

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 1981¹. In Kenya, the first case was recognized in 1984² 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 epicenter³. 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 treatment⁴. 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 2007⁴.

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 elsewhere⁵.

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 viruses⁶. The group N HIV-1 strains have been identified in infected Cameroonians⁷. 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 cases⁸."

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 retroviruses¹⁰. 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 virion¹¹.

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 viruses¹².

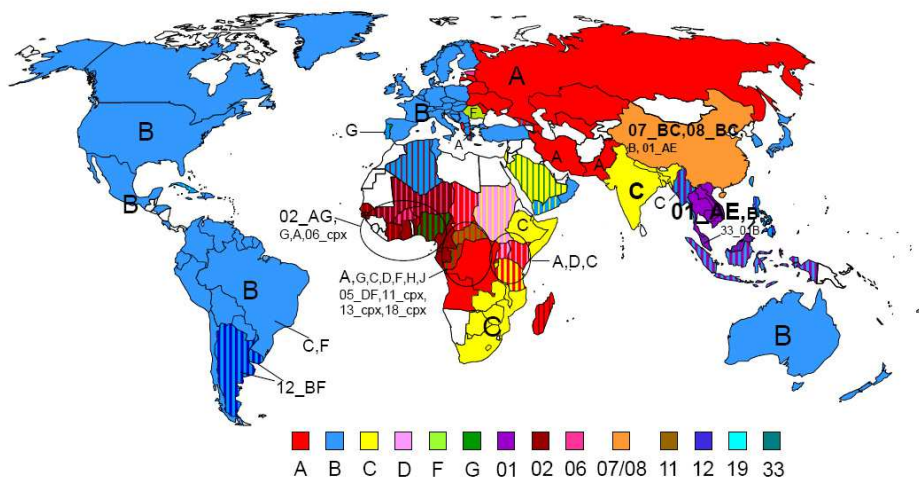


Fig. 1. Geographical distribution of HIV-1 subtypes (Adapted from WHO-UNAIDS HIV Vaccine Initiative)

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 infected¹⁴. 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 strains¹⁵.

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 affiliation¹⁶. 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 Kenya¹⁷.

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 analyzed¹⁸. 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 form¹⁹. 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 unclassified²⁰. In order to investigate the *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 form²¹.

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%)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) sequences²³. 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%)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 A1²⁵. 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 monotherapy²⁶. 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^{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 termination²⁹.

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 cells²⁹. 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 HIV³⁰.

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 delaviridine (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 inhibitors³¹. 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 virions³². 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)³³. 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 responses³⁴. 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 decreased³⁵.

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^{36,37}.

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 day³⁸. 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 nucleotides³⁹.

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 present⁴⁰.

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 population⁴¹.

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 blood⁴².

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 virions⁴³.

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* infection⁴⁴. 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 breastfeeding⁴⁵.

Maternal plasma HIV-1 viral load is one of the strongest predictors of MTCT⁴⁶. 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 pregnant⁴⁷. Prolonged labour accounts for MTCT during delivery. An increased risk of MTCT has been observed in first-born twins⁴⁸. 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 load⁴⁹.

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 infants⁵⁰. 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^{51, 52}.

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-1⁵³. In Malawi, women with increased milk sodium concentrations consistent with subclinical mastitis had higher milk viral load⁴⁷. 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 transmission⁵⁴. 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 breastfeeding⁵⁵.

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 milk⁵⁶. Among HIV-infected pregnant women, low selenium status increases risk of MTCT and poor pregnancy outcomes⁵⁷. 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 outcome⁵⁸. 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 delivery⁵⁹.

7.4 Antiretroviral prophylaxis

The use of antiretroviral prophylactic therapies to reduce MTCT came into effect following studies by Paediatrics AIDS Clinical Trial Group 076⁶⁰. 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 labour⁶¹.

An identical regimen on breastfeeding populations in two areas of West Africa showed high efficacy rates by 3-6 months^{62, 63}. In the perinatal transmission trial (PETRA[®]) carried out in Eastern and Southern African countries, a combination of zidovudine and lamivudine had efficacies beyond 65% at 18 months⁶⁴. 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 *intra 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%⁶⁵. In the ultra-short nevirapine (NVP) HIVNET 012[®] 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%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^{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 indefinitely⁶⁸. 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 resistance⁶⁹. Accessory (or minor) mutations may not result in a significant decrease in susceptibility⁷⁰, 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 drugs⁷¹.

