pulmonary TB, with suitable chemoprophylaxis

have become key components towards achieving the end TB strategy.

The aim should be to combine the ideal anti-tuberculosis treatment (ATT) with mutually compatible highly active antiretroviral therapy (HAART) combinations to maximize efficacy, avoiding drug–drug interaction. Despite wide spread scale up of antiretroviral therapy (ART), only about one-third (392,000 or 77 % of the notified TB cases known to be HIV infected) were put on antiretroviral therapy.

When antiretroviral therapy is initiated in HIV infected subjects, a major complication that could arise is the onset of antiretroviral therapy related immune reconstitution inflammatory syndrome or IRIS, requiring, early detection and prompt treatment. [85, Rank 5]

Estimated rates of TB among children with HIV also vary widely, partly depending on whether the study is taking place in a TB endemic area or not and on highly active anti-retroviral treatment (HAART) coverage in that area, but also due to the problems of reaching a definitive diagnosis of TB in children with HIV and under-ascertainment. In one large paediatric HIV clinic in London, UK, there was an average of two children with HIV per year who presented with active TB over a 15 year period (18/328, 5.5% of HIV infected

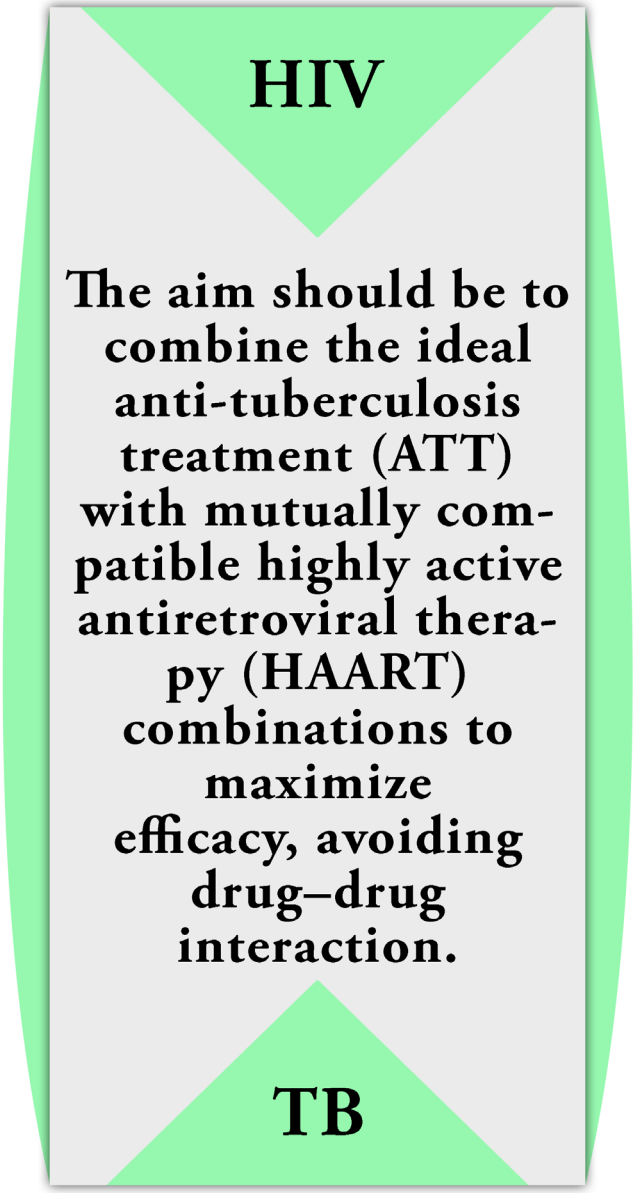


Figure 28: HIV Associated TB- Treatment

patients were treated for active TB) and in a US cohort of nearly 1500 HIV infected children, TB disease was found 3%, with an incidence of 0.61 per 100 child-years. In contrast, in high prevalence countries, the incidence of TB disease in HIV positive children is much higher. Thus, in a South African retrospective study, incidence of TB disease was estimated to be 23 per 100 child-years among HIV positive children

receiving HIV care. With increasing coverage with ART, the incidence of TB has been decreasing, but remains substantially higher in HIV positive children than in the general paediatric population

The Impact of HIV on Pathogenesis of TB

In the HIV-uninfected population, only around 10% of people infected with TB will develop TB disease. However, in HIV positive people, there is a 20-30 fold increased relative risk of developing TB disease from latent state compared with that in people without HIV, an increase that outweighs those of other risk factors such as malnutrition. The mechanisms promoting susceptibility of people with HIV to TB disease are incompletely understood.

