Contents available at **PubMed**
www.aidsreviews.com

PERMANYER

AIDS Rev. 2015;17:3-20

Update on HIV-1 Acquired and Transmitted Drug Resistance in Africa

Deogratius Ssemwanga[1], Raphael W. Lihana[2], Chinenye Ugoji[4], Alash'le Abimiku[4,5], John Nkengasong[3], Patrick Dakum[4] and Nicaise Ndembi[4]

[1]MRC/UVRI Uganda Research Unit on AIDS, Entebbe, Uganda; [2]Center for Virus Research, Kenya Medical Research Institute (KEMRI), Nairobi, Kenya; [3]US Centre for Disease Control and Prevention, Division of Global HIV/AIDS, International Laboratory Branch, Atlanta, USA; [4]Institute of Human Virology (IHV)-Nigeria, Abuja, Nigeria; [5]Institute of Human Virology, University of Maryland School of Medicine, Baltimore, USA

Abstract

The last ten years have witnessed a significant scale-up and access to antiretroviral therapy in Africa, which has improved patient quality of life and survival. One major challenge associated with increased access to antiretroviral therapy is the development of antiretroviral resistance due to inconsistent drug supply and/or poor patient adherence. We review the current state of both acquired and transmitted drug resistance in Africa over the past ten years (2001-2011) to identify drug resistance associated with the different drug regimens used on the continent and to help guide affordable strategies for drug resistance surveillance. A total of 161 references (153 articles, six reports and two conference abstracts) were reviewed. Antiretroviral resistance data was available for 40 of 53 African countries. A total of 5,541 adult patients from 99 studies in Africa were included in this analysis. The pooled prevalence of drug resistance mutations in Africa was 10.6%, and Central Africa had the highest prevalence of 54.9%. The highest prevalence of nucleoside reverse transcriptase inhibitor mutations was in the west (55.3%) and central (54.8%) areas; nonnucleoside reverse transcriptase inhibitor mutations were highest in East Africa (57.0%) and protease inhibitors mutations highest in Southern Africa (16.3%). The major nucleoside reverse transcriptase inhibitor mutation in all four African regions was M184V. Major nonnucleoside reverse transcriptase inhibitor as well as protease inhibitor mutations varied by region. The prevalence of drug resistance has remained low in several African countries although the emergence of drug resistance mutations varied across countries. Continued surveillance of antiretroviral therapy resistance remains crucial in gauging the effectiveness of country antiretroviral therapy programs and strategizing on effective and affordable strategies for successful treatment.

(AIDS Rev. 2015;17:3-20)

Corresponding author: Nicaise Ndembi, ndembinic@yahoo.fr; nndembi@ihvnigeria.org

Key words

Acquired drug resistance. Africa. Antiretroviral therapy. HIV-1. Drug resistance. Transmitted drug resistance.

Correspondence to:
Nicaise Ndembi, PhD
Institute of Human Virology-Nigeria
Pent House, Maina Court
Plot 252, Herbert Macaulay Way
Central Business District, Abuja, Nigeria
E-mail: ndembinic@yahoo.fr
nndembi@ihvnigeria.org

Introduction

With the support of international funding, more than four million HIV patients in Africa receive life-saving antiretroviral treatment[1-3]. This is an unprecedented success in medical history and represents a 100-fold increase as compared to the situation in Africa 10 years ago[3-5]. However, the widespread use of antiretroviral (ARV) drugs can introduce drug resistance, which eventually can make drugs ineffective. Drug resistance is caused by mutations in pathogens, which can develop when the patient uses insufficient or sub-quality drugs. This risk is particularly true in resource-limited settings (RLS), where treatment of diseases is challenged by drug stock-outs[6,7], lack of laboratory monitoring[8], insufficient information for patients, lack of adherence to drugs[9,10], use of counterfeit drugs, and lack of qualified medical staff, among others[11]. It is remarkable that to date there has been little attention paid to this evolving problem and that much-needed documentation on HIV drug resistance in Africa remains poor.

Over the past decade, worldwide antiretroviral therapy (ART) coverage has been scaled up significantly with sub-Saharan Africa having the greatest increase in the number of people accessing it[2,12,13]. In 2010, the revised WHO treatment guidelines[14] advocated treatment of patients whose CD4 count was ≤ 350 cells/mm^3; these guidelines were revised in 2013[15] to initiate treatment at CD4 ≤ 500 cells/mm^3. Whereas this immediately increases the number of people in need of treatment and costs, it is anticipated that it will reduce HIV-related morbidity, mortality[16], and hospitalization in the long term. However, ART can lead to HIV drug resistance[17]. With the revised guidelines, by the end of 2011, the majority (> 8 million, 54%) of people eligible for ART in low- and middle-income countries received it, representing a 26-fold increase since 2003[3].

There have been some reports on the effects of HIV subtype on the development of drug resistance mutations (DRM). Several DRMs are more likely to occur in certain HIV-1 subtypes. For example, V106M occurs more commonly in subtype C viruses in patients treated with nevirapine or efavirenz than in viruses belonging to other subtypes because V106M requires a single base-pair change in subtype C viruses (GTG [V] => ATG [M]), but a two base-pair change in all other subtypes (GTA [V] => ATG [M])[18,19]. By a similar mechanism, subtype G viruses are more likely to develop the protease inhibitor (PI) resistance mutation V82A[20] and subtype A viruses from the countries of the Former Soviet Union develop G190S more commonly than any other nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance mutation. By virtue of a different mechanism, subtype C viruses may be predisposed to develop the nucleoside reverse transcriptase inhibitor (NRTI) resistance mutation K65R[21]. However, most DRMs have been reported in nearly all subtypes and there is no evidence that any DRMs have different phenotypic effects in different subtypes. Therefore, the nature of HIV care and treatment requires that monitoring strategies be dynamic and should blend well with prevalent subtypes[22] to achieve maximum benefit. Furthermore, ART programs should be geared at achieving maximum benefit for patients through continuous monitoring of drug resistance to inform therapeutic change[23]. Increased access to ART in many African countries has brought many challenges regarding which monitoring of therapy response would be appropriate: independent virologic, immunologic, or drug resistance testing[24-27]. While many countries have adopted the former two, it has been shown that this may not be enough unless drug resistance is tested to determine the extent and to choose appropriate regimens[24,27]. The availability of affordable viral load and HIV-1 drug resistance testing would be best suited for patient care, treatment, and monitoring in resource-limited settings and this was strongly recommended in the new WHO treatment guidelines[15].

According to the 2011 UNAIDS World AIDS Day report, there are 6.6 million people receiving treatment in low- and middle-income countries, nearly half of those eligible for therapy, and this has subsequently led to a reduction in AIDS-related deaths to 1.8 million (1.6-1.9 million) in 2010, down from a peak of 2.2 million (2.1-2.5 million) in the mid-2000s[28]. One major challenge to ART scale up in Africa is development of drug resistance as a result of poor adherence, which is mainly due to failure to maintain uninterrupted supplies of ARVs leading to drug stock-outs[29]. In 2009 a WHO survey showed that 38% (36/94) of reporting countries had documented at least one stock-out of ARV drugs in health facilities[12]. Though many of the ART country programs are donor funded, drug stock-outs are reported and this has been attributed to poor procurement and supply chain management systems in these countries[29]. The report further points out the procurement difficulties in projecting ARV requirements when patients start alternative first-line, second-line, and other pediatric regimens[29] and this outlines the importance of investing in effective procurement and supply chain management systems in Africa.

The WHO has developed a continuously updated consensus list of resistance mutations recommended for global surveillance of HIV transmitted drug resistance

(TDR)[30,31]; however, simulations have shown that TDR estimates can be overestimated as a result of natural sequence polymorphisms[32]. This has, therefore, called for a more accurate estimation of polymorphisms and adjustments for these in TDR surveillance studies[32]. A recent review (early 2000 to 2009) on the global prevalence of TDR showed prevalence in rank order: North America (12.9%), Europe (10.9%), Latin America (6.3%), Africa (4.7%), and Asia (4.2%). The TDR prevalence was shown to have significantly increased in Asia ($p = 0.047$) and Africa ($p < 0.001$) and this was attributed to ART becoming more available in these continents[33].

The various available drug resistance interpretation algorithms may have a limitation as they are based on evaluation of each drug separately. However, the use of these different HIV-1 drug resistance interpretation algorithms (like IAS-USA mutation list of 2013[34], or the Stanford HIVdb version 4.3.0, 2007, or the Shafer list of 2007[35]) was shown not to have a difference in levels of TDR[36], but it remains important to have harmony across the various algorithms to get an accurate estimate of TDR.

In this review we explore the extent and challenges of ART in Africa, with a focus on studies on both acquired and transmitted drug resistance mutations between the year 2001 and 2011.

Search strategies and statistical analysis

We searched for available drug resistance data in peer-reviewed articles written in English from PubMed, conference abstracts, and technical reports published in the 10-year period from 2001 to 2011 following the format published by Nkengasong, et al.[37]. We included studies in drug-naive and experienced adult, child, and infant patients in sub-Saharan Africa.

Analysis of the overall prevalence of drug resistance mutations and proportion of total mutations due to each class of drug (NNRTI, NRTI, PI) in each region of Africa was done. The pooled proportions of individuals with DRMs among those genotyped was done for each of the African regions by assessing the heterogeneity in the proportions between studies and where the studies showed significant heterogeneity by the I^2 statistic, the random effects estimate of the pooled proportions using DerSimonian-Laird weighting was reported. The same weighting method as described above was used to estimate the pooled prevalence of each type of mutation in each of the African regions. The fixed effects (inverse variance) proportion as opposed to the DerSimonian-Laird estimates was used to estimate the pooled proportions for mutations that showed homogeneity within studies.

East and Southern Africa

Angola

Surveillance data on both acquired and transmitted drug resistance in Angola is very limited[38,39]. A study in 2001 among 196 untreated HIV-1-infected patients found a TDR prevalence of 1.6% (n = 2) to NRTI (M41L, D67N, M184V, L210W, T215Y/F) and NNRTI (K103N) drug resistance mutations[38]. A study among 35 recently HIV-1-diagnosed pregnant women attending antenatal clinics in Luanda found an overall TDR prevalence of 5.7%, with one woman harboring NRTI (M184V) and NNRTI (G190A) mutations and the second woman harboring a G190A NNRTI mutation[39]. In the above two studies, no PI resistance mutations have been reported from Angola and it emphasizes the need for continued periodic surveillance of TDR.

Botswana

One of the earliest studies in 2001 among 71 subtype C-infected ART-naive individuals in 11 northern and southern districts of Botswana found no resistance mutations to all three drug classes[40]. Mathematical models have been used to predict the evolution of drug-resistant epidemics during ART roll-out in Africa, and a study published in 2005 predicted low rates of TDR (< 5%) until 2015 in RLS[41]. Another study based on the Botswana treatment program predicted that TDR could reach 15% by 2009 if acquired resistance rates were high[42]. Such conflicting predictions highlight the importance of effective and routine surveillance.

As part of the 2007 national sentinel survey, the prevalence of TDR among women presenting for routine antenatal care was found to be less than 5% with no resistance mutations found in one site, but prevalence could not be ascertained using the WHO strategy at the second site due to small sample size[43].

Ethiopia

Similar to most other countries, information on acquired and transmitted drug resistance from Ethiopia is limited[44,45]. A study among 92 ART-naive HIV-1-infected patients in northwest Ethiopia found one patient harboring the V75I NRTI mutation, two patients harbored the G190A NNRTI resistance mutation, and there was no PI resistance mutation[45]. A study following the WHO guidelines to access TDR among 39 of the 75 recently infected individuals in Addis Ababa in 2005 found the prevalence of TDR below 5%, with no TDR to any of the three drug classes[44].

Kenya

The prevalence of HIV drug resistance (HIVDR) was investigated among 53 Kenyans initiating therapy in 2005 and four (7.5%) were found to harbor NRTI mutations (M184V, K65R, D67N, K70R, and K219Q) and NNRTI mutations (K103N and Y181C)[46]. This study showed the importance of HIVDR testing prior to initiation of therapy. A study among 16 HIV-1-infected patients to evaluate treatment success and development of ART drug resistance in Mombasa, Kenya, found no major protease mutations but 14/16 (87.5%) patients were found with drug resistance mutations in the reverse transcriptase. The M184V (n = 12), K103N (n = 9), Q151M (n = 1) and the K65R (n = 2) mutations were found[47].

Another study looked at the naturally occurring polymorphisms within the *pol*-integrase among 42 Kenyan ART-experienced and naive patients and found no primary mutations to integrase inhibitors[48]. The emergence of HIV-1 drug resistance among 32 infants born to HIV-1-infected mothers after six months of breastfeeding was found in 16 infants: 13 (81%) had at least one NRTI resistance mutation (M184 I/V, n = 12; K65R, n = 2; and D67G, n = 1), and six (38%) had NNRTI resistance mutations (K103N, n = 2; Y181, n = 2; and G190A, n = 2). No primary PI mutations were detected in any infant[49].