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^{72,73}.

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, respectively⁷⁴.

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^{75,76,77,78}. 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 NNRTIs⁷⁹.

A rapid selection of K65R is observed in subtype C strains compared with the slow evolution of K65R in subtype B⁸⁰. 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^{81,82}.

Nevirapine prophylaxis used in the HIVNET 012⁶⁶ 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 infants⁸³. By contrast with HIVNET 012⁶⁶, 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 occur⁸⁴.

Viral genetic diversity seems to have an important role on MTCT and in timing of transmission. In a study by Kweek 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 transmission⁸⁵.

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 gp41⁸⁶. 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 D⁸⁷. 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 vaccine⁸⁸. 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 differs⁸⁹.

9. References

- [1] Centres for Disease Control (1981). *Pneumocystis pneumonia*--Los Angeles. *Morbidity and Mortality Weekly Report*; 30: 250-252.
- [2] Obel A., Shariff S.M., Gitonga E., Shah M. and Gitau W. (1984). Acquired immune deficiency syndrome in an African. *East African Medical Journal*; 61: 724-730.
- [3] UNAIDS/WHO AIDS epidemic update December 2008. www.unaids.org.
- [4] *Kenya AIDS Indicator Survey 2007* Nairobi Kenya: National AIDS and STI Control Programme, Ministry of Health Kenya (NASCOP); 2008.
- [5] Peeters M., Piot P. and van der Groen G (1991). Variability among HIV and SIV strains of African origin. *AIDS*; 5 (Suppl.1): S29-S36.
- [6] Subbarao S. and Schochetman G. (1996). Genetic variability of HIV-1. *AIDS*; 10 (Suppl. A): S13-S23.
- [7] Simon F., Maucleere P., Roques P., Loussert-Ajaka I., Muller-Trutwin M.C., Saragosti S., Georges-Courbot M.C., Barre-Sinoussi F. and Brun-Vezinet F.(1998). Identification of a new Human Immunodeficiency Virus type 1 distinct from group M and group O. *Nature Medicine*; 4 (9): 1032-1037.
- [8] Plantier J.C., Leoz M., Dickerson J.E., De Oliveira F., Cordonnier F., Lemée V., Damond F., Robertson D.L. and Simon F. (2009). "A new human immunodeficiency virus derived from gorillas". *Nature Medicine*; 15 (8): 871-2.

