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HIV-1 Diversity and Its Implications in Diagnosis, Transmission, Disease Progression, and Antiretroviral Therapy

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1. Introduction

Due to an error prone reverse transcriptase, HIV-1 has diversified into multiple variants. Currently, there are four phylogenetic groups named M, N, O and P (Gurtler et al., 1994; Plantier et al., 2009b; Simon et al., 1998). HIV-1 group M, which is responsible for most of the infections in the world, has diversified into nine subtypes named A, B, C, D, F, G, H, J and K, seven sub-subtypes (A1-A5 and F1-F2), multiple circulating recombinant forms (CRFs) and countless unique recombinant forms (UFRs) (Gao et al., 2001; Meloni et al., 2004; Triques et al., 1999; Vidal et al., 2009; Vidal et al., 2006). At present, 49 CRFs were recognized of which 37 are first generation recombinants and 12 are second generation recombinants (Los Alamos Sequence Database, 2011).

Five HIV-1 strains dominate the global epidemic: subtypes A, B, and C, along with CRF01_AE and CRF02_AG, with subtype C accounting for almost 50% of all HIV-1 infections worldwide (Buonaguro, Tornesello, and Buonaguro, 2007; McCutchan, 2006; Santos and Soares, 2010; Taylor and Hammer, 2008). Molecular epidemiological studies show that, with the exception of sub-Saharan Africa where almost all subtypes, CRFs and several URFs have been detected there is a specific geographic distribution pattern for HIV-1 subtypes (Buonaguro, Tornesello, and Buonaguro, 2007; McCutchan, 2006; Santos and Soares, 2010; Taylor and Hammer, 2008). Subtype A is prevalent in Central and Eastern Africa (Kenya, Uganda, Tanzania, and Rwanda) (Harris et al., 2002; Morison et al., 2001; Songok et al., 2004), Iran (Tagliamonte et al., 2007), Eastern Europe (Bobkov et al., 1997; Bobkov et al., 2004), and Central Asia (Beyrer et al., 2009; Eyzaguirre et al., 2007). Subtype B predominates in developed countries, such as United States of America (USA) and Canada (Akouamba et al., 2005; Brennan et al., 2010; Carr et al., 2010a; Jayaraman et al., 2003), in Brazil (Dumans et al., 2004; Monteiro-Cunha et al., 2011; Santos et al., 2006), countries of Western and Central Europe (Abecasis et al., 2011; Castro et al., 2010; De Mendoza et al., 2009; Easterbrook et al., 2010; Galimand et al., 2010; Habekova et al., 2010; Kousiappa, Van

De Vijver, and Kostrikis, 2009; Lai et al., 2010; Parczewski et al., 2010) and Australia (Herring et al., 2003; Ryan et al., 2004), and is also common in several countries of Southeast Asia (Chen et al., 2010; Lau et al., 2010), northern Africa (Annaz et al.) and the Middle East (Sarrami-Forooshani et al., 2006). Subtype C is the overwhelming prevailing strain in Southern Africa (Bartolo et al., 2009b; Gonzalez et al., 2010; Lahuerta et al., 2008; Papathanasopoulos et al., 2010), in India and neighbor countries (Neogi et al., 2009a; Neogi et al., 2009b) and in the southern region of Brazil (Monteiro-Cunha et al., 2011). Subtype D strains are found mainly in East Africa, and to a lesser extent in West Africa (Conroy et al., 2010; Harris et al., 2002; Laukkanen et al., 2000; Songok et al., 2004). Subtype F predominates in Central Africa (Carr et al., 2010b; Soares et al., 2010), South America (Avila et al., 2002; Munerato et al., 2010) and Eastern Europe (Fernandez-Garcia et al., 2009; Paraschiv, Foley, and Otelea, 2011). Subtype G viruses are prevalent in Central and Western Africa (Hawkins et al., 2009; Kalish et al., 2004), as well as in Portugal (Abecasis et al., 2011; Esteves et al., 2003; Esteves et al., 2002; Palma et al., 2007) and Spain (De Mendoza et al., 2009; Trevino et al., 2011). Subtypes H and J were described in Central Africa (Janssens et al., 2000; Mokili et al., 1999; Yamaguchi et al., 2010) and in Angola (Bartolo et al., 2005; Bartolo et al., 2009d). Subtype K was identified in DRC and Cameroon (Triques et al., 2000).

Some CRFs have high impact in local AIDS epidemics, such as CRF01_AE in Southeast Asia (Gao et al., 1996; Magiorkinis et al., 2002) and CRF02_AG in Western and Central Africa (Cornelissen et al., 2000; Fischetti et al., 2004a; Fischetti et al., 2004b). CRF11_cpx was the first second generation CRF described in 2000 in patients from Cameroon (Tscherning-Casper et al., 2000). This CRF circulates in Cameroon, Central African Republic, Gabon, DRC, and Angola although its exact prevalence rate remains to be determined (Djoko et al., 2011). Second generation CRFs are becoming common in complex epidemics with multiple subtypes and recombinant forms. At present they have been detected in Africa, East Asia, Thailand, Malaysia, Estonia and Saudi Arabia (Djoko et al., 2011).

HIV-1 group O seems to be endemic in Cameroon and neighboring countries in West-Central Africa and represents only about 1-5% of HIV-1 positive samples in this region (Peeters et al., 1997; Yamaguchi et al., 2004). Elsewhere in the world, group O viruses have been identified mainly from people with epidemiological links to the referred Central African countries (Lemey et al., 2004). HIV-1 groups N and P circulate exclusively in Cameroon (Brennan et al., 2008; Plantier et al., 2009b; Vallari et al., 2010; Vallari et al., 2011). In some regions of the world, little information is available about HIV diversity, particularly in North Africa, the Middle East, and parts of Central Asia.

Differential characteristics of viral subtypes and their interactions with the human host may influence HIV transmission and disease progression. HIV-1 genetic diversity may also impact the susceptibility and resistance to antiretroviral drug as well as the performance of diagnostic and viral load assays. The aim of this Chapter was to review the current knowledge on HIV-1 diversity and its implications in diagnosis, transmission, disease progression, and antiretroviral therapy and resistance.

2. Impact of HIV-1 diversity in transmission

Although earlier studies found an association between CRF01_AE and heterosexual transmission and between subtype B and intravenous drug use (Gao et al., 1996; Soto-

Ramirez et al., 1996), a more recent longitudinal study performed in Thailand found an increased probability of CRF01_AE transmission among IDUs compared with subtype B (Hudgens et al., 2002). A recent study performed in HIV-discordant couples in Uganda found that subtype A was associated with a significant higher rate of heterosexual transmission than subtype D (P=0.01) (Kiwanuka et al., 2009). The rate of transmission may reflect differences in subtype-specific coreceptor tropism. HIV-1 can use as coreceptors CCR5 (R5 variants), CXCR4 (X4 variants) or both (R5X4 variants or dual tropic) to enter the cells (Schuitemaker, van 't Wout, and Lusso, 2011). R5 variants are largely prevalent during primary infection and seem to be more easily transmitted or established in the newly infected host than X4 strains (Schuitemaker, van 't Wout, and Lusso, 2011). An increased prevalence of X4 variants has been reported for subtype D which may in part explain their reduced heterosexual transmissibility when compared to other genetic forms (Huang et al., 2007; Kaleebu et al., 2007; Kiwanuka et al., 2009; Tscherning et al., 1998).

