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Virological outcome among HIV-1 infected patients on first-line antiretroviral treatment in semi-rural HIV clinics in Togo

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Abstract

Background: Access to antiretroviral treatment (ART) in resource-limited countries has increased significantly but scaling-up ART into semi-rural and rural areas is more recent. Information on treatment outcome in such areas is still very limited notably due to additional difficulties to manage ART in these areas.

Results: 387 HIV-1 infected adults (≥18 years) were consecutively enrolled when attending healthcare services for their routine medical visit at 12 or 24 months on first-line ART in five HIV care centers (four semi-rural and one rural). Among them, 102 patients were on first-line ART for 12 ± 2 months (M12) and 285 for 24 ± 2 months (M24). Virological failure was observed in 70 (18.1%) patients ranging from 13.9 to 31.6% at M12 and from 8.1 to 22.4% at M24 across the different sites. For 67/70 patients, sequencing was successful and drug resistance mutations were observed in 65 (97%). The global prevalence of drug resistance in the study population was thus at least 16.8% (65/387). Moreover, 32 (8.3%) and 27 (6.9%) patients were either on a completely ineffective ART regime or with only a single drug active. Several patients accumulated high numbers of mutations and developed also cross-resistance to abacavir, didanosine or the new NNRTI drugs like etravirine and rilpivirine.

Conclusion: The observations on ART treatment outcome from ART clinics in semi-rural areas are close to previous observations in Lomé, the capital city suggesting that national ART-programme management plays a role in treatment outcome.

Keywords: HIV, Antiretroviral treatment, Drug resistance, Semi-rural, Public health, Togo, Africa

Findings

Background

Scale-up of antiretroviral treatment (ART) programs in resource-limited countries was possible because standardized first and second line antiretroviral (ARV) combinations and clinical and/or immunological criteria to start and monitor ART were used as recommended by WHO [1]. However, heterogeneous treatment outcomes have been observed in the national ART programs from different countries, most likely related to ART-programme management [2]. As such, virological failure can range from less than 3 % to more than 20 % in patients on ART for 12 or 24 months [2–4].

In Togo, a country of six million inhabitants in West Africa, scaling-up of ART started in 2007 in Lomé, the capital city, and has expanded to semi-rural areas in 2008. In 2013, almost 50 % of patients who were in need for ART according to WHO guidelines from 2010 (CD4 count <350) were receiving ART [5]. Previous studies in ART clinics in Lomé showed high virological failure related to ARV drug resistance, i.e. in 13 to 25 % of the patients receiving ART for 12 or 24 months [2, 6]. Given the additional difficulties to manage ART in these areas
(distances to clinics, scarce human resources, drug stock-outs, etc.) together with high rates of ARV drug resistance in the capital city, it was important to evaluate also virological outcome and emergence of drug resistance in ART clinics located in semi-urban and rural areas in Togo.

Methods

Study sites and population
A cross-sectional study was conducted in 2012 between January and July in five HIV care centers that administer ARV drugs and monitor treatment. They were located in four semi-rural cities: Aného (AN), Kpalimé (KP), Atakpamé (AT) and Kara (KA) at respectively 60, 120, 160 and 410 km from Lomé, the capital city, and in one rural city, Kouvé (KO) at 70 km distance from Lomé (Fig. 1). HIV-1 infected adults (>18 years) were consecutively enrolled when attending clinics for their routine medical visit at 12 ± 2 months or 24 ± 2 months on first-line ART. This study was approved by the National Ethics Committee (nº751/2014/MS/CAB/DGS/DPLET/CBRS). Informed consent was obtained from each participating patient. Questionnaires were used to collect epidemiological and demographic information and ART history was obtained from on-site medical records. Whole blood was drawn and plasma was separated by centrifugation. Plasma aliquots were stored at −20 °C for maximum 1 week on site and were subsequently transported by road in a cool box to the Laboratoire de Biologie Moléculaire et d’Immunologie (BIOLIM/FSS-UL) where they were stored at −80 °C until use.