- [9] Tatt I.D., Barlow K.L., Nicoll A. and Chewley J.P. (2001). The public health significance of HIV-1 subtypes. *AIDS*; 15(Suppl.5): S59-S71.
- [10] Coffin J.M. (1986). Genetic variation in AIDS viruses. *Cell*; 46 (1): 1-4.
- [11] Mild M., Esbjornsson J., Fenyo E., and Medstrand P. (2007). Frequent intrapatient recombination between human Immunodeficiency virus type 1 R5 and X4 envelopes: implications for coreceptor switch. *Journal of Virology*; 81: 3369-3376.
- [12] Gao F., Robertson D.L., Carruthers C.D., Morrison S.G., Jian B., Chen Y., Barre-Sinoussi F., Girard M., Srinivasan A., Abimiku A.G., Shaw G.M., Sharp P.M. and Hahn B.H. (1998). A comprehensive panel of near-full-length clones and reference sequences for non-subtype B isolates of Human Immunodeficiency Virus type 1. *Journal of Virology*; 72(7): 5680-5698.
- [13] Carr J.K., Salminen M.O., Koch C., Gotte D., Artenstein A.W., Hegerich P.A., St Louis D., Burke D.S. and McCutchan F.E. (1996). Full-length sequence and mosaic structure of a Human Immunodeficiency Virus type 1 isolate from Thailand. *Journal of Virology*; 70 (9): 5935-5943.
- [14] Central Bureau of Statistics (2003). Kenya demographic and health survey 2003. Calverton, Maryland, USA: CBS, MOH, ORC MARCO.
- [15] Janssens W., Heyndrickx L., Franssen K., Temmerman M., Leonaers A., Ivens T., Motte J., Piot P. and Van der Groen G. (1994). Genetic variability of HIV type 1 in Kenya. *AIDS Research and Human Retroviruses*; 10 (11):1577-9.
- [16] Poss M., Gosink J., Thomas E., Kreiss J.K., Ndinya-Achola J., Mandaliya K., Bwayo J. and Overbaugh J. (1997). Phylogenetic evaluation of Kenyan HIV type 1 isolates. *AIDS Research and Human Retroviruses*; 13(6):493-9.
- [17] Carr J.K., Salminen M.O., Albert J., Sanders-Buell E., Gotte D., Birx D.L. and McCutchan F. E. (1998). Full genome sequences of human immunodeficiency virus type 1 subtypes G and A/G intersubtype recombinants. *Journal of Virology*; 247(1):22-31.
- [18] Neilson J.R., John G.C., Carr J.K., Lewis P., Kreiss J.K., Jackson S., Nduati R.W., Mbori-Ngacha D., Panteleeff D.D., Bodrug S., Giachetti C., Bott M.A., Richardson B.A., Bwayo J., Ndinya-Achola J. and Overbaugh J. (1999). Subtypes of human immunodeficiency virus type 1 and disease stage among women in Nairobi, Kenya. *Journal of Virology*; 73(5):4393-4403.
- [19] Dowling W.E., Kim B., Mason C.J., Wasunna K.M., Alam U., Elson L., Birx D.L., Robb M.L., McCutchan F.E. and Carr J.K. (2002). Forty-one near full-length HIV-1 sequences from Kenya reveal an epidemic of subtype A and A-containing recombinants. *AIDS*; 16(13):1809-1820.
- [20] Songok E.M., Lihana R.W., Kiptoo M.K., Genga I.O., Kibaya R., Odhiambo F., Kobayashi K., Ago Y., Ndembu N., Okoth F., Fujiyama Y., Imanishi J. and Ichimura H. (2003). Identification of env CRF-10 among HIV variants circulating in rural western Kenya. *AIDS Research and Human Retroviruses*; 19(2):161-1655.
- [21] Songok E.M., Lwembe R.M., Kibaya R., Kobayashi K., Ndembu N., Kita K., Vulule J., Oishi I., Okoth F., Kageyama S. and Ichimura H. (2004). Active generation and selection for HIV intersubtype A/D recombinant forms in a co-infected patient in Kenya. *AIDS Research and Human Retroviruses*; 20(2):255-258.
- [22] Yang C., Li M., Shi Y.P., Winter J., van Eijk A.M., Ayisi J., Hu D.J., Steketee R., Nahlen B.L. and Lal R.B. (2004). Genetic diversity and high proportion of intersubtype recombinants among HIV type 1-infected pregnant women in Kisumu, western Kenya. *AIDS Research and Human Retroviruses*; 20(5):565-574.
- [23] Khamadi S.A., Ochieng W., Lihana R.W., Kinyua J., Muriuki J., Mwangi J., Lwembe R., Kiptoo M., Osman S., Lagat N., Pelle R., Muigai A., Carter J.Y., Oishi I., Ichimura H.,