Several studies have looked for variations between clades in mother-to-child HIV-1 transmission (MTCT) rates. In Kenya, MTCT appeared to be more common among mothers infected with subtype D compared with subtype A (P=0.002) and this association was independent of other risk factors for MTCT, such as maternal HIV viral load, episiotomy or perineal tear, and low birth weight (Yang et al., 2003). On the other hand, in Tanzania HIV-1 subtypes A (odds ratio, 3.8; 95% CI, 0.8-24.7%) and C (odds ratio, 5.1; 95% CI, 1.3-30.8%) were more frequently transmitted from mother-to-child than subtype D (Renjifo et al., 2001). In another study, the risk of MTCT was higher in women infected with subtype C, followed by subtype A, and was lowest in women infected with subtype D (John-Stewart et al., 2005). It was found that pregnant women, infected with subtype C were more likely than those infected with subtype A or D (P=0.006) to shed HIV-1–infected vaginal cells even after adjusting for age, CD4 cell count, and plasma HIV-1 viral load. Another study in Tanzania presented similar results, with preferential in-utero transmission of HIV-1 subtype C compared to HIV-1 subtype A or D (P=0.026) (Renjifo et al., 2004). Other researchers, however, found no association between subtype and rates of MTCT (Martinez et al., 2006; Murray et al., 2000; Tapia et al., 2003). Moreover, in studies where pregnant women received a single-dose nevirapine (sdNVP) prophylaxis no significant differences were observed in the rate of MTCT in women infected with HIV-1 subtype A, D or C (Eshleman et al., 2006; Eshleman et al., 2005a).

Many factors, such as maternal stage of the disease, maternal immunological status, viral load, mode of delivery, duration of breast-feeding, ARV prophylaxis, maternal plasma vitamin A (associated with AIDS progression), and close maternal-child Human Leukocyte Antigen (HLA) matching, can contribute to these differences (Fowler and Rogers, 1996; MacDonald et al., 1998; McGowan and Shah, 2000). Nevertheless, the role of viral determinants in MTCT has yet to be well established (Dickover et al., 2001). Several studies have shown that viral diversity in the mother is generally higher than that present in the infant, suggesting that maternal viruses are selected before transmission (Ahmad, 2005; Zhang et al., 2010b). Several factors like specific viral selection (Wolinsky et al., 1992), neutralization resistance (Dickover et al., 2006; Wu et al., 2006; Zhang et al., 2010a) and enhanced replicative capacity of the transmitted viruses (Kong et al., 2008) have been

associated with a bottleneck type transmission. The basis for the MTCT bottleneck is an issue that needs further clarification.

In summary, it remains to be determined whether there is a true association between subtypes and adult or MTCT transmission of HIV-1 or whether the differences in transmission probabilities found in some studies are associated with several other factors that can influence HIV transmission, e.g. behavioral, epidemiological and immunological (Attia et al., 2009). More longitudinal and well controlled studies, preferentially performed in a single area and with a single ethnic group of HIV-1 infected patients, are needed to identify HIV-1 determinants for adult and vertical transmission and to evaluate the potential association of subtype with transmission.

3. Impact of HIV-1 diversity in disease progression

Another important question is whether clade differences result in variable rates of disease progression. There have been several prospective, observational studies of the course of HIV-related disease in cohorts infected with various HIV-1 genetic forms. Although some studies did not find an association between HIV-1 clades and disease progression (Alaeus et al., 1999; Amornkul et al., 1999; Galai et al., 1997; Laurent et al., 2002; Taylor and Hammer, 2008), more recent studies established this association (Easterbrook et al., 2010; Keller et al., 2009; Kiwanuka et al., 2010). A retrospective cohort study (1996-2007) reported that Africans patients infected with HIV-1 non-B subtypes (A, C, F-K, AC, AE, AG, BF and DF) had slower rates of disease progression compared to Haitians (P=0.0001) and Canadians (P=0.02) infected with subtype B viruses (Keller et al., 2009).

Earlier studies found that subtype D was associated with the most rapid disease progression relative to other subtypes (Taylor and Hammer, 2008). A very recent study in patients from Rakai, Uganda, reported that infection with subtype D is associated with significantly faster rates of CD4 T-cell loss than subtype A (P<0.001), which might explain the more rapid disease progression for subtype D compared with subtype A (Kiwanuka et al., 2010). Along the same lines, a study conducted in 2010 in an ethnically diverse population of HIV-1-infected patients in South London showed a faster CD4 cell decline and higher rate of subsequent virological failure with subtype D infection than with subtypes B (P=0.02), A (P=0.004) or C (P=0.01) (Easterbrook et al., 2010).

An important unanswered question is the biological basis for these differences. A possible clue comes from data suggesting that emergence of X4 variants, which in subtype B are associated with increased CD4 depletion and disease progression [302-304], was more common in HIV-1 subtype D compared with subtype A (P=0.040) (Kaleebu et al., 2007; Tscherning et al., 1998). Other study found that subtype D may be dual tropic more frequently than the other subtypes (Huang et al., 2007). The earlier switch to X4 usage in subtype D isolates may explain the faster rate of CD4 decline and disease progression with this subtype (Kaleebu et al., 2007; Tscherning et al., 1998).

One study reported the presence of X4 or R5X4 isolates at early stages of infection, in addition to a decrease in CD4+ counts, in all patients infected with CRF14_BG (Perez-Alvarez et al., 2006). We have shown recently that most CRF14_BG strains (78.9%)

sequenced to date use CXCR4 (Bártolo et al., 2011) and that patients infected with this CRF can progress very quickly to AIDS and death (Bartolo et al., 2009a). Together, these results suggest that, like HIV-1 subtype D, CRF14_BG may be highly pathogenic (Kuritzkes, 2008; Sacktor et al., 2009). The rapid disease progression associated with CRF14_BG may be due to an earlier switch to X4 phenotype driven by the selective pressure of neutralizing antibodies (Bártolo et al., 2011). However, the relationship between higher tendency for X4 use and higher disease progression may not hold for other subtypes. For instance, the percentage of X4 virus appears to be lower in subtype C than in subtype B, even when the viruses are obtained from patients with AIDS (Casper et al., 2002; Cilliers et al., 2003; Ping et al., 1999).

It is important to note that most of these studies of disease progression have confounder factors such as access to medical care, nutritional status, host genetic factors, and mode of viral transmission, which may contribute to the divergent results (Pereyra et al., 2010). More studies are needed to confirm previous conflicting results, and to elucidate the host–viral interactions that may lead to more favorable outcomes in individuals infected with various genetic forms of HIV-1. This kind of studies should be longitudinal, performed with a higher number of patients, preferentially in primary infection, in a single country to better control ethnic and genetic factors of the patients, and with several genetic forms of HIV-1.