Studies have also shown that HIV positive individuals in high TB incidence regions have an increased risk of developing active TB in the first year after HIV seroconversion, i.e. with high CD4 T-cell counts. In addition, HIV positive individuals on antiretroviral therapy with high CD4 T-cell counts continue to have an increased risk of developing TB compared with uninfected controls. This suggests that although the loss of cell-mediated immunity with HIV disease progression is likely to be an important factor with respect to

> **"According to recent World Health Organization (WHO) estimates, 9.6 million cases of tuberculosis (TB) occurred all over the world with 12 % (1.2 million) being co-infected with human immunodeficiency virus (HIV); with 37 % of these new TB cases going undiagnosed."**

the increased risk of active TB associated with HIV, this is likely to be caused by multifactorial processes.

Studies have demonstrated depletion of TB-specific CD4 T cells in peripheral blood and in the lung at early stages of HIV disease, suggesting that TB-specific adaptive immunity may be especially susceptible to HIV-associated immune damage. The essential role of CD4 T cells in generation of granulomas, and the depletion of such cells with HIV disease progression, may explain the increased risk of extra-pulmonary TB (EPTB) in HIV-positive patients.

Furthermore, the failure of the declining CD4 T cell population to regulate and maintain granulomas is one of the mechanisms proposed to be behind the increasing risk of re-activation disease in latently infected individuals with HIV. Turning to innate immunity, apoptosis or programmed cell

death of an infected macrophage is an important host immune response to TB infection. Recent work has suggested that in the context of HIV infection, apoptosis of alveolar macrophages is decreased, possibly due to raised IL-10 (an anti-inflammatory cytokine) in the lung, which may be a mechanism behind the increased susceptibility of those with HIV to TB. Genetic variants are also known to influence TB development in HIV positive patients. A recent case-control study in Brazil showed the novel association between certain inflammasome gene polymorphisms (i.e. CARD8 genetic variants) and the development of TB infection in HIV positive subjects. [57, Rank 5]

> "HIV alters the pathogenesis of TB, increasing the risks of developing active TB in those with latent infection as well as in those newly exposed to TB. Risk of active TB increases with depletion of CD4 T-cells"

Challenges of Diagnosis of TB in Patients with HIV

WHO guidelines state that diagnosis of TB in an HIV positive child should follow the same approach as for HIV-uninfected children, with taking into account the history of TB contact, clinical features suggestive of TB, positive tuberculin skin test (TST) ≥5mm are considered to be positive in HIV infected individuals, and suggestive chest X-ray signs.

Paediatric TB and HIV have overlapping clinical manifestations, including fever, weight loss and lymphadenopathy, which combined with persistent cough, could lead to missed or late diagnosis, or alternatively a misdiagnosis of either infection or concomitant infections with similar clinical features. TB generally has a more severe clinical presentation in HIV positive individuals than in those uninfected. The risk of EPTB or disseminated TB is increased in HIV positive adults, particularly with low CD4 T cell counts.

In a US study of HIV positive adults with extra-pulmonary TB, there was a significantly increased risk of central nervous system, meningeal or disseminated TB disease compared to lymph node disease in those with severe immunosuppression (CD4 <100 cells/mm3). In the limited paediatric literature, studies have reported no significant differences in the frequency of extra-pulmonary TB between HIV positive and negative children. However, others have suggested that HIV infected children with more advanced HIV disease are at higher risk of extra-pulmonary TB and combination of extrapulmo-

nary and pulmonary TB disease. Overall, the clinical presentation of TB in HIV infected children, may depend on degree of immunocompromise, and with severe, disseminated forms more frequently found in patients with advanced HIV infection; however this link is less well reported than in adults.

