HIV Antiretroviral Drug Resistance in Africa

John N. Nkengasong[1,2], Christiane Adje-Toure[3] and Paul J. Weidle[2]

[1]Division of HIV/AIDS, STD, TB Laboratory Research. [2]Division of HIV/AIDS Prevention, Surveillance, and Epidemiology. National Center for HIV, STD and TB Prevention, Centers for Disease Control and Prevention, Atlanta, GA, USA. [3]Projet RETRO-CI, Abidjan, Côte d'Ivoire

Abstract

Highly active antiretroviral therapy (HAART) has dramatically reduced mortality and morbidity in HIV-infected persons in developed countries. Although the use of HAART remains limited in Africa, there are global efforts to make available these drugs to several million HIV-infected persons on the continent. In this review we examine the impact of HIV genetic diversity on the occurrence of drug-resistance mutations among non-B subtypes, and discuss the implication of resistant strains in programs aimed at implementing antiretroviral treatment (ART) in Africa, with respect to factors that may favor the occurrence of treatment-acquired drug-resistant viruses, ways to monitor for drug resistance, and strategies to limit its occurrence. We assert that antiretroviral drug resistance is an inevitable consequence when providing long-term treatment, and should not be seen as a limitation of providing antiretrovirals to patients in resource-poor settings, but rather a necessary challenge to be incorporated into the rational design of programs that provide ART in Africa. **(AIDS Rev 2004;6:4-12)**

Key words

Drug resistance. Africa. Antiretroviral therapy. HIV subtypes.

Introduction

The demonstration of dramatic improvements in HIV-1 mortality and morbidity as a result of HAART in North America[1], Europe[2], and more recently Brazil[3], has steered the international community to increase access to these drugs in resource-limited settings[4,5]. However, in Africa it is estimated that only about 30,000-75,000 of the millions of HIV-infected patients who need antiretroviral treatment currently receive it[4,5]. A series of efforts and circumstances are combining to enable HIV-infected patients in Africa to access ART, including individual country drug-access initiatives; the Global Fund against AIDS, TB, and Malaria; The World Health Organization's '3 by 5 initiative'; the U.S. Government's Emergency Plan for AIDS Relief; the accelerated-access care initiative; UNAIDS-led price observatory; the availability of generic drugs; and the drastic reduction in prices of ART drugs by pharmaceutical companies. Moreover, ART is presently used in Africa in programs to prevent mother-to-child transmission (MTCT) of HIV-1.

The main constraints for access to ART in Africa have been the high cost of drugs, the lack of infrastructure to procure and distribute drugs, inadequate numbers of trained health-care staff, and the lack of adequate laboratory facilities to monitor patients receiving ART. These limitations have raised concerns for the possibility of emergence of drug-resistant viral strains in patients and the subsequent occurrence of community-acquired resistant strains if ART is widely used in Africa.

This review examines the implication of access to ART on the occurrence of drug resistance in Africa with respect to tools for monitoring drug resistance in Africa; possible differences in HIV genetic types and subtypes; occurrence of drug-resistant viruses in drug-access initiatives in Africa and in MTCT prevention programs; the need to monitor for drug-resistant viruses for public health purposes; and strategies to limit the occurrence of drug resistance in Africa.

Correspondence to:
John N. Nkengasong
Division of HIV/AIDS, STD, TB Laboratory Research (MS A 25)
Centers for Disease Control and Prevention
Atlanta, GA, USA
Phone: 404-6390871
Fax: 404-639 2108
E-mail: jcn5@cdc.gov

Mechanism of occurrence of drug resistance

The polymerase *(pol)* gene of HIV consists of protease and reverse transcriptase (RT) genes, which produce enzymes necessary for the replication of HIV. The emergence of HIV-resistance mutations in the viral protease and RT genes is a major cause for treatment failure of ART. HIV drug resistance is the outcome of the high replication and mutation rates of HIV. Approximately 10 billion copies of HIV can be generated in a single day in untreated persons, and because the HIV RT lacks proofreading capacity, an average of one mutation occurs during each replication cycle. Genotypic resistance refers to the identification of mutations at specific nucleic acid positions, which are associated with phenotypic resistance. Antiretroviral drug resistance is a result of substitution of some amino acids that encode the RT and protease enzymes. For example, a methionine (M) to valine (V) substitution at position 184 of the RT gene is associated with high-level phenotypic resistance to lamivudine, and is referred to as M184V.