In a multicentre study to determine the prevalence of transmitted drug resistance mutations (TDR) among recently infected African volunteers in the coastal town of Kilifi in Kenya, it was found that in 64 recently infected volunteers, the prevalence of TDRs was 3.1% (n = 2)[50]. In this study, the two patients were males, both reporting having had sex with men, and one harbored the D67N NRTI mutation whereas the other harbored the K101E NNRTI mutation[50]. The other multicentre study among drug-naive individuals in six African countries including Kenya found an overall TDR prevalence of 4.7% (19/404) in the two Kenyan sites of Mombasa and Nairobi[23].

A recent survey among 68 newly diagnosed HIV-1-infected ART-naive adults in Mombasa using HIVDR threshold surveillance strategy found a high prevalence of 13.2% (n = 9) of TDR (7.4% for NNRTIs, 4.4% for PIs, and 1.5% for NRTIs). The mutations K70R (n = 1) and K103N (n = 5) in reverse transcriptase and I85V (n = 1), N88D (n = 1) and L90M (n = 1) in protease were identified[51].

Madagascar

The only study so far reported in Madagascar, among 31 seropositive people identified during the 2005 HIV surveillance using the ANRS 2005 DRM list, identified no NRTI or NNRTI mutations, but one patient harbored three (M46I, I84V and L90M) PI mutations[52].

Malawi

The earliest studies in samples collected between 1996 and 2001 in 21 ART-naive Malawians did not find any DRMs[53]. A study to compare and determine the presence of minority resistance mutations among 47 HIV-infected pregnant women after single-dose nevirapine found no major resistance mutations using the ViroSeq® and LigAmp® assays[54]. Using the WHO threshold surveillance method in 2006, dried blood spots were collected from HIV-positive women aged < 25 years attending primagravida antenatal clinics in Lilongwe to determine prevalence of TDR[55]. From the 54 samples that were sequenced, no major DRM was found for any of the three drug classes[55]. A recent PEPFAR funded study to determine the prevalence of TDR among 53 patients using the WHO-recommended method found no TDR mutations[56].

Mozambique

Earlier studies on resistance in Maputo, Mozambique, were done in 58 drug-naive HIV-1-positive individuals eligible for ART in 2003 and no major resistance mutations were detected for any of the three drug classes[57]. In the city of Beira in Mozambique, the prevalence of drug resistance among 43 ART-naive patients was investigated in 2003 and an overall prevalence of 14% (6/43) in protease and reverse transcriptase mutations was found: PIs 2.3% (1/42, I84V), NRTIs 4.7% (2/43, V75A, M184I) and NNRTIs 7.0% (3/43, K103N, Y181C, P236L)[58].

In 2002 among 75 HIV ART-naive pregnant women in Mozambique, no primary resistance to all the three drug classes was found[59]. A study done between 2002-2004 to determine TDR in healthcare settings in Maputo among 144 drug-naive patients attending public hospitals and private clinics using the Stanford Genotypic Resistance Interpretation Algorithm and a published list of TDR mutations[35] found no PI-associated resistance mutations in the 68 samples that were fully analysed[60]. However 5.9% (4/68) of the patients harbored one or more NRTI mutations (M41L, D67N, M184V, L210W, T215F, T215Y and K219Q) and one patient in addition harbored the K103N NNRTI mutation[60].

Rwanda

An earlier study done in Rwanda among 43 treatment-naive HIV-positive women who were about to

enroll in a prevention of mother-to-child transmission (PMTCT) program in 2000 found no TDRs[61]. A study among 37 untreated HIV-1-positive women from Rwanda found one woman with the G190A NNRTI mutation[62].

A multicentre study among recently infected African volunteers recruited between 2006 and 2009 found a prevalence of 7.7% (6/78) in Kigali, Rwanda[50]. In this study, one patient was found to harbor the M46L PI resistance mutation; there were no NRTI mutations, five harbored NNRTI mutations (two with L100I, two with K103N and one with both K103N and Y181C)[50].

Seychelles

Data on TDR is not readily available from the Seychelles; however, one study among 40 remnant sera has shown no evidence of resistance to PI and RTI using the ANRS 2006 DRM list[63].

South Africa

Due to the existence of an advanced healthcare system in South Africa, there have been many published reports with regard to prevalence of acquired and transmitted drug resistance[23,64-74]. In 2001 the prevalence of primary resistance was determined in the Limpopo province, a region that was found to have an increased HIV-1 prevalence, and no DRMs were found[64].

A study among 72 treatment-naive patients (16 children and 56 adults) found no major NRTI or PI mutations; however, three patients harbored NNRTI mutations: one patient with A98G, another patient with K103N, and her partner with G190A in addition to the K103N mutation[75]. Between 2001 and 2004, 40 protease and 35 reverse transcriptase patient sequences from ART-naive HIV-1 subtype C-infected individuals were analyzed for DRMs[65]. There were 5% PI mutations (2.5% M46L, 2.5% G73S) that were detected, and in the RT mutations, V118I (8.5%) and Y318F (5.7%) were observed[65]. In Gauteng province between 2002 and 2004, the prevalence of resistance was determined using the WHO surveillance methodology among drug-naive HIV-1-infected pregnant women[73]. Among the 65 samples analyzed in 2002, none was found with any resistance mutations, and in 2004, 4.2% (2/48) were found to harbor T69D and K70R mutations[73]. The rapid accumulation of RTI resistance mutations was shown among patients initiating ART, indicating prior TDR infection[76]. In this study, among the 21 patients with virologic failure, only two didn't have any resistance mutations, indicating poor ART adherence, whereas 58%, 26%, and one patient had at least two, three, and five NNRTI (K103N, V106M, Y181C, and V190A) mutations, respectively, using the IAS-USA 2007 resistance list; the M184V NRTI mutation was also common[76].

In a randomized clinical trial between 2003 and 2007 to reduce nevirapine resistance in PMTCT, NNRTI resistance mutations were found in 12 of the 393 women who were fully analyzed: 12 had one NNRTI: A98G (n = 2), V101E (n = 2), K103N (n = 2), V106IM (n = 1), V108I (n = 1), V179D (n = 2), M230L (n = 1) and one had V106M, Y181C and G190A[77]. The prevalence of drug resistance among 140 HIV-1-positive treatment-naive patients in Cape Town was analyzed in samples collected from 2002 to 2004 and it was found that five samples (3.6%) had RTI resistance mutations, of which three samples had NNRTI mutations[68]. A cohort of 120 treatment-naive HIV-1-infected patients recruited between 2003 and 2006 in Cape Town showed four patients (3.3%) with NRTI mutations K65R (n = 1; 0.8%) and V118I (n = 3; 2.5%) in addition to two patients (1.7%) with Y181C and G190A NNRTI mutations[71]. In the Free State among 425 HIV-1-infected treatment-naive patients attending district centers for assessment to commence therapy in 2006, a low prevalence (2.3%) was found, representing nine patients with a total of 11 resistance mutations[67]. Surveillance of TDR among 49 HIV-1-infected ART-naive infants aged < 18 months in the Western Cape Province found only three NNRTI mutations with no NRTI or PI mutations[74]. In the study, the three infants with NNRTI mutations had received ART as part of the PMTCT program[74].

An HIV-1 subtype C-specific assay was assessed to determine the prevalence of major integrase inhibitor mutations among 51 integrase-naive patient plasma samples (collected in 2009) and 22 ARV-naive patients from South Africa (collected in 2005) and no primary mutations associated with resistance to integrase inhibitors were found[66]. Resistance testing in young, newly diagnosed, treatment-naive, HIV-positive women in KwaZulu-Natal during the 2009 threshold survey revealed that only one woman out of the 47 that were fully analyzed had the K103N NNRTI mutation[72]. Another study in the Limpopo province among newly diagnosed ART-naive patients in 2008 found a low prevalence (3.5%) of TDR comprising of Y181C and L33F mutations[69].

In one multicentre study that included sites from South Africa among ART-naive adults found an overall prevalence of 3.6% in the three sites of Pretoria, White River, and Johannesburg[23]. In northeastern South Africa, the prevalence of ART drug resistance among 54 HIV-1-infected individuals attending voluntary counseling and testing clinics was 9.3% (n = 5)[70]. Four (7.4%) were NRTI mutations (D67G, D67E, T69D and T215Y)

and one (1.9%) was a M46I PI mutation, but no NNRTI mutations were detected[70].

In a study to determine the long-term outcome in 101 children receiving ART in rural South Africa, among 23 children with virologic failure, 78% (n = 18) were found to have the M184V mutation whereas 52% (n = 12) had the K103N mutation[78]. A study among 44 ART-naive individuals in the Limpopo Province of northeastern South Africa found a prevalence of 4.5% (n = 2) with the K103N NNRTI mutation, but no NRTI or PI mutations were found[79].

A study among 165 adults failing NNRTI-based regimens found 28 (17%) with no resistance mutations and 137 (82%) with NNRTI mutations: K103N (n = 59), V106N (n = 35), V108I (n = 15), G190A (n = 23), Y181C (n = 25), K101E (n = 12), and P225H (n = 10)[80]. In addition, the M184I/V (n = 101), K65R (n = 7) and thymidine analogue mutations (TAM, n = 20) were found, but no PI mutations were found[80].

A survey among 72 seroconverters in KwaZulu-Natal province during the 2010 WHO surveillance found no TDR[81]. Analysis of 10 data sets including 1,618 sequences collected between 2000 and 2010 to determine trends in prevalence of TDR in South Africa found that the prevalence of TDR was highest in 2002 (6.67%; 95% CI: 3.09-13.79%; n = 6/90), but was found to reduce to less than 5% after 2002 and did not have any significant increase after 2002 to 2010. The commonest NNRTI mutations were K103N, Y181C and Y188C/L[81].

Swaziland

Published work on the prevalence of HIV-1 TDR in Swaziland is also limited[82,83]. A study among 47 ART-naive patient samples stored in Mbabane between 2002 and 2003 following the WHO guidelines identified only one NNRTI mutation (Y181I), which was representative of < 5% prevalence; there were no NRTI or PI mutations detected in this population[82]. In another study in Mbabane in 2006 following the WHO truncated sequential sampling method, prevalence of TDR was assessed in 70 primigravidas aged < 25 years attending antenatal clinics, and there were no NRTI or NNRTI mutations after analysis of the first consecutive 34 samples analysed[83]. On analysis of the first consecutive 44 samples, only one PI mutation (M46I) was identified and the study showed a TDR prevalence of < 5%[83].

Uganda

Since the scale-up of ART in early 2000, a number of surveys have been carried out to determine the prevalence of TDR in Uganda[23,84-88]. A study to determine the development of phenotypic and genotypic resistance of ART in 150 patients on therapy in Uganda showed 24 (16%) of the patients developing phenotypic NRTI (zidovudine and stavudine) resistance; 22 of the 24 (92%) had genotypic resistance mutations: T215Y (n = 18), T215F (n = 4), M41L (n = 19), K70R (n = 10), D67N (n = 16), and L210W (n = 9)[89]. In the same study, 74 of 77 (96%) patients with phenotypic resistance to lamivudine had genotypic resistance mutations: M184V (n = 64), M184M/V (n = 8), M184I (n = 2). There were 21 patients with phenotypic NNRTI resistance and the commonest mutations were K103N/K, M230L, and Y188Y/H. In addition, 17 patients had PI phenotypic resistance, with D30N, M46I, N88S and L90M mutations present[89]. In Entebbe between 2006 and 2007, a study to determine TDR among 37 of 46 newly diagnosed HIV-1-infected pregnant women aged < 25 years found no evidence of resistance mutations for any of the three drug classes[87]. Among 104 drug-naive, recently HIV-1-infected adults in Rakai district between 1998 and 2003, six (5.8%) samples had resistance mutations: three NRTI (two with M41L, one with K219R), three PI (I47V, F53L and N88D), but there were no NNRTI mutations[84].

A study to document the evolution of HIV-1 drug resistance among 15 patients with virological failure of first-line ART in Uganda, 13 (86%) of the patients were found with lamivudine resistance mutations; the K103N and M184V mutations were the most common[90]. A study that combined results from four PMTCT clinical trials in Uganda among 80 infants using the ViroSeq HIV genotyping system and a sensitive point mutation assay found 45% (n = 36) with nevirapine resistance mutations: Y181C (n = 28), K103N (n = 9), Y188C (n = 3), G190A (n = 30), V106A (n = 2), V106M (n = 2), and K101E (n = 1)[91].

Among 401 drug-naive individuals initiating NNRTI-based regimens in western Uganda, nine (2.2%) were found with resistance mutations: five had K103N NNRTI mutation, three NRTI mutations K219K/Q, T69A/D/N/T, M184V, and one had both NNRTI and NRTI mutations (T69A/D/N/T with Y181C/Y)[92]. In the DART trial to determine the evolution of drug resistance during 48 weeks of zidovudine/lamivudine/tenofovir in the absence of real-time viral load monitoring, of the 62 patients followed up, 41 had the M184V mutation and eight had the K65R mutation in addition to other mutations that occurred at lower frequencies[93]. Analysis of 74 HIV-1-infected children prior to initiation of ART showed two (2.7%) of the children with NRTI mutations (T215A) and NNRTI mutations

(Y181C)[94]. In this study, among 12 children who initiated ART and had detectable viral load at week 48, all had the M184V NNRTI mutation. In addition, three samples had other NNRTI mutations: one sample each had K65R, D67G/T69N mutations and T251S=Y[94].