The presence of HIV co-infection compounds the well-recognised challenges of reaching a definitive diagnosis in children with suspected TB. Although every effort should be made to obtain a microbiologically-confirmed TB diagnosis in children, in reality this may only be achieved in a minority, reflecting the paucibacillary nature of much childhood TB, the inability of young children to expectorate sputum, the difficulties of obtaining gastric aspirates and the low yield of such samples. Sputum induction with hypertonic saline was found to be safe and useful for microbiological confirmation of pulmonary TB in both HIV positive and HIV negative children in a study: overall, 24% of children had a positive smear or culture for Mycobacterium tuberculosis and induced sputum (IS) samples had a three-times greater yield than gastric lavage (GA), with no difference in yield by HIV infection status.

This was later evaluated in the community setting with 16.9% of clinically diagnosed TB cases confirmed microbiologically, highlighting the usefulness of this diagnostic

tool in the outpatient settings. However the need for electrical supply and special technical equipment, together with the high work load and infectious hazard are substantial obstacles for widespread use of this method. It is important to note that low rates of microbiological confirmation in paediatric TB are in part due to low rates of obtaining the samples from children. For example, European Centre for Disease Prevention and Control (ECDC) surveillance demonstrated that only 42% of children with TB reported to ECDC had mycobacterial cultures sent in 2000-2009, however of those who had their cultures sent, 40% were culture positive. It is important to highlight that every effort needs to be undertaken to collect samples from children with suspected TB for microbiological confirmation.

Rapid polymerase chain reaction (PCR) tests, such as ***Xpert MTB/RIF (Mycobacterium tuberculosis DNA and resistance to rifampicin)*** assay, are increasingly used in children with TB and are recommended by WHO as the initial diagnostic test in patients suspected of multi drug resistant TB or HIV/TB. The test is an important advance in rapid detection of TB disease and detection of drug resistance.

The few prospective studies evaluating it in children have showed that it is much more sensitive than microscopy, with sensitivity being reported from 75 to 90% on sputum samples and nearly 70% on gastric aspirates, with comparable performance in HIV positive and HIV negative children. Although the sensitivity of Xpert MTB/RIF test is higher than microscopy, a substantial proportion of children with negative test had positive MTB cultures. Hence Xpert MTB/RIF test cannot be used to rule out TB, and MTB culture remains a necessary diagnostic tool.

The use of ***less or non invasive methods of sample collection, such as naso-pharyngeal aspirates (NPA) and stool samples for a PCR-based diagnostic test tests and MTB cultures is promising technique*** which was evaluated in HIV negative and HIV positive children. Small pilot studies in South Africa reported on Xpert MTB/RIF assay on stool in childhood TB. The first study assessed Xpert on decontaminated stool sediment. It showed that stool Xpert was equally sensitive to the assay on GA, detecting 75% of children with intra-thoracic culture confirmed TB.

In another pilot study, stool Xpert, which was performed directly on stool detected 47% culture-confirmed TB (80% in HIV-infected children and 33% in HIV-uninfected children) compared to 65% cases detected by Xpert on IS. The study used small stool volumes, and the authors concluded that the sensitivity may be increased by an improved protocol. Another paediatric study from the South Africa compared Nasopharyngeal aspirate with induced sputum: the sensitivity of two Xpert MTB/RIF tests were comparable, however the culture yield from Nasopharyngeal aspirate was significantly less than from induced sputum. Stool and Nasopharyngeal aspirate can be useful add on or alternative specimens in the settings where is unavailable. Urine lipoarabinomannan has been recently shown to be useful in diagnosing TB in severely immunocompromised adults, detecting up to 61% of culture-confirmed TB cases with CD4<50 cells/mm3. There are no reported studies in children to date.

With respect to tuberculin skin test there is a high rate of false negative results in HIV positive children. In a study in Cape Town, among nearly 300 paediatric TB cases, those with HIV were significantly less likely to have a positive TST than those HIV negative (36% versus 59%). In a further study among HIV-infected children with culture-confirmed TB, only 56% had a positive TST (tuberculin skin test). There is considerable discrepancy between current recommendations on use of interferon-γ release assays (IGRA) and tuberculin skin

test in diagnosis of TB infection and TB disease in children.