Resistance mutations have been classified as minor or major, based on the amino acid sequences of HIV-1 subtype-B viruses. In them, minor mutations have little discernible effect on viral susceptibility to a drug *in vitro:* they are predominantly compensatory, resulting in increased fitness of the particular viral isolate. In non-B subtypes, minor mutations can exist as natural polymorphisms in viruses from drug-naive patients. Major mutations develop during the course of virologic failure, and have a measurable impact on *in vitro* susceptibility of HIV to a particular drug or class of drugs.

Although many resistance mutations are harmful to viral replication in the absence of drugs, they can be selected because they allow HIV to replicate better in the presence of antiretroviral therapy. Certain specific single mutations can directly diminish drug binding to the enzyme's active site and thereby impact on a drug's inhibitory effect. This is exemplified by the M184V and Y181C mutations of the RT gene that confer resistance to lamivudine and nevirapine (NVP), respectively. However, for resistance to other drugs such as zidovudine (ZDV), a selection of multiple, sequential mutations has to occur before high-level resistance results. Once selected, the capacity of HIV for genomic integration and dormancy means that the mutants may persist, perhaps for later reselection. For patients who have undergone antiretroviral therapy, resistance selected by previously used drugs can lead to cross-resistance to other drugs and can have a significant impact on subsequent therapy.

Techniques for resistance detection

In vitro, viral resistance can be detected using genotypic and phenotypic assays. Phenotypic testing measures the ability of an HIV-1 isolate to replicate in the presence of a drug. Phenotypic resistance can be measured by a recombinant virus assay or enzymatic susceptibility of RT/protease to inhibition by a drug.

Presently, two recombinant virus phenotypic assays exist: Phenosense HIV (ViroLogic Inc, South San Francisco, CA, USA) and Antivirogram (Virco Ltd, Melchelen, Belgium). These assays use reporter genes to measure the levels of recombinant virus replication at a given drug concentration. Phenotypic resistance is usually reported in terms of the inhibitory concentration of the drug required to reduce viral replication 50 or 90% (the IC_{50} or the IC_{90}). The most challenging aspect of phenotypic assays is interpreting the data in terms of choosing the appropriate cutoff for fold change in IC_{50}. Because these assays are time consuming, expensive and require specialized laboratory facilities, they are unlikely to become widely available as clinical assays in the near future in Africa.

An enzymatic-based in-house assay for phenotypic RT susceptibility testing, referred to as Amp-RT, detects RT activity by using a known heterologous RNA template from the encephalomyocarditis virus (EMCV) RNA genome. The RT-derived EMCV cDNA is detected by PCR amplification and ELISA-based hybridization with an internal EMCV-specific probe[6,7]. In contrast to the recombinant virus phenotypic assays, drug susceptibility by Amp-RT provides rapid information on resistance in one to two days, and can also be used to monitor for drug resistance in persons infected with highly divergent viruses such as HIV-1 group O[8]. This assay may be more convenient for use in regional specialized laboratories in Africa. One limitation of this assay is that a template for determining protease activities does not exist.

