High prevalence of HIV-1 drug resistance among patients on first-line antiretroviral treatment in Lomé, Togo

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Abstract

**Background:** With widespread use of antiretroviral (ARV) drugs in Africa, one of the major potential challenges is the risk of emergence of ARV drug-resistant HIV strains. Our objective is to evaluate the virological failure and genotypic drug-resistance mutations in patients receiving first-line highly active antiretroviral therapy (HAART) in routine clinics that use the World Health Organization public health approach to monitor antiretroviral treatment (ART) in Togo.

**Methods:** Patients on HAART for one year (10-14 months) were enrolled between April and October 2008 at three sites in Lomé, the capital city of Togo. Plasma viral load was measured with the NucliSENS EasyQ HIV-1 assay (Biomérieux, Lyon, France) and/or a Generic viral load assay (Biocentric, Bandol, France). Genotypic drug-resistance testing was performed with an inhouse assay on plasma samples from patients with viral loads of more than 1000 copies/ml. CD4 cell counts and demographic data were also obtained from medical records.

**Results:** A total of 188 patients receiving first-line antiretroviral treatment were enrolled, and 58 (30.8%) of them experienced virologic failure. Drug-resistance mutations were present in 46 patients, corresponding to 24.5% of all patients enrolled in the study. All 46 patients were resistant to non-nucleoside reverse-transcriptase inhibitors (NNRTIs): of these, 12 were resistant only to NNRTIs, 25 to NNRTIs and lamivudine/emtricitabine, and eight to all three drugs of their ARV regimes. Importantly, eight patients were already predicted to be resistant to etravirine, the new NNRTI, and three patients harboured the K65R mutation, inducing major resistance to tenofovir.

**Conclusions:** In Togo, efforts to provide access to ARV therapy for infected persons have increased since 2003, and scaling up of ART started in 2007. The high number of resistant strains observed in Togo shows clearly that the emergence of HIV drug resistance is of increasing concern in countries where ART is now widely used, and can compromise the long-term success of first- and second-line ART.

Background

Implementation of antiretroviral therapy (ART) is recognized as a public health priority in resource-limited countries. In order to allow a rapid roll out of ART, countries use the World Health Organization (WHO) public health approach, which proposes standard first-line therapy, together with treatment initiation and switch guided by clinical disease progression and, where possible, with monitoring of CD4 cell counts [1]. The standard therapy consists of two nucleoside reverse transcriptase inhibitors (NRTIs) (3TC+AZT/d4T) and one non-nucleoside reverse transcriptase inhibitor (NNRTI) (EFV/NVP).

In 2010, these guidelines were revised and recommended less toxic drugs in first-line therapy by replacing stavudine (d4T) with tenofovir (TDF) [2]. Although a more strategic monitoring for ART efficacy is now also recommended, virological monitoring is still not
feasible for the majority of patients on ART in sub-Saharan Africa due to the absence of adequate laboratory facilities and insufficient financial means. In addition, deficiencies in health systems and resources, such as unreliable supply systems, storage and the lack of qualified personnel to prescribe and monitor patients on ART, could also create conditions for accelerated development of HIV resistance to antiretroviral (ARV) drugs. It is thus important to evaluate the outcome and effectiveness of ART programmes in routine care settings in resource-limited countries to evaluate whether the empirical second-line treatment recommended by WHO would still be effective.

Togo is a small country of 5.5 million inhabitants, located in west Africa, with an estimated HIV prevalence of around 3% in the general population [3]. Scaling up of ART started in 2007, and approximately 7000 HIV-1-infected individuals were receiving ART by the end of 2007. Treatment became free of charge by the end of 2008 and, today, more than 17,000 people are receiving ART, which corresponds to coverage of 33%. Here we describe virological outcome and emergence of drug resistance in a cross-sectional study among HIV-1-infected patients treated according to the national guidelines in hospitals in Lomé, the capital city of Togo.