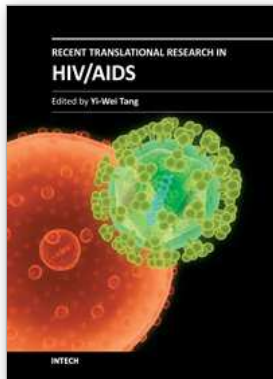
- Mwaniki D.L., Okoth F.A., Mpoke S. and Songok E.M. (2005). HIV type 1 subtypes in circulation in northern Kenya. *AIDS Research and Human Retroviruses*; 21(9): 810-4.
- [24] Lihana R.W., Khamadi S.A., Kiptoo M.K., Kinyua J.G., Lagat N., Magoma G.N., Mwau M.M., Makokha E.P., Onyango V., Osman S., Okoth F.A. and Songok E.M. (2006). HIV type 1 subtypes among STI patients in Nairobi: a genotypic study based on partial pol gene sequencing. *AIDS Research and Human Retroviruses*; 22(11):1172-7.
- [25] Kiptoo M.K., Ichimura H., Raphael L., Ng'ang'a Z., Mueke J., Kinyua J., Lagat N., Okoth F. and Songok E.M. (2008). Prevalence of Nevirapine-Associated Resistance Mutations after Single Dose Prophylactic Treatment among Antenatal Clinic Attendees in North Rift Kenya. *AIDS Research and Human Retroviruses*; 24(12):1555-1559.
- [26] Volberding P.A., Lagakos S.W., Koch M.A., Pettinelli C., Myers M.W., Booth D.K., Balfour H.H. Jr, Reichma R.C., Bartleth J.A. and Hirsch M.S. (1990). Zidovudine in asymptomatic HIV infection. A controlled trial in persons with fewer than 500 CD4-positive cells per cubic millimeter. *New England Journal of Medicine*; 322(14): 941-949.
- [27] Rusconi S., Scozzafava A., Mastrolorenzo A. and Supuran C.T. (2007). An update in the development of HIV entry inhibitors. *Current Topics in Medicinal Chemistry*; 7(13): 1273-1289.
- [28] Barbaro G., Scozzafava A., Mastrolorenzo A. and Supuran C.T. (2005). Highly active antiretroviral therapy: current state of the art, new agents and their pharmacological interactions useful for improving therapeutic outcome. *Current Pharmaceutical Design*; 11(14): 1805-1843.
- [29] Richman D.D. (2001). HIV chemotherapy. *Nature*; 410(6831): 995-1001.
- [30] Bean P. (2005). New Drug Targets for HIV. *Clinical Infectious Diseases*; 41: S96-S100.
- [31] Eron J.J. Jr. (2000). HIV-1 protease inhibitors. *Clinical Infectious Diseases*; 30 (Suppl. 2): S160-S170.
- [32] Venaud S., Yahi N., Fehrentz J.L., Guettari N., Nisato D., Hirsch I. and Chermann J.C. (1992). Inhibition of HIV by anti-HIV protease synthetic peptide blocks an early step of viral replication. *Research in Virology*; 143(5): 311-319.
- [33] Burton A. (2003). Enfuvirtide approved for defusing HIV. *Lancet Infectious Diseases*; 3 (5): 260.
- [34] Gupta R.K., Loveday C., Kalindi U., Lechelt M., Skinner C. and Orkin C. (2007). Tipranavir/T20-based salvage regimens highly effective and durable against HIV-1 with evidence for genotypic predictability of response in clinical practice. *International Journal of STD & AIDS*; 18(9): 630-632.
- [35] Hogg R.S., Heath K.V., Yip B., Craib K.J., O'Shaughnessy M.V., Schechter M.T. and Montaner J.S. (1998). Improved survival among HIV-infected individuals following initiation of antiretroviral therapy. *Journal of the American Medical Association*; 279(6): 450-454.
- [36] Murphy D.A., Greenwell L. and Hoffman D. (2002). Factors associated with antiretroviral adherence among HIV-infected women with children. *Journal of Women & Health*; 36(1): 97-111.
- [37] Miller V. and Larder B.A. (2001). Mutational patterns in the HIV genome and cross-resistance following nucleoside and nucleotide analogue drug exposure. *Antiviral Therapy*; 6 (Suppl.3): 25-44.
- [38] Perelson A.S., Neumann A.U., Markowitz M., Leonard J.M. and Ho D.D. (1996). HIV-1 dynamics in vivo: virion clearance rate, infected cell life span, and viral generation time. *Science*; 271(5255): 1582-1586.

