The Changing Trends of HIV Subtypes and Its Implication on Mother-to-Child Transmission

Michael Kiptoo
Kenya Medical Research Institute
Kenya

1. Introduction

The first cases of Acquired Immune Deficiency Syndrome (AIDS) were described in the United States in 1981\(^1\). In Kenya, the first case was recognized in 1984\(^2\) and since that time, Human Immunodeficiency Virus (HIV)/AIDS still remains a huge barrier to social and economic development. It is estimated that 33.4 million people worldwide were living with HIV by December 2008. During 2008 more than two and a half million adults and children became infected with HIV. Sub-Saharan Africa remains the epicenter\(^3\). Recent data show HIV prevalence in Kenya of 7.4\%, resulting in 1.4 million Kenyans living with HIV. An estimated 190,000 HIV-infected Kenyans receive Antiretroviral therapy (ART), representing 44\% of those in need of treatment\(^4\). Access to ART in Kenya has significantly increased since the start of the World Health Organization (WHO) 3 by 5 initiative. The Kenya AIDS indicator survey of 2007 showed that of the estimated 392,000 Kenyan adults in need of ART, 138,000 (35\%) had received the treatment by September 2007\(^4\).

Human immunodeficiency virus is a highly variable virus due to rapid mutation. This results in many different strains of HIV, even within the body of a single infected person. There are two types of HIV: HIV-1 and HIV-2. Both types are transmitted by sexual contact, through blood, and from mother to child, and they cause clinically indistinguishable AIDS. However, HIV-2 is less easily transmitted, and the period between initial infection and illness is longer in the case of HIV-2. Worldwide, the predominant virus is HIV-1. The relatively uncommon HIV-2 type is concentrated in West Africa and is rarely found elsewhere\(^5\).

The strains of HIV-1 are classified into three groups: the "major" group M, the "outlier" group O and the "new" group N. These three groups represent three separate introductions of SIV into humans. Members of HIV-1 group O have been recovered from individuals living in Cameroon, Gabon, and Equatorial Guinea with the genomes sharing less than 50\% identity with group M viruses\(^6\). The group N HIV-1 strains have been identified in infected Cameroonian\(^7\). In 2009, a newly-analyzed HIV sequence was reported to have greater similarity to a Simian Immunodeficiency Virus (SIV) recently discovered in wild gorillas (SIVgor) than to SIVs from chimpanzees (SIVcpz). The virus had been isolated from a Cameroonian woman residing in France who was diagnosed with HIV-1 infection in 2004. The scientists reporting this sequence placed it in a proposed Group P "pending the identification of further human cases.\(^8\)

More than 90\% of HIV-1 infections belong to HIV-1 group M. Within group M there are nine genetically distinct subtypes (or clades) of HIV-1. These are subtypes A, B, C, D, F, G, H, J
and K9. The HIV-1 population present within an individual can vary from 6% to 10% in nucleotide sequences. Human immunodeficiency virus type 1 isolates within a clade may exhibit nucleotide distances of 15% in gag and up to 30% in gp 120 coding sequences. One obvious consequence of the genetic diversity of HIV-1 is the potential impact on the efficacy of a future vaccine. Less obvious and largely controversial is the impact of genetic diversity on disease progression, vertical transmission, response to antiretroviral therapy and drug-resistance pathways.

2. Viral variation

High rates of genetic variation are a hallmark of retroviruses. The molecular basis for variation is the error-prone nature of the reverse transcriptase enzyme and the absence of any exonucleolytic proof-reading mechanisms to correct the errors. The ability of HIV to generate extremely large numbers of diverse variants is an advantage to the virus in its continuous effort to adapt to local environments or respond to selection pressures. Viral variation in HIV is as a result of mutation and recombination. Due to the lack of proof-reading ability of the HIV-1 reverse transcriptase enzyme, several mutations are generated. These point mutations are base-pair substitutions, and base-pair insertions or deletions. Recombination occurs frequently during reverse transcription, a consequence of having two RNA genomes packaged per virion.

A significant fraction of the HIV-1 group M global diversity includes interclade viral recombinants (Figure 1). These HIV-1 recombinants are found in geographic areas such as Africa, South America and Southeast Asia where multiple subtypes co-exist and account for 10% of circulating HIV-1 strains. The HIV-1 recombinants are known as "circulating recombinant forms" or CRFs. Most HIV-1 recombinants have arisen from Africa and a majority contains segments originally derived from clade A viruses.