4. Impact of HIV-1 diversity in diagnosis and disease management

Acute infection with HIV-1 can be identified and quantified using several virological and immunological markers (Figure 1) (Fiebig et al., 2003). In the first eleven days after infection viral markers are undetectable in the blood (window period). Plasma HIV RNA levels begin to increase at the 10^{th} day, peaking around 20 days after infection. HIV p24 levels typically peak around 20 days after infection. Antibody response starts to be detectable by ELISA assays after 20 days of infection, on average. Serological and molecular assays have been designed to detect and/or quantify one or more of these HIV infection markers. These assays should be able to detect all genetic forms of HIV but the very high genetic and antigenic evolution of this virus along with the continued diversification and global redistribution of HIV groups, subtypes and recombinants may affect their performance.

4.1 Immunoassays

HIV fourth-generation assays detect both HIV antibodies and the p24 antigen. These assays provide an advantage for detection of infection during the window period prior to seroconversion since the diagnostic window may be reduced by an average of 5 days relative to an IgM-sensitive EIA (Fiebig et al., 2003; Weber et al., 1998). However, some fourth-generation assays showed low sensitivity in the detection of p24 antigen from some non-subtype B HIV-1 strains (A, C, F, H, CRF01_AE, O) (Kwon et al., 2006; Ly et al., 2007; Ly et al., 2004; Ly et al., 2001; Weber, 2002). This low sensitivity in antigen detection may be attributed to differences in viral epitopes of the different HIV genetic forms which may not be recognized by the monoclonal antibody used in the assay (Plantier et al., 2009a).

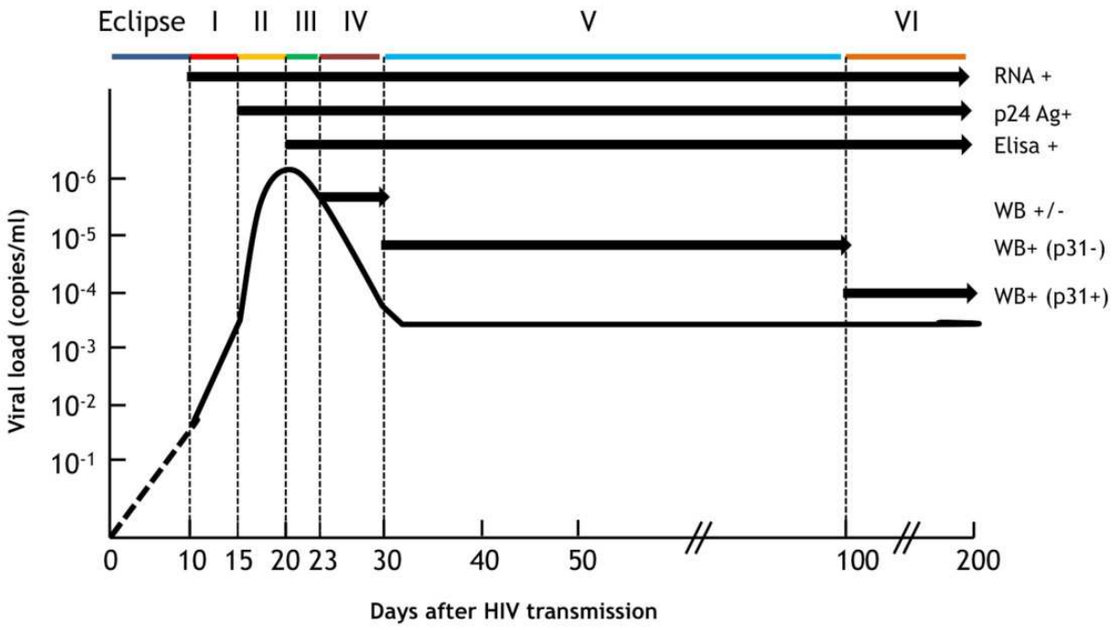

Fig. 1. Progression of HIV-1 markers in acute infection. WB, Western blot; RNA, HIV RNA; LS–Ab, HIV antibody determined by sensitive/less sensitive enzyme immunoassay testing strategy; p24 Ag, HIV p24 antigen, from time of exposure (day 0) through the first 200 days of infection. Eclipse, eclipse period (undetectable viral markers in blood samples); Stage I (definitive HIV RNA viremia), stage II (p24 antigenemia), stage III (HIV EIA antibody reactive), stage IV (I, Western blot indeterminate), stage V (Western blot positive without p31 pol band) and stage VI (P, Western blot positive with p31 pol band). Adapted from (Fiebig et al., 2003).

The major target for HIV-1 antibodies in immunoassays is the *env* gp41 immunodominant region (IDR). Key epitope(s) targeted by these assays might be modified or eliminated by the occurrence of natural polymorphisms within the IDR region associated with the genetic variation of HIV-1, ultimately leading to reduced sensitivity or lack of antibody detection (Brennan et al., 2006; Gaudy et al., 2004). A few cases of false-negative results involving, for example, subtypes B, C, and F, and resulting from major mutations of the IDR epitope have been described (Aghokeng et al., 2009; Gaudy et al., 2004; Ly et al., 2007; Ly et al., 2004; Ly et al., 2001; Zouhair et al., 2006).

Earlier analysis of specimens from patients infected with group O viruses revealed that some commercial immunoassays failed to detect group O infections (Eberle et al., 1997; Loussert-Ajaka et al., 1994; Schable et al., 1994; Simon et al., 1994). This ultimately led to incorporation of group O specific antigens and/or peptides into the assays to improve detection of group O infections (van Binsbergen et al., 1996). Nonetheless, false-negative results continue to be reported for some patients infected with HIV-1 group O (Henquell et al., 2008; Plantier et al., 2009a; Zouhair et al., 2006).

Despite the high genetic divergence between HIV-1 groups M and N, all group N infections studied until now were detected by five commercial HIV immunoassays (Vallari et al., 2010). Group P infections may not be efficiently detected by the current HIV screening tests due to the absence of group P-specific reagents for antibody detection (Vallari et al., 2011). Nevertheless, Plantier et al., in the first report regarding detection of group P infections, found that several HIV-1 screening tests were reactive against this group (Plantier et al., 2009b). Despite the absence of either HIV-1 group N or group P specific antigens in most assays, antibodies targeting some group M specific antigens may cross-react with group N and P antigens allowing for the serologic detection of infections by HIV-1 isolates from these groups.

Serological diagnosis of HIV-1 infection in Sub-Saharan Africa is mostly done with rapid tests (Plate, 2007). This kind of assay is simple, rapid, instrument-free and relatively cheap. However some of these assays have shown problems in detecting HIV-1 subtypes D, F, H, CRF02_AG, group O and HIV-2 (Aghokeng et al., 2009; Beelaert and Fransen, 2010; Chaillet et al., 2010; Holguin et al., 2009; Laforgerie et al., 2010; Pavie et al., 2010). Minor antigenic differences between isolates of different clades and the peptides/recombinant proteins used in these assays could explain the problems in the detection of some HIV genetic forms (Aghokeng et al., 2009; Laforgerie et al., 2010; Makuwa et al., 2002; Pavie et al., 2010). Low sensitivity of some of these tests can also be associated with low level of HIV-specific antibodies due to recent seroconversion, early and stringent control of viral replication by antiretroviral therapy, or immune exhaustion in end-stage AIDS patients (Apetrei et al., 1996; Ferreira Junior et al., 2005; Jurriaans et al., 2004; Laforgerie et al., 2010; Makuwa et al., 2002; Pavie et al., 2010; Spivak et al., 2010).