A systemic review and meta-analysis on interferon-γ release assays in childhood tuberculosis showed improved specificity of interferon-γ release assays compared with tuberculin skin test and similar accuracy between interferon-γ release assays and Tuberculin skin test in detection of TB infection or TB disease; however the tests showed high level of discordant results and had lower sensitivity for HIV positive children. In a recent South African study comparing performance of the tuberculin skin test and interferon-γ release assays in children recruited from hospital outpatient settings, while the proportion with a positive tuberculin skin test did not vary according to HIV infection status, HIV positive children were significantly less likely to have a positive interferon-γ release assays than HIV negative children after adjusting for degree of TB exposure; in addition, HIV negative children had an increasing probability of a positive tuberculin skin test with increasing age compared to HIV positive children, after adjusting for degree of TB exposure, Bacillus Calmette–Guérin (BCG) vaccination, malnutrition and past TB.

The authors concluded that caution is needed in interpreting interferon-γ release assays results in the context of HIV infection, given their findings that the test performance compared with tuberculin skin test is differentially affected by age and HIV infection. Some studies demonstrated that enzyme-linked immunospot assay is more sensitive than tuberculin skin test in detection of active TB in HIV positive children however the sensitivity was not sufficiently high to rule out active TB.

Although in adults with TB and HIV, particularly those with severe immunodeficiency, there may be atypical chest X-ray findings, the limited studies in children have not identified key differences in the radiological presentation of TB according to HIV status. HIV positive children may frequently have other respiratory opportunistic infections such as Pneumocystis jirovecii pneumonia, lymphoid interstitial pneumonitis or other bacterial or viral pneumonias, which can further complicate diagnosis of pulmonary TB, for example, due to similar clinical or radiological manifestations. However, the presence of one such opportunistic infection does not preclude concurrent infection with another, and the challenge is to identify all respiratory infections present and to treat appropriately. [44, Rank 3]

Challenges of Current Antiretroviral Therapy and HIV Prognosis

An examination of the lifecycle of HIV-1 informs the discussion of new approaches to antiretroviral therapy (ART), in the context of the array of small molecule inhibitors that already provide remarkably effective treatment for HIV-1 infection. HIV infection is characterized by cycles of virus production and reinfection, a process that occurs optimally within activated CD4+ T lymphocytes. Viral expression begins with the transcription and translation of early, regulatory viral gene products from the integrated proviral genome within the infected cell. This leads to a cascade of expression of late, structural viral proteins, and the assembly and budding of infectious viral particles.

Persistent HIV Infection Despite Effective Treatment

Antiretroviral drugs can be divided into classes based on their antiviral molecular mechanism (as shown in Table 2)

Virions spread within the host to infect new, susceptible target cells. The process of infection can occur directly by cell-to-cell spread in vitro, but how often this occurs in vivo is unknown. Predominantly, HIV particles enter new host cells via direct contact across the "immunological synapse" of an infected cell apposed to

ANTIRETROVIRAL DRUGS

1	Nucleoside Reverse Transcriptase Inhibitors(NRTIs)	Abacavir Emtricitabine Zidovudine Tenofovir disoproxil fumarate
2	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Efavirenz Doravirine Nevirapine Etravirine
3	Protease Inhibitors (PIs)	Atazanavir Darunavir Ritonavir Fosamprenavir
4	Fusion Inhibitors	Enfuvirtide
5	CCR5 Antagonists	Maraviroc
6	Integrase Inhibitors	Raltegravir Dolutegravir
7	Attachment Inhibitors	Fostemsavir
8	Post-Attachment Inhibitors	Ibalizumab-uiyk
9	Pharmacokinetic Enhancers	Cobicistat
10	Combination HIV Medicines	Epzicom Symtuza Trizivir Biktarvy

Table 2: Antiretroviral Drugs

a target cell, or once the budded virion has travelled free from the producer cell. In either case, the HIV particle first engages the CD4 receptor in a weak interaction with the HIV envelope glycoprotein that docks the virion at the target cell. Then a second interaction of HIV envelope with a cellular chemokine receptor, principally the C-C chemokine receptor type 5 receptor, induces a conformation shift in the HIV envelope structure that allows a fusion event to occur between the viral and cellular membranes.