![Fig. 1. Geographical distribution of HIV-1 subtypes (Adapted from WHO-UNAIDS HIV Vaccine Initiative)](www.intechopen.com)
In Thailand, for example, the predominant circulating strain consists of a clade A gag plus pol gene segment and a clade E env gene (CRF01_AE)\(^{13}\). Within subtypes A and F, there are separate sub-clusters that are related closely to each other than to other subtypes. They are designated A1, A2 and F1, F2 respectively. Within subtypes B, C and G there are geographically localized sub-clusters that share a common ancestry as suggested in phylogenetic trees: subtype B from Thailand, subtype C from India and Ethiopia, and subtype G from Spain and Portugal. The classification of HIV strains into subtypes, sub-subtypes and CRFs is a complex issue and the definitions are subject to change as new discoveries are made. These subtypes are generally confined to specific geographical regions with some of these subtypes having been characterized in Kenya.

### 3. HIV-1 diversity in Kenya

Kenya has about 2.2 million people living with HIV/AIDS. In 2003, the first national HIV prevalence survey was carried out, which estimated that 7\% of adults aged 15-49 years in Kenya were infected\(^{14}\). Several studies on the HIV molecular epidemiology in Kenya has been done mostly based on partial sequencing of the env, gag or pol regions.

In a study carried out between 1990 and 1992, 22 HIV-1-seropositive pregnant women and 1 HIV-1-infected baby attending the Pumwani Maternity Hospital of Nairobi were studied as part of a cohort study of maternal risk factors in mother-to-child transmission. A 250-base pair (bp) fragment of the env gene encoding C2V3 was amplified mostly from Deoxyribonucleic Acid (DNA) isolated from primary peripheral blood mononuclear cells and subsequently sequenced. The results revealed that 19 were classified in subtype A versus 3 in subtype D, together with a much larger variation between subtype A strains as compared to subtype D strains, which suggested an earlier introduction of a subtype A strain, multiple introductions of subtype A strains, and/or faster diversification of subtype A strains as compared to subtype D strains\(^{15}\).

Another study carried out in 1996 revealed that 71\% of the viruses were clade A and 29\% were clade D. The most divergent clade A isolate identified in the study grouped closely with two other taxa previously reported as having no distinct clade affiliation\(^{16}\). These findings signaled the emergence of an outlier group of clade A variants or a new subtype of HIV-1. The first two virtually full-length genome sequences from HIV-1 subtype G were isolated in Sweden and Finland but originated in Congo and Kenya\(^{17}\).

In another study, HIV-1 subtype was determined among 320 women from Nairobi by a combination of heteroduplex mobility assays and sequence analyses of envelope genes, using geographically diverse subtype reference sequences as well as envelope sequences of known subtype from Kenya. The distribution of subtypes in this population was as follows: subtype A, 225 (70.3\%); subtype D, 65 (20.5\%); subtype C, 22 (6.9\%); and subtype G, 1 (0.3\%). Intersubtype recombinant envelope genes were detected in 2.2\% of the sequences analyzed\(^{18}\). This study also addressed whether infection with a particular subtype is associated with differences in disease stage. It was found out that the plasma viral RNA levels were highest in women infected with subtype C virus, and women infected with subtype C virus had significantly lower CD4 lymphocyte levels than women infected with the other subtypes.

To further define the genetic diversity of HIV-1 in Kenya, purified peripheral blood mononuclear cell DNA from 41 HIV-1 positive blood donations collected from six hospitals across southern Kenya was used to amplify near full-length genomes by nested PCR.
Among 41 near full-length genomes, 25 were non-recombinant (61%) and 16 were recombinant (39%). Of the 25 pure subtypes, 23 were subtype A, one was subtype C and one was subtype D. Most recombinants consisted of subtype A and either subtype C or subtype D; a few contained A2, a recently identified sub-subtype. Two A2/D recombinants had identical breakpoints and may represent a circulating recombinant form. A third A2/D recombinant had the same structure as a previously described Korean isolate, and these may constitute a second A2-containing circulating recombinant form\textsuperscript{19}. The latter has been designated as CRF16.