A study to compare the viral rebound and emergence of drug resistance in the absence of viral load testing using zidovudine/lamivudine plus nevirapine and zidovudine/lamivudine plus abacavir found that at week 48, 88% of patients had one or more resistance mutations in the abacavir arm compared to 82% in the nevirapine arm[93]. It was also shown that the M184V mutation was present in all samples, except three samples in the nevirapine arm that had only NNRTI mutations[93].

In a study among 70 newly HIV-1 diagnosed young individuals attending voluntary counseling and testing clinics between 2009 and 2010 in Kampala, the prevalence was 8.6% (6/70): two had NRTI mutations (D67G and L210W), three had NNRTI mutations (G190A, G190S and K101E), and one had the N88D PI mutation[86]. In a multicenter cross-sectional survey (2007-2009) in six African countries to determine prevalence of primary resistance among drug-naive HIV-1-infected adults, the overall prevalence in all three Ugandan sites was 11.6% (66/570)[23]. The other multicentre study (2006-2009) among recently infected African volunteers found an overall prevalence of 6.7% (6/89) in the two Ugandan sites: three had PI mutations (two with I85V and one with M46L), two had NRTI mutations (L210W and V118I), and two had the K103N NNRTI mutation[50]. In the study, one patient had both I85V and V118I mutations[50].

Studies among high-risk sexual behavior populations have been done in Uganda to determine the prevalence of TDR[88,95]. A study among 38 newly HIV-1-diagnosed female sex workers in Kampala between 2008 and 2010 found a TDR prevalence of 2.6% (1/38) with the K103N NNRTI mutation; there were no NRTI or PI mutations detected in this study[88]. The prevalence of TDR among 47 recently infected fisher-folks around the Lake Victoria basin in Uganda was 6.4% (3/47); only NNRTI mutations (two with K103N and one with V106A) were detected[95]. Early virologic failure and emergence of ART DRMs was documented in 14 Ugandan children and M184V mutation along with other mutations (E138A, Y181C and G190A) was shown to emerge within six months of early virologic failure[96].

United Republic of Tanzania

In the Kagera and Kilimanjaro regions, the prevalence of drug resistance among 100 drug-naive HIV-1-infected pregnant women was investigated and found to be 7% (7/100): three with NRTI mutations (two with V118I and one with both V118I/T69D), four with NNRTI mutations (two with E138K, one V179E and P225H)[97]. Using the WHO surveillance methodology in Dar es Salaam between 2005 and 2006, analysis of the first 39 dried blood spot (DBS) specimens found no primary mutations to any of the three drug classes[98]. The virological efficacy and emergence of resistance among 22 adults on ART for one to four years in rural Tanzania found an overall prevalence of mutations M184I/V (64%), K103N (27%), Y181C (27%), and G190A (27%)[99].

A study to determine drug resistance among 19 children receiving long-term ART in a rural Tanzanian hospital found 11 children with RT resistance mutations: M184V (n = 11), Y181C (n = 4), G190A/S (n = 4) and K103N (n = 4) mutations were found[100]. The feasibility and reliability of using DBS to test for HIV-1 drug resistance in patients who fail therapy was done in rural Tanzania and this showed a high concordance between DBS and plasma testing[101,102] and the use of DBS has been adopted in some settings.

The other study in Dar es Salaam was done among 44 of 75 recently HIV-1-infected treatment-naive youths where three (7%) had NRTI mutations and four (9%) had NNRTI mutations: there were cross-resistance mutations, with the first having M184V, T215F/K103N, Y181C, the second having M184V/K103N, the third with only Y181C, and the fourth with K65R/Y181C[103]. Among 88 HIV-1-infected ART-naive patients in Tanzania not eligible for the WHO threshold HIVDR survey, the prevalence of resistance was high at 14.8% (n = 13), with NRTI mutations present in seven patients: M41L (n = 2), M184I (n = 3), and one each of V75A and T215I. Six patients had NNRTI mutations: G190E (n = 2), k103n (n = 3), and one Y188H. Five patients harbored PI mutations: G73S (n = 2) and one each of D30N, V82T and V82A[104].

Zambia

One of the earliest studies among 28 ART-naive Zambians found no TDRs; however, most patients harbored secondary mutations in the protease and RT genes[105]. On assessing the presence of resistance among patients initiating therapy in Lusaka in 2007-2008, it was found at 5.2% (27/523 participants) among drug-naive patients: NRTI 1.0% (5/523), NNRTI 3.6% (19/523), and PI 1.1% (6/523)[106]. There is a study that compared two cohorts with HIV-1-infected therapy naive patients that were enrolled in 1998-2002 before the

rollout of ART (cohort A) and in 2005 after the rollout of ART (cohort B)[107]. Analysis of 30 patients in cohort A found no major mutations to any of the three drug classes, whereas analysis in cohort B among the 86 patient samples showed one (1.16%) NRTI (M184V) and one (1.16%) K103N NNRTI mutation[107]. Drug resistance among 26 Zambian children receiving adult fixed-dose combination stavudine, lamivudine and nevirapine found 25 (96%) with NNRTI resistance: 22 (84%) with M184V, two (8%) with Q151M and one (4%) each had K65R, L74V, or K70E[108]. In the multicentre study (2006-2009) among newly HIV-1-diagnosed African volunteers, in 169 patients from Zambia, 2.4% (n = 4) had TDR: three with NRTI mutations (K70R, M184V and M41L), two with the K103N NNRTI mutation, and one patient had both the M184V and K103N mutations[50]. The other multicentre study (2007-2009) showed the overall prevalence of primary resistance in Lusaka at 5.0% (26/525)[23].

Zimbabwe

In a study among 21 Zimbabwean patients failing ART, 17 (81%) had at least one known resistance mutation; seven (33%), eight (38%), and two (10%) patients had resistance to one, two, and three drug classes, respectively[109]. The NRTI mutations were M184V (n = 11), T215Y/I/S/F (n = 8), K70R (n = 7), M41L (n = 6), and D67N/G (n = 6). The NNRTI mutation was Y181C (n = 2) and PI mutations included L90M (n = 4) and V82I (n = 3)[109]. To study the extent of breast milk shading of drug-resistant HIV-1 in 32 women exposed to single-dose nevirapine, resistance profiles in the plasma was compared to breast milk[110]. In plasma, 11 (34%) women had at least one NNRTI mutation, with the K103N mutation being present in nine (82%) of the 11 sequences. Breast milk was analyzed from 20 women, and 13 (65%) had at least one NNRTI mutation, with 11 (85%) of the 13 sequences harboring the K103N mutation[110]. The DART trial that included sites from Uganda and Zimbabwe, among 18 patients that had viral rebound at week 24, found that all 18 had at least one major NRTI mutation: four had M184V alone, and one had three nucleoside analogue associated mutations (NAM) alone; 10 had M184V and additional NAMs, and three had K65R (one with T215Y, one with Y115F, and one K65R alone)[111]. A study done in 2006-2007 among 236 HIV-1-infected drug-naive pregnant women attending antenatal clinics, the prevalence of primary resistance was 0.8% (2/236) with NNRTI (Y181C) and PI (I85V) mutations[112]. The multicenter study to determine prevalence of TDR among newly HIV-1-infected individuals found an overall prevalence of 2.6% (5/190) in Zimbabwe[23].

From our literature search there is paucity of data on TDR available from countries like Comoros, Eritrea, Lesotho, Mauritius, and Namibia. This may be attributed to several factors that might include, but are not limited to, lack of the necessary infrastructure and resources to carry out surveillance of TDR.

Western and Central Africa

Provision of ARVs has improved but remains much lower in West and Central Africa (23%) compared to East and Southern Africa (68%) (http://www.usaid.gov/our_work/global_health/aids/Countries/africa/hiv_summary_africa.pdf). Reports of drug resistance among those newly infected and receiving ART have emerged and the available country estimates are discussed below.

Benin

In a study among 129 participants from Cotonou, Benin, (73 selected from the general population and 56 from commercial sex workers) of HIV-positive drug-naive individuals, the prevalence of surveillance DRMs was 3.9%. No NRTI mutations were detected in this population. According to the WHO surveillance DRM algorithm, 2009, four individuals had NNRTI mutations (K103N [n = 3] and G190A [n = 1]), while one had resistance mutation F53Y[113].

Burkina Faso

Several studies carried out in Burkina Faso have reported varied prevalence of HIV-1 drug resistance. In a multicenter study that included 51 antenatal clinic attendees in Bobo-Dioulasso, the prevalence of HIVDR was reported to be low in 2006[114]. A study in 2003/2004 among non-HAART and HAART patients (n = 33) in Ouagadougou showed presence of minor mutations only in the non-HAART group (n = 17), while 33.3% (n = 11) of the HAART group harbored major NNRTI mutation K103N after six months of ART[115]. In another study among drug-naive patients, the prevalence of HIVDR was reported to be 8.2% and most patients were resistant to NNRTIs[116]. In another multicenter study of HIVDR among treatment-experienced individuals in Mali and Burkina Faso, high prevalence of mutations was reported among individuals exposed to ART for > 6 months, with M184V/I and K103N being most common[117]. Studies on HIVDR in Ouagadougou among 75 samples collected in

2007 from HAART-exposed patients with suboptimal virological response showed high-level resistance to NRTI (85%), with dominant mutations being M41L (37.3%), T215F/Y (48%), L210W (34.6%), and M184V (57.3%); NNRTI mutations were detected in 76%, with dominant mutations being K103N (44.4%), G190S/A (16%), and Y181C/I (16%); and PI mutations (40% of 43 sequences) showing M46I/V/L (37.2%), V82A/T/F (30.2%), and L90M and I84V (18.6% each) as predominant[118,119].

Burundi

In an HIV surveillance study performed in 2002 among the general population of urban and rural districts of Burundi, HIV-1 subtype C was reported as the major circulating strain (81.2%)[120]. Drug resistance analysis among 101 *pol* sequences revealed presence of NNRTI mutation G190E (n = 1, 1%) based on the 2005 classification of HIVDR[120].

Cameroon

Cameroon is one of the countries in west-central Africa with the highest HIV genetic diversity and reports of drug resistance[121,122]. As early as 2004, a year after the WHO's 3 by 5 initiative, a study among 79 drug-naive individuals in Yaoundé, showed the prevalence of PI and RTI mutations to be 2.6 and 9.3%, respectively[122]. Almost at the same time (2002/2003), a study on 57 samples collected from drug-naive individuals did not show major RTI mutations; only polymorphisms associated with drug resistance were detected in seven patients (12.3%). These included V118I (n = 1), G333E (n = 1), and G190E (n = 1) among others[123]. Similarly, another study in rural western Cameroon reported presence of PI and RTI DRM among 54 newly diagnosed individuals: primary PI mutations were detected in 7.4% and RTI mutations in 9.8%[121]. Another study among newly diagnosed patients showed a prevalence of 7.8%, with PI mutation M46I/L being detected in two individuals[116]. A similar study carried out between 2006 and 2007 among newly diagnosed antenatal clinic attendees in Yaoundé (n = 47) and Douala (n = 34) showed a moderate HIVDR prevalence based on the WHO HIVDR threshold survey[124], with detection of both NRTI and NNRTI mutations: D67D/N (n = 2), K103N (n = 2), and M184V/K101E/G190A (n = 1).

In a study to determine baseline genotypic and phenotypic susceptibilities of HIV-1 group O viruses, a panel of 171 samples was analyzed. Presence of T20 resistance mutations was analyzed and showed that 98% (168/171) of samples had mutation N42D in *gp41*. Other mutations included N42S (n = 1), N42D (n = 1) and N43K (n = 1). One sample had no mutation[125]. A cross-sectional survey of 573 HIV-1-infected patients undergoing treatment at the military hospital in Yaoundé showed that of the 84 successfully genotyped samples, the frequency of mutations increased with time of ART. The NRTI mutations detected included: M41L (n = 5), K65R (n = 2), D67G/N/S (n = 5), K70E/R (n = 5), L74V (n = 1), Y115F (n = 1), Q151L/M (n = 3), M184V (n = 36), T215F9 (n = 14), and K219E/N/Q (n = 4). Observed NNRTI mutations included K101E/H/N/Q (n = 8), K103N (n = 20), V106A (n = 4), V108I/M (n = 8), Y181C/I/V (n = 18), Y188L (n = 1), G190A/V (n = 8), P225H (n = 2), F227L (n = 2), and M230L (n = 3). No major protease mutations were detected[126].