**Methods**

A total of 188 HIV-1-positive patients receiving first-line ART for 12 months (+/-2 months) were consecutively enrolled between April and October 2008 in three sites in Lomé: the University Hospital Tokoin; and two non-governmental organizations for HIV care, (EVT (Espoir Vie Togo) and CRIPS (Centre de Réflexion et d’Initiative pour la Promotion de la Santé). The study was approved by the National Ethics Comitee and Ministry of Health (N°0269/2007/MS/DGS/DPLET/CBRS). Only patients who declared that they were ARV treatment naïve prior to the start of first-line treatment and those without prior use of ARVs for prevention of mother to child transmission of HIV were included in this study. After written informed consent, whole blood was collected and plasma was separated from cells by centrifugation at 3000rpm for five minutes and stored at -80°C in three aliquots.

Whole blood less than six hours old was used to determine the CD4 lymphocyte count using a FACSCALIBUR flow cytometer (Becton Dickinson, San Jose, CA). Plasma viral load was measured with the NuclisENS EasyQ HIV-1 assay (Biomérieux, Lyon, France) and/or a Generic viral load assay (Biocentric, Bandol, France) [4]; the detection limits of the tests are 50 and 300 copies/ml, respectively. Genotypic drug-resistance testing was performed on samples with HIV-1 RNA levels equal to or above 1000 copies/ml using a previously described in-house assay [5]. Amino acid sequences were analyzed for the presence of mutations in protease and RT genes with the drug-resistance interpretation algorithm from ANRS (version July 2010) (http://www.hivfrenchresistance.org/). HIV-1 subtypes/CRFs were determined by phylogenetic tree and recombination analysis as previously described [6].

**Results**

During the study period, 580 HIV-1-infected patients attended one of the three clinics for their follow-up visit at M12, and a total of 188 were included in this study. The median duration of ARV therapy prior to study enrollment was 12 months, ranging from 10 to 14 months. The median age of patients was 37 years (IQR 32-43), and only 66 (35.1%) were male (Table 1). National guidelines for patient monitoring recommend monthly clinical visits and CD4 counts at start and every six months. CD4 counts were available for 160 patients at treatment initiation; a median CD4 cell count of 100 cells/mm³ (IQR 54-173) was seen, which increased to a median of 293 cells/mm³ (IQR 188-431) among the same 160 patients at the time of enrolment in this study, i.e., about 12 months later.

However, CD4 count increases were lower for the patients with virological failure, i.e., from 98 cells/mm³ (IQR 97-154) to 121 cells/mm³ (IQR 50-249) versus 112

| Characteristic                              | Patients (n = 188) Number (%) |
|--------------------------------------------|-------------------------------|
| Age, median years                          | 37 (IQR 32-43)               |
| Male sex                                   | 66 (35.1)                    |
| Treatment interruption (days)              |                               |
| [1-30]                                     | 82 (43.6)                    |
| >30                                        | 22 (11.7)                    |
| Total                                      | 104 (55.3)                   |
| CD4 lymphocyte at enrolment (n = 160)      |                               |
| CD4 count, median cells/mm³                | 100 (IQR 54-173)             |
| CD4 lymphocyte at end point (n = 160)      |                               |
| CD4 count, median cells/mm³                | 293 (IQR 188-431)            |
| Viral load at end point ≥1000 copies/ml    | 58 (30.9)                    |
| Genotypic drug-resistance mutations        | 46 (24.5)                    |
| HIV subtypes/CRFs                          |                               |
| CRF02                                      | 26                            |
| CRF06                                      | 6                             |
| G                                          | 1                             |
| Unique recombinant forms a                 | 13                            |