Viral fusion with the target cell membrane then allows the deposition of the viral nucleocapsid within the newly infected cell, which delivers the HIV genome in its RNA form, along with molecules of HIV reverse transcriptase (RT) and integrase, in the cellular cytoplasm. HIV reverse transcriptase then co-opts cellular nucleosides and directs transcription of viral RNA into double-stranded linear DNA copies of the HIV genome. Viral integrase then forms a pre-integration complex with the HIV DNA and travels through nuclear pores to find a site for integration into the host genome. This is a vulnerable time for the infection process, as reverse transcription of the ***HIV genome must be complete and accurate in the face of the host apolipoprotein B mRNA editing enzyme,*** catalytic polypeptide-like (ApoBEC) factors, which induce hypermutation of the incoming viral RNA genome as it is reversed transcribed in to viral DNA. Further, the new viral DNA genome must rapidly achieve successful integration before it falls prey to degradation by host nucleases, or anneals in an auto-ligation event that recreates a dead-end circular viral genome.

HIV infection is then irreversibly established within the new target cell by a surviving viral genome that has entered the host genome without being marked by lethal hypermutation. Viral gene expression may then proceed in the cascade that leads to production of a new swarm of virions, or the viral genome may lapse in to a state of latency. ***Overall, while the establishment of durable viral latency is a rare event and robust viral expression may ensue in most cells immediately following infection,*** a significant number of newly infected cells—perhaps those infected while in a less activated state—may express viral particles after a delay or over a prolonged period of time.

Viral replication leads, directly or indirectly, to the loss of CD4+ T cells and immune dysfunction. Poised to interrupt this relentless process that gradually leads to fatal immunodeficiency in most infected humans, is an arsenal of more than three dozen Food and Drug Administration–approved drugs and co-formulations

available for treatment of HIV-1 infection. The vast majority of HIV-infected people on antiretroviral therapy around the world receive combination therapy using drugs from the first three classes that target the viral Reverse transcriptase, integrase, or protease enzymes. These widely used inhibitors target the HIV lifecycle after viral entry and before viral particles are expressed (N-NRTIs, NRTIs, and integrase and protease inhibitors).

Once combination Antiretrovirals (cART) is employed in a combination potent enough to ablate ongoing viral replication and prevent the emergence of drug resistance, an event documented clinically by the suppression of plasma viremia to fewer than 50 copies of HIV-1 RNA/μl, immune recovery often ensues, and AIDS-related clinical events become rare. The ongoing implementation of antiretroviral therapy throughout the world has been one of the greatest success stories of modern medicine. However, current antiretroviral therapy has burdens that include the cost of drugs and medical care, adherence to lifelong therapy, the potential for the emergence of drug-resistant HIV if adherence is not maintained, and the potential long-term toxicities of small-molecule drugs.It is in this context that we may consider the possible benefits and challenges of humoral Antiretrovirals using broadly neutralizing anti-HIV antibodies (bnAbs). Therapy with bnAbs uniquely targets the viral lifecycle at its two poles: viral entry and viral particle expression. Of note, these two stages of HIV-1 lifecycle can be targeted by monoclonal antibodies (mAbs) recognizing the CD4 inducible (CD4i) constant region 1 and 2 (C1/C2) and the gp41 cluster I region that are non-neutralizing Abs (non-nAb). Therefore, both bnAbs and non-nAbs can be used to generate molecules that can target infected cells. While fusion inhibitors and coreceptor antagonists block viral entry, these drugs have thus far found limited use in the clinic. Fusion inhibitors have not gained traction in the clinic largely due to manufacturing cost and the challenges of frequent subcutaneous injection required for their use. Coreceptor antagonists, mAbs, and mAb-based molecules share the potential benefit of blocking infection at an early stage, which prevents the transcription of viral DNA or viral proteins within the target cells, though clinical data has yet to bear this out. [90, Rank 2]

HIV-1 infection remains incurable despite the maintenance of viremia suppression, the prevention of drug resistance, and durable clinical benefits of standard antiretroviral therapy. Persistent HIV infection despite antiretroviral therapy is also marked by mild but persistent abnormalities of the

immune system, and broadly neutralizing antibodies might contribute to efforts to eradicate infection, or more fully resolve the effects of HIV infection on immune function