Data on HIVDR obtained from ART-naive individuals in both rural and urban areas of Cameroon (n = 369) between 1996 and 2007 showed an increasing prevalence in Yaoundé (from 0% in 1996 to 12.3% in 2007)[127]. In rural areas, the prevalence in 2006-2007 was 4.8%[127]. A study among 49 randomly selected individuals in southwest and northwest regions of Cameroon showed the prevalence of DRMs in 28 patients on therapy to be 39% (11/28) for NRTIs, and 46% (13/28) for NNRTIs after a median of 12 months of therapy[128]. Among 21 drug-naive individuals studied, five (24%) were infected with viruses that harbored genotypic DRMs, two of which had mutations to both the NRTI and NNRTI[128].

A study to determine trends in virus evolution and drug resistance among 61 blood donors and HIV patients revealed presence of DRMs in 10/18 (55.5%) patients with ART exposure, while 19/43 (44%) drug-naive individuals harbored mutations, but only 8/19 had mutations known to confer drug resistance. These were: M184V (n = 2), V108I (n = 2), Y181C (n = 2), K219Q (n = 1), V179E (n = 2), G190A (n = 1), V118I (n = 1), Q151M (n = 1), H221K (n = 1) and F116Y (n = 1). Among drug-naive individuals, observed mutations included: M184V/I (n = 5), TAMs (D67N, K70R [n = 2]), K103N (n = 3), Y181C (n = 2), G190A (n = 3), Q151M (n = 2), A62V (n = 2), and Y188L (n = 1). In the protease region, no mutation was detected in drug-naive individuals, but the I54L mutation was detected in ART-exposed individuals[129]. An analysis of 59 HIV-1 samples collected between 2002 and 2005 in Yaoundé showed presence of mutations in the HIV-1 protease; two patients each harbored D30N and M46I mutations, respectively, while only one showed mutation (K219Q) in RT. In the RNaseH region, two samples had mutations: Q509L (n = 1) and Q547K (n = 1)[130]. Further, a 2004 survey

among 96 drug-naive HIV-1-infected pregnant women in Yaoundé showed presence of NRTI mutation L210W in one case. Sequence analysis of other regions of the HIV *pol* gene did not reveal presence of any other major mutations except for polymorphisms[131].

Cape Verde

The first study to characterize the genetic diversity of HIV (HIV-1, n = 41, HIV-2, n = 14) in the Cape Verde Islands was done in samples collected in 2005 (n = 37), 2006 (n = 14), and 2007 (n = 4)[132]. Drug resistance profiles from 41 samples with high genetic diversity showed presence of the M41L and K103N mutations, conferring resistance to NRTIs and NNRTIs, respectively, in 2/17 (12%) untreated patients while it was detected in 3/10 (30%) patients undergoing comprehensive ART[132].

Central African Republic

In the Central African Republic, CRF06_cpx and CRF22_01A1 have been documented to be predominant subtypes, with the first data on HIVDR obtained in 2008-2009[133]. Though the exact number of patients was not reported, 12 developed resistance to either NRTIs, NNRTIs, or to both, while two patients on a PI-containing regimen developed PI resistance mutations[133]. A study carried out in 2005 among antenatal clinic attendees in Bangui showed increased HIV-1 polymorphic diversity but no drug resistance mutation[134]. In a study among 242 children in Bangui who were mostly infected with CRF11_cpx, 83% of 59 sequenced samples harbored NRTI drug resistance mutations while 85% developed NNRTI resistance[135]. Similarly, in a study to assess the rate of virological failure among 386 adults in Bangui, the prevalence of HIVDR was 76%[136].

Chad

In a study to evaluate the extent of TDR among newly infected antenatal clinic attendees (n = 34) in N'djamena, Chad, the prevalence was < 5% according to WHO HIVDR threshold survey[124]. At the time, country ART coverage was 27% and the 2005 HIV prevalence in antenatal clinics was 3.5%[124]. However, in a study among 88 infected adults on first-line ART, 56 (64%) had developed DRMs at six months[137].

Côte d'Ivoire

Several studies in Cote d'Ivoire have documented HIVDR[1,114,138]. In a multicenter study that included 48 antenatal clinic attendees in Abidjan, the prevalence of HIVDR was reported to be < 5% in 2006[114]. In a study among 395 children receiving HAART in Abidjan (Cote d'Ivoire HIV treatment program), it was reported that 47 of the 68 children (69%) followed up for one year had resistance mutations[1]. Sampling was done between August 1998 and September 2003; the most common mutations were M184V/I, T215Y/F, K103N, and L90M[1]. In the same period, HIVDR among 645 adults receiving ART was detected in 131 (20%), of which 115 (88%) were resistant to NRTIs, 42 (32%) to NNRTIs, and 28 (21%) to PIs[138]. The most common PI, NRTI, and NNRTI mutations were L90M (54%), M184V (75%), and K103N (95%), respectively[138].

Similarly, between 2003 and 2005, a study among 247 HIV-infected women who had exposure to ART (for PMTCT of HIV) showed emergence of lamivudine resistance in 15.1% and nevirapine resistance in 17.1%, four weeks after delivery[139]. The most common NRTI and NNRTI mutations were M184V and K103N, respectively[139]. In blood donors, a study carried out between 2002 and 2006 among 100 infected volunteers showed the prevalence of HIVDR to be 6% where all six patients were infected with HIV-1 CRF02_AG[140,141].

Democratic Republic Congo

The first study on the genetic diversity among uniformed personnel in Kinshasa in 2007 documented an extensive diversity of HIV-1 (n = 94), with one strain (1.2%) harboring a single PI mutation, I54V[142]. In a cross-sectional survey among patients on ART in four major cities in 2008 (Kinshasa, n = 289; Matadi, n = 198; Lubumbashi, n = 77; and Mbuji-Mayi, n = 103), drug resistance was shown in 83.9% of 93 samples that were successfully sequenced[143]. Similarly, among recently diagnosed individuals (n = 243), the prevalence of resistance was 7.9%[143].

Equatorial Guinea

In characterizing HIV strains circulating among the military in Malabo, a high diversity of HIV was reported among 41 blood samples and HIVDR was detected in two samples: PI mutation M46I (n = 1) and NRTI mutation D67N (n = 1) from a 24-year-old woman and a 26-year-old man, respectively[144].

Gabon

Gabon is one of West Africa's countries with the lowest HIV prevalence[145]. A study conducted among miners (n = 857) at the Comilog Company in Moanda, in the

province of Haut-Ogouée in southeastern Gabon in 2007 showed a prevalence of HIVDR of 0%[145]. Testing for HIVDR revealed presence of *pol* and RT polymorphisms that were not or less associated with drug resistance. In another study among ART-naive (n = 13) and ART-experienced (n = 22) patients in Libreville, none of the ART-naive patients had HIVDR mutations, while 58% of treated patients (11/19) had at least one mutation conferring resistance to available regimens[146].

Ghana

The prevalence of HIV in Ghana is relatively low (http://www.usaid.gov/our_work/global_health/aids/Countries/africa/hiv_summary_africa.pdf). Few studies on HIVDR have been conducted: in a national ART program between 2002 and 2004, data from 207 patients showed presence of RTI mutations in 20 of them[147]. Of the 20, six had major resistance mutations according to the HIVDR guidelines at that time; five of them had been exposed to ART. No PI mutations were detected[147].

Guinea

In Conakry, a recent report on drug resistance among HIV-positive drug-naive individuals showed a prevalence of 8.6%[148]. In the report, eight major DRMs were reported with multi-resistant NRTIs being identified in one case.

Mali and Mauritania

In a study to determine genetic diversity and drug resistance among drug-naive patients in Bamako, 2/98 (2%) drug-naive patients harbored drug-resistant HIV-1; one patient had NRTI mutation T215S and another K103N. The samples were collected in 2005[149]. A study among 109 treatment-experienced patients treated with stavudine/lamivudine/nevirapine between January 2004 and August 2005 in Segou showed detectable viral load in 26 patients after 20 months on treatment. Drug resistance from 22/26 patient samples that were amplified showed presence of mutations in 11 (50%). Observed mutations included: M184V (n = 10), Y181C (n = 6), G190A (n = 3), K103N (n = 2) and V106A (n = 1). No TAMs were observed in this study[150]. In a study among 97 HIV-infected children attending the Gabriel Toure hospital, 22/30 (73%) samples that were genotypically analyzed showed presence of DRMs. The children had been on ART for 12 months[151]. Observed mutations included: M184V/I (n = 19), K103N (n = 11), Y181C (n = 5), Y188L (n = 3), V106A (n = 3), K101E/Q (n = 1), G190A (n = 4), K70R (n = 1), D67N (n = 1) and L210W (n = 1). Data from a multicenter study of HIVDR that included treatment-experienced individuals from Mali showed high prevalence of mutations among individuals exposed to ART for > 6 months[117]. Predominant mutations among the 46 successfully sequenced samples included NRTI mutations M184V/I (82.6%), TAMs (TAM1, 21.7%; TAM2, 30.4%), and NNRTI mutations K103N (50%), Y181C (19.6%), P225H (19.6%), G190A/S (17.4%) and K101E (13%)[117].

Niger

The first report on ARV drug resistance among drug-naive patients in Niamey, Niger, showed prevalence of resistance at 6.5%[148].

Nigeria

Several studies on drug resistance have been conducted in Nigeria. In a multicenter study that included patients recruited between 2007 and 2009, the overall drug resistance among drug-naive individuals in Lagos, Nigeria was 1.6% (3/186)[23]. Of this, NNRTIs accounted for most mutations, with TAMs and NRTIs appearing in equal proportions[23]. In a study among drug-naive antenatal clinic attendees in north-central Nigeria (n = 28) conducted in 2007, no major PI or NRTI DRMs were found; however, K101E mutation was detected in one individual and V179E together with Y181C in another, making the prevalence of DRMs to be 7%[152].

In a study among 338 ART-exposed individuals from Lagos (Lagos State), Ibadan (Oyo State), Jos (Plateau State), and Maiduguri (Borno State), the most common NRTI mutations observed in 2005 were M184V (301, 89.1%), K70R (91, 26.9%), D67N (75, 22.2%), T215Y (61, 18.0%), T215F (51, 15.1%), M41L (46, 13.6%), K219Q (45, 13.3%), S68G (43, 12.7%), and K65R (37, 10.9%)[153]. The most common NNRTI mutations included: Y181C (168, 49.7%), K103N (123, 36.4%), G190A (89, 26.3%), A98G (66, 19.5%), K101E (59, 17.5%), V108I (52, 15.4%), and V90I (41, 12.1%). One patient had virus with a major PI-resistant mutation L90M[153,154].

A study to assess DRMs among 175 treatment-experienced individuals showed high level drug resistance after 30.5 months of ART. In the study, 90% of patients had the M184V/I mutation, 62% had TAMs, while 14% had the K65R mutation. The NNRTI resistance mutations were detected in 97%, with 47% harboring etravirine-associated mutations[155]. In a study among patients on efavirenz- or nevirapine-based therapy in Plateau state,

Table 1 A. Characteristics of included studies; contribution of different classes of antiretrovirals to drug resistance mutations in Africa (3 regions)

	Number of genotypes (number of studies)*	Median number of genotypes per study (range)	Prevalence of drug resistance fraction (%)	Proportion of total mutations to NNRTIs	Proportion of total mutations to NRTIs	Proportion of total mutations to PIs
East Africa	1,863 (24)	59 (19-401)	138/1,863 (7.4)	66.2	26.3	7.5
Southern Africa	3,393 (34)	56 (13-548)	99/3,393 (2.9)	50.0	37.5	12.5
West and Central Africa	285 (39)	6 (1-20)	102/285 (35.8)	33.0	58.6	8.4

NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: nonnucleoside reverse transcriptase inhibitor; PI: protease inhibitor.
Total number of studies = 99.
*2 studies did not record number of genotypes assayed.

and who were in virological failure after 24 weeks, the prevalence of NNRTI mutations M184V/I and TAMs were 38.9% (37/95) and 11.6% (11/95), respectively[156]. Among NNRTI mutations, Y181C/I/V was predominant (26.3%) followed by K103N (18.9%), G190S/A (11.6%), and K101E/H/P (8.4%)[156]. In a study among 14/102 infants born to HIV-infected women, 4/13 successfully genotyped samples had NNRTI mutations: V179I (two infants), Y181C, and V179E[157].

Republic of Congo

In a WHO HIVDR threshold survey among pregnant women from Congo, the prevalence of HIVDR in Brazzaville (n = 31) and Pointe-Noire (n = 44) could not be determined because the eligible sample number was not reached. This was due to serology outcome after sample collection, which showed that 26 samples were HIV-1 negative. Only 15/31 and 23/44 samples from Brazzaville and Pointe-Noire, respectively, were HIV-1 positive. Since the two sites were 400 km apart, the samples could not be pooled to represent Congo for classification of HIVDR[124].