Virological analyses

HIV-1 viral load (VL) was determined with EasyQ HIV assay (Biomerieux, Capronne, France) or RealTime m2000rt (Abbott Pack, IL, USA) in Lomé (BIOLIM/FSS-UL). According to WHO recommendations, genotypic drug resistance testing was done in a WHO accredited laboratory (IRD, Montpellier, France) on patients with VL ≥1000 copies/ml. Protease and partial Reverse Transcriptase (RT) were amplified with the in-house protocol from the Agence Nationale de Recherche sur le Sida et les Hépatites en France (ANRS) [2, 7]. Drug resistance mutations (DRM) were identified using the ANRS interpretation algorithm, version 24 [7]. The newly reported sequences are available in GenBank under the following accession numbers: KR047793–KR047859.

Results

A total of 387 patients were consecutively enrolled during their follow-up visit at 12 ± 2 (M12, n = 102) or 24 ± 2 (M24, n = 285) months on ART. Table 1 shows patients characteristics at each site. Overall, more women were enrolled than men: 84/102 (82.4 %) at M12 and 205/285 (71.9 %) at M24. The median age of patients was 36 (IQR 31–42) and 39 years (IQR 33–45) at M12 and M24, respectively. More than 97 % (277/285) of patients have been exposed to the following drugs in their first line regimen: stavudine (d4T) and/or zidovudine (AZT) plus lamivudine (3TC) plus nevirapine (NVP) and/or efavirenz (EFV). For 302 (78 %) patients, d4T was replaced by AZT because national guidelines were changed. Only eight (2.8 %) patients switched to tenofovir (TDF) instead of AZT or d4T. At ART initiation the overall median CD4 count/mm³ was 176 (IQR 86–261) and 152 (IQR 88–219) for the patients who were on ART for 12 ± 2 and 24 ± 2 months, respectively. Overall, 153/373 (41.1 %) and 220/373 (58.9 %) of the patients were in WHO stages 1 or 2 and WHO stages 3 or 4, respectively at ART start. However, CD4 counts and WHO stages at ART initiation could vary across the different sites (Table 1).

Seventy patients (18.1 %; CI95 14.5–22.2 %) had VL >1000 copies/ml; 20/102 (19.6 %; CI95 13.4–29.2 %) at M12 and 50/285 (17.5 %; CI95 13.5–22.4 %) at M24. Virological failure ranged from 13.9 to 31.6 % at M12 and from 8.1 to 22.4 % at M24. For 67 (95.7 %) patients, sequencing was successful and DRM were observed in 65 (97 %) of them; i.e. 20/20 at M12 and 45/47 at M24. Among the 65 drug resistant HIV strains, 59 were resistant to NRTIs and NNRTIs, two to NRTIs only and four to NNRTIs only. The global prevalence of drug resistance in the study population was thus at least 16.8 % (13.4–20.9 %, 95 % CI) (65/387), but 27 patients (6.9 %; 4.8–9.9 %, 95 % CI) were infected with HIV strains resistant to two of the three first line ARVs and 32 (8.3 %; 5.9–11.4 %, 95 % CI) to all three first line ARVs.