4.2 Viral load assays

A variety of nucleic acid based diagnostic assays that quantify plasma HIV-1 RNA levels have been developed and used to monitor disease progression and response to antiviral therapy, detect primary infection [plasma HIV RNA levels begin to be detectable about 11 days after infection (Figure 1)], detect HIV infection among perinatally exposed infants and HIV vaccine recipients, and detect HIV infection in the absence of antibodies (Table 1)(Bill & Melinda Gates Foundation, 2009; European AIDS Clinical Society, 2009; Korenromp et al., 2009; Mellors et al., 1997; Thompson et al., 2010). These assays rely on HIV-1 sequence-specific primers and/or probes and use technologies such as reverse transcriptase polymerase chain reaction (RT-PCR) amplification, isothermal nucleic acid sequence-based amplification (NASBA), branched-chain DNA signal amplification (bDNA) and real-time (RT) PCR (Collins et al., 1997; de Mendoza et al., 2005; Dyer et al., 1999; Johanson et al., 2001; Rouet et al., 2005; Stevens et al., 2005; Sun et al., 1998; Yao et al., 2005). The genetic variation of HIV-1 presents challenges to the design of quantitative assays that measure HIV-1 RNA or DNA levels. Reliable quantification can be compromised by natural polymorphisms occurring in primer/probe sequences that have the potential to reduce or abolish hybridization (Christopherson, Sninsky, and Kwok, 1997; Kwok et al., 1990). Genetically divergent variants may go unrecognized since, usually, subtype and target sequence information is not known at the time of testing.

Several comparative studies have shown that the sensitivity and specificity of viral load assays varies depending on HIV-1 group or subtype, especially in non-B subtypes, complex recombinant forms and groups O, N, and P viruses (Bourlet et al., 2011; Church et al., 2011;

Assays	Technology	Probe target	Linear range (RNA copies/ml)	HIV-1 clade recognition
Abbot Real Time HIV-1	RT-PCR	*pol*-INT	40-10,000,000	Group M (subtypes A-H), several CRFs and Groups O and N
Amplicor HIV-1 Monitor Test v1.5	RT-PCR	*gag*-p24	Standard protocol: 400 to >750,000; Ultra-sensitive: 50 - >100,000	HIV-1 Group M (subtypes A-H)
Cobas Amplicor HIV-1 Monitor Test, v1.5	RT-PCR	*gag*	Standard protocol: 400 to >750,000; Ultrasensitive: 50 - >100,000	HIV-1 Group M (subtypes A-H)
Cobas AmpliPrep/Cobas TaqMan HIV-1 Test, v2.0	RT-PCR	*gag*-p41 and 5´LTR	20-10,000,000	Group M, several CRFs, and Group O
Versant HIV-1 RNA 1.0 Assay (kPCR)	RT-PCR	*gag*-p24	37-11,000,000	HIV-1 Groups M and O
Versant HIV-1 RNA 3.0 Assay	bDNA	*pol*-INT	50-500,000	HIV-1 Group M
NucliSens EasyQ HIV-1 v2.0	NASBA	*gag*-p24	10- 10,000,000	HIV-1 Group M (subtypes A-J), CRF01_AE, and CRF02_AG

Adapted from (World Health Organization, June 2010).

Table 1. Viral load assays approved by FDA and recommended by WHO

Geelen et al., 2003; Gottesman et al., 2006; Holguin et al., 2008; Katsoulidou et al., 2011; Plantier et al., 2009b; Rouet et al., 2010; Scott et al., 2009; Swanson et al., 2005; Swanson et al., 2006; Swanson et al., 2007; Tang et al., 2007; Wirden et al., 2009; Xu et al., 2008). However, the newer quantitative real-time PCR (qRT-PCR) methods (i.e., m2000rt Abbot Real Time HIV-1 Assay or Cobas AmpliPrep/COBAS TaqMan) showed a higher performance on HIV viral load testing of patients with subtype B as well as patients with non-B subtype infections (Bourlet et al., 2011; Church et al., 2011; Katsoulidou et al., 2011; Swanson et al., 2007; Tang et al., 2007). Abbot Real Time HIV-1 Assay seems to be the only assay prepared to detect all HIV-1 subtypes, several CRFs, as well as group N, and O viruses (Church et al., 2011; Swanson et al., 2007; Tang et al., 2007). This is probably related with the high level of genetic conservation of the integrase gene that this test amplifies (Young et al., 2011). In contrast, bDNA (Versant v3.0) and NASBA (EasyQ) assays are considerably less reliable for accurate viral load measurements across HIV clades (Bourlet et al., 2011; Church et al., 2011; Katsoulidou et al., 2011; Swanson et al., 2007; Tang et al., 2007). In summary, available data indicates that HIV-1 assays targeting the highly conserved *pol* integrase region of the HIV-1 genome may be subject to less variability than assays targeting the *gag* gene (Geelen et al.,

2003; Swanson et al., 2005; Swanson et al., 2006; Swanson et al., 2007). As HIV genetic diversity evolves, evaluations of all commercially licensed HIV-1 viral load assays should be performed regularly in populations with patients infected with all viral subtypes.

Failed detection or unreliable quantification of HIV infection can have significant consequences in early detection of MTCT (Creek et al., 2007; Geelen et al., 2003). Early diagnosis in infants can only be achieved with tests that detect HIV-1 DNA or RNA, since maternal HIV antibodies can persist in the infant until month 18 (Read, 2007) thereby precluding the use of antibody detection tests. It has been recommended that diagnostic testing with HIV-1 DNA or RNA assays be performed within the first 14-21 days of life, at 1-2 months and at 4-6 months of age (AIDSinfo, May 24, 2010). Additionally, if any of these test results are positive, repeat testing on a second sample has to be done to confirm the diagnosis of HIV-1 infection. A diagnosis of HIV-1 infection can be made on the basis of 2 separate positive HIV-1 DNA or RNA assay results (New York State Department of Health AIDS Institute, 2010).