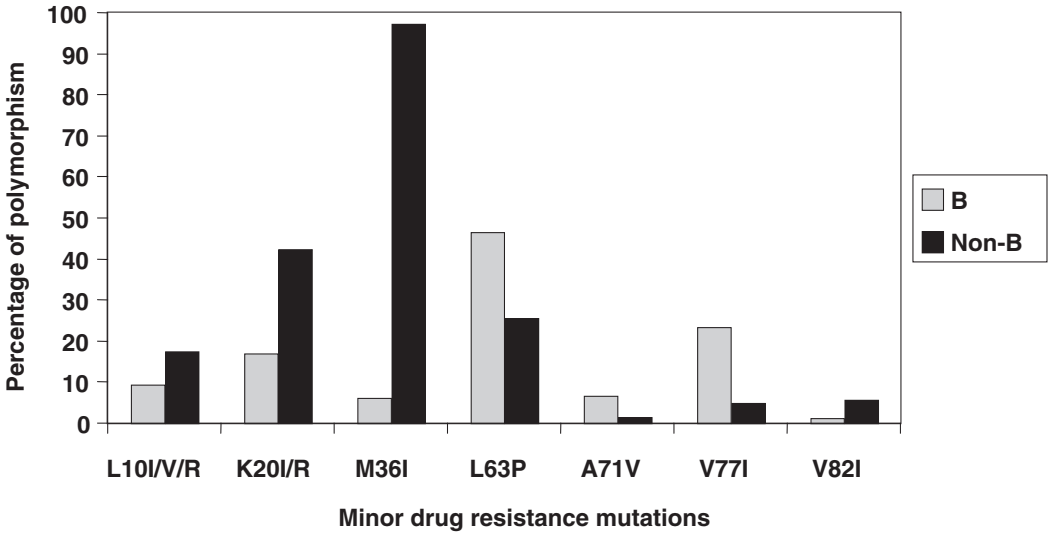
DNA sequencing analysis provides information on all positions of the RT and protease genes associated with drug resistance. Presently, four assays based on DNA sequencing are being extensively used for testing for drug-resistance mutations: TRUGENE™ (Visible Genetics, Toronto, Ontario, Canada), the ViroSeq kit (Applied Biosystems Inc., Foster City, CA), VircoGEN™ (Virco Ltd., Mechelen, Belgium), and GeneSeq HIV

(Virologic Inc., South San Francisco, CA). These assays are based on cycle sequencing and require amplification of HIV-1 sequences from plasma containing at least 500 to 1000 HIV RNA copies/ml. DNA sequences obtained from these assays can later be used to determine HIV-1 subtype. Although these assays have been shown to perform well on patients infected with non-B subtypes present in Africa[9], the high cost and the need for expensive equipment, well trained technicians, laboratory quality assurance and expert clinicians to interpret genotypic results, limits their use in managing patients receiving ART in Africa, or using them as tools for surveillance of drug resistance in individual countries.

At least two simpler and cheaper assays have been developed as alternatives to DNA sequencing: 1) a sensitive, highly specific and high-throughput oligonucleotide ligation assay (OLA) resistance; this ligation-based assay uses differentially modified oligonucleotides specific for wild-type or mutant sequences, allowing sensitive and simple detection of both genotypes in a single well of a microtiter plate[10]; 2) the reverse hybridization line probe assay (LiPA) which is a rapid and simple assay that can be used to detect mutations in the RT gene at codons 41, 69, 70, 74, 184 and 215 of HIV-1[11]. The LiPA assay has some limitations in recognizing mutations selected by RT inhibitors that may be due to the limited number of probes for each position utilized in this test. Also, HIV-1 heterogeneity may affect its performance[12].