Our group further analyzed samples from pregnant women in rural western Kenya based on the envelope region (C2V3) and we identified for the first time the presence of CRF10 which had been identified previously in Tanzania. The following were the other subtypes: 20 subtype A1, 2 subtype D, 1 subtype C, 1 subtype G, 2A/D, 2A/C, and 2 were unclassified\textsuperscript{20}. In order to investigate the \textit{in vivo} evolution of recombinant HIV, we followed up on a mother who was initially co-infected with subtypes A and D in Kenya. Blood samples were obtained in 1996 and 2002, and HIV pol and env genes were amplified by PCR, cloned, sequenced, and phylogenetically analyzed. In this study, the clones (1996) generated from the pol and env genes clustered either with subtypes A and D reference strains. However, two clones from the pol gene were found to be independent recombinants between subtypes A and D by RIP analysis, suggesting active generation of recombinant forms. As for the 2002 sample, all the clones from the pol gene clustered only with the subtype A reference strain, while all the env clones clustered only with subtype D, denoting a dominance of an A/D recombinant form\textsuperscript{21}.

A detailed molecular epidemiological investigation on HIV-1-infected women attending an antenatal clinic in Kisumu, based on gag-p24 region from 460 specimens revealed that 310 (67.4%) were A, 94 (20.4%) were D, 28 (6.1%) were C, 9 (2.0%) were A2, 8 (1.7%) were G, and 11 (2.4%) were unclassifiable. Analysis of the env-gp41 region revealed that 326 (70.9%) were A, 85 (18.5%) D, 26 (5.7%) C, 9 (2.0%) each of A2 and G, 4 (0.9%) unclassifiable, and 1 (0.2%) CRF02\_AG. Parallel analyses of the gag-p24 and env-gp41 regions indicated that 344 (74.8%) were concordant subtypes, while the remaining 116 (25.2%) were discordant subtypes. The most common discordant subtypes were D/A (40, 8.7%), A/D (27, 5.9%), C/A (11, 2.4%), and A/C (8, 1.7%) \textsuperscript{22}.

In 2003/4, we carried out a study in northern Kenya, especially areas bordering Ethiopia, Sudan and Somalia to determine the circulating HIV-1 subtypes. This study revealed that 50% were subtype A, 39% subtype C and 11% subtype D based on the analysis of partial env (C2V3) sequences\textsuperscript{23}. This showed that subtype A and C are the dominant strains in circulation unlike the other regions with subtype A being dominant and followed by subtype D. We carried out a study in 2005 to establish HIV-1 subtype diversity among patients with sexually transmitted infections in Nairobi. In this study, 140 samples were collected and partial pol gene sequencing done. From the analysis it was established that subtype A1 was the major subtype (64%) followed by D (17%), C (9%), G (1%), and recombinants AD (4%), AC (3%), CRF02\_AG (1%), and CRF16\_A2D (1%) \textsuperscript{24}.

From April 2005 to July 2006 we carried a study in North Rift to determine the subtypes circulating based on the pol region (RT). This was part of a study to explore the status of nevirapine resistant HIV genotypes in rural hospitals in North Rift Valley Province of Kenya. Of the total of 39 HIV infected mother and child samples successfully amplified and sequenced, 28 were subtype A1 (72%), 5 subtype D (13%), 3 subtype C (8%), 1 subtype A2 (3%) and one subtype G (3%). Our analysis shows that like other parts of the country the
predominant circulating subtype in North Rift was A1\textsuperscript{25}. This clearly shows that the HIV epidemic in Kenya is a dynamic one and is continually evolving. This observation is applicable to other countries where different subtypes are circulating.

4. Antiretroviral therapy

The development of antiretroviral therapy has been one of the most dramatic progressions in the history of medicine. The early years, 1987-90, brought great hope and the first modest advances using monotherapy\textsuperscript{26}. The use of combination therapies became widely used in 1996. Within only three years, from 1994-1997, the proportion of untreated patients in Europe decreased from 37\% to 9\%, whilst the proportion of highly active antiretroviral therapy (HAART) patients rose from 2\% to 64\%. Almost all compounds used as part of HAART are either nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), or protease inhibitors (PIs). These three classes of drugs target intracellular steps in the viral life cycle mediated by two viral enzymes, reverse transcriptase (RT) and HIV protease. The fusion inhibitors have been introduced recently and block the viral entry\textsuperscript{27,28}.