a The following unique recombinant forms were observed: CRF02/A3 (n = 2), CRF02/CRF06 (n = 1), CRF02/U (n = 2), G/A (n = 1), G/CRF02 (n = 1), G/CRF06 (n = 1), G/CRF02 (n = 2), CRF02/CRF06/U (n = 1), J/K/U (n = 1), U = Unknown subtype/CRF.
cells/mm³ (IQR 54-176) to 347 cells/mm³ (IQR 269-475). With the exception of two patients, all received the generic drug, Triomune, a fixed-dose combination of stavudine (d4T), lamivudine (3TC) and nevirapine (NVP). The other two patients received AZT+3TC+EFV or AZT+3TC+IDV. Importantly, during the 12-month ART period, 104 (52.7%) patients had interrupted their treatment; the duration of this interruption ranged from one to 168 days, and for 22 patients, this period exceeded one month. Treatment interruption was reported for patients with and without virological failure at comparable rates.

For 58 (30.8%) patients, plasma viral load (VL) was above 1000 copies/ml, and for nine of them, VL was between 1000 and 5000 copies/ml. Genotypic drug-resistance testing analyses were done on 56 samples for which sufficient material was available. Mutations conferring resistance to NRTIs were detected in 46 of 56 (82.2%) patients with VLs above 1000 copies/ml, including seven of the nine patients with VLs between 1000 and 5000 copies/ml. This corresponds to at least 24.5% of patients receiving ART for 12 months.

Details of the drug-resistance profiles and corresponding patient characteristics are shown in Table 2. All patients were resistant to NNRTIs: 12 were resistant only to NNRTIs, with the remainder resistant to NNRTIs and other drugs. Among the NNRTI-associated resistance mutations, 29 (60.4%) occurred at position Y181, 17 (35.4%) at K103 and 10 (20.8%) at G190 (Table 2). V106A/M, K101E and Y188C/L were noted in four, three and two patients, respectively. Importantly, eight patients were already predicted to be resistant to etravirine, the new NNRTI, either because they harboured the single Y181V mutation (n = 3) or due to the presence of both Y181C and H221Y mutations (n = 5). Among the 46 ARV-resistant patients, 25 also harboured the M184V mutation conferring resistance to 3TC/FTC; among them, eight patients were also resistant to the other NRTI drug in their regimen because of the high number of TAMs (n = 4), or the presence of the Q151M (n = 1) or the K65R (n = 3) mutation. This implied that they were resistant to all three drugs of their ARV regimes.

The presence of the K65R also means that tenofovir (TDF) will not be effective when used in the second-line regime, and the Q151M mutation commonly confers multi-drug resistance to NRTIs (AZT, ABC, ddi and d4T). In seven patients, the presence of one or two NRTI mutations (M41L, D67N) was also seen, but this had not yet resulted in drug resistance. Two patients had virus mutations indicative of the TAM-1 profile (M41L, L210W, T215S), and two of the TAM-2 profile (D67N, K70R, T215F, K219Q/R/E). No major mutations were seen in the protease gene.

The predominant HIV-1 variant in this study population was CRF02_AG (n = 26, 56.5%). Other variants were CRF06_cpx (n = 6, 13%), subtype G (n = 1, 2.1%), and 13 (28.3%) were unique recombinant forms.

Scaling up highly active antiretroviral therapy (HAART) to achieve universal access is the current priority of WHO and the Joint United Nations Programme on HIV/AIDS (UNAIDS). Several cohort studies, using virological monitoring, have shown that ART treatment in resource-poor settings has efficacy rates similar to those reported for developed countries [7-12]. However, the few studies reporting on ART using the public health approach showed more contrasted results, with virological success after 12 months ranging from 50% to more than 90% [13,14]. But among these patients with virological failure, a significant proportion can be due to adherence problems, as shown in a study in Cameroon, where only 25% of patients with VLs over 1000 copies/ml were resistant to ARVs after 12 months [15].