As expected, the observed DRM were associated with the drugs used in first-line regimens (Table 2). M184 V selected by 3TC was the most frequent NRTI mutation, 56/65 (86.2 %). Frequent TAMs included K65R and K219E/Q and T215Y/F. The K65R mutation was seen in two patients. One-third of the patients accumulated at least three NNRTI mutations, and several patients were already predicted to be resistant to ABC (n = 12), DDI (n = 2) or tenofovir (TDF) (n = 3). Among NNRTI mutations, Y181C/Y and K103N were most frequently observed and 15 (23.1 %) patients accumulated at least three NNRTI mutations, with 31.5 (21.5 %) and 44 (67.7 %) that were predicted to be resistant to second line NNRTIs ETV and RPV, respectively.
Discussion
Overall, we showed that 18% of patients on ART for 12 or 24 months in semi-rural and rural ART clinics were on virological failure and almost all of them (97%) were infected with drug resistant HIV-1 strains. These observations are high and close to what has been noticed in previous studies from Lomé, the capital city; for example in a survey conducted about 1 year earlier in 2010/2011 using the same cross-sectional approach, 19% (124/642) of patients for 12 or 24 months on ART were infected with HIV drug resistant strains [2]. Our study confirms thus a high ART failure in Togo in general and which is higher than observed in other countries, when comparing with studies that used a similar approach [2]. Scale-up of ART started in 2007 in the capital city and was expanded to semi-rural areas in 2008. Between 2006 and 2012, the number of patients on ART increased from 6700 to 31,500 but tools to monitor patients did not follow this scale-up and training of medical personnel was insufficient to allow early detection of side effects of certain ARVs, evaluate adherence or recognize rapidly decline of clinical status. In addition, the national
| Characteristics                      | M12 |               | M24 |               |               | M12 |               | M24 |               | M24 |               |
|--------------------------------------|-----|---------------|-----|---------------|---------------|-----|---------------|-----|---------------|-----|---------------|
|                                      | Aného (AN) | Kpalimé (KP) | Atakpamé (AT) | Kara (KA) | Total | Aného (AN) | Kouvé (KO) | Kpalimé (KP) | Atakpamé (AT) | Kara (KA) | Total |
| Number of patients (n)               | 19  | 14            | 26  | 43            | 102            | 58  | 103          | 37  | 50            | 37  | 285            |
| Women (%)                            | 17 (89.5 %) | 13 (92.8 %) | 20 (76.9 %) | 34 (79.1 %) | 84 (82.4 %) | 42 (72.4 %) | 74 (71.9 %) | 26 (70.3 %) | 39 (78.0 %) | 24 (64.9 %) | 205 (71.9 %) |
| Median age years (IQR)               | 42 (35–51) | 38 (36–49)   | 35 (33–42) | 36 (31–40) | 35 (31–42) | 35 (31–42) | 38 (32–45) | 36 (30–46) | 37 (33–42) | 35 (31–42) | 39 (33–45) |
| WHO stages                           | 1/2 | 9/14 (64.3 %) | 15/24 (62.5 %) | 20/42 (47.6 %) | 46/99 (46.4 %) | 13/58 (22.4 %) | 24/102 (23.5 %) | 18/34 (52.9 %) | 39/43 (90.7 %) | 13/37 (35.1 %) | 107/274 (39.1 %) |
| CD4 counts at baseline (n)           | 18 (94.7 %) | 14 (100 %)   | 26 (100 %) | 43 (100 %) | 101 (100 %) | 56/58 (96.6 %) | 103/103 (100 %) | 31/37 (83.8 %) | 42/50 (84 %) | 35/37 (94.6 %) | 667/274 (93.7 %) |
| Median CD4 counts at baseline (IQR)  | 107 (86–181) | 109 (71–235) | 197 (111–277) | 202 (101–274) | 176 (86–261) | 134 (110–210) | 154 (75–232) | 120 (80–158) | 201 (167–242) | 135 (106–185) | 152 (88–219) |
| First line drugs n (%)               | AAZT‑3TC‑EFV | –             | 1 (3.8 %) | 1 (2.3 %) | 3 (2.9 %) | 1 (1.7 %) | 6 (5.8 %) | 2 (5.4 %) | 10 (20.0 %) | 3 (8.1 %) | 23 (81 %) |
|                                      | AAZT‑3TC‑NVP | –             | 1 (23.3 %) | 11 (10.8 %) | 7 (12.1 %) | –             | –             | –             | –             | 13 (46 %) |
|                                      | AAZT‑3TC‑NVP/EFV | –             | –             | –             | –             | –             | 2 (1.9 %) | –             | –             | –             | 2 (07 %) |
|                                      | D4T‑3TC‑NVP | 15 (53.5 %) | 7 (26.9 %) | 2 (4.7 %) | 15 (14.7 %) | 4 (6.9 %) | 3 (2.9 %) | –             | 1 (2.0 %) | 1 (2.7 %) | 9 (32 %) |
|                                      | D4T/AZT‑3TC‑NVP | 16 (84.2 %) | 7 (20.0 %) | 15 (57.7 %) | 28 (85.1 %) | 66 (64.7 %) | 43 (75.8 %) | 86 (83.5 %) | 32 (64.0 %) | 33 (89.2 %) | 226 (79.3 %) |
|                                      | D4T/AZT‑3TC‑NVP/EFV | –             | 2 (10.0 %) | 1 (3.8 %) | 3 (2.9 %) | 3 (5.2 %) | 1 (098 %) | 3 (81 %) | –             | –             | 7 (25 %) |
|                                      | D4T/AZT‑3TC‑NVP/EFV | –             | –             | 1 (3.8 %) | 1 (2.3 %) | 2 (1.9 %) | –             | 2 (19 %) | –             | –             | 2 (07 %) |
|                                      | TDF‑3TC‑NVP | 15 (53.5 %) | 7 (26.9 %) | 2 (4.7 %) | 15 (14.7 %) | 4 (6.9 %) | 3 (2.9 %) | –             | 1 (2.0 %) | 1 (2.7 %) | 9 (32 %) |
|                                      | TDF/AZT‑3TC‑NVP | –             | –             | –             | –             | –             | 1 (098 %) | –             | –             | –             | 1 (03 %) |
|                                      | AAZT‑3TC‑NVP/EFV | –             | –             | 1 (2.3 %) | 1 (099 %) | –             | 1 (099 %) | –             | –             | –             | 1 (03 %) |
|                                      | D4T/AZT‑3TC‑NVP/EFV | –             | –             | –             | –             | –             | 1 (098 %) | –             | –             | –             | 1 (03 %) |
|                                      | AAZT‑3TC‑NVP/EFV | –             | –             | –             | –             | –             | 1 (098 %) | –             | –             | –             | 1 (03 %) |
|                                      | TDF/AZT‑3TC‑NVP/EFV | –             | –             | –             | –             | –             | 1 (098 %) | –             | –             | –             | 1 (03 %) |
|                                      | VL > 1000 copies/ml (n %) | 3/14 (23.1 %) | 5/26 (19.2 %) | 6/43 (13.9 %) | 20/102 (19.6 %) | 13/58 (22.4 %) | 14/103 (13.6 %) | 11/37 (29.7 %) | 9/50 (180 %) | 3/37 (8.1 %) | 50/285 (17.5 %) |
| Obtained pol sequences (n/n tested)  | 6/6 | 3/3            | 5/5 | 6/6            | 20/20          | 14/14          | 10/11          | 8/9             | 23/28 (82.1 %) | 23/31 (74.2 %) | 45/50 (90.0 %) |
Table 1 continued