4.1 Reverse transcriptase inhibitors

The reverse transcriptase inhibitors (RTI) are divided into nucleoside/nucleotide reverse transcriptase inhibitors (NRTI/NtRTI) and non-nucleoside reverse transcriptase inhibitors (NNRTI). The NRTI mimic the naturally occurring building blocks of DNA. After conversion to their triphosphate form, they compete with natural deoxynucleoside for binding to reverse transcriptase (RT), the necessary enzyme for HIV multiplication within the human cell. The NRTI also compete with deoxynucleoside triphosphates for incorporation into newly synthesized viral DNA chains, resulting in chain termination\textsuperscript{29}. Seven compounds of the NRTI class have been approved by the US Food and Drug Administration (FDA): zidovudine (ZDV/AZT), stavudine (d4T), didanosine (ddI), zalcitabine (ddc), lamivudine (3TC), abacavir (ABC) and emtricitabine (FTC). The NRTI are divided into thymidines such as zidovudine (ZDV) and stavudine (d4T) which act preferentially on activated CD4 cells and non-thymidines such as didanosine (ddI), zalcitabine (ddc) and lamivudine (3TC) which act on resting and activated CD4 cells\textsuperscript{29}. There is also a new class of anti-HIV drugs called nucleotide reverse transcriptase inhibitors which includes tenofovir. The concentration of NRTIs in cerebrospinal fluid (CSF) varies, but, thus far, zidovudine is the only drug with proven efficacy against the neurological complications of HIV\textsuperscript{30}. The NNRTI target the reverse transcriptase enzyme. The NNRTI bind directly and non-competitively to the enzyme at a position in close proximity to the substrate-binding site for nucleosides. The resulting complex blocks the catalyst-activated binding site of the reverse transcriptase, which can thus bind fewer nucleosides, and polymerization is slowed down significantly. These include efavirenz (EFZ), nevirapine (NVP) and delavirdine (DLV).

4.2 Protease inhibitors

The HIV protease cleaves the viral gag-pol polyprotein into its functional subunits. Inhibition of the protease, preventing proteolytic splicing and maturation, leads to the release of virus particles, which are non-infectious. Knowledge of the protease substrate and protease inhibitor structures has led to successful development of protease inhibitors\textsuperscript{31}. The protease inhibitors (PI) work against HIV in the late stage of viral replication to prevent infectious virus
production from infected cells. They block the protease enzyme, which is necessary for the production of mature virions. Seven compounds of the PI class have been approved by the US Food and Drug Administration (FDA): saquinavir (SQV), indinavir (IDV), ritonavir (RTV), nelfinavir (NFV), amprenavir (AMP), lopinavir/ritonavir (LPV), and atazanavir (ATV).

4.3 Fusion inhibitors
The fusion inhibitors block the attachment of the viral envelope to the cell membrane and the first to be approved was enfuvirtide (Fuzeon) by the US Food and Drug Administration (FDA). The availability of these drugs has changed the treatment of HIV-1 infected patients. Escalating drug resistance in treatment-experienced HIV-1-infected patients has made management increasingly difficult. In clinical trials, tripanavir/enfuvirtide based salvage regimens have produced potent and durable responses. Multiple observations in a variety of settings have demonstrated a decrease in mortality due to HIV related illnesses, and the incidence of HIV-1 related opportunistic infections has decreased. However, the efficacy of these antiretroviral treatments is impaired by poor compliance with treatment regimens, sub-optimal antiviral potency and drug concentrations, and selection of drug-resistant HIV quasi species.

5. Mechanisms of HIV drug resistance
Human immunodeficiency virus replication is a highly dynamic process whereby large numbers of virions are created and destroyed by the immune system each day. Mutations in the HIV genome are primarily generated during the initial steps of HIV replication cycle. The genomic ribonucleic acid (RNA) carried by HIV is copied into DNA early in the replication cycle. The RT makes spontaneous errors when copying the RNA, placing the incorrect nucleotide in the growing DNA strand about once in every 10,000 to 30,000 nucleotides. These nucleotide errors may cause changes in the amino-acid coding of the HIV proteins made from the HIV DNA, potentially altering the structure and/or function of these proteins and affecting the replication competence of the viral strain. Since mutations in the proteins cause changes in drug susceptibility, the nomenclature for drug resistance mutations refers to the changes in the amino acid sequence of the proteins. Viral mutations are described in the format M184V, where the initial letter represents the wild-type amino-acid of the particular protein, the number represents the mutated codon, or position of the protein and the end letter represents the mutant amino acid that is present.