- [39] Mansky L.M. and Temin H.M. (1995). Lower in vivo mutation rate of Human Immunodeficiency Virus type 1 than that predicted from the fidelity of purified reverse transcriptase. *Journal of Virology*; 69(8): 5087-5094.
- [40] Naeger L.K., Margot N.A. and Miller M.D. (2001). Increased susceptibility of HIV-1 reverse transcriptase mutants containing M184V and zidovudine-associated mutations: analysis of enzyme processivity, chain-terminator removal and viral replication. *Antiviral Therapy*; 6 (2): 115-126.
- [41] Coffin J.M. (1995). HIV population dynamics *in vivo*: Implications for genetic variation, pathogenesis, and therapy. *Science*; 367: 483-489.
- [42] Van Dyke R., Korber B., Popek E., Macken C., Widmayer S.M., Bardeguet A., Hansan I.C., Wiznia A., Luzuriaga K., Visareello R.R. and Wolinsky S. (1999). The Arie Project: A prospective cohort study of maternal-child transmission of Human Immunodeficiency Virus type 1 in the era of maternal antiretroviral therapy. *Journal of Infectious Diseases*; 179(2): 319-328.
- [43] Lewis P., Nduati R., Kreiss J.K., John G.C., Richardson B.A., Mbori-Ngacha D., Ndinya-Achola J. and Overbaugh J. (1998). Cell free HIV-1 in breast milk. *Journal of Infectious Diseases*; 177(1): 34-39.
- [44] Luzuriaga K. and Sullivan J. (1996). DNA polymerase chain reaction for the diagnosis of vertical HIV infection. *Journal of the American Medical Association*; 275: 1360-1361.
- [45] De Cock K.M., Fowler M.G., Mercier E., de Vincenzi I., Saba J., Hoff E., Alnwick D.J., Rogers M. and Shaffer N. (2000). Prevention of mother-to-child transmission of HIV in resource poor countries: translating research into policy and practice. *Journal of the American Medical Association*; 283: 1175-1182.
- [46] Garcia P., Kalish L., Pitt J., Minkoff H., Quinin T.C., Burchett S.K., Kornegay J., Jackson B., Moye J., Hanson C., Zorilla C. and Lewis J.F. (1999). Maternal levels of plasma Human Immunodeficiency Virus type 1 RNA and the risk of perinatal transmission. *New England Journal of Medicine*; 341(6): 394-402.
- [47] Sperling R.S., Shapiro D.E., Coombs R.W., Todd J.A., Herman S.A., McSherry G.D., O'Sullivan M.J., Van Dyke R.B., Jimenez E., Rouzioux C., Flynn P.M. and Sullivan J.L. (1996). Maternal viral load, zidovudine treatment and risk of transmission of HIV from mother to child. *New England Journal of Medicine*; 335: 1621-1629.
- [48] Goedert J., Duliege A.M. and Amos C. (1991). High risk HIV-1 infection for first-born twins. *Lancet*; 338(8781): 1471-1475.
- [49] John G.C., Nduati R., Mbori-Ngacha D., Richardson B.A., Panteleff D., Mwatha A., Overbaugh J., Bwayo J., Ndinya-Achola J.O. and Kreiss J.K. (2001). Correlates of mother-to-child Human Immunodeficiency Virus type 1 (HIV-1) transmission: association with maternal plasma HIV-1 RNA load, genital HIV-1 DNA shedding, and breast infections. *Journal of Infectious Diseases*; 183 (2): 206-212.
- [50] Miotti P.G., Taha T.E., Kumwenda N.I., Broadhead R., Mtimavalye L.A., Van der Hoeven L., Chipangwi J.D., Liomba G. and Biggar R.J. (1999). HIV transmission through breastfeeding: a study in Malawi. *Journal of the American Medical Association*; 282(8): 744-749.
- [51] Semba R.D., Kumwenda N., Hoover D.R., Taha T.E., Quinn T.C., Mtimavalye L., Biggar R.J., Broadhead R., Miotti P.G., Sokoll L.J., Hoeven L. and Chipangwi J.D. (1999). Human Immunodeficiency Virus load in breast milk, mastitis, and mother-to-child transmission of Human Immunodeficiency Virus type 1. *Journal of Infectious Diseases*; 180(1): 93-98.