Latent and persistent infection by a small population of quiescent, replication-competent proviruses is founded within a long-lived population of memory T cells, capable of reigniting new rounds of infection if therapy is interrupted. This latent pool of virus is established within days of infection and is unaffected by the antiviral immune response or current therapy. The latent pool is maintained in part by the quiescent state of the infected cell, the enforcement of proviral latency by host cellular factors, and the long lifespan of such cells. Homeostatic proliferation of latently infected cells may also contribute to latent infection. HIV DNA integrants are enriched in or near host genes associated with cell cycle control, suggesting that the integration of HIV-1 into such sites could lead to proliferation of these latently infected cells.

Although one study examining a limited number of integrants suggests that these proliferating integrants are defective, a recent clinical observation calls this conclusion into question. Should rare latently infected cells transiently display viral proteins while undergoing proliferation,

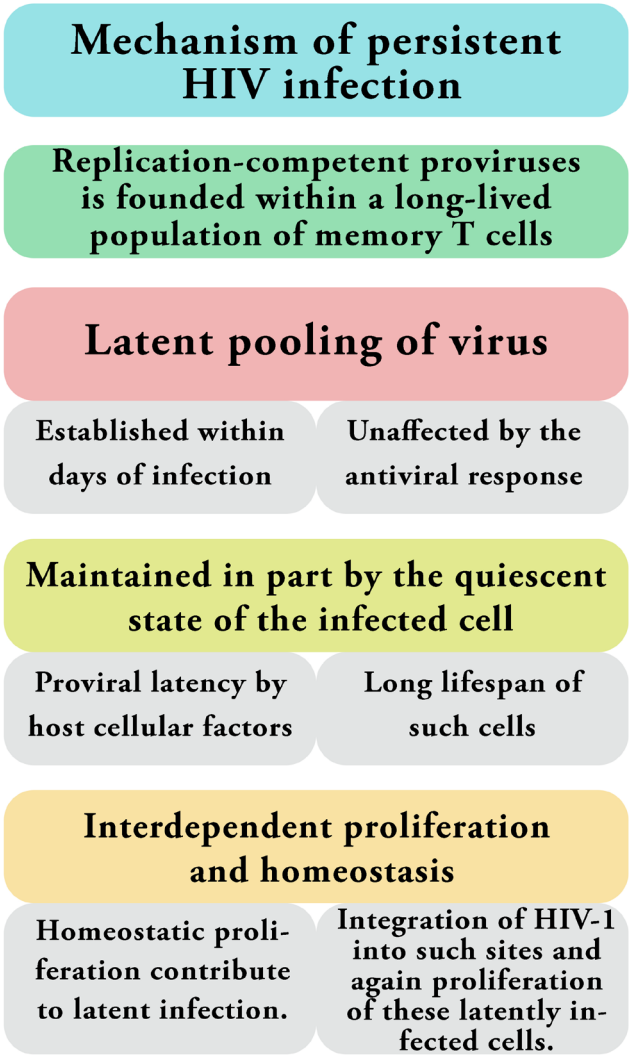


Figure 29: Persistent HIV Infection despite Effective Treatment

anti-HIV antibodies with antibody-dependent cell-mediated cytotoxic (ADCC) activity could allow clearance of these persistently infected cells. Indeed, some evidence suggests that residual viremia observed with suppressive ART may originate from viral species in the resting CD4+ T cell reservoir.

The potential contribution of residual virus replication despite ongoing ART remains controversial in some quarters. Multiple controlled studies of therapy intensification have failed to demonstrate

> "The Xpert MTB/RIF assay is a nucleic acid amplification (NAA) test that uses a disposable cartridge with the GeneXpert Instrument System. A sputum sample is collected from the patient with suspected TB. The sputum is mixed with the reagent that is provided with the assay, and a cartridge containing this mixture is placed in the GeneXpert machine. All processing from this point on is fully automated."

an effect of any of the current antiretroviral agents on low-level viremia, suggesting that such viremia is generated by cells infected prior to the implementation of therapy, and not through residual replication. Two studies of integrase inhibitor intensification found transient changes in forms of HIV 2-LTR DNA or reductions in immune activation. And one study found HIV sequence evolution within lymph node tissue in patients treated for 6 months, a relatively short period of time after initiating antiretroviral therapy. However, other studies found no evidence of viral evolution in plasma or tissues following years of suppression of viremia. If Broadly neutralizing antibodies can provide a novel and

Risk of Adverse Outcomes in HIV

It is important to address modifiable factors that contribute to the risks of adverse pregnancy outcomes for all women and pose additional risks for women with HIV.