| Characteristics | M12 | M24 |
|-----------------|-----|-----|
|                 | Aného (AN) | Kpalimé (KP) | Atakpamé (AT) | Kara (KA) | Total | Aného (AN) | Kouvé (KO) | Kpalimé (KP) | Atakpamé (AT) | Kara (KA) | Total |
| Frequency of drug resistant HIV (n/n tested) | 6/6 | 3/3 | 5/5 | 6/6 | 20/20 | 12/12 | 13/14 | 10/10 | 7/8 | 3/3 | 45/47 |
| NRTI only       | 0   | 0   | 0   | 0   | 0/20 | 0     | 0     | 1     | 1   | 0   | 2    |
| NNRTI only      | 0   | 0   | 0   | 0   | 0/20 | 3     | 1     | 0     | 0   | 0   | 4    |
| NRTI + NNRTI    | 6   | 3   | 5   | 6   | 20/20 | 9     | 12    | 9     | 6   | 3   | 39   |
| Global drug resistance n (%) | 6/19 (31.6 %) | 3/14 (23.1 %) | 5/26 (19.2 %) | 6/43 (13.9 %) | 20/102 (19.6 %) | 12/58 (20.7 %) | 13/103 (12.6 %) | 10/37 (27.0 %) | 7/50 (14.0 %) | 3/37 (8.1 %) | 45/285 (15.8 %) |
| Resistance to 2 drugs of first line ART | 4 | 3 | 3 | 2 | 12/20 | 2 | 6 | 5 | 2 | 0 | 15/45 |
| Resistance to 3 drugs of first line ART | 2 | 0 | 2 | 4 | 8/20 | 7 | 6 | 5 | 4 | 3 | 25/45 |
| Cross-resistance to second line NNRTI | ETV | 1 | 0 | 1 | 1 | 3/20 | 3 | 3 | 3 | 1 | 1 | 11/45 |
| RPV             | 3   | 1   | 3   | 6   | 13/20 | 9     | 8     | 6     | 5   | 3   | 31/45 |
| Cross-resistance to other NRTIs | ABC | 2(1) | 0 | 2 | 1 | 3/20 | 2 | 1 | 3 | 1 | 2 | 9/45 |
| DDI             | 0   | 0   | 1   | 0   | 1/20 | 2     | 0     | 0     | 0   | 0   | 2/45 |
| TDF             | 0   | 0   | 1   | 0   | 1/20 | 1     | 1     | 0     | 0   | 0   | 2/45 |
Table 2  Drug resistance mutations to the first line antiretroviral drugs after 12 and 24 months on ART