Senegal

Studies on HIVDR in Senegal have documented differing outcomes among different populations. In the initial years of the Senegalese government initiative of access to ART, no major HIVDR among 68 drug-naive individuals was observed after a follow up of 12-30 months, while NRTI mutations were detected in one treated (1/6 tested out of 12) patient. The NRTI mutations in this patient included M41L, D67N, L210W, and T215Y[158]. In a study among 200 ART-naive patients, of which 96 samples were collected between 1998 and 2001, NRTI drug resistance mutations were detected in four patients: K65R (n = 1), V75S (n = 1), M41L (n = 1), and K219N (n = 1). There were no NNRTI mutations. One patient had PI resistance mutation M46L. Among the

Table 1 B. Characteristics of included studies; contribution of different classes of antiretrovirals to drug resistance mutations in Africa (4 Regions)

Region	Number of genotypes (number of studies)*	Median number of genotypes per study (range)	Prevalence of drug resistance fraction (%)	Proportion of total mutations to NNRTIs	Proportion of total mutations to NRTIs	Proportion of total mutations to PIs
East Africa	1,863 (24)	59 (19-401)	138/1,863 (7.4)	66.2	26.3	7.5
Southern Africa	3,393 (34)	56 (13-548)	99/3,393 (2.9)	50.0	37.5	12.5
West Africa	231 (33)	6 (1-20)	74/231 (32.0)	33.1	58.9	7.9
Central Africa	54 (6)	9 (5-12)	28/54 (51.9)	30.7	51.4	17.9

NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: nonnucleoside reverse transcriptase inhibitor; PI: protease inhibitor.
Total number of studies = 99.
*2 studies did not record number of genotypes assayed.

Table 2. Pooled prevalence of drug resistance mutations in Africa and in each region

Region	Prevalence (%), (95% CI)
Africa	10.6 (8.1-13.4)
East Africa	7.4 (4.0-11.8)
Southern Africa	2.5 (1.7-3.4)
West Africa	46.3 (34.4-58.4)
Central Africa	54.9 (16.3-90.3)
West and Central Africa	48.6 (36.1-61.2)

Number of genotypes with WHO drug resistance mutation/total number of genotypes.

104 samples collected between 2003 and 2007, no DRMs were identified in RT, but PI mutations were present in two strains, G73S (n = 1) and I54T (n = 1)[159]. In a multicenter study that included 48 voluntary counseling and testing attendees in Dakar, the prevalence of HIVDR was reported to be low (0/48) in 2006[114].

Sierra Leone

The WHO estimates that 20-39% of HIV-infected individuals in Sierra Leone are on treatment. There is not much data on the diversity of HIV or treatment outcomes in Sierra Leone. This is probably due to the past political instability. However, a case report of a patient harboring CRF02_AG with multi-NRTI resistance has been reported[160]. In this 33-year-old patient, multi-NRTI resistance mutations Q151M, K65R, M184I and Y181I were reported after 36 months of stavudine/lamivudine/nevirapine treatment.

Togo

The prevalence of drug resistance mutations in Togo was reported as 10.7%, with M41L being most common[161]. In one patient, PI mutation L90M was detected[161]. A similar study among 188 patients on first-line ART showed the prevalence of resistance mutations to be 24.5%[162]. Of 46 patients with resistance, 25 were resistant to NRTIs while 12 were resistant to NNRTIs, with eight patients resistant to all first-line drug classes. M184V was the most common mutation in this population[162].

Data on HIV drug resistance was available for 21 of the 24 west and central African countries; Gambia, Guinea-Bissau and Liberia had no readily available data. Absence of data from these countries may be attributed to low or absence of HIV prevalence data, socio-political and cultural practices.

Table 3 A. Pooled prevalence of each type of mutation in each region

	NRTI Prevalence (95% CI)	NNRTI Prevalence (95% CI)	PI Prevalence (95% CI)	p-value
East Africa	32.5 (18.3-48.5)	57.0 (38.6-74.5)	12.8 (5.9-21.8)	< 0.0001
Southern Africa	41.1 (28.2-54.7)	46.4 (33.3-59.8	16.3 (11.0-22.3	< 0.0001
West and Central Africa	55.0 (50.6-59.4)	33.3 (27.7-39.3)	12.4 (7.0-19.0)	< 0.0001
West Africa	55.3 (51.1-59.5)	33.9 (27.6-40.4)	11.9 (6.3-19.1)	< 0.0001
Central Africa	54.8 (32.1-76.5)	31.0 (16.0-48.5)	14.7 (3.2-32.7)	< 0.0001

Table 3 B. Pooled prevalence of each type of mutation in each region

	East Africa Prevalence (95% CI)	Southern Africa* Prevalence (95% CI)	West and Central Africa Prevalence (95% CI)	p value
NRTI	32.5 (18.3-48.5)	41.1 (28.2-54.7)	55.0 (50.6-59.4)	0.005
NNRTI	57.0 (38.6-74.5)	46.4 (33.3-59.8)	33.3 (27.7-39.3)	0.003
PI	12.8 (5.9-21.8)	16.3 (11.0-22.3)	12.4 (7.0-19.0)	0.565

NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: nonnucleoside reverse transcriptase inhibitor; PI: protease inhibitor.
Number of PI or NNRTI or NRTI mutations/total number of drug resistance mutations.
*For Southern Africa (PIs), the fixed effects (inverse variance) proportion was used as inconsistency between studies was not significant, I^2 (inconsistency) = 6.9% (95% CI: 0-39.4%); p = 0.3528.

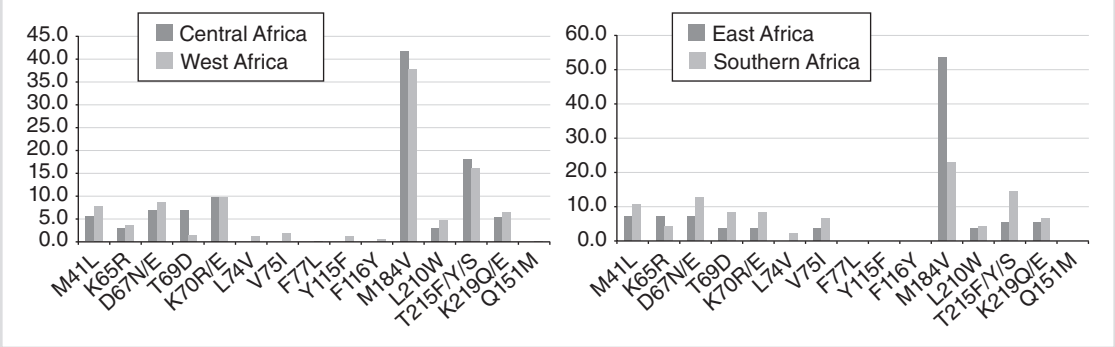

Figure 1. *Prevalence of nucleoside reverse transcriptase inhibitor mutations.*

Overall prevalence of HIV drug resistance in Africa

We analyzed datasets from 99 studies carried out in the four (East, Central, South, and Western) African regions. A total of 5,541 patients were included in this analysis. The overall proportion of DRMs to NNRTIs was highest (66.2%) in East Africa, whereas the highest mutations to NRTIs was observed in West (58.9%) and Central (51.4%) Africa. The highest proportion of mutations to PIs was observed in Central (17.9%) and Southern Africa (12.5%) (Table 1 A and 1 B). The pooled prevalence of DRMs in Africa was 10.6% (95% CI: 8.1-13.4), and Central Africa had the highest pooled prevalence of 54.9% (95% CI: 16.3-90.3) (Table 2). The highest observed pooled prevalence of NRTI mutations was in the West (55.3% CI: 51.1-59.5) and Central (54.8% CI: 32.1-76.5); NNRTIs was East Africa (57.0% CI: 38.6-74.5), and PIs was Southern Africa (16.3% CI: 11.0-22.3) (Table 3).

With respect to the contribution of the various classes of drugs, NRTIs were the major causes of DRMs in West and Central Africa, whereas NNRTIs were the major causes in East and Southern Africa (Fig. 1). The major NRTI mutation in all four regions was M184V (Fig. 2). In West and Central Africa, the major NNRTI mutation was K103N, in East Africa it was K103N and Y181C, and in Southern Africa it was also K103N (Fig. 3). The major PI mutation(s) in Central Africa was V82A, in West Africa M46I/L, in East Africa N88D and I85V, and in Southern Africa it was L90M. The regional distributions of individual subtypes and recombinants are broadly stable, although unique recombinant forms/circulating recombinant forms may play an increasing role in the HIV pandemic. Few subtypes, namely, A (A1, A2, A3, A4 and A5), C, CRF02_AG, and D accounted for about 85% of new infections. Subtype A and D have been stable in East Africa; C in Southern Africa; A, G, CRF02_AG and CRF06_cpx in Western Africa, subtype B and CRF02_AG in Northern Africa.

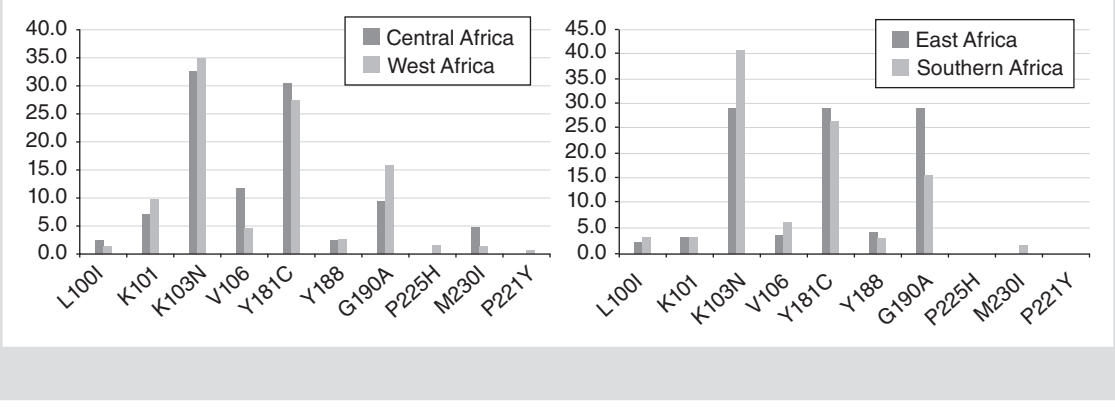

Figure 2. *Prevalence of nonnucleoside reverse transcriptase inhibitor mutations.*

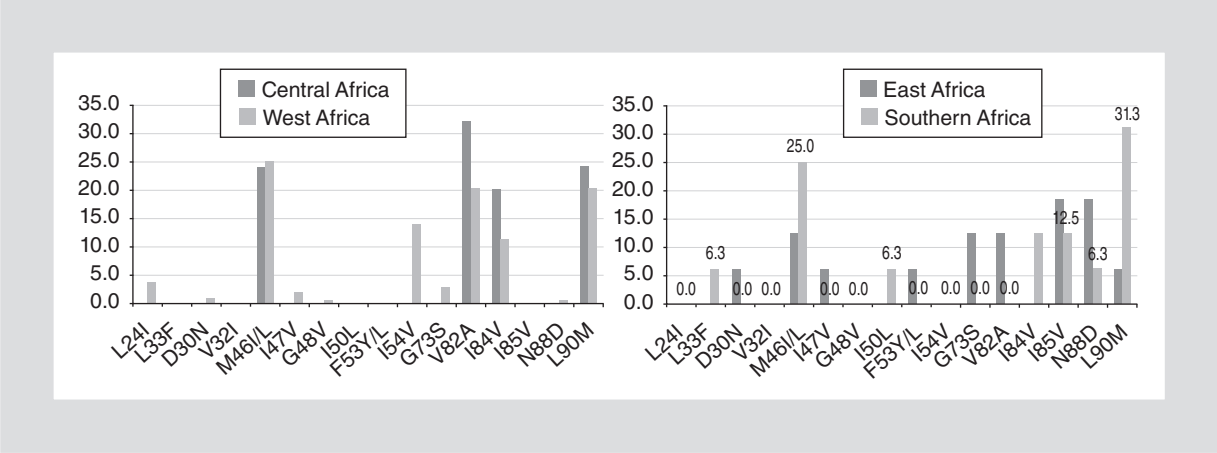

Figure 3. *Prevalence of protease inhibitor mutations.*

With the overall regional distributions of HIV subtypes and recombinants being stable, it was expected that HIV drug resistance would follow similar trends. However, it was observed that in West, Central, and Southern Africa where subtypes A, G, CRF02_AG and CRF06_cpx and subtype C are predominant, respectively[22], the major NNRTI mutation was K103N. In East Africa, where Subtype A and D have been stable, K103N, Y181C and G190A were the major NNRTI mutations. The major PI mutations in each region were V82A in Central Africa, M46I/L in West Africa, N88D and I85V in East Africa and L90M in Southern Africa. This outcome would likely be attributable to different countries having adopted different strategies in treating patients. This differences were, however, not significant.