Smoking and alcoholism

About 40% of persons with HIV are current smokers in contrast to 19% of adults in the US. Among persons with HIV who are in care, data indicate that about half drink alcohol, and while statistics vary, studies indicate that alcohol abuse or dependence is a common problem. ***Alcohol consumption has been linked to increased HIV disease progression and reduced adherence to antiretroviral therapy.*** Although the majority of women become HIV-infected through sexual contact, 12% of Black African/American and Latino women and 25% of white women acquire HIV through injection drug use. Studies have shown that alcohol and drug use are associated with risky sexual behaviors that can contribute to acquisition of sexually transmitting infections or transmission of HIV. A study using the Enhanced Perinatal Surveillance system in 15 US jurisdictions for birth years 2005 through 2008 found that ***women with HIV who abused substances (smoking, alcohol, or drugs) were***

twice as likely to have an infected infant compared to women who did not.

Tobacco, alcohol, and drug abuse are all associated with poor maternal health but are also associated with adverse pregnancy and fetal outcomes if mother is HIV infected. In an analysis of hospital discharge records linked to birth records from the state of Florida for 1998–2007, cigarette use and maternal HIV status were independent predictors of LBW, preterm birth, and small for gestational age (SGA), with the greatest risks, approximately a two-fold increase, among mothers who were HIV positive and smoked during pregnancy.

Opioid dependency

Opiate-dependent HIV clients have a significant increase in neurobehavioral deficits, and increased mortality. Cocaine use significantly increases risk of preterm birth, low birth weight, miscarriage, placental abruption, obstetrical and neonatal complications, including preeclampsia, low birth weight, neonatal withdrawal. If Associated with HIV it shows a double risk to the mother and child. Identifying and addressing both legal and illicit substances of abuse is critical to deal with prior to conception whenever possible. [58, Rank 3]

Neurocognitive Disorders

Central nervous system involvement in HIV infection is a major public health issue in resource-poor settings; however, in this Review we focus on HIV-associated neurocognitive disorders in populations with access to antiretroviral therapy. Cross-sectional studies show that HIV-associated neuro-cognitive disorders are common in industrialised countries with widely available antiretroviral therapy. The largest and most detailed study to examine cognitive impairment in HIV is the Central nervous system HIV Anti-retroviral Therapy Effects Research (CHARTER) cross-sectional cohort study that showed cognitive impairment in 814 (52%) of 1555 HIV-seropositive patients.

This cohort was selected to reflect the HIV-seropositive population receiving treatment in clinics and as such included all causes of impaired cognitive function that occur in people with HIV. Among the 843 people in this cohort who had minimally confounding neuropsychiatric disorders (unrelated to HIV infection) 40% met the criteria for impaired cognitive function. Several other studies estimate the prevalence of HIV-associated neurocognitive disorders in patients with access to ART as 20–50%, and some studies estimate that it is as high

as 69%.This wide range in prevalence estimates has resulted in uncertainty about the actual prevalence of cognitive impairment due to HIV pathology in populations with access to ART.

Several factors might predispose HIV-seropositive individuals to cognitive impairment. Cerebrovascular disease can result from the metabolic and systemic effects of HIV and Central nervous system on endothelial function and cardiovascular risk factors. These mechanisms might become increasingly important as the HIV-seropositive population ages. ***Hepatitis C infection is associated with cognitive dysfunction independently of HIV infection, and this effect is compounded in patients with HIV.*** Patients with HIV and hepatitis C co-infection are almost twice as likely to have cognitive impairment as HIV-seropositive individuals without hepatitis C infection. The use of psychoactive drugs, particularly methamphetamine, has deleterious effects on cognition, which is more pronounced when combined with HIV infection. [69, Rank 5]

Cognitive changes related to ageing might be compounded by HIV infection, and low educational level can contribute to poor cognitive function. Mood disorders might masquerade as, or be caused by, cognitive impairment. The extent to which each factor contributes to the prevalence of cognitive impairment in various populations is unclear.