In contrast, in this study in Togo, more than 80% of patients with virological failure at M12 were already resistant to ARVs, corresponding to 24.5% of all the patients enrolled in this study. Moreover, since the first-line regimen included two drugs with low genetic barriers, the majority of patients with HIV harbouring drug-resistance mutations were resistant to two of the three drugs from their regimens (25 of 46, or 54.3%); eight of 46 (17.4%) were resistant to all drugs in their ARV treatments. A total of 11 (23.9%) patients already harboured mutations conferring resistance to drugs for second-line regimes, such as TDF (n = 3) or the new NNRTI, etravirine (n = 8).

This is in agreement with observations from a recent study in Malawi, which also showed clearly that when only clinical and CD4 count cell criteria are used to monitor first-line ART failure, extensive NRTI and NNRTI resistance emerges, with 23% patients having resistance profiles that compromise second-line therapy [16]. Importantly, our estimates of drug resistance in treated patients in Togo are most likely minimal estimates because we used a cross-sectional approach and only patients who are still under treatment were studied. Our study does not provide any information on how many patients dropped out of care or died and how many of those patients harbour drug-resistance mutations. However, the observed information is useful for clinicians managing patients and can serve as an indicator of ARV programme efficiency in patients still on treatment.

In Togo, efforts to provide access to ARV therapy for infected persons have increased since 2003, and scaling up of ART started in 2007. However, during the scaling-up period, the national programme encountered...
| ID     | Age | Sex  | CD4 (cells/mm³) | Viral Drug-resistance Mutations | Predictions of high level resistance to following ARVs |
|--------|-----|------|----------------|-------------------------------|-------------------------------------------------------|
| T3003  | 28  | F    | 175            | M184V                         | EFV/NVP, 3TC/FTC, D4T, AZT                            |
| T3008  | 32  | F    | 30 36          | M184V (A98G), K103N            | EFV/NVP, 3TC/FTC                                      |
| T3013  | 23  | M    | 21 145         | M184V (A98G), K103N            | EFV/NVP, 3TC/FTC                                      |
| T3016  | 67  | M    | nt             | M184V (A98G), K103N            | EFV/NVP, 3TC/FTC                                      |
| T3023  | 32  | F    | 57 112         | M184V (A98G), K103N            | EFV/NVP, 3TC/FTC                                      |
| T3024  | 37  | F    | 276 255        | M184V (A98G), K103N            | EFV/NVP, 3TC/FTC                                      |
| T3037  | 47  | M    | 97 490         | M184V (A98G), K103N            | EFV/NVP, 3TC/FTC                                      |
| T3040  | 60  | F    | 154 209        | M184V (A98G), K103N            | EFV/NVP, 3TC/FTC                                      |
| T3042  | 36  | M    | 10 106         | M184V (A98G), K103N            | EFV/NVP, 3TC/FTC                                      |
| T3046  | 42  | M    | 348 218        | M184V (A98G), K103N            | EFV/NVP, 3TC/FTC                                      |
| T3050  | 34  | M    | 41 84          | M184V (A98G), K103N            | EFV/NVP, 3TC/FTC                                      |
| T3052  | 42  | F    | 35 84          | M184V (A98G), K103N            | EFV/NVP, 3TC/FTC                                      |
| T3055  | 35  | M    | 118 40         | M184V (A98G), K103N            | EFV/NVP, 3TC/FTC                                      |
| T3056  | 31  | F    | 34 72          | M184V (A98G), K103N            | EFV/NVP, 3TC/FTC                                      |
| T3058  | 30  | F    | 152 339        | M184V (A98G), K103N            | EFV/NVP, 3TC/FTC                                      |
| T3060  | 36  | F    | 98 288         | M184V (A98G), K103N            | EFV/NVP, 3TC/FTC                                      |
| T3061  | 33  | M    | 72 12          | M184V (A98G), K103N            | EFV/NVP, 3TC/FTC                                      |
| T3062  | 33  | M    | 70 13          | M184V (A98G), K103N            | EFV/NVP, 3TC/FTC                                      |
| T3064  | 39  | M    | 147 365        | M184V (A98G), K103N            | EFV/NVP, 3TC/FTC                                      |
| T3065  | 39  | M    | 57 112         | M184V (A98G), K103N            | EFV/NVP, 3TC/FTC                                      |
| T3066  | 35  | M    | 99 66          | M184V (A98G), K103N            | EFV/NVP, 3TC/FTC                                      |
| T3068  | 41  | M    | 118 40         | M184V (A98G), K103N            | EFV/NVP, 3TC/FTC                                      |
| T3070  | 31  | F    | 64 310         | M184V (A98G), K103N            | EFV/NVP, 3TC/FTC                                      |
| T3072  | 30  | F    | 154 209        | M184V (A98G), K103N            | EFV/NVP, 3TC/FTC                                      |
| T3074  | 35  | M    | 70 13          | M184V (A98G), K103N            | EFV/NVP, 3TC/FTC                                      |
| T3075  | 32  | F    | 72 12          | M184V (A98G), K103N            | EFV/NVP, 3TC/FTC                                      |
| T3076  | 30  | F    | 154 209        | M184V (A98G), K103N            | EFV/NVP, 3TC/FTC                                      |
| T3078  | 33  | M    | 72 12          | M184V (A98G), K103N            | EFV/NVP, 3TC/FTC                                      |