- [52] Richardson B.A., John-Stewart G.C., Hughes J.P., Nduati R., Mbori-Ngacha D., Overbaugh J. and Kreiss J.K. (2003). Breast-milk infectivity in Human Immunodeficiency Virus type 1. *Journal of Infectious Diseases*; 187(5): 736-740.
- [53] John G.C., Richardson B.A., Nduati R.W., Mbori-Ngacha D. and Kreiss J.K. (2001). Timing of breast milk HIV-1 transmission: a meta-analysis. *East African Medical Journal*; 78 (2): 75-79.
- [54] Embree J.E., Njenga S., Datta P., Nagelkerke N.J., Ndinya-Achola J.O., Mohammed Z., Ramdahin S., Bwayo J.J. and Plummer F.A. (2000). Risk factors for postnatal mother-to-child transmission of HIV-1. *AIDS*; 14(16): 2535-2541.
- [55] Ekpini E.R., Wiktor S.Z., Satten G.A., Adjorlolo-Johnson G.T., Sibailly T.S., Ou C.Y., Karon J.M., Brattegaard K., Whitaker J.P., Gnaore E., De Cock K.M. and Greenberg A.E. (1997). Late postnatal mother-to-child transmission of HIV-1 in Abidjan, Cote d'Ivoire. *Lancet*; 349(9058): 1054-1059.
- [56] Mills E. J., Wu P., Seely D. and Guyatt G.H. (2005). Vitamin supplementation for prevention of mother-to-child transmission of HIV and pre-term delivery: a systematic review of randomized trial including more than 2800 women. *AIDS Research and Therapy*; 2(1):4.
- [57] Gupta R., Garland M., Msamanga G., Spiegelman D., Hunter D. and Fawzi W. (2005). Selenium status, pregnancy outcomes and mother-to-child transmission of HIV-1. *Journal of Acquired Immune Deficiency Syndrome*; 39 (2): 203-210.
- [58] Taha T.E., Biggar R.J., Broadhead R.L., Mtimavalye L.A., Justesen A.B., Liomba G.N., Chipangwi J.D. and Miotti P.G. (1997). Effect of cleansing the birth canal with antiseptic solution on maternal and newborn morbidity and mortality in Malawi: clinical trial. *British Medical Journal*; 315(7102): 216-219.
- [59] The International Perinatal HIV Group (1999). The mode of delivery and risk of vertical transmission of Human Immunodeficiency Virus type 1 a meta-analysis of 15 prospective cohort studies. *New England Journal of Medicine*; 340(13): 977-987.
- [60] Connor E.M., Sperling R.S., Gelbert R., Kiseleu P., O'Sullivan M.J., Van Dyke R., Bey M., Shearer W., Jacobson R.L., Jimenez E., Basin B., Delfraissy J.F., Culnane M., Coombs R., Elkins M., Moya J., Stratton P. and Basley J. (1994). Reduction of maternal-infant transmission of Human Immunodeficiency Virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Protocol 076 study group. *New England Journal of Medicine*; 331: 1173-1180.
- [61] Wiktor S.Z., Ekpini E., Karon J.M., Nkengasong J., Maurice C., Severin S.T., Roels T.H., Kouassi M.K., Lackritz E.M., Coulibaly I.M. and Greenberg A.E. (1999). Short course oral zidovudine for prevention of mother-to-child transmission of HIV-1 in Abidjan, Cote d'Ivoire: a randomised trial. *Lancet*; 353(9155): 781-785.
- [62] Dabis F., Msellati P., Meda N., Welffens-Ekra C., You B., Manigart O., Leroy V., Simonon A., Cartoux M., Combe P., Ouangre A., Ramon R., Ky-Zebro O., Montcho C., Salamon R., Rouzioux C., Van de Perre P. and Mandelbrot L. (1999). Six-month efficacy, tolerance and acceptability of a short regimen of oral Zidovudine to reduce vertical transmission of HIV in breastfed children in Cote d'Ivoire and Burkina Faso: a double-blind placebo-controlled multicentre trial. *Lancet*; 353: 786-792.
- [63] Leroy V., Karon J.M., Alioum A., Ekpini ER., Meda N., Greenberg A.E., Msellati P., Hudgens M., Dabis F. and Wiktor S.Z. (2002). 24-month efficacy of a maternal short course zidovudine regimen to prevent mother-to-child transmission of HIV-1 in West Africa. *AIDS*; 16(4): 631-641.
- [64] 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