Immunosuppression before ART is initiated, as estimated by the nadir CD4+ T-cell count, is strongly associated with cognitive impairment. This might be due to irreversible nervous system injury before treatment, a so-called legacy effect. Alternatively there might be a process of immune or glial cell activation that occurs during advanced immunosuppression, which persists after treatment and immune recovery.

Comorbidities are important to consider in the clinical assessment of HIV-positive individuals with cognitive impairment and in studies of HIV-associated neuro cognitive disorders. Risk factors, such as a low nadir CD4+ T-cell count, are potentially preventable, whereas others, such as depression and systemic HIV replication might be amenable to treatment. Although comorbidities are linked with impaired cognitive function, they are not strictly the underlying cause of HIV-associated neuro cognitive disorders. The widely used research classification, the Frascati criteria, proposed the terms asymptomatic neurocognitive impair ment and mild neuro cognitive disorder to characterise the neuro cognitive deficits in patients with mild HIV-associated neurocognitive disorders and state that the

diagnosis is possible only if cognitive impairment is not explained by comorbidities. [53, Rank 3]

Neuropsychiatric complications

HIV usually affects the peripheral neurologic system as neuropathy - distal sensory polyneuropathy-or radiculopathy. These conditions may be exacerbated by antiretroviral drug use or other conditions such as diabetes. ***Polyradiculopathy may also be caused by cytomegalovirus in patients with AIDS.*** Patients with distal sensory polyneuropathy generally present with symptoms of paresthesia, dysesthesia, or numbness of the bilateral extremities, whereas patients with lumbosacral radiculopathy typically experience radiating back pain, occasional asymmetric leg weakness, sacral or lower extremity sensory loss, and possible bowel or bladder dysfunction. Studies estimate that up to 50 percent of patients with HIV infection have concurrent chronic psychiatric and substance use disorders. Such conditions are not directly related to infection, but occasionally decrease quality of life and interfere with treatment adherence. Therefore, many HIV clinics routinely screen for these conditions at the initial visit and at regular intervals thereafter

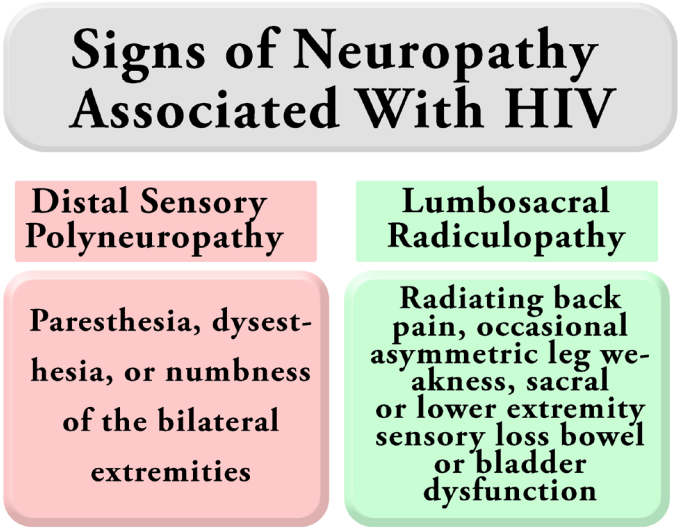


Figure 30: Signs of Neuropathic complications in HIV

Cardiopulmonary complications

Higher rates of myocardial infarction and atherosclerosis are seen in patients with HIV infection. HIV appears to independently increase the risk of cardiovascular disease via elevated cytokine levels, chronic vascular inflammation, and endothelial dysfunction. Virally mediated vascular effects may then be compounded by lipid or metabolic changes caused by infection and antiretroviral use. In addition, some experts suggest that extra attention be paid to current and previous antiretroviral exposure (i.e., abacavir, protease inhibitors) when evaluating patients for cardiovascular disease.

Other HIV-associated cardiac complications - cardiomyopathy, myocarditis, and pericarditis are still reported, although their incidence has decreased as