| Patient code | Months on ART | NNRTI mutations | NRTI mutations | Subtype/CRF | Accession |
|--------------|---------------|-----------------|----------------|-------------|-----------|
| AN021        | 12            | Y181V           | M41LM, M184V, T215F | A3          | KR047796  |
| AN026        | 12            | A98S, Y181C, G190A | M41L, A62V, M184V, K219N | CRF02_AG | KR047798  |
| AN052        | 12            | K103KN          | M184V          | CRF06_cpx  | KR047805  |
| AN058        | 12            | V106A           | A62A, M184V    | CRF02_AG   | KR047807  |
| AN059        | 12            | K103N           | M41L, M184V, T215Y | CRF02_AG | KR047808  |
| AN074        | 12            | K101E, G190A    | M184V          | CRF06_cpx  | KR047810  |
| AT407        | 12            | K101E, G190A    | M41L, D67N, K70R, V75I, T215F, K219Q | URF | KR047840  |
| AT411        | 12            | Y181C, G190A    | M184V          | URF        | KR047841  |
| AT423        | 12            | K103N           | M184V          | CRF06_cpx  | KR047843  |
| AT426        | 12            | V90I, K101EQ, Y181C, G190S | K65R | CRF02_AG | KR047844  |
| AT477        | 12            | K103N           | M184I          | G           | KR047850  |
| KA305        | 12            | Y181C           | M41L, M184V    | CRF06_cpx  | KR047851  |
| KA308        | 12            | K103N, Y181C, H221Y | M184V, T215Y | CRF06_cpx  | KR047852  |
| KA348        | 12            | Y181C           | M184V          | CRF06_cpx  | KR047855  |
| KA350        | 12            | K101E, G190A    | M41L, M184V    | URF        | KR047856  |
| KA378        | 12            | Y181C           | M41L, M184V, L210W, T215Y | URF | KR047858  |
| KA379        | 12            | K103N, Y181C    | M184I          | CRF02_AG   | KR047859  |
| KP206        | 12            | A98S, K103N, P225H | M184V | C           | KR047826  |
| KP218        | 12            | K101EK, G190A   | M184V          | CRF06_cpx  | KR047829  |
| KP280        | 12            | K103N           | M184V          | CRF02_AG   | KR047837  |
| AN008        | 24            | V179I, Y181C, G190AG | –          | URF        | KR047793  |
| AN012        | 24            | K103N           | –              | CRF02_AG   | KR047794  |
| AN019        | 24            | Y181C, H221Y    | M41L, V75I, M184V, T215F | CRF02_AG | KR047795  |
| AN022        | 24            | Y181C           | M184V          | URF        | KR047797  |
| AN028        | 24            | A98S, Y181C     | D67N, K70R, T215F, K219E | CRF02_AG | KR047799  |
| AN032        | 24            | Y181C, G190AG, H221HY | –          | URF        | KR047800  |
| AN041        | 24            | K103N, Y181C    | A62V, K65R, K70T, V75I, F116Y, Q151M, M184V | CRF02_AG | CRF02_AG |
| AN043        | 24            | K101E, Y181C, G190A | M184V, T215F | CRF02_AG   | KR047802  |
| AN048        | 24            | Y181C           | D67N, K70R, T215F, K219E | CRF02_AG | KR047803  |
| AN049        | 24            | K103N           | M184V          | CRF06_cpx  | KR047804  |
| AN054        | 24            | K103N           | M41L, E44D, L74I, M184V, L210W, T215Y | CRF02_AG | KR047806  |
| AN068        | 24            | Y181C, H221Y    | M41LM, M184V, T215Y | CRF02_AG | KR047809  |
| AT400        | 24            | Y181C           | K70KR, M184V   | CRF02_AG   | KR047838  |
| AT403        | 24            | –               | M184V          | A3          | KR047839  |
| AT420        | 24            | K103N           | M184V          | CRF02_AG   | KR047842  |
| AT435        | 24            | Y181C, H221Y    | M41LM, D67DN, K70KR, T215Y, K219EK | CRF02_AG | KR047845  |
| AT442        | 24            | Y181C           | M184V, T215FST | CRF02_AG   | KR047846  |
| AT452        | 24            | Y181C           | M41L, M184V, T215Y | CRF02_AG | KR047847  |
| AT456        | 24            | K101E, G190A    | M184V, T215F   | CRF02_AG   | KR047848  |
| AT463        | 24            | –               | –              | CRF02_AG   | KR047849  |
| KA319        | 24            | A98S, K103N, Y181C | D67N, K70R, M184V, T215F, K219Q | URF | KR047853  |
| KA344        | 24            | K101E, G190A    | M41L, D67DN, K70KR, M184V, T215Y | G          | KR047854  |
| KA366        | 24            | K101E, Y181C, G190A | M41L, M184V, L210W, T215Y | URF        | KR047857  |
| KO100        | 24            | Y181C           | M41L, M184V, T215F | CRF06_cpx  | KR047811  |
| KO112        | 24            | K103N, P225H    | K70DEKN, M184V | CRF02_AG   | KR047812  |
| KO116        | 24            | K103N           | M184V          | URF        | KR047813  |
| KO122        | 24            | Y181C, H221Y    | M41L, D67N, K70R, M184V, T215Y | G          | KR047814  |
| KO130        | 24            | K103N, E138K    | M184V, T215F   | CRF02_AG   | KR047815  |
| KO137        | 24            | V179I, G190A, M230L | M184V, T215Y | A3          | KR047816  |
program encountered problems with stock management resulting in ARV drug substitution with the same molecules, administered separately as individual pills instead as a fixed dosed combination, or even interruption of the treatment. It is known that non-adherence and treatment interruption may favor emergence of drug resistance.