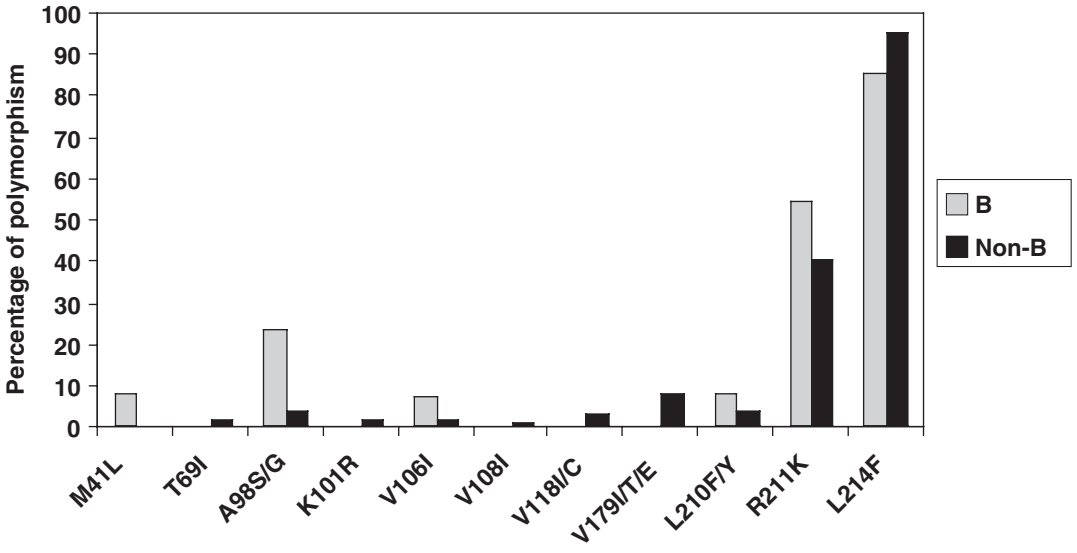
HIV genetic diversity and drug resistance

Two main types of HIV have been identified: HIV-1 and HIV-2. HIV-1 consists of group M, group N and group O. At least nine different HIV-1 group M subtypes and 15 circulating recombinant forms (CRFs) have been documented[13-15]. Antiretroviral drugs were designed, tested and validated primarily in North America and Europe where HIV-1 group M subtype B strains predominate, but non-B subtypes predominate in Africa and the world. CRF02_AG predominate in West Africa, multiple subtypes exist in Central Africa, subtypes A and D predominate in East Africa, and subtype C in Southern Africa[13]. These subtypes differ from one another by 10-15% in their *pol* gene, which includes the coding regions for the viral protease and RT, the current targets of most antiretroviral drugs. Figures 1 and 2 show the differences between HIV-1 subtype B and non-B subtypes in the RT and protease



Differences in amino acid substitutions in the protease gene for subtypes B and non-B were compiled from several published HIV-1 strains: 108 subtypes B and 348 non-B subtypes (87A, 74C, 31D, 8F1, 13F2, 11G, 10J, 4O, 26CRF02_AE and 84CRF02_AG).

Figure 1. *Comparison of amino acid substitutions associated with minor protease resistance among drug-naive persons infected with HIV-1 subtype B and non-B viruses.*



Differences in amino acid substitutions in the reverse transcriptase gene for subtypes B and non-B were compiled from several published HIV-1 strains: 13 subtypes B and 206 non-B subtypes (8A, 74C, 5D, 25F, 3G, 3J, 4O, 3CRF02_AE and 81CRF02_AG).

Figure 2. *Comparison of amino acid substitutions associated with minor RT resistance among drug-naive persons infected with HIV-1 subtype B and non-B viruses.*

regions, with significant differences at different protease positions: L10I/V/R, K20I/R, M36I, L63P, and V77I. Amino acid substitutions are not so different in the RT region.

HIV-1 group M resistance to ART

Until recently, due to lack of data on ART use in Africa, there was speculation whether persons infected with HIV-1 group M non-B subtypes had similar patterns of drug-resistance mutations as those infected with subtype B strains. Some limited studies on ART drug resistance in Africa, or on non-B subtypes in Europe, have shown a strong correlation between the presence of major mutations and phenotypic resistance, similar to mutations seen in subtype B infections under similar treatment regimens[16]. However, studies have documented some salient differences among patients infected with non-B subtypes:

1. In non-B subtypes, natural polymorphisms, which have been identified as minor genotypic resistance mutations in subtype B, are often found in the protease gene at amino acid positions L10I/V, K20I, and M36I and in the RT gene at positions V179I/T/E and L214F[17,18] (Figs. 1 and 2).
2. Compared to patients infected with subtype B, those infected with CRF14_BG have a high frequency of polymorphisms for mutations within the B region of gp41 at L9F and K144R, which is the binding domain for enfuvirtide (also known as T-20), a new drug for treating HIV patients that blocks cell fusion and viral entry. Also, polymorphisms of gp41 at positions T115L and M118V may be more frequent for subtype G viruses[19].
3. Although V82I is not a major protease inhibitor (PI) mutation, this mutation is a naturally occurring polymorphism in subtype G strains[20,21].
4. Tissue culture experiments with efavirenz (but not NVP or delavirdine) have shown that subtype C isolates developed the V106M mutation, conferring high-level cross-resistance to all NNRTIs. Thus, V106M seems to be a signature mutation in subtype C patients treated with efavirenz[22].
5. A study of single-dose NVP to prevent mother-to-child transmission of HIV, conducted in Uganda, showed that selection of genotypic mutations associated with resistance to NVP occurred more frequently at 6-8 weeks postpartum in women infected with subtype D than in women infected with subtype A viruses[23].

6. In some non-B subtypes, nelfinavir treatment may select for mutations such as the L90M mutation, which confers resistance to nelfinavir as well as cross-resistance to all other PIs, potentially making nelfinavir less clinically useful in many non-B subtypes compared to subtype B. However, in HIV-1 subtype B strains, D30N is the signature mutation[24].

Despite these documented differences between HIV-1 group M subtype B and non-B strains, virologic and immunologic responses to ART appear to be similar for subtype B infected patients and those treated in drug-access initiatives in West Africa, where CRF06_cpx, CRF02_AG and subtype A are predominant[25,26]; in East and Southern Africa, where subtypes A, C and D are most frequent[27,28]; and in studies of African patients in Europe[29].

HIV-2 and HIV-1 group O resistance to ART

West and West-Central Africa are the epicenters of HIV-2 and HIV-1 group O strains, respectively. HIV-2 infection accounts for about 2% of HIV infections in some countries in West Africa[28] and 2.5% in South India[31], with at least seven genetic subtypes documented so far. The nucleotide sequences of HIV-1 and HIV-2 are approximately 50% identical in the protease and about 60% in the RT gene, and their catalytic properties are also very similar[32,33]. This similarity in the amino acid sequence and in the enzymatic properties suggests that the structure of HIV-2 RT is likely to be very similar to that of HIV-1 and, thus, may have similar resistance profiles.

From a clinical viewpoint, because very few patients have been treated with ART drugs in Africa, limited data exist on the patterns of drug-resistant mutations for HIV-2 and HIV-1 group O infected patients. HIV-2 and HIV-1 group O strains are naturally resistant to NNRTIs[34,35], with the naturally occurring mutation Y181C. Information regarding HIV-2 infected patients treated in Europe has shown that, as for HIV-1 infections, treatment with suboptimal antiretroviral agents can lead to the development of drug-resistance mutations[36,37].

Some similarities exist for antiretroviral resistance mutations in HIV-1 and HIV-2. For instance, in the RT gene the M184V mutation is rapidly selected for and is present in HIV-2 in 70 to 83% of patients receiving a 3TC-containing regimen[38,39] and is also associated with phenotypic resistance to 3TC[38]. Development of PI resistance in HIV-2 appears to be similar in some ways to that in HIV-1. As in HIV-1 infection, HIV-2 infected patients receiving PIs develop resistance mutations at positions 82, 84 and 90[38,39]. The polymorphism in the protease gene M36I, a minor mutation thought to be associated with ritonavir and nelfinavir resistance, occurs at a similar rate in HIV-2 and HIV-1 non-B strains[40].