- Tanzania, South Africa and Uganda (Petra study): a randomised, double-blind placebo-controlled trial. *Lancet*; 359(9313): 1178-1186.
- [65] Songok E.M., Fujiyama Y., Adungo N., Vulule J., Kiptoo M., Kobayashi N., Mpoke S., Genga I., Tukei P.M. and Ichimura H. (2003). The use of short course Zidovudine to prevent mother-to-child transmission of Human Immunodeficiency Virus in rural Kenya. *American Journal of Tropical Medicine and Hygiene*; 69 (1): 8-13.
- [66] Guay L.A., Musoke P., Fleming T., Bagenda D., Allen M., Nakabiito C., Sherman J., Bakaki P., Ducar C., Desevve M., Emel L., Mirochnick M., Fowler M.G., Mofenson L., Miotti P., Dransfield K., Bray D., Mmiro F. and Jackson B. (1999). Intrapartum and neonatal single dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomized trial. *Lancet*; 354(9181): 795-802.
- [67] Fowler M.G. (2000). Prevention of perinatal infection. What do we know? Where should future research go? *Annals of the New York Academy of Sciences*; 918: 45-52.
- [68] Fortin J.F., Cantin R., Lamontagne G. and Tremblay M. (1997). Host-derived ICAM-1 glycoproteins incorporated on Human Immunodeficiency Virus type 1 are biologically active and enhance viral infectivity. *Journal of Virology*; 71(5): 4847-4851.
- [69] Kantor R. and Katzenstein D. (2003). Polymorphism in HIV-1 non-subtype B protease and reverse transcriptase and its potential impact on drug susceptibility and drug resistance evolution. *AIDS Reviews*; 5(1): 25-30.
- [70] Adje-Toure C., Bile C.E., Borget M.Y., Hertog K., Maurice C., Nolan M.L. and Nkengasong J.N. (2003). Polymorphism in protease and reverse transcriptase and phenotypic drug resistance of HIV-1 recombinant CRF02_AG isolates from patients with no prior use of antiretroviral drugs in Abidjan, Cote d'Ivoire. *Journal of Acquired Immune Deficiency Syndrome*; 34(1): 111-113.
- [71] Jülg B. and Goebel F.D. (2005). HIV genetic diversity: any implications for drug resistance? *Infection*; 33(4):299-301.
- [72] Abecasis A.B., Deforche K. and Bacheler L.T. (2005). Lack of reduced susceptibility to PIs in wild-type non-B subtypes and detection of hypersusceptibility to nelfinavir in HIV-1 patients infected with CRF02_AG. *Third European HIV Drug Resistance Workshop*, Athens, Abstr. 28.
- [73] Kinomoto M., Appiah-Opong R. and Brandful J.A. (2005). HIV-1 Proteases from drug-naïve West African patients are differentially less susceptible to protease inhibitors. *Clinical Infectious Diseases*; 41: 243-251.
- [74] Brenner B. (2007). Resistance and viral subtypes: how important are the differences and why do they occur? *Current Opinion HIV/AIDS*; 2: 94-102.
- [75] Eshleman S.H., Hoover D.R., Chen S., Hudelson S.E., Guay L.A., Mwatha A., Fiscus S.A., Mmiro F., Musoke P., Jackson J.B., Kumwenda N., and Taha T. (2005a). Nevirapine (NVP) resistance in women with HIV-1 subtype C, compared with subtypes A and D, after the administration of single-dose NVP. *Journal of Infectious Diseases*; 192(1): 30-36.
- [76] Flys T., Nissley D.V., Claasen C.W., Jones D., Shi C., Guay L.A., Musoke P., Mmiro F., Strathern J.N., Jackson J.B., Eshleman J.R. and Eshleman S.H. (2005). Sensitive drug-resistance assays reveal long-term persistence of HIV-1 variants with the K103N nevirapine (NVP) resistance mutation in some women and infants after the administration of single-dose NVP: HIVNET 012. *Journal of Infectious Diseases*; 192: 24-29.
- [77] Loubser S., Balfe P., Sherman G., Hammer S., Kuhn L. and Morris L. (2006). Decay of K103N mutants in cellular DNA and plasma RNA after single-dose nevirapine to reduce mother-to-child HIV transmission. *AIDS*; 20(7): 995-1002.