**Table 2** Details of observed drug mutations and prediction of resistance to ARVs according to ANRS algorithm (version July 2010) and corresponding patient characteristics, CD4 counts and viral load values.
Table 2 Details of observed drug mutations and prediction of resistance to ARVs according to ANRS algorithm (version July 2010) and corresponding patient characteristics, CD4 counts and viral load values (Continued)

| C7030 | 30  | F  | 190 | 603 | 351  | G190AG | EFV/NVP |
|-------|-----|----|-----|-----|------|--------|---------|
| C7044 | 55  | F  | 204 | 3.38| -    | M184V  | Y181C, H221Y | ETV, EFV/NVP, 3TC/FTC |

Viral load is expressed as log_{10} copies/mL. The abbreviations are for the following drugs: AZT - zidovudine; 3TC - lamivudine; FTC - emtricitabine; ddI - didanosine; d4T - stavudine; ABC - abacavir; TDF - tenofovir; EFV - efavirenz; NVP - nevirapine; ETV - etravirine

problems with stock management involving ARV drug substitution with the same molecules, administered separately as individual pills instead of as fixed-dosed combinations, or even interruption of the treatment.

Overall, our study shows major problems with the ART programme in Togo during the first year of scaling up HAART in the country, but does not reflect the situation in Togo three years later, which could be different. In a previous study, we reported also that 10% of recently diagnosed ARV-naive HIV-1 positive patients in 2007 were infected with HIV strains that already harboured a drug-resistance mutation [6]. However, the possibility cannot be excluded that some of the patients included in this and our previous study [6] were not ART naive and already harboured ARV-resistant strains because this was based on self-reported information by the patients.

Conclusions

Our results show clearly that the emergence of HIV drug resistance is of increasing concern in countries where ART is now widely used, and can compromise long-term success in treatment outcomes. Since individual patient monitoring for viral load and drug resistance is not yet possible, the system that WHO (HIVRESNET) has established for the surveillance of transmitted drug resistance and the monitoring of ART resistance at sentinel sites should be implemented in order to inform health authorities on the efficiency of first- and second-line ART and allow recommendations on future ART strategies [17]. The high number of resistant strains observed in Togo among ARV-naive patients and patients on ART at the onset of ART scaling up in the country needs further attention, and additional studies are needed to evaluate actual drug-resistance rates.

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Authors’ contributions

AYD and NV carried out the viral load assays, genotypic drug-resistance test and phylogenetic analysis. MM organized quality assurance for viral load between different sites. AM, AP, KO and MS enrolled patients and collected data on patient history. PP, AS, AYD, MPD, MP and ED participated in the design of the study. AYD, MPD and PP coordinated the study. AYD, NV, ED and MP drafted the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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