In uncontrolled HIV infection, the high HIV replication rate generates a large pool of genetically but distinct HIV strains called quasispecies, each with potential to develop into the dominant strain. A strain possessing a mutation that provides a growth advantage in a particular environment such as in the presence of antiretroviral drugs out competes the other quasispecies and become the dominant viral strain in the population.

6. Mother-To-Child Transmission of HIV (MTCT)
6.1 Pathogenesis of MTCT
Human Immunodeficiency Virus can be transmitted from a HIV-infected mother to the infant during pregnancy (in utero), during delivery (intra partum) or via breastfeeding (post partum). The precise mechanisms responsible for in utero and intra partum MTCT remain
uncertain. The placenta is an effective barrier to infection, but conditions that compromise the placental unit such as vasoactive drug use or chorio-amnionitis, may allow mixture of maternal and foetal blood.

Virus in vaginal secretions, mother’s blood and breast milk may penetrate the infant’s mucosal tissues either during or after delivery. After penetrating the mucosal tissues, langerhans cells and key immune cells such as dendritic cells, macrophages and lymphocytes (CD4 T cells) take up the virus. These cells transport the virus to the lymph nodes where it replicates. In 5-7 days post exposure, HIV appears in the blood within infected CD4 T cells or as free virions.

6.2 Risk factors for MTCT
In non-breastfed populations, 25-30% of infected infants have detectable provirus in their peripheral blood lymphocytes at birth, suggesting in utero infection. The detection of HIV RNA or provirus after a week or two suggests intra partum transmission of HIV-1. In breastfed populations, approximately 15% of infections are thought to occur in utero, 65-70% during delivery, and 15-20% during post partum through breastfeeding.

Maternal plasma HIV-1 viral load is one of the strongest predictors of MTCT. Mother-to-child transmission of HIV can occur at any maternal viral load, but the risk of transmission increases with increasing maternal plasma HIV-1 load. Mothers with a high viral load during pregnancy are more likely to transmit virus to their infants during the in utero or intra partum periods, particularly if they seroconvert while pregnant. Prolonged labour accounts for MTCT during delivery. An increased risk of MTCT has been observed in first-born twins. In addition, cervico-vaginal ulcers or high maternal cervical or vaginal HIV-1 proviral copy numbers have been significantly associated with MTCT, independent of maternal plasma HIV-1 load.

Available data suggests that most breast milk transmission occurs within the first months of life. Longer durations of breastfeeding are associated with increased risk of HIV-1 transmission to infants. The maternal factors associated with breastfeeding transmission include younger age and higher parity, maternal HIV disease stage and breast health. Advanced disease stage is a risk factor associated with postnatal transmission of HIV-1. This is associated with low blood CD4+ cell counts and higher maternal peripheral blood or milk viral load.

Several studies have established the association between transmission of HIV-1 through breastfeeding with maternal breast abnormalities such as breast abscesses, mastitis and nipple lesions. In Kenya, for example, mastitis and breast abscesses were associated with late postnatal transmission of HIV-1. In Malawi, women with increased milk sodium concentrations consistent with subclinical mastitis had higher milk viral load. In another study in Kenya, maternal nipple lesions and mastitis were associated with increased risk of postnatal transmission. Oral candidiasis in infants before 6 months of age was associated with postnatal transmission. A study in the Ivory Coast suggested maternal breast abscesses, cracked nipples and oral candidiasis in infants as risk factors for late postnatal transmission of HIV-1 through breastfeeding.

7. Strategies for reduction of MTCT
7.1 Behavioural Intervention
Counselling and testing in the antenatal clinic offers an opportune time to discuss prevention of primary HIV infection. For women who are found to be HIV-negative, safe sexual behaviour should be reinforced.
7.2 Nutritional intervention
Low Vitamin A levels have been associated with higher rates of MTCT and with higher levels of virus in breast milk\textsuperscript{56}. Among HIV-infected pregnant women, low selenium status increases risk of MTCT and poor pregnancy outcomes\textsuperscript{57}. Therefore, HIV positive pregnant women should maintain adequate nutritional status.