- [78] Chaix M.L., Ekouevi D.K., Rouet F., Tonwe-Gold B., Viho I., Bequet L., Peytavin G., Toure H., Menan H., Leroy V., Dabis F. and Rouzioux C. (2006). Low risk of nevirapine resistance mutations in the prevention of mother-to-child transmission of HIV-1: ANRS Study, Abidjan, Cote d'Ivoire. *Journal of Infectious Diseases*; 193(4): 482-487.
- [79] Brenner B., Turner D., Oliveira M, Moisi D., Detorio M., Carobene M., Marlink R.G., Schapiro J., Roger M. and Wainberg M.A. (2003). A V106M mutation in HIV-1 clade C viruses exposed to efavirenz confers cross-resistance to nonnucleoside reverse transcriptase inhibitors. *AIDS*; 17(1): F1-F5.
- [80] Brenner B., Oliveira M., Doualla-Bell F., Moisi D.D., Ntemgwa M., Frankel F., Essex M. and Wainberg M.A. (2006). HIV-1 subtype C viruses rapidly develop K65R resistance to tenofovir in cell culture. *AIDS*; 20 (9): F9-F13.
- [81] Descamps D., Collin G., Letourneur F., Apetrei C., Damond F., Loussert-Ajaka I., Simon F., Saragosti S. and Brun-Vezinet F. (1997). Susceptibility of Human Immunodeficiency Virus type 1 group O isolates to antiretroviral agents. *Journal of Virology* 71(11): 8893-8898.
- [82] Eshleman S.H., Hoover D.R., Chen S., Hudelson S.E., Guay L.A., Mwatha A., Fiscus S.A., Mmiro F., Musoke P., Jackson J.B., Kumwenda N., and Taha T. (2005). Nevirapine (NVP) resistance in women with HIV-1 subtype C, compared with subtypes A and D, after the administration of single-dose NVP. *Journal of Infectious Diseases*; 192(1): 30-36.
- [83] Jackson J.B., Becker-Pergola G., Guay L.A., Musoke P., Mracna M., Fowler M.G., Mofenson L.M., Mirochnick M., Mmiro F. and Eshleman S.H. (2000). Identification of the K103N resistance mutation in Ugandan women receiving nevirapine to prevent HIV-1 vertical transmission. *AIDS*; 14(11): F111-F115.
- [84] Beckerman K.P. (2002). Mothers, orphans and prevention of pediatric AIDS. *Lancet* 359: 1168-1169.
- [85] Kwiek J.J., Russell E.S., Dang K.K., Burch C.L., Mwapasa V., Meshnick S.R. and Swanstrom R. (2008). The molecular epidemiology of HIV-1 envelope diversity during HIV-1 subtype C vertical transmission in Malawian mother-infant pair. *AIDS*; 22:863-871.
- [86] Yang C., Li M., Newman R.D., Shi Y.P., van Eijk A.M., Otieno J., Misore A.O., Steketee R.W. Nahlen B.L. and Lal R.B. (2003). Genetic diversity of HIV-1 in western Kenya: subtype-specific differences in mother-to-child transmission. *AIDS*; 17(11):1667-1674.
- [87] Eshleman S.H., Guay L.A., Mwatha A., Brown E., Musoke P., Mmiro F. and Jackson J.B. (2005). Comparison of mother-to-child transmission rates in Ugandan women with subtype A versus D HIV-1 who received single-dose nevirapine prophylaxis: HIV Network for Prevention Trials 012. *Journal of Acquired Immune Deficiency Syndrome*; 39(5): 593-597.
- [88] Bulterys P.L., Dalai S.C. and Katzenstein D.A. (2010). Viral sequence analysis from HIV-infected mothers and infants: molecular evolution, diversity, and risk factors for mother-to-child transmission. *Clinical Perinatology*; 37 (4): 739-750.
- [89] Renaud Becquet, Didier K. Ekouevi, Elise Arrive, Jeffrey S. A. Stringer, Nicolas Meda, Marie-Laure Chaix, Jean-Marc Treluyer, Valérie Leroy, Christine Rouzioux, Stéphane Blanche, and Francois Dabis (2009). Universal Antiretroviral Therapy for Pregnant and Breast-Feeding HIV-1-Infected Women: Towards the Elimination of Mother-to-Child Transmission of HIV-1 in Resource-Limited Settings. *Clinical Infectious Diseases*; 49: 1936-1945.



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The collective efforts of HIV/AIDS research scientists from over 16 countries in the world are included in the book. This 27-chapter Open Access book well covers HIV/AIDS translational researches on pathogenesis, diagnosis, treatment, prevention, and also those beyond conventional fields. These are by no means inclusive, but they do offer a good foundation for the development of clinical patient care. The translational model forms the basis for progressing HIV/AIDS clinical research. When linked to the care of the patients, translational researches should result in a direct benefit for HIV/AIDS patients.

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No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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