Today, only very few studies reported observations on ART outcome from semi-rural or rural areas in resource limited settings, especially from Africa [2, 8, 9]. In Cameroon, 10% of patients were infected with drug resistant HIV strains after a median of 12 months on ART in rural district hospitals at 50 to 150 km distance from Yaoundé, the capital city [10], which is close to rates observed in Yaoundé [2]. However, in a rural health center in Kolofata, at the extreme north of Cameroon at 1200 km from the capital city and with difficult connections, almost 30% of patients on ART (median of 24 months) were resistant to ARV drugs [11]. Another report showed equal proportions of drug resistance in urban and rural areas, between 9.2 to 15.9% after a median of 36 months on ART in Senegal, Mali and Guinea [12]. In rural and semi-rural settings in Gabon, 21% of patients were resistant after a median of 33 months on ART [13]. In a rural clinic in Tanzania, rates of drug resistance were low and ranged from 4 to 8% of patients after 1 or 2 years on ART, respectively [14]. Although, it is important to note that comparing results among the different studies mentioned above has to be taken with caution, because study design can differ as well as viral load capacities and techniques to identify virological failure.

Overall it seems that treatment outcome varies among countries, but within countries treatment outcome in semi-rural settings seem to be similar to those in urban settings except in extreme conditions. These observations are in line with the fact that national ART-programme management plays a role in treatment outcome in resource-limited countries [2]. It is important to note that we provided only information on the proportion of drug resistance in HIV infected patients who are still on ART and have no information on follow-up or mortality rates. Prospective studies where loss of follow-up are considered as treatment failures, would probable yield higher virological failure rates. Previous studies showed a higher mortality rate and loss of follow up in rural areas during the first 3 years [15].

Like in other reports on treatment outcome, several patients in our survey accumulated high numbers of mutations and developed also cross-resistance to potential second and/or third line drugs [16–18]. In addition these multi-drug resistant strains can also be transmitted and have a negative impact on future efficiency of first line regimens.

Conclusions

The observations on ART treatment outcome in semi-rural areas show high failure rate