Conclusion

This review has shown varying geographic trends of prevalence of DRMs in Africa, with West and Central Africa having predominantly NRTI mutations and East and Southern Africa with NNRTIs. It remains important to understand the geographic HIVDR trends in relation to subtypes and at-risk populations such as men who have sex with men, commercial sex workers and heterosexual populations. Several published works across Africa have shown low levels of both acquired and transmitted drug resistance and this is a possible indication of successful ART roll-out in these countries. The increasing reports of HIVDR in some countries highlight the importance of routine surveillance of HIVDR as part of national ART programs. The major cause of poor adherence in Africa has mainly been due to ART drug stock-outs as a result of poor procurement and supply chain practices and these have to be urgently addressed to improve on the ART roll-out programs. Unfortunately, a few countries that are affected by the HIV/AIDS epidemic and are rolling out therapy do not have resistance data and such countries should initiate surveillance studies before the roll-out programs are compromised.

References

1. Adje-Toure C, Hanson D, Talla-Nzussouo N, et al. Virologic and immunologic response to antiretroviral therapy and predictors of HIV type 1 drug resistance in children receiving treatment in Abidjan, Cote d'Ivoire. AIDS Res Hum Retroviruses. 2008;24:911-17.
2. WHO HIV drug resistance report 2012. Available at: http://www.who.int/hiv/pub/drugresistance/report2012/en/index.html. [Accessed June 2012].
3. UNAIDS, J.U.N.P.o.H.A., UNAIDS Report on the Global AIDS Epidemic 2012. Available at: http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2012/gr2012/20121120_UNAIDS_Global_Report_2012_en.pdf. [Accessed Jan 2013, 2012].
4. UNAIDS, J.U.N.P.o.H.A., Report on the global HIV/AIDS epidemic, June 2000, 2000.
5. UNAIDS, J.U.N.P.o.H.A., UNAIDS Report on the Global AIDS Epidemic 2010, 2010.
6. Oyugi J, Byakika-Tusiime J, Ragland K, et al. Treatment interruptions predict resistance in HIV-positive individuals purchasing fixed-dose combination antiretroviral therapy in Kampala, Uganda. AIDS. 2007;21:965-71.
7. Bateman C. Drug stock-outs: inept supply-chain management and corruption. S Afr Med J. 2013;103:600-2.
8. Gupta R, Hill A, Sawyer A, et al. Virological monitoring and resistance to first-line highly active antiretroviral therapy in adults infected with HIV-1 treated under WHO guidelines: a systematic review and meta-analysis. Lancet Infect Dis. 2009;9:409-17.
9. Bangsberg D, Hecht F, Charlebois E, et al. Adherence to protease inhibitors, HIV-1 viral load, and development of drug resistance in an indigent population. AIDS. 2000;14:357-66.
10. Haberer J, Kiwanuka J, Nansera D, Wilson I, Bangsberg D. Challenges in using mobile phones for collection of antiretroviral therapy adherence data in a resource-limited setting. AIDS Behav. 2010;14:1294-301.
11. Rasschaert F, Philips M, Van Leemput L, Assefa Y, Schouten E, Van Damme W. Tackling health workforce shortages during antiretroviral treatment scale-up--experiences from Ethiopia and Malawi. J Acquir Immune Defic Syndr. 2011;57(Suppl 2):S109-12.
12. WHO/UNAIDS/UNICEF. Towards universal access. Available at: http://www.who.int/hiv/pub/2010progressreport/report/en/index.html, 2010.
13. PEPFAR. Technical note on PEPFAR's reporting methodology. Available at: http://www.pepfar.gov/2009results/. [Accessed Jan 2012].
14. WHO. Antiretroviral therapy for HIV infection in adults and adolescents. Recommendations for a public health approach (2010 revisions), Geneva, Switzerland, World Health Organization. Available at: http://www.who.int/hiv/pub/arv/adult2010/en/index.html.

15. WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Available at: http://www.who.int/hiv/pub/guidelines/arv2013/en/.
16. Jahn A, Floyd S, Crampin A, et al. Population-level effect of HIV on adult mortality and early evidence of reversal after introduction of antiretroviral therapy in Malawi. Lancet. 2008;371:1603-11.
17. Grant R, Hecht F, Warmerdam M, et al. Time trends in primary HIV-1 drug resistance among recently infected persons. JAMA. 2002;288:181-8.
18. Brenner B, Turner D, Oliveira M, et al. A V106M mutation in HIV-1 clade C viruses exposed to efavirenz confers cross-resistance to non-nucleoside reverse transcriptase inhibitors. AIDS. 2003;17:F1-5.
19. Grossman Z, Istomin V, Averbuch D, et al. Genetic variation at NNRTI resistance-associated positions in patients infected with HIV-1 subtype C. AIDS. 2004;18:909-15.
20. Palma A, Covens K, Snoeck J, Vandamme AM, Camacho R, Van Laethem K. HIV-1 protease mutation 82M contributes to phenotypic resistance to protease inhibitors in subtype G. J Antimicrob Chemother. 2012;67:1075-9.
21. Coutsinos D, Invernizzi C, Xu H, et al. Template usage is responsible for the preferential acquisition of the K65R reverse transcriptase mutation in subtype C variants of human immunodeficiency virus type 1. J Virol. 2009;83:2029-33.
22. Lihana R, Ssemwanga D, Abimiku A, Ndembi N. Update on HIV-1 diversity in Africa: a decade in review. AIDS Eev. 2012;14:83-100.
23. Hamers R, Wallis C, Kityo C, et al. HIV-1 drug resistance in antiretroviral-naive individuals in sub-Saharan Africa after rollout of antiretroviral therapy: a multicentre observational study. Lancet Infect Dis. 2011;11:750-9.
24. Kambugu A. Pre-ART HIV resistance testing in Africa: are we there yet? Lancet Infect Dis. 2012;12:261.
25. Mugyenyi P, Walker A, Hakim J, et al. Routine versus clinically driven laboratory monitoring of HIV antiretroviral therapy in Africa (DART): a randomised non-inferiority trial. Lancet. 2010;375:123-31.
26. Castelnuovo B, Kiragga A, Schaefer P, Kambugu A, Manabe Y. High rate of misclassification of treatment failure based on WHO immunological criteria. AIDS. 2009;23:1295-6.
27. Sigaloff K, Hamers R, Wallis C, Unnecessary antiretroviral treatment switches and accumulation of HIV resistance mutations; two arguments for viral load monitoring in Africa. J Acquir Immune Defic Syndr. 2011; 58:23-31.
28. UNAIDS, J.U.N.P.o.H.A., UNAIDS World AIDS Day Report. Available at: http://www.unaids.org/en/resources/unaidspublications/2011/. [Accessed January 2012].
29. Schouten E, Jahn A, Ben-Smith A, et al. Antiretroviral drug supply challenges in the era of scaling up ART in Malawi. J Int AIDS Soc. 2011; 14(Suppl 1):S4.
30. Bennett D, Camacho R, Otelea D. Drug resistance mutations for surveillance of transmitted HIV-1 drug-resistance: 2009 update. PLoS One. 2009;4:e4724.
31. Bennett D, Myatt M, Bertagnolio S, Sutherland D, Gilks C. Recommendations for surveillance of transmitted HIV drug resistance in countries scaling up antiretroviral treatment. Antivir Ther. 2008;13(Suppl 2):25-36.
32. Frentz D, van de Vijver D, Boucher C, Albert J. Estimates of HIV transmitted drug resistance can be inflated due to natural sequence polymorphisms. J Acquir Immune Defic Syndr. 2011;58:e135-7.
33. Frentz D, Boucher C, van de Vijver D. Temporal changes in the epidemiology of transmission of drug-resistant HIV-1 across the world. AIDS Rev. 2012;14:17-27.
34. Johnson V, Calvez V, Gunthard H, et al. Update of the drug resistance mutations in HIV-1: March 2013. Top Antivir Med. 2013;21:6-14.
35. Shafer R, Rhee S, Pillay D, et al. HIV-1 protease and reverse transcriptase mutations for drug resistance surveillance. AIDS. 2007;21:215-23.
36. Green H, Tilston P, Fearnhill E, Pillay D, Dunn D. The impact of different definitions on the estimated rate of transmitted HIV drug resistance in the United Kingdom. J Acquir Immune Defic Syndr. 2008;49:196-204.
37. Nkengasong J, Adje-Toure C, Weidle P. HIV antiretroviral drug resistance in Africa. AIDS Rev. 2004;6:4-12.
38. Bartolo I, Rocha C, Bartolomeu J, et al. Antiretroviral drug resistance surveillance among treatment-naive human immunodeficiency virus type 1-infected individuals in Angola: evidence for low level of transmitted drug resistance. Antimicrob Agents Chemother. 2009;53:3156-8.
39. Castelbranco E, da Silva Sousa E, Cavalcanti A, Martins A, de Alencar L, Tanuri A. Frequency of primary resistance to antiretroviral drugs and genetic variability of HIV-1 among infected pregnant women recently diagnosed in Luanda-Angola. AIDS Res Hum Retroviruses. 2010;26:1313-16.
40. Bussmann H, Novitsky V, Wester W, et al. HIV-1 subtype C drug-resistance background among ARV-naive adults in Botswana. Antivir Chem Chemother. 2005;16:103-15.
41. Blower S, Bodine E, Kahn J, McFarland W. The antiretroviral rollout and drug-resistant HIV in Africa: insights from empirical data and theoretical models. AIDS. 2005;19:1-14.
42. Vardavas R, Blower S. The emergence of HIV transmitted resistance in Botswana: "when will the WHO detection threshold be exceeded?". PLoS One. 2007;2:e152.
43. Bussmann H, de la Hoz Gomez F, Roels T, et al. Prevalence of transmitted HIV drug resistance in Botswana: lessons learned from the HIVDR-Threshold Survey conducted among women presenting for routine antenatal care as part of the 2007 national sentinel survey. AIDS Res Hum Retroviruses. 2011;27:365-72.
44. Abegaz W, Grossman Z, Wolday D, et al. Threshold survey evaluating transmitted HIV drug resistance among public antenatal clinic clients in Addis Ababa, Ethiopia. Antivir Ther. 2008;13(Suppl 2):89-94.
45. Kassu A, Fujino M, Matsuda M, Nishizawa M, Ota F, Sugiura W. Molecular epidemiology of HIV type 1 in treatment-naive patients in north Ethiopia. AIDS Res Hum Retroviruses. 2007;23:564-8.
46. Lihana R, Khamadi S, Lubano K, eta al. HIV type 1 subtype diversity and drug resistance among HIV type 1-infected Kenyan patients initiating antiretroviral therapy. AIDS Res Hum Retroviruses. 2009;25:1211-17.
47. Steegen K, Luchters S, Dauwe K, et al. Effectiveness of antiretroviral therapy and development of drug resistance in HIV-1 infected patients in Mombasa, Kenya. AIDS Res Ther. 2009;6:12.
48. Nyamache A, Muigai A, Nganga Z, Khamadi S. HIV-1 genetic diversity and naturally occurring polymorphisms in HIV-1 Kenyan isolates: Implications for integrase inhibitors. AIDS Res Hum Retroviruses, 2012;28:933-6.
49. Zeh C, Weidle P, Nafisa L, et al. HIV-1 drug resistance emergence among breastfeeding infants born to HIV-infected mothers during a single-arm trial of triple-antiretroviral prophylaxis for prevention of mother-to-child transmission: a secondary analysis. PLoS Med. 2011;8:e1000430.
50. Price M, Wallis C, Lakhi S, et al. Transmitted HIV type 1 drug resistance among individuals with recent HIV infection in East and Southern Africa. AIDS Res Hum Retroviruses. 2011;27:5-12.
51. Sigaloff K, Mandaliya K, Hamers R, et al. High prevalence of transmitted antiretroviral drug resistance among newly HIV-1 diagnosed adults in Mombasa, Kenya. AIDS Res Hum Retroviruses. 2012;28:1033-7.
52. Razafindratsimandresy R, Rajaonatahina D, Soares J, Rousset D, Reynes J. High HIV type 1 subtype diversity and few drug resistance mutations among seropositive people detected during the 2005 second generation HIV surveillance in Madagascar. AIDS Res Hum Retroviruses. 2006;22:595-7.
53. Petch L, Hoffman I, Jere C, et al. Genotypic analysis of the protease and reverse transcriptase of HIV type 1 subtype C isolates from antiretroviral drug-naive adults in Malawi. AIDS Res Hum Retroviruses. 2005;21:799-805.
54. Church J, Hudelson S, Guay L, et al. HIV type 1 variants with nevirapine resistance mutations are rarely detected in antiretroviral drug-naive African women with subtypes A, C, and D. AIDS Res Hum Retroviruses. 2007;23:764-8.
55. Kamoto K, Aberle-Grasse J. Surveillance of transmitted HIV drug resistance with the World Health Organization threshold survey method in Lilongwe, Malawi. Antivir Ther. 2008;13(Suppl 2):83-7.
56. Chunfu YangB, Bile E, Marum L, Wagar N, Nkengasong J. Global surveillance of transmitted HIV-1 drug resistance in PEPFAR-supported countries using a broadly sensitive genotyping assay. In 18th CROI, 2011, Boston, USA.
57. Bellocchi M, Forbici F, Palombi L, et al. Subtype analysis and mutations to antiviral drugs in HIV-1-infected patients from Mozambique before initiation of antiretroviral therapy: results from the DREAM programme. J Med Virol. 2005;76:452-8.
58. Parreira R, Piedade J, Domingues A, et al. Genetic characterization of human immunodeficiency virus type 1 from Beira, Mozambique. Microbes Infect. 2006;8:2442-51.
59. Abreu CM, Brindeiro P, Martins A, et al. Genotypic and phenotypic characterization of human immunodeficiency virus type 1 isolates circulating in pregnant women from Mozambique. Arch Virol. 2008;153:2013-7.
60. Bartolo I, Casanovas J, Bastos R, et al. HIV-1 genetic diversity and transmitted drug resistance in health care settings in Maputo, Mozambique. J Acquir Immune Defic Syndr. 2009;51:323-31.
61. Servais J, Lambert C, Karita E, et al. HIV type 1 pol gene diversity and archived nevirapine resistance mutation in pregnant women in Rwanda. AIDS Res Hum Retroviruses. 2004;20:279-83.
62. Galluzzo C, Germinario E, Bassani L, et al. Antiretroviral resistance mutations in untreated pregnant women with HIV infection in Uganda and Rwanda. AIDS Res Hum Retroviruses. 2007;23:1449-51.
63. Razafindratsimandresy R, Hollanda J, Soares J, Rousset D, Chetty A, Reynes J. HIV type 1 diversity in the Seychelles. AIDS Res Hum Retroviruses. 2007;23:761-3.
64. Bessong P, Obi C, Cilliers T, et al. Characterization of human immunodeficiency virus type 1 from a previously unexplored region of South Africa with a high HIV prevalence. AIDS Res Hum Retroviruses. 2005;21:103-9.
65. Bessong P, Mphahlele J, Choge I, et al. Resistance mutational analysis of HIV type 1 subtype C among rural South African drug-naive patients prior to large-scale availability of antiretrovirals. AIDS Res Hum Retroviruses. 2006;22:1306-12.
66. Fish M, Hewer R, Wallis C, Venter W, Stevens W, Papathanasopoulos M. Natural polymorphisms of integrase among HIV type 1-infected South African patients. AIDS Res Hum Retroviruses. 2010;26:489-93.
67. Huang K, Goedhals D, Fryer H, et al. Prevalence of HIV type-1 drug-associated mutations in pre-therapy patients in the Free State, South Africa. Antivir Ther. 2009;14:975-84.