Despite the similarities, HIV-2 viruses have several unique patterns of drug-resistance mutations. First, sequences from untreated patients have different amino acids than tyrosine at position 181 and 188 in the RT gene, which is considered the primary cause of the natural resistance of HIV-2 to NNRTI drug classes[41]. Second, HIV-2 patients failing ZDV-containing therapy rarely develop the classical T215Y/F mutation that is common in HIV-1 infected patients failing ZDV-containing therapy[38]. Rather, the S215Y, which is not associated with phenotypic resistance to ZDV[38] and the E219D mutation[42], occurs in patients failing ZDV-containing therapy. However, the phenotypic significance of the E219D mutation has not been demonstrated; thus, it is not known if these are the major ZDV-resistance mutations in HIV-2. One *in vitro* study has shown that HIV-2 strains seem to be naturally resistant to ZDV[43]. Third, whereas in HIV-1 infection the multi-drug resistant mutation Q151M usually develops in 3 to 17% of patients after more than two years of therapy with DDI in combination with ZDV or D4T[44,45], it occurs in about 17-33% of HIV-2-infected patients receiving ART drug regimens containing DDI and ZDV or D4T within 12 months of therapy[38,39]. These preliminary observations indicate that the Q151M mutation may represent a major pathway for NRTI resistance for HIV-2 viruses. As for HIV-1 viruses, the occurrence of Q151M in HIV-2 infection resulted in 5- to 10-fold lower sensitivity to ZDV, DDI, D4T and DDC, suggesting that the presence of this mutation leads to NRTI cross-resistance for HIV-2 as well[38]. Fourth, resistance to PIs appears to involve mutations at several positions in the protease gene (T43I, K45R, I54M, V71I, A92T and L99F)[40], many of which are not considered as major or minor resistance mutations in HIV-1. The substitution M46I, a major mutation in HIV-1 associated with indinavir resistance, appears to occur in about 90% of HIV-2 subtypes A and B[40]. Of concern are some recent studies that have shown, among a small number of patients, that nelfinavir-based PI regimens may have limited virologic benefits in HIV-2 patients[38,39]. A database for HIV-2 drug-resistance mutations, similar to what ex-

ists for HIV-1, is needed to be able to correctly interpret HIV-2 drug-resistance profiles.

The potential implications for the treatment of persons infected with HIV-2 of different amino acids than tyrosine at position 181 and 188 in the RT gene that are thought to be the primary cause of natural resistance of HIV-2 to NNRTI drug classes, is that this natural resistance precludes the use of currently available NNRTIs. Moreover, if further studies confirm that HIV-2 strains may be naturally resistant to ZDV, therapeutic options for RT inhibitors may be further limited for patients infected with HIV-2. Likewise, some PI regimens may have limited virologic benefits in HIV-2 patients, thus limiting therapeutic options for that class of drugs as well. Further research is needed to ascertain the impact of these early findings.

Drug resistance in ART pilot drug-access programs in Africa

Unregulated use of ART

Unregulated and widespread use of ART may lead to the rapid emergence of resistant viral strains that will limit therapeutic options for patients, create community-wide resistant viruses, and increase the risk of transmission of resistant strains. Studies in African countries where ART has been administered without the proper infrastructure to monitor patients, has shown a high prevalence of drug-resistance strains. For instance, in Côte d'Ivoire, of the approximately 1,000 HIV-infected patients screened for eligibility assessment at the start of the Drug Access Initiatives (DAI), about 10% reported having already received ART. In this population, the prevalence of genotypic drug-resistance mutations to at least one of the RT or PIs was 57%, with major mutations to ZDV (T215Y/F and K70R) and 3TC (M184V) being the most common[16]. In Côte d'Ivoire, prior to 1998, no official policy existed to import ARV drugs; thus, HIV-infected patients relied on friends or relatives in Europe, the United States, and elsewhere for supplies of ART. Also, no laboratory infrastructure to monitor response to therapy, especially changes in HIV-1 RNA viral load and CD4 counts, existed in the country. Similarly, in Gabon, Vergne, et al. showed that 58% of patients who had received unsupervised ART without an adequate health infrastructure to monitor for clinical and laboratory follow-up, developed major ART-resistance mutations, mainly to nucleoside RT inhibitors[46]. These observations strongly highlight the need to have guidelines for administering and monitoring patients on ART put in place before ART is widely implemented in Africa.