Viral load assay	Extraction method	Lower detection limit (log10 HIV-1 RNA copies/ml)	Reference
COBAS TaqMan RT-PCR Assay	Nuclisens MiniMAG	3.0 (96.4% detected)	(Andreotti et al., 2010)
COBAS TaqMan RT-PCR Assay	Primagen	3.0 (96 % detected)	(Waters et al., 2007)
Nuclisens EasyQ HIV-1 v2.0	Nuclisens EasyMAG	2.9 (95% detected)	(van Deursen et al., 2010)
Nuclisens EasyQ HIV-1 v2.0	Manual Nuclisens	3.5 (100% detected)	(Johannessen et al., 2009)
Nuclisens EasyQ HIV-1	Nuclisens MiniMAG	2.9 (100% detected)	(Kane et al., 2008)
Amplicor HIV-1 Monitor Test v1.5	In-house method	3.0 (100% detected)	(Ikomey et al., 2009)
Abbot Real Time HIV-1	m2000 RT system	3.7 (100% detected)	(Garrido et al., 2009)
Abbot Real Time HIV-1	m2000 RT system	2.6 (99% detected)	(Lofgren et al., 2009)
Abbot Real Time HIV-1	m2000 RT system	3.0 (100% detected)	(Mbida et al., 2009)

Adapted from (Johannessen, 2010).

Table 2. Recent studies comparing HIV-1 viral load assays in DBS and plasma

Amplicor HIV-1 DNA PCR test version 1.0 (Roche Diagnostic), the first commercial HIV-1 qualitative DNA PCR assay, lacked optimal sensitivity to detect non-B HIV-1 subtypes (Bogh et al., 2001; Kline, Schwarzwald, and Kline, 2002; Obaro et al., 2005). In May 2005,

Roche Diagnostics replaced Amplicor HIV-1 DNA PCR version 1.0 by version 1.5, which has been shown to have excellent sensitivity and specificity in testing adult venous blood samples and infant DBS (Germer et al., 2006; Patton et al., 2007). This test is highly accurate in detecting the multiple HIV-1 subtypes circulating in Africa (Stevens et al., 2008), is standardized and supported for use in Africa, and has been used by researchers and infant diagnosis pilot programs in several countries (Creek et al., 2007). However, Amplicor HIV-1 DNA PCR 1.5 uses primers for the relatively variable *gag* gene and was developed to amplify HIV-1 group M strains (Roche Diagnostics). So, it is likely that sensitivity problems arise with groups O, N and P. New DNA amplification assays that cover all HIV-1 genetic forms are needed

5. Impact of HIV-1 diversity in response to antiretroviral therapy

Differences in amino acid composition between HIV-1 clades can lead to differences in susceptibility to ARV drugs. This is best illustrated by HIV-1 group O and HIV-2 isolates that show high-level of innate resistance to NNRTIs and T20 (Descamps et al., 1997; Poveda et al., 2004; Smith et al., 2009). This innate resistance is due to resistance mutations that are present as natural polymorphisms. For instance, HIV-1 group O isolates naturally present a cysteine at RT position 181 (Y181C) which is considered a major drug resistance mutation (DRM) to NNRTIs; the secondary NNRTI DRM A98G is also a natural polymorphism in group O (Descamps et al., 1997; Poveda et al., 2004) (Table 3).

Susceptibility of non-B subtypes to ARV drugs has been less well studied than subtype B mainly because of the predominance of subtype B in developed countries where ARVs first became available, coupled with the availability of genotypic and phenotypic ARV drug resistance testing (Brenner, 2007). Some studies of sdNVP for prevention of MTCT have demonstrated a statistically significant disparity in the overall drug resistance among subtypes, with frequencies of 69-87%, 55.3-36%, 19-42%, and 21% resistance against NVP in women with subtypes C, D, A, and CRF02_AG infections, respectively (Eshleman et al., 2005b; Flys et al., 2006; Johnson et al., 2005; Toni et al., 2005). There were no significant differences in the pre-NVP frequency of NVP resistance mutations or the pre-NVP levels of K103N-containing variants in women with subtypes A, C, and D that could explain the subtype-based differences in mutations after sdNVP exposure (Flys et al., 2006). However, there are other factors that may be associated with NVP resistance in women after the administration of sdNVP and which include: higher viral load and lower CD4+ T cell count prior to NVP exposure, increased pharmacokinetic exposure to NVP (e.g., longer half-life and decreased oral clearance of NVP), and the timing of sample collection (Eshleman et al., 2005b). Additional studies are needed that take in account all these factors to better understand the biological causes of these subtype differences in sdNVP resistance.

In the Pediatric European Network for Treatment of AIDS (PENTA) 5 trial, where 128 children were enrolled in a randomised trial to evaluate the antiviral effect of NRTI combinations (3TC+Abacavir, 3TC+ZDV, Abacavir+ZDV) and the tolerability of adding NFV, there was no significant difference according to HIV-1 subtype in the virologic response to treatment or in the frequency of development of resistance among children (Pillay et al., 2002). A French cohort study of 416 adult patients, 24% of whom carried non-B subtypes, showed that at 3, 6 and 12 months after initiation of ARV therapy (first line

regimens, subtype B: 65% PI-based regimens, 25% NNRTI-based regimens, 10% NRTI only; non-B subtype: 65% PI-based regimens, 30% NNRTI-based regimens, 5% NRTI only) HIV-1 subtype did not affect clinical progression, CD4 cell count, or viral load in response to treatment (Bocket et al., 2005). Frater *et al.* studied patients of African origin who were infected with a non-B subtype of HIV-1 and were living in London, and found no significant difference in the response to therapy (first line regimens, 50% PI-based regimens, 50% NNRTI-based regimens) among patients infected with subtypes A, C and D (Frater et al., 2001). Geretti and collaborators reported that patients infected with subtypes A, C, D and CRF02_AG were as likely to achieve viral load suppression (NRTI backbone: AZT+3TC or TDF+FTC or TDF+3TC or 3TC+d4T or d4T+ddI or ABC+3TC; third drug: EFV or NVP or RTV boosted PI) as those infected with subtype B and showed comparable rates of CD4 cell count recovery (Geretti et al., 2009). Other studies have analyzed virologic and immunologic responses to antiretroviral therapy according to the HIV-1 subtype and also did not find any differences (Alexander et al., 2002; Atlas et al., 2005; Bannister et al., 2006; De Wit et al., 2004; Nicastri et al., 2004). Thus, overall, it appears that HIV-1 subtypes do not have major differences in the response to ARV therapy. However, further studies should be designed, firstly to assess the efficacy of specific drug regimens in patients with non-B subtypes and secondly to evaluate the efficacy of these regimens in patients infected with particular non-B subtype species including the highly divergent H, J and K subtypes, complex CRFs and URFs which are common in African countries as wells as in patients infected with group O, N and P viruses. These studies should be performed within a single country in order to control for the many variables that might influence response to therapy, namely, adherence, ethnicity, psychosocial support and drug regimens.

Polymorphisms	Prevalence in subtype B	Prevalence in non-B subtypes
A98S	5%	70% G and 98% O
K103R	2.7%	98% O
V179E	0.4%	98% O
V179I	3.2%	50% A
Y181C	0%	100% O

Adapted from (Wainberg and Brenner, 2010).