7.3 Obstetric intervention
Studies have shown that vaginal cleansing with antiseptic is associated with reduced MTCT and improved perinatal outcome\textsuperscript{58}. The other obstetric intervention is elective caesarean section (CS). Prospective cohort studies have shown that the rate of perinatal transmission among women undergoing elective CS delivery was significantly lower than among women undergoing non-elective CS or vaginal delivery\textsuperscript{59}.

7.4 Antiretroviral prophylaxis
The use of antiretroviral prophylactic therapies to reduce MTCT came into effect following studies by Paediatrics AIDS Clinical Trial Group 076\textsuperscript{60}. In this trial, zidovudine (ZDV) was given to mothers beginning at 14-34 weeks of pregnancy, intravenously during labour and for 6 weeks to infants. This resulted in 68\% reduction in MTCT. Owing to the high cost and complexity of the regimen, recommendations were made for shorter and simplified forms to be tried in developing countries. A trial in Thailand showed a 50\% reduction in mother-to-child transmission of HIV in non-breastfeeding women who took an exclusive oral ZDV regimen twice a day beginning at 36 weeks gestation and every 3 hours during labour\textsuperscript{61}.

An identical regimen on breastfeeding populations in two areas of West Africa showed high efficacy rates by 3-6 months\textsuperscript{62, 63}. In the perinatal transmission trial (PETRA\textsuperscript{®}) carried out in Eastern and Southern African countries, a combination of zidovudine and lamivudine had efficacies beyond 65\% at 18 months\textsuperscript{64}. In Kenya, a study was carried out to determine the feasibility of using short-course zidovudine to prevent MTCT in a breastfeeding population in a rural area. The mothers were given a daily dose of 400 mg of ZDV starting at 36 weeks of gestation and another 300 mg every three hours in\textit{tra partum}. No ZDV was administered to infants after delivery. Even though not all the mothers took ZDV, the HIV vertical transmission rate was reduced by 65.6\% \textsuperscript{65}. In the ultra-short nevirapine (NVP) HIVNET 012\textsuperscript{®} trial in Uganda, one dose given to the mother during labour combined with one dose given to the neonate within 72 hours of birth reduced 3-month transmission by 47\% \textsuperscript{66}. These studies have formed the basis of recommendations on the use of short course antiretroviral therapies for prevention of mother-to-child transmission of HIV in developing countries\textsuperscript{45, 67}.

8. Drug resistance, viral subtypes and implications on MTCT
Drug resistance is one of the greatest threats to successful long-term antiretroviral therapy (ART). Combination ART delays the onset of drug resistance, but drug resistance can still develop and lead to a reduction in drug efficacy. Once resistance has developed to a drug or drug class, resistant viruses are archived in lymphoid tissue, and responses to the drug or drug class are compromised indefinitely\textsuperscript{68}. Because cross-resistance may also limit the efficacy of unused ART agents, many persons infected with HIV can exhaust effective ART treatment options quickly if careful selection and monitoring of initial ART are not undertaken.

Many studies have shown the existence of polymorphisms among non-B strains, especially naturally occurring minor mutations in the protease gene, as well as atypical substitutions in
protease (PR) and reverse transcriptase (RT) at positions associated with resistance. Accessory (or minor) mutations may not result in a significant decrease in susceptibility, but may be associated with an increase in viral fitness (replication capacity) and/or increase in resistance level associated with major mutations, and thus long-term failure of therapy. It is not clear whether differences exist among the various forms of HIV-1 (groups, subtypes, and CRFs) in terms of transmissibility, pathogenicity, and responses to antiretroviral therapy, but some in vitro and in vivo observations suggest that certain variants may respond differently to certain antiretroviral drugs.

There is a solid body of evidence to indicate that drug resistance pathways vary between different subtypes. One classic example is that of the development of NFV resistance in subtypes B and G. Patients with subtype B tend to preferentially develop the D30N mutation, whereas those with other subtypes including G tend to preferentially develop L90M. Even in cases where the first mutation is L90M in both B and G subtypes, subsequent mutations differ significantly. In subtype B, L63P is the second mutation and occurs in almost 100% of cases, suggesting that the progression of resistance is dependent on the emergence of this mutation, followed by the selection of V77I and other mutations. In subtype G, L89I follows the emergence of L90M, and is present in almost 100% of cases suggesting a role in subtype G similar to that of L63P in subtype B. The third mutation can be either A71V or I54V.