68. Jacobs G, Laten A, van Rensburg E, et al. Phylogenetic diversity and low level antiretroviral resistance mutations in HIV type 1 treatment-naive patients from Cape Town, South Africa. AIDS Res Hum Retroviruses. 2008;24:1009-12.
69. Nwobegahay J, Bessong P, Masebe T, et al. Prevalence of drug-resistant mutations in newly diagnosed drug-naive HIV-1-infected individuals in a treatment site in the waterberg district, Limpopo province. S Afr Med J. 2011;101:335-7.
70. Nwobegahay J, Bessong P, Masebe T, Mavhandu L, Iweriebor B, Selabe G. Prevalence of antiretroviral drug resistance mutations and HIV-I subtypes among newly-diagnosed drug-naive persons visiting a voluntary testing and counselling centre in northeastern South Africa. J Health Popul Nutr. 2011;29:303-9.
71. Orrell C, Walensky R, Losina E, Pitt J, Freedberg K, Wood R. HIV type-1 clade C resistance genotypes in treatment-naive patients and after first virological failure in a large community antiretroviral therapy programme. Antivir Ther. 2009;14:523-31.
72. Parboosing R, Naidoo A, Gordon M, Taylor M, Vella V. Resistance to antiretroviral drugs in newly diagnosed, young treatment-naive HIV-positive pregnant women in the province of KwaZulu-Natal, South Africa. J Med Virol. 2011;83:1508-13.
73. Pillay V, Ledwaba J, Hunt G, et al. Antiretroviral drug resistance surveillance among drug-naive HIV-1-infected individuals in Gauteng Province, South Africa in 2002 and 2004. Antivir Ther. 2008;13(Suppl 2):101-7.
74. van Zyl G, Cotton M, Claassen M, Abrahams C, Preiser W. Surveillance of transmitted resistance to antiretroviral drug classes among young children in the Western Cape Province of South Africa. Pediatr Infect Dis J. 2010;29:370-1.
75. Gordon M, De Oliveira T, Bishop K, et al. Molecular characteristics of human immunodeficiency virus type 1 subtype C viruses from KwaZulu-Natal, South Africa: implications for vaccine and antiretroviral control strategies. J Virol. 2003;77:2587-99.
76. Barth R, Wensing A, Tempelman H, Moraba R, Schuurman R, Hoepelman A. Rapid accumulation of nonnucleoside reverse transcriptase inhibitor-associated resistance: evidence of transmitted resistance in rural South Africa. AIDS. 2008;22:2210-12.
77. McIntyre J, Hopley M, Moodley D, et al. Efficacy of short-course AZT plus 3TC to reduce nevirapine resistance in the prevention of mother-to-child HIV transmission: a randomized clinical trial. PLoS Med. 2009; 6:e1000172.
78. Barth R, Tempelman H, Smelt, Wensing A, Hoepelman A, Geelen S. Long-term outcome of children receiving antiretroviral treatment in rural South Africa: substantial virologic failure on first-line treatment. Pediatr Infect Dis J. 2011;30:52-6.
79. Iweriebor B, Mavhandu L, Masebe T, et al. Molecular epidemiology of HIV in two highly endemic areas of northeastern South Africa. Arch Virol. 2012;157:455-65.
80. van Zyl G, van der Merwe L, Claassen M, Zeier M, Preiser W. Antiretroviral resistance patterns and factors associated with resistance in adult patients failing NNRTI-based regimens in the Western Cape, South Africa. J Med Virol. 2011;83:1764-9.
81. Manasa J, Katzenstein D, Cassol S, Newell M, de Oliveira T. Primary drug resistance in South Africa - data from 10 years of surveys. AIDS Res Hum Retroviruses. 2012;28:558-65.
82. Deho L, Walwema R, Cappelletti A, et al. Subtype assignment and phylogenetic analysis of HIV type 1 strains in patients from Swaziland. AIDS Res Hum Retroviruses. 2008;24:323-5.
83. Maphalala G, Okello V, Mndzebele S, et al. Surveillance of transmitted HIV drug resistance in the Manzini-Mbabane corridor, Swaziland, in 2006. Antivir Ther. 2008;13(Suppl 2):95-100.
84. Eshleman S, Laeyendecker O, Parkin N, et al. Antiretroviral drug susceptibility among drug-naive adults with recent HIV infection in Rakai, Uganda. AIDS. 2009;23:845-52.
85. Gale C, Yirrell D, Campbell E, Van der Paal L, Grosskurth H, Kaleebu P. Genotypic variation in the pol gene of HIV type 1 in an antiretroviral treatment-naive population in rural southwestern Uganda. AIDS Res Hum Retroviruses. 2006;22:985-92.
86. Ndembi N, Hamers R, Sigaloff K, et al. Transmitted antiretroviral drug resistance among newly HIV-1 diagnosed young individuals in Kampala. AIDS. 2011;25:905-10.
87. Ndembi N, Lyagoba F, Nanteza B, et al. Transmitted antiretroviral drug resistance surveillance among newly HIV type 1-diagnosed women attending an antenatal clinic in Entebbe, Uganda. AIDS Res Hum Retroviruses. 2008;24:889-95.
88. Ssemwanga D, Ndembi N, Lyagoba F, et al. Transmitted antiretroviral drug resistance among drug-naive female sex workers with recent infection in Kampala, Uganda. Clin Infect Dis. 2012;54(Suppl 4):S339-42.
89. Weidle P, Downing R, Sozi C, et al. Development of phenotypic and genotypic resistance to antiretroviral therapy in the UNAIDS HIV Drug Access Initiative--Uganda. AIDS. 2003;17(Suppl 3):S39-48.
90. Reynolds S, Kityo C, Mbamanya F, et al. Evolution of drug resistance after virological failure of a first-line highly active antiretroviral therapy regimen in Uganda. Antivir Ther. 2009;14:293-7.
91. Church J, Mwatha A, Bagenda D, et al. In utero HIV infection is associated with an increased risk of nevirapine resistance in Ugandan infants who were exposed to perinatal single dose nevirapine. AIDS Res Hum Retroviruses. 2009;25:673-7.
92. Lee G, Kizogi I, Bangsberg D, et al. Prevalence and virologic consequences of transmitted drug resistance mutations in Uganda. In 17th CROI, 2010, San Francisco.
93. Ndembi N, Goodall R, Dunn D, et al. Viral rebound and emergence of drug resistance in the absence of viral load testing: a randomized comparison between zidovudine-lamivudine plus Nevirapine and zidovudine-lamivudine plus Abacavir. J Infect Dis. 2010;201:106-13.
94. Towler W, Barlow-Mosha L, Church J, et al, Analysis of drug resistance in children receiving antiretroviral therapy for treatment of HIV-1 infection in Uganda. AIDS Res Hum Retroviruses. 2010;26:563-8.
95. Nazziwa J, Njai H, Ndembi N, et al. HIV-1 transmitted drug resistance and evidence of transmission clusters among recently infected antiretroviral naive individuals from Ugandan fishing communities of Lake Victoria. AIDS Res Hum Retroviruses. 2013;29:788-95.
96. Ruel T, Kamya M, Li P, et al. Early virologic failure and the development of antiretroviral drug resistance mutations in HIV-infected Ugandan children. J Acquir Immune Defic Syndr. 2011;56:44-50.
97. Nyombi B, Holm-Hansen C, Kristiansen K, Bjune G, Muller F. Prevalence of reverse transcriptase and protease mutations associated with antiretroviral drug resistance among drug-naive HIV-1 infected pregnant women in Kagera and Kilimanjaro regions, Tanzania. AIDS Res Ther. 2008;5:13.
98. Somi G, Kibuka T, Diallo K, et al. Surveillance of transmitted HIV drug resistance among women attending antenatal clinics in Dar es Salaam, Tanzania. Antivir Ther. 2008;13(Suppl 2):77-82.
99. Johannessen A, Naman E, Kivuyo S, et al. Virological efficacy and emergence of drug resistance in adults on antiretroviral treatment in rural Tanzania. BMC Infect Dis. 2009;9:108.
100. Bratholm C, Johannessen A, Naman E, et al. Drug resistance is widespread among children who receive long-term antiretroviral treatment at a rural Tanzanian hospital. J Antimicrob Chemother. 2010;65:1996-2000.
101. Johannessen A, Garrido C, Zahonero N, Naman E, de Mendoza C. HIV-1 drug resistance testing from dried blood spots collected in rural Tanzania using the ViroSeq HIV-1 Genotyping System. J Antimicrob Chemother. 2011;66:260-4.
102. Johannessen A, Holberg-Petersen M, Lovgaarden G, et al. HIV type-1 drug resistance testing on dried blood spots is feasible and reliable in patients who fail antiretroviral therapy in rural Tanzania. Antivir Ther. 2010;15:1003-9.
103. Mosha F, Urassa W, Aboud S, et al. Prevalence of genotypic resistance to antiretroviral drugs in treatment-naive youths infected with diverse HIV type 1 subtypes and recombinant forms in Dar es Salaam, Tanzania. AIDS Res Hum Retroviruses. 2011;27:377-82.
104. Kasang C, Kalluvya S, Majinge C, et al. HIV drug resistance (HIVDR) in antiretroviral therapy-naive patients in Tanzania not eligible for WHO threshold HIVDR survey is dramatically high. PLoS One. 2011;6:e23091.
105. Handema R, Terunuma H, Kasolo F, et al. Prevalence of drug-resistance-associated mutations in antiretroviral drug-naive Zambians infected with subtype C HIV-1. AIDS Res Hum Retroviruses. 2003;19:151-60.
106. Hamers R, Siwale M, Wallis C, et al. HIV-1 drug resistance mutations are present in six percent of persons initiating antiretroviral therapy in Lusaka, Zambia. J Acquir Immune Defic Syndr. 2010;55:95-101.
107. Gonzalez S, Gondwe C, Tully D, et al. Short communication: antiretroviral therapy resistance mutations present in the HIV type 1 subtype C pol and env regions from therapy-naive patients in Zambia. AIDS Res Hum Retroviruses. 2010;26:795-803.
108. Gupta R, Ford D, Mulenga V, et al. Drug resistance in human immunodeficiency virus type-1 infected Zambian children using adult fixed dose combination stavudine, lamivudine, and nevirapine. Pediatr Infect Dis J. 2010;29:e57-62.
109. Kantor R, Zijenah L, Shafer R, et al. HIV-1 subtype C reverse transcriptase and protease genotypes in Zimbabwean patients failing antiretroviral therapy. AIDS Res Hum Retroviruses. 2002;18:1407-13.
110. Lee E, Kantor R, Zijenah L, et al. Breast-milk shedding of drug-resistant HIV-1 subtype C in women exposed to single-dose nevirapine. J Infect Dis. 2005;192:1260-4.
111. DART Virology Group and Trial Team. Virological response to a triple nucleoside/nucleotide analogue regimen over 48 weeks in HIV-1-infected adults in Africa. AIDS. 2006;20:1391-9.
112. Tshabalala M, Manasa J, Zijenah L, et al. Surveillance of transmitted antiretroviral drug resistance among HIV-1 infected women attending antenatal clinics in Chitungwiza, Zimbabwe. PLoS One. 2011;6:e21241.
113. Chamberland A, Diabate S, Sylla M, et al. Transmission of HIV-1 drug resistance in Benin could jeopardise future treatment options. Sex Transm Infect, 2012;88:179-83.
114. Ayouba A, Lien T, Nouhin J, et al. Low prevalence of HIV type 1 drug resistance mutations in untreated, recently infected patients from Burkina Faso, Cote d'Ivoire, Senegal, Thailand, and Vietnam: the ANRS 12134 study. AIDS Res Hum Retroviruses. 2009;25:1193-6.