Table 3. Polymorphisms in the RT that may impact HIV-1 resistance to NNRTIs

6. Impact of HIV-1 diversity in drug resistance

In the absence of any drug exposure, RT and PR sequences from B and non-B subtypes are polymorphic in about 40% of the first 240 RT amino acids and 30% of the 99 PR amino acids (Bartolo et al., 2009b; Bartolo et al., 2009c; Kantor and Katzenstein, 2004). Polymorphisms in the RT of non-B subtype viruses normally do not occur in known sites of resistance to NRTIs (Kantor and Katzenstein, 2003); in contrast, the PR from drug naive patients may contain amino acid substitutions associated with secondary resistance to some PIs in subtype B (ex. K20R, M36I, H69KQ) (Table 4) (Grossman et al., 2001; Holguin et al., 2004). However, these genotypic changes by themselves do not consistently confer decreased susceptibility to PIs when viral strains are subject to phenotypic testing (Descamps et al., 2005; Grossman et al., 2004; Ly et al., 2005; Maljkovic et al., 2003; Nkengafac et al., 2007; Palma et al., 2007; Paraskevis et al., 2005; Roudinskii et al., 2004; Tee, Kamarulzaman, and Ng, 2006; Vazquez

de Parga et al., 2005; Wensing et al., 2005). Consistent with this, most observational studies performed *in vitro* and *in vivo* suggest that the currently available PR and RT inhibitors are as active against non-B subtype viruses as they are against subtype B viruses (Santos and Soares, 2010).

Different HIV genetic forms carry in their genomes genetic signatures and polymorphisms that could alter the structure of viral proteins which are targeted by drugs, thus impairing ARV drug binding and efficacy (Tables 3 and 4). A single nucleotide substitution from the wild-type codon found in subtype C can generate the mutation V106M, which is associated with NNRTIs resistance, while at least two substitutions are needed for the wild-type subtype B codon (Brenner et al., 2003; Loemba et al., 2002). This suggested that subtype C could have a lower genetic barrier to resistance to NNRTIs than subtype B, and that this V106M mutation could be more frequent in subtype C infected patients failing therapy, than in subtype B infected patients. Indeed, the clinical importance of the V106M mutation in non-B subtypes has been confirmed in several studies showing that V106M is more frequently seen in subtype C (and CRF01_AE) after therapy with EFV or NVP (Deshpande et al., 2007; Hsu et al., 2005; Marconi et al., 2008; Rajesh et al., 2009). The G190A mutation was also relatively more frequent in subtype C Indian and Israeli patients failling NNRTI-based regimens than in subtype B (Deshpande et al., 2007; Grossman et al., 2004).

In vitro, the emergence of the K65R mutation after therapy with TDF is faster in subtype C (15 weeks after TDF) than in subtype B (34-74 weeks) (Brenner et al., 2006; Coutsinos et al., 2010; Coutsinos et al., 2009). In contrast, K65R may be less frequent in subtype A than in all other subtypes (Gupta et al., 2005). Several studies suggest that there is a higher risk of development of K65R in subtype C infected patients failing ddI and d4T-containing regimens (Brenner and Coutsinos, 2009; Deshpande et al., 2010; Doualla-Bell et al., 2006; Hosseinipour et al., 2009; Orrell et al., 2009). A study from Israel reported a high frequency of K65R in subtype C viruses from Ethiopian immigrants in ARV therapy (Turner et al., 2009). However, K65R did not appear to emerge frequently in subtype C patients who participated in large clinical trials in which they received either TDF or TDF/FTC as part of a triple therapy regimen (Miller et al., 2007). In Malawi, in patients with subtype C viruses, differences observed in the emergence of the K65R mutation were significantly related to treatment regimen and disease stage (Hosseinipour et al., 2009). In addition, development of K65R in subtype C and CRF01_AE has been associated with the Y181C NVP mutation within the viral backbone (Brenner and Coutsinos, 2009; Zolfo et al., 2010 Set 22 [Epub ahead of print].). The presence of higher rates of the K65R mutation in subtype C in some studies (Doualla-Bell et al., 2006; Hosseinipour et al., 2009; Orrell et al., 2009) suggests that these viruses may have a particular predisposition toward acquiring this mutation. It has been proposed that a RNA template mechanism could explain the higher rates of K65R in subtype C viruses than in other subtypes. In this subtype, there is an intrinsic difficulty in synthesizing pol-A homopolymeric sequences that leads to template pausing at codon 65, facilitating the acquisition of K65R under selective drug pressure (Coutsinos et al., 2010; Coutsinos et al., 2009). The natural polymorphisms found in the RT of treatment-naive patients (10% in 726 patients) infected with HIV-1 non-B subtypes had no significant impact on susceptibility to ETR (Cotte et al., 2009; Derache et al., 2008; Maiga et al., 2010).

In PR, polymorphisms do not impair drug susceptibility but may affect the genetic pathway of resistance as soon as the virus generates a major resistant mutation (Martinez-Cajas et al., 2008). The rare minor V11I mutation, which is associated with DRV resistance, is a natural polymorphism in all CRF37_cpx isolates and some subtype A isolates (Bartolo et al., 2009b; Bartolo et al., 2009c; de Meyer et al., 2008; Poveda et al., 2007; Powell et al., 2007a), suggesting that these viruses may have a lower genetic barrier to DRV resistance. The V82I natural polymorphism in subtype G led to the emergence of I82M/T/S with treatment failure to IDV (Camacho et al., 2005). A study suggested that polymorphisms at position 36 in PR may play important roles in determining the emergence of specific patterns of resistance mutations among viruses of different subtypes (Lisovsky et al., 2010). Gonzáles *et al.* (Gonzalez et al., 2003) compared clinical isolates of C subtype with and without the I93L polymorphism, finding that hipersusceptibility to LPV in subtype C is strongly associated with the presence of that mutation.

Minor mutations	ARV	Prevalence in subtype B	Prevalence in non-B viruses
V11I	DRV	1%	100% CRF37_cpx and 4% in subtype A
I13V	TPV	13%	90%–98% in subtypes A, G and CRF02_AG, 4%–78% in other non-B subtypes
K20I	ATV	2%	93%–98% in subtypes G and CRF02_AG, 1%–3.5% in subtypes A, F and CRF01_AE
M36I	ATV, IDV, NFV and TPV	13%	81%–99% in several non-B subtypes
H69K	TPV	2%	96%–97% in subtypes A, C and G, CRF01_AE and CRF02_AG, 2% in subtype F
V82I	ATV	2%	87% in subtype G, 1%–6% in several non-B subtypes
I93L	ATV	33%	94% in subtype C, 5%–40% in several non-B subtypes

DRV, darunavir; TPV, tripranavir; ATV, atazanavir; IDV, indinavir; NFV, nelfinavir. Adapted from (Santos and Soares, 2010).

Table 4. Polymorphisms on the PR of HIV-1 non-B subtypes associated with resistance to PIs

The D30N mutation was not observed in CRF02_AG and CRF02_AE isolates from patients failing NFV therapy; rather, the N88S mutation emerged after NFV use in CRF01_AE and after IDV use in subtype B (Ariyoshi et al., 2003; Chaix et al., 2005). The M89I/V mutations have been observed in C, F and G subtypes in PI experienced patients (NFV, APV, IDV, LPV, ATV) but not in other subtypes (Abecasis et al., 2005). The L90M mutation, that confers resistance to NFV and SQV, is rare in subtype F but common in subtype B in patients from Brazil (Calazans et al., 2005). D30N has a stronger negative impact in the replicative capacity

of C subtype than in B subtype (Gonzalez et al., 2004), which could explain the low frequency of this mutation observed in subtype C infected individuals failing NFV-containing regimens. A recent study in Portuguese patients, reported that mutation I54V/L was selected by NFV in subtype G isolates, a mutation not previously described for this drug in subtype B (Santos et al., 2009).