The HIV-1 group O and HIV-2 strains are naturally resistant to non-nucleoside reverse transcriptase inhibitors (NNRTIs). Human immunodeficiency virus type 2 variants carry the major NNRTI resistance mutations, Y181I, Y188L, and G190A, in addition to the minor mutations, K101A, V106I, and V179I. Human immunodeficiency virus type 2 isolates show 1000–10,000-fold resistance to first and second-generation NNRTIs. These observations clearly show that the use of NNRTIs to reduce the transmission rates of mother-to-child will not work among women infected with HIV-2. Subtype O viruses show resistance to NNRTIs through two distinct mutational profiles involving the NNRTI secondary mutations, A98G, K103R, and I79E, in the presence or absence of Y181C. Subtype O viruses without Y181C show greater than 100-fold and greater than 500-fold resistance to nevirapine and efavirenz, respectively.

Clinical trials demonstrate a disparity in the frequency of primary nevirapine resistance, involving K103N or Y181C in 65–69, 36, 19 and 21% in women with subtype C, D, A and CRF02_AG infections, respectively. Subtype C viruses have a signature valine codon polymorphism absent in other non-B subtypes. This subtype C polymorphism facilitates the acquisition of V106M upon selective drug pressure with efavirenz but not nevirapine. The V106M confers cross-resistance to NNRTIs.

A rapid selection of K65R is observed in subtype C strains compared with the slow evolution of K65R in subtype B. Subtype G strains are less susceptible in vitro to protease inhibitors (PIs), the rate of occurrence of nevirapine resistance-associated mutations after a single dose is significantly higher in women with HIV-1 subtype C than in women with subtype A or D.

Nevirapine prophylaxis used in the HIVNET 012 has been reported to result in selection of single point mutations strongly associated with high resistance to non-nucleoside reverse transcriptase inhibitors that were detectable in 19% of the mothers and 46% of the infants. By contrast with HIVNET 012, where intra partum and neonatal exposure to nevirapine or zidovudine was limited, the PETRA interventions led to ongoing maternal exposure to zidovudine plus lamivudine from 36 weeks gestation. It has been postulated that induction of significant single mutation (M184V) lamivudine resistance will occur.
Viral genetic diversity seems to have an important role on MTCT and in timing of transmission. In a study by Kwiek and colleagues, among HIV-1 subtype C infected mothers, they observed different diversity patterns during intrauterine and intrapartum transmissions. Intrauterine infected-infants tended to be infected by one single variant that was more detected in the mother’s plasma, whereas intrapartum infected-infants showed multiple variants of detected and undetected variants of the mother’s quasispecies. Regardless of the time of transmission, nearly 50% of the quasispecies included the transmission of variants that were not detected in the mother’s blood plasma, suggesting a genetic bottleneck and arguing against a stochastic model of vertical transmission.

A number of studies have been carried out to determine the role of HIV-1 subtypes on MTCT. A study carried out in Kenya among 414 women, MTCT rates were higher among women with subtype D compared with subtype A in either the gp41. Such differences may be caused by altered cellular tropism for placental cell types. However, a study carried out in Uganda found no significant difference in the rate of MTCT in women with subtype A versus D. Several HIV-1 structural, regulatory and accessory genes are highly conserved following MTCT. In addition, HIV-1 sequences from non-transmitting mothers are less heterogeneous compared with transmitting mothers, suggesting that a higher level of viral heterogeneity influences MTCT.

The mechanism through which MTCT occurs seems not to be fully clear, and should be a focus point for researches to understand the biology of viral transmission and also attempt to eliminate one of transmission routes. Further studies are needed regarding the mechanisms that determine the moment of transmission, and the influence of the viral subtype, the influence of host immunity, recombination and drug resistance on MTCT may provide insight into new prevention strategies and the development of an effective vaccine. Early and universal access to ARV during pregnancy is the most important measure to achieve a decrease in vertical transmission in areas where clade distribution differs.

9. References

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PETRA® (2002). Efficacy of three short-course regimens of Zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother-to-child in...


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