115. Nadembega W, Giannella S, Simpore J, et al. Characterization of drug-resistance mutations in HIV-1 isolates from non-HAART and HAART treated patients in Burkina Faso. J Med Virol. 2006;78:1385-91.
116. Vergne L, Diagbouga S, Kouanfack C, et al. HIV-1 drug-resistance mutations among newly diagnosed patients before scaling-up programmes in Burkina Faso and Cameroon. Antivir Ther. 2006;11:575-9.
117. Sylla M, Chamberland A, Boileau C, et al. Characterization of drug resistance in antiretroviral-treated patients infected with HIV-1 CRF02_AG and AGK subtypes in Mali and Burkina Faso. Antivir Ther. 2008;13:141-8.
118. Tebit D, Sangare L, Makamtse A, et al. HIV drug resistance pattern among HAART-exposed patients with suboptimal virological response in Ouagadougou, Burkina Faso. J Acquir Immune Defic Syndr. 2008;49:17-25.
119. Tebit D, Sangare L, Tiba F, et al. Analysis of the diversity of the HIV-1 pol gene and drug resistance associated changes among drug-naive patients in Burkina Faso. J Med Virol. 2009;81:1691-701.
120. Vidal N, Niyongabo T, Nduwimana J, et al. HIV type 1 diversity and antiretroviral drug resistance mutations in Burundi. AIDS Res Hum Retroviruses. 2007;23:175-80.
121. Koizumi Y, Ndembi N, Miyashita M, et al. Emergence of antiretroviral therapy resistance-associated primary mutations among drug-naive HIV-1-infected individuals in rural western Cameroon. J Acquir Immune Defic Syndr. 2006;43:15-22.
122. Ndembi N, Abraha A, Pilch H, et al. Molecular characterization of human immunodeficiency virus type 1 (HIV-1) and HIV-2 in Yaounde, Cameroon: evidence of major drug resistance mutations in newly diagnosed patients infected with subtypes other than subtype B. J Clin Microbiol. 2008;46: 177-84.
123. Youngpairoj A, Alemnji G, Eno L, et al. Prevalence of drug resistance-related polymorphisms in treatment-naive individuals infected with non-subtype B HIV type 1 in Cameroon. AIDS Res Hum Retroviruses. 2012;28:675-84.
124. Aghokeng A, Vergne L, Mpoudi-Ngole E, et al. Evaluation of transmitted HIV drug resistance among recently-infected antenatal clinic attendees in four Central African countries. Antivir Ther. 2009;14:401-11.
125. Depatureaux A, Charpentier C, Collin G, et al. Baseline genotypic and phenotypic susceptibilities of HIV-1 group O to enfuvirtide. Antimicrob Agents Chemother. 2010;54:4016-9.
126. Soria A, Porten K, Fampou-Toundji J, et al. Resistance profiles after different periods of exposure to a first-line antiretroviral regimen in a Cameroonian cohort of HIV type-1-infected patients. Antivir Ther. 2009;14:339-47.
127. Aghokeng A, Kouanfack C, Laurent C, et al. Scale-up of antiretroviral treatment in sub-Saharan Africa is accompanied by increasing HIV-1 drug resistance mutations in drug-naive patients. AIDS. 2011;25:2183-8.
128. Burda S, Viswanath R, Zhao J, et al. HIV-1 reverse transcriptase drug-resistance mutations in chronically infected individuals receiving or naive to HAART in Cameroon. J Med Virol. 2010;82:187-96.
129. Ragupathy V, Zhao J, Wood O, et al. Identification of new, emerging HIV-1 unique recombinant forms and drug resistant viruses circulating in Cameroon. Virol J. 2011;8:185.
130. Soares E, Makamche M, Siqueira J, et al. Molecular diversity and polymerase gene genotypes of HIV-1 among treatment-naive Cameroonian subjects with advanced disease. J Clin Virol. 2010;48:173-9.
131. Vessiere A, Nerrienet E, Kfutwah A, et al. HIV-1 pol gene polymorphism and antiretroviral resistance mutations in drug-naive pregnant women in Yaounde, Cameroon. J Acquir Immune Defic Syndr. 2006;42:256-8.
132. Oliveira V, Bartolo I, Borrego P, et al. Genetic diversity and drug resistance profiles in HIV type 1- and HIV type 2-infected patients from Cape Verde Islands. AIDS Res Hum Retroviruses. 2012;28:510-22.
133. Moussa S, Pinson P, Pelembi P, et al. First data on HIV-1 resistance mutations to antiretroviral drugs in Central African Republic. AIDS Res Hum Retroviruses. 2010;26:1247-8.
134. Marechal V, Jauvin V, Selekon B, et al. Increasing HIV type 1 polymorphic diversity but no resistance to antiretroviral drugs in untreated patients from Central African Republic: a 2005 study. AIDS Res Hum Retroviruses. 2006;22:1036-44.
135. Charpentier C, Gody J, Mbitikon O, et al. Virological response and resistance profiles after 18 to 30 months of first- or second-/third-line antiretroviral treatment: A cross-sectional evaluation in HIV type 1-infected children living in the Central African Republic. AIDS Res Hum Retroviruses. 2012;28:87-94.
136. Pere H, Charpentier C, Mbelesso P, et al. Virological response and resistance profiles after 24 months of first-line antiretroviral treatment in adults living in Bangui, Central African Republic. AIDS Res Hum Retroviruses. 2012;28:315-23.
137. Koyalta D, Charpentier C, Beassamda J, et al. High frequency of antiretroviral drug resistance among HIV-infected adults receiving first-line highly active antiretroviral therapy in N'Djamena, Chad. Clin Infect Dis. 2009;49:155-9.
138. Hanson D, Adje-Toure C, Talla-Nzussouo N, et al. HIV type 1 drug resistance in adults receiving highly active antiretroviral therapy in Abidjan, Cote d'Ivoire. AIDS Res Hum Retroviruses. 2009;25:489-95.
139. Coffie P, Ekouevi D, Chaix M, et al. Maternal 12-month response to antiretroviral therapy following prevention of mother-to-child transmission of HIV type 1, Ivory Coast, 2003-2006. Clin Infect Dis. 2008;46:611-21.
140. Toni T, Masquelier B, Minga A, et al. HIV-1 antiretroviral drug resistance in recently infected patients in Abidjan, Cote d'Ivoire: A 4-year survey, 2002-2006. AIDS Res Hum Retroviruses. 2007;23:1155-60.
141. Toni T, Asahchop E, Moisi D, et al. Detection of human immunodeficiency virus (HIV) type 1 M184V and K103N minority variants in patients with primary HIV infection. Antimicrob Agents Chemother. 2009;53:1670-2.
142. Djoko C, Rimoin A, Vidal N, et al. High HIV type 1 group M pol diversity and low rate of antiretroviral resistance mutations among the uniformed services in Kinshasa, Democratic Republic of the Congo. AIDS Res Hum Retroviruses. 2011;27:323-9.
143. Muwonga J, Butel C, Vidal N, et al. Resistance to antiretroviral drugs in treated and drug-naive patients in the Democratic Republic of Congo. J Acquir Immune Defic Syndr. 2011;57:27-33.
144. Djoko C, Wolfe N, Vidal N, et al. HIV type 1 pol gene diversity and genotypic antiretroviral drug resistance mutations in Malabo, Equatorial Guinea. AIDS Res Hum Retroviruses. 2010;26:1027-31.
145. Caron M, Makuwa M, Souquiere S, Descamps D, Brun-Vezinet F, Kazanji M. Human immunodeficiency virus type 1 seroprevalence and antiretroviral drug resistance-associated mutations in miners in Gabon, central Africa. AIDS Res Hum Retroviruses. 2008;24:1225-8.
146. Vergne L, Malonga-Mouellet G, Mistoul I, et al. Resistance to antiretroviral treatment in Gabon: need for implementation of guidelines on antiretroviral therapy use and HIV-1 drug resistance monitoring in developing countries. J Acquir Immune Defic Syndr. 2002;29:165-8.
147. Delgado E, Ampofo W, Sierra M, et al. High prevalence of unique recombinant forms of HIV-1 in Ghana: molecular epidemiology from an antiretroviral resistance study. J Acquir Immune Defic Syndr. 2008; 48:599-606.
148. Charpentier C, Bellecave P, Cisse M, et al. High prevalence of antiretroviral drug resistance among HIV-1-untreated patients in Guinea-Conakry and in Niger. Antivir Ther. 2011;16:429-33.
149. Derache A, Traore O, Koita V, et al. Genetic diversity and drug resistance mutations in HIV type 1 from untreated patients in Bamako, Mali. Antivir Ther. 2007;12:123-9.
150. Marcelin A, Jarrousse B, Derache A, et al. HIV drug resistance after the use of generic fixed-dose combination stavudine/lamivudine/nevirapine as standard first-line regimen. AIDS. 2007;21:2341-3.
151. Germanaud D, Derache A, Traore M, et al. Level of viral load and antiretroviral resistance after 6 months of non-nucleoside reverse transcriptase inhibitor first-line treatment in HIV-1-infected children in Mali. J Antimicrob Chemother. 2010;65:118-24.
152. Ajoge H, Gordon M, Ibrahim S, Shittu O, Ndung'u T, Olonitola S. Drug resistance pattern of HIV type 1 isolates sampled in 2007 from therapy-naive pregnant women in North-Central Nigeria. AIDS Res Hum Retroviruses. 2012;28:115-18.
153. Chaplin B, Eisen G, Idoko J, et al. Impact of HIV type 1 subtype on drug resistance mutations in Nigerian patients failing first-line therapy. AIDS Res Hum Retroviruses. 2011;27:71-80.
154. Hawkins C, Chaplin B, Idoko J, et al. Clinical and genotypic findings in HIV-infected patients with the K65R mutation failing first-line antiretroviral therapy in Nigeria. J Acquir Immune Defic Syndr. 2009;52:228-34.
155. Etiebet M, Shepherd J, Nowak R, et al. Tenofovir-based regimens associated with less drug resistance in HIV-1-infected Nigerians failing first-line antiretroviral therapy. AIDS. 2013;27:553-61.
156. Taiwo B, Idoko J, Marcelin A, et al. Patient-selected treatment partners did not protect against drug resistance during first-line NNRTI-based HAART in a randomized trial. J Acquir Immune Defic Syndr. 2010;54:563-5.
157. Ojesina A, Mullins C, Imade G, et al. Characterization of HIV type 1 reverse transcriptase mutations in infants infected by mothers who received peripartum nevirapine prophylaxis in Jos, Nigeria. AIDS Res Hum Retroviruses. 2007;23:1587-92.
158. Vergne L, Kane C, Laurent C, et al. Low rate of genotypic HIV-1 drug-resistant strains in the Senegalese government initiative of access to antiretroviral therapy. AIDS. 2003;17(Suppl 3):S31-8.
159. Diop-Ndiaye H, Toure-Kane C, Leye N, et al. Antiretroviral drug resistance mutations in antiretroviral-naive patients from Senegal. AIDS Res Hum Retroviruses. 2010;26:1133-8.
160. Hamers R, Wensing A, Back N, Arcilla M, Frissen J. Multi-nucleoside reverse transcriptase inhibitor resistant HIV type-1 in a patient from Sierra Leone failing stavudine, lamivudine and nevirapine. Antivir Ther. 2011;16:115-18.
161. Yaotse D, Nicole V, Roch N, Mireille P, Eric D, Martine P. Genetic characterization of HIV-1 strains in Togo reveals a high genetic complexity and genotypic drug-resistance mutations in ARV naive patients. Infect Genet Evol. 2009;9:646-52.
162. Dagnra A, Vidal N, Mensah A, et al. High prevalence of HIV-1 drug resistance among patients on first-line antiretroviral treatment in Lome, Togo. J Int AIDS Soc. 2011;14:30.