The frequency of polymorphisms in gp41 among different HIV-1 clades from T20 drug-naive patients is higher in non-B subtypes and recombinants than in subtype B viruses ($P<0.001$) especially at positions Q32L/T/N/K, R46K/Q, N43H, I37L, and V69L that are associated with resistance to T20 (Carmona et al., 2005). The N42S polymorphism, associated with increased susceptibility to T20, is detected more frequently in non-B subtypes than in B subtype (13% in B, 73% in A and 90% in G) (Carmona et al., 2005). A30V (in subtype G and CRF06_cpx) and Q56K/R (in subtypes A and J, CRF04_cpx, CRF09_cpx, CRF11_cpx, and CRF13_cpx), Q56R and S138A in group O, and S138A in group N are natural polymorphisms associated with T20 resistance (Holguin, De Arellano, and Soriano, 2007).

Integrase inhibitor-associated mutations (primary and secondary) are normally absent from HIV-1 subtype B isolates from patients receiving ARV regimens without raltegravir (RAL) and from untreated patients (Ceccherini-Silberstein et al., 2010a; Ceccherini-Silberstein et al., 2010b). A study found integrase gene polymorphisms present in more than 10% of the 97 analyzed sequences (subtype B and non-B) from patients treated with RAL but these polymorphisms showed no impact on virological outcome either at week 24 or at week 48 (Charpentier et al., 2010). N155H, Q148H/R/K with G140S/A, and Y143R/C are the described mutational patterns that confer resistance to RAL, with or without secondary mutations (Garrido et al., 2010). A study on natural polymorphisms and mutations associated with resistance to RAL in drug-naive and ARV-treated patients (all RAL naive) found that CRF02_AG and subtype C isolates could have a higher genetic barrier to the development of G140C or G140S compared to subtype B (Brenner et al., 2011). On group O viruses, natural presence of the E157Q mutation or E157E/Q mixture seems to confer resistance to RAL (Leoz et al., 2008).

These observations in non-B subtype viruses suggest that differences in drug resistance pathways between HIV-1 subtypes do exist. However, the accumulated evidence is insufficient to adequately assess the contribution of the innate genetic diversity of HIV-1 to resistance. Larger and more rigorous prospective studies in drug naive and treated patients are required to validate these hypotheses and it will be necessary to evaluate these mutations by the analysis of site-directed mutants in phenotypic resistance assays.

7. Impact of HIV-1 diversity in the performance of genotypic and phenotypic drug resistance assays

Drug resistance testing is extremely important for the management of ART therapy failure in HIV patients (Grant and Zolopa, 2009; Shafer, 2002; Taylor, Jayasuriya, and Smit, 2009). Genotypic and phenotypic assays are both used to detect resistance to ARV drugs that could compromise response to treatment (Vandamme et al., 2011). All current clinically used genotypic assays involve sequencing the genes whose proteins are targeted by the different antiretroviral drugs [*pol* (RT, PR and IN) and *env*], to detect mutations that are known to

confer phenotypic drug resistance. There are two approved genotyping resistance assays commercially available, the ViroSeq HIV-1 genotyping system, version 2.0 (Eshleman et al., 2004) and the Trugene HIV-1 genotyping kit for drug resistance (Grant et al., 2003). Phenotypic assays measure the ability of an HIV-1 isolate to grow *in vitro* in the presence of an inhibitor, in comparison with a known susceptible strain.

The European HIV Drug Resistance Guidelines Panel recommends genotyping in most situations using updated and clinically evaluated interpretation systems (Vandamme et al., 2011). Genotypic assays are faster and cheaper than phenotypic assays (Vandamme et al., 2004). Nonetheless, the commercial genotypic tests are too expensive to be used in low-income countries. In-house methods for genotyping drug resistance mutations are recommended by WHO for surveillance of primary and secondary drug resistance (Bennett et al., 2008). The reported rate of success in amplification and sequencing with these methods in low-income countries ranges from 41 up to 100 % with non-B isolates (Bartolo et al., 2009b; Bartolo et al., 2009c; Bennett et al., 2008; Oliveira et al., 2011).

Several studies analyzed the performance of commercially available genotypic resistance assays and in-house methods in B and non-B strains (Aghokeng et al., 2011; Beddows et al., 2003; Fontaine et al., 2001; Jagodzinski et al., 2003; Maes et al., 2004). In commercial kits a greater degree of success was obtained when sequencing subtype B isolates compared to non-B isolates, and some studies report that alternative amplification/sequencing primers had to be used for some samples belonging to non-B subtypes. A Belgian study analyzed the performance of the ViroSeq HIV-1 Genotyping System in 383 samples comprising 12 different subtypes (Maes et al., 2004). Amplification failed in 8.4% of the samples and there was a lower performance in the amplification of non-B subtypes. The sequencing performance on the different subtypes showed a significant decrease of positive results for subtypes A, G and recombinant strains. As a result of sequencing problems, 18.5% of the samples had to be processed with in-house procedures. In Cameroon, where all groups of HIV-1 circulate, the sequencing efficiency of the ViroSeq assay was also evaluated (Aghokeng et al., 2011). The sequencing failures involved mainly the 5´end of the PR and the 3` end of the RT genes because of the high failure rate of primers A, D, F, and H. There was a high degree of polymorphism in non-B isolates in the areas for which these primers are designed. One study compared the two commercially available sequencing kits with a in-house genotyping system in HIV-1 samples from treated and untreated patients belonging to subtypes A through J (Fontaine et al., 2001). All the samples could be amplified and sequenced by the three systems; however, for all systems, alternative amplification/sequencing primers had to be used for some samples belonging to non-B subtypes.

Several studies have evaluated the use of DBS for HIV-1 genotypic resistance testing (reviewed in (Johannessen, 2010)). Nucleotide similarity between the two sample types ranged from 98.1 to 99.9%. Drug-resistant mutations found in plasma were detected in 82–100% of the corresponding DBS specimens. In all, these findings indicate that the performance of amplification and sequencing primers must be improved to allow good sequencing results and consequently fast and reliable resistance testing for all HIV-1 genetic forms. Validated in-house methods with primers designed on the basis of the local HIV genetic diversity are needed for low–resources settings.