Use of non-suppressive ART

The use of non-suppressive ART may also contribute to the occurrence of drug-resistant strains. When the UNAIDS-WHO Drug Access Initiative started in Côte d'Ivoire in 1998, because of the high cost of the drugs most patients were treated with a combination of two drugs. The use of a combination of two antiretroviral drugs was associated with a tenfold increase in occurrence of drug resistance[47] and 79% of the patients failing therapy, with a rebound in viral load after at least six months of therapy, had major genotypic drug resistance mutations to at least one RT or PI. The most frequent genotypic resistant mutations were to ZDV (T215Y/F) and lamivudine (M184V)[47].

Likewise, in the Uganda pilot UNAIDS-WHO DAI, which also started in 1998, the choice of drugs was also constrained by cost, and the use of two NRTIs was associated with a less potent virologic response[27] and more frequent development of resistance[48]. Approximately one third of those prescribed HAART and just over one half of those prescribed two NRTIs, had resistance to at least one drug. Most of the documented resistance was to lamivudine, commonly used at that time, and was associated with a genotypic mutation that would be predicted from what is seen in subtype B. This was similar to earlier findings from Uganda where the major genotypic mutation associated with lamivudine resistance (M184V) was present for all nine specimens with phenotypic resistance to that drug, most of those from patients who had taken two NRTIs[49].

In contrast, in the Senegalese DAI, where 86% of patients received HAART, after 24 months follow-up with careful clinical and biological monitoring, drug-resistance mutations were seen in only 16% of the patients[50]. However, 42% of patients who had received ART prior to the start of the DAI had major drug-resistant viruses. In this population where about 50% of the patients were infected with CRF02_AG, major mutations, such T215Y, similar to those observed in subtype-B infected patients, were seen.

Drug resistance in MTCT prevention programs in Africa

In 2001, it was estimated that 90% of the estimated 800,000 people who were newly infected with HIV

through MTCT, were born in Africa. Short-course antiretroviral regimens to prevent mother-to-infant transmission are presently being used extensively in Africa. These regimens include ZDV, NVP or lamivudine. In fact, mass treatment of an intrapartum and neonatal single-dose NVP regimen has been suggested as an effective strategy in MTCT prevention programs[51].

It is conceivable that extensive use of short-term dual- or monotherapy in MTCT prevention programs has the potential to select antiretroviral resistance mutations and may compromise treatment options in the mothers or infants later on in life. In fact, in view of the high fertility rate in many African nations, even among HIV-infected women, a woman might require ART to prevent MTCT of HIV-1 during more than one pregnancy. MTCT prevention studies in Africa have shown that the rate of occurrence of drug resistance varies by drug: a study conducted in Abidjan, Côte d'Ivoire, did not find any ZDV resistance after six weeks of therapy[52]. In the United States, only 2.6% of women developed ZDV resistance in the ACTG 076 study at approximately 12 weeks of ZDV treatment[53].

Single-dose NVP is associated with induction of NVP resistance in women with unsuppressed virus. Results from several studies have shown that, for mothers receiving single-dose NVP, the risk of developing transient detectable genotypic NVP-resistant virus (usually K103N or Y181C) among women with replicating virus is between 15-19%[54]. Resistance mutations decrease to undetectable levels in the absence of drug selection pressure. In the Uganda HIVNET 012[55] this mutation was no longer detectable when reassessed at 12 months. Results from the Uganda studies also suggest that women with subtype D are more likely to develop NVP resistance[55]. The long-term implications of NVP-related mutant selection following single-dose therapy are as yet undefined. Research is needed to address the drug's efficacy during subsequent pregnancies and when used as part of future treatment options.