Drug resistance interpretation algorithms are user friendly and helpful in the clinical setting to follow up HIV-infected patients. These algorithms have been developed to interpret complex patterns of resistance mutations in HIV-1 subtype B. The most frequently used clinically available systems are listed in Table 5. There are two types of systems, geno2pheno and *Virtual*Phenotype which try to predict viral phenotype under the assumption that phenotype predicts treatment response, whereas all others algorithms try primarily to predict treatment response based on information extracted from databases of genotypic and correlated phenotypic or treatment response data (Vandamme et al., 2011). Several studies have compared these algorithms in drug naive and treated patients infected with non-B subtypes to examine the influence of pre-existing polymorphisms on predictions of drug susceptibilities and the subsequent choice of therapy (Champenois et al., 2008; Depatureaux et al., 2011; Snoeck et al., 2006; Vergne et al., 2006a; Vergne et al., 2006b; Yebra et al., 2009). Most of these studies found some discordance between algorithms, which was related to the presence of naturally occurring polymorphisms in non-B subtypes (Champenois et al., 2008; Depatureaux et al., 2011; Snoeck et al., 2006; Vergne et al., 2006a; Vergne et al., 2006b; Yebra et al., 2009). A study showed that, according to available resistance algorithms, both B and non-B subtypes from drug naive patients were considered fully susceptible to PIs, except for TPV/RTV for which the ANRS algorithm scored non-B subtypes as naturally resistant (Champenois et al., 2008). The discordant results for TPV/RTV were due to differences in the mutations that are considered by the algorithms in the analysis. The ANRS algorithm takes in account TPV/RTV mutations that are considered natural polymorphisms in non-B subtypes (e.g. M36I, H69K and L89M). In another study, 68 drug naive and 9 highly ARV-experienced HIV-1 group O infected patients were analyzed (Depatureaux et al., 2011). Twelve minor resistance mutations, present in more than 75% of the PR sequences, led to the different algorithms giving discrepant results for NFV and SQV susceptibility.

A large study (5030 patients infected with different HIV-1 clades) found that the four algorithms analyzed agreed well on the level of resistance scored and that the discordances could be attributed to specific (subtype-dependent) combinations of mutations (Snoeck et al., 2006). In a comparison of five algorithms in HIV-1 sequences from drug naive patients, discordances were significantly higher in non-B vs. B variants for ddI, NVP, TPV, and fAPV, and were attributed to natural patterns of mutations in non-B subtypes (Yebra et al., 2009). Several other studies demonstrated that there was a lack of concordance between algorithms that predict treatment response based on phenotype and genotype (Holguin, Hertogs, and Soriano, 2003; Ross et al., 2005; Santos et al., 2009). These discrepancies indicate that the patterns of drug resistance mutations have not yet been completely clarified in non-B subtype variants. The use of certain algorithms could lead to an overestimation of the resistance in the analysis of specific non-B subtypes because of the lack of consensus in the resistance mutations considered although with increasing knowledge such discrepancies tend to diminish.

Tropism testing is recommended before the use of a CCR5 antagonist drug (Vandekerckhove et al., 2011). In general, the enhanced sensitivity Trofile (ESTA) assay (phenotypic assay) and V3 population genotyping are the recommended methods. A multicenter prospective study evaluated the performance of genotypic algorithms for prediction of HIV-1 coreceptor usage in comparison with a phenotypic assay for the determination of coreceptor usage (Recordon-Pinson et al., 2010). Researchers reported important differences between 13 algorithms in the sensitivity of detection of X4 isolates.

The most sensitive were PSSM and Geno2pheno, with sensitivities of about 60%; on the other hand the specificity was high for most algorithms. In other studies, higher sensitivities could be found for the same genotypic algorithms (Chueca et al., 2009; Raymond et al., 2008). Geno2pheno presented sensitivities of 88-93.7% and specificity of 87%, and PSSM with sensitivities of 77% and specificity of 94%. Overall, these studies validate genotypic algorithms for prediction of HIV-1 coreceptor use in antiretroviral-experienced patients infected with subtype B. Few studies have evaluated the performance of genotypic algorithms for prediction of HIV-1 coreceptor use in non-B subtype viruses. An initial report showed a poor performance of genotypic tools for non-B subtypes (A-J, CRF01_AE, CRF02_AG, CRF11, CRF12_BF, CRF14_BG, URFs, and U samples), where they particularly failed to detect X4 strains (Garrido et al., 2008). Other studies found that main genotypic algorithms perform well when applied to CRF02_AG (Raymond et al., 2009) and subtype C viruses (Raymond et al., 2010). Additional studies are needed to evaluate the performance of these genotypic tools to predict coreceptor use in non-B subtypes.

System	Levels of resistance	Web Site
HIV DB Stanford	S, PL, LL, IR, HR	http://hivdb.stanford.edu/
REGA	S, I, R	http://www.kuleuven.ac.be/rega/cev/links/
ANRS	S, I, R	http://www.hivfrenchresistance.org/index.html
GenoSure	S, RP, R	http://www.monogramhiv.com
ResRis	S, I, R	http://www.retic-ris.net
HIVGrade	S, I, LS, R	http://www.hiv-grade.de
AntiRetroScan	100/75/50/25/0#	http://www.hivarca.net/includeGenpub/AntiRetroScan.html
HIV-TRePS	Quantitative*	http://www.eurist.org
EuResist Network	Quantitative*	http://www.eurist.org
Geno2pheno	Quantitative, S, I, R	http://www.geno2pheno.org
Virco	Quantitative+	http://www.vircolab.com
ViroSeq	S, P, R	http://www.abbotmolecular.com
TruGene	S, I, R	http://www.labnews.com

S, susceptible; PL, possible low-level resistance; LL, low-level resistance; IR or I, intermediate resistance; HR, high level resistance; R, resistance; RP or P, resistance possible; LS, low susceptibility; #100/75/50/25/0 in %activity with drug-GSS weighting factor; *probability for short-term response with specific drug combinations; +lower clinical cut-off at 20% of loss of response, upper to 80%. Adapted from (Vandamme et al., 2011).

Table 5. Drug resistance interpretation algorithms

8. References

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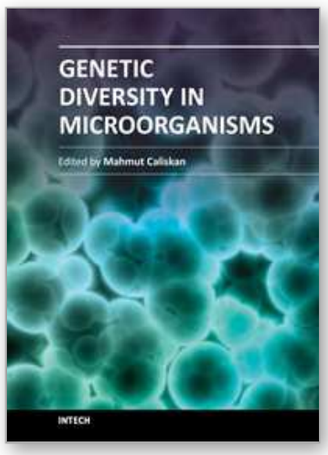

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Genetic Diversity in Microorganisms presents chapters revealing the magnitude of genetic diversity of microorganisms living in different environmental conditions. The complexity and diversity of microbial populations is by far the highest among all living organisms. The diversity of microbial communities and their ecologic roles are being explored in soil, water, on plants and in animals, and in extreme environments such as the arctic deep-sea vents or high saline lakes. The increasing availability of PCR-based molecular markers allows the detailed analyses and evaluation of genetic diversity in microorganisms. The purpose of the book is to provide a glimpse into the dynamic process of genetic diversity of microorganisms by presenting the thoughts of scientists who are engaged in the generation of new ideas and techniques employed for the assessment of genetic diversity, often from very different perspectives. The book should prove useful to students, researchers, and experts in the area of microbial phylogeny, genetic diversity, and molecular biology.

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