Monitoring for drug resistance for public health

As more people receive ART in Africa, concerted international efforts are being put in place to monitor for drug resistance. For instance, the International AIDS Society (IAS) and the World Health Organization (WHO) have established a global network to monitor for drug resistance, and the WHO Regional Office on Africa has also initiated a program to monitor for drug resistance in Africa. These programs aim to standardized methods for monitoring ART resistance in both treated and untreated patients in drug-access programs, and also strengthen regional capacity to monitor drug resistance. Information gained in these programs may help countries make appropriate decisions in selecting first- and second-line regimens, and may provide important data for program management and policy. It is also hoped that these initiatives will provide information on drug-resistance patterns of HIV strains circulating in Africa.

To accomplish this goal requires the development of a standardized protocol for implementation of resistance monitoring. This involves further determining whether the relationships between genotypic assays and phenotypic resistance among HIV-1, group M, non-B subtypes are, in fact, consistent across subtypes and for multiple drugs. Any surveillance program will likely be based on detecting 'signature' genotypic mutations for resistance. These mutations appear to be consistent across subtypes for some drugs, however, some subtype-specific mutations may need to be considered to avoid under or over reporting resistance rates. Additionally, algorithms for monitoring genotypic mutations for HIV-1 group O and HIV-2, which co-circulate with HIV-1 group M in some African countries, need to be developed. Though all this effort will yield more accurate and complete reporting, the interpretation of these reports may become quite complex. The level of sophistication necessary to decipher resistance-surveillance reports may not be available to all levels of program managers and clinicians. Careful dissemination of the reports, accompanied by a clear and adequate summary, will be necessary to avoid the untoward consequence of incorrect interpretation of the reports and potentially inappropriate changes to program design.

Antiretroviral strategies to address drug resistance

Several factors contribute to the occurrence of drug resistance: disruption in supplies of antiretroviral drugs; inappropriate use and practices of drugs; changing medication frequently; administering and taking the wrong dose; and interruptions in treatment due to financial constraints. However, considerations of resistance are only one of many issues that program managers at a country, regional, or local level must consider when designing ART programs. Other issues include drug availability, cost, storage requirements, drug-drug interactions, and toxicity. Standardized and simplified antiretroviral treatment strategies are being

advocated and implemented in many resource-limited settings. The advantages of this approach include simplified training of program staff, delivery of consistent messages to the community, ease of patient education for adherence, streamlined monitoring for toxicity, and predictable patterns of resistance.

With regard to resistance, the regimens can be constructed to take advantage of known resistance and cross-resistance patterns among the circulating strains of HIV. Many programs where HIV-1 group M is predominant are utilizing two NRTIs plus an NNRTI as the first-line regimen. In such scenarios, the second-line regimen can contain two different NRTIs plus a PI. In this manner, real-time resistance testing is not necessary, since the expected resistance pattern to the first-line regimen can be addressed with an appropriate second-line regimen. However, difficulties arise if HIV develops multi-drug resistant mutations to NRTIs, or if patients develop toxicity to individual drugs, requiring alteration of a regimen. The program may have limited options for drug substitution that still maximize the chance of optimal success with a second regimen. Lastly, providing appropriate training on the use of ART to health care providers, and ensuring that there is good clinical and biologic monitoring of patients receiving ART, are critical in limiting the occurrence of drug resistance.

Conclusions

Antiretroviral drug resistance is an inevitable consequence when providing long-term treatment, and should not be seen as a limitation of providing antiretrovirals to patients in resource-poor settings. Financial constraints that limit the use of maximally suppressive therapy may promote more rapid emergence of resistance. Efforts should be focused on the use of maximally suppressive ART and appropriate measures to enhance adherence to limit occurrence of drug resistance. Moreover, there is a need to provide adequate training to health care providers to be able to properly administer and monitor patients receiving ART. A better understanding of drug-resistant mutations for persons infected with HIV-2, and in those dually infected with HIV-1 and HIV-2, is needed to inform practitioners and program managers about the optimal use of ART in settings where these viruses co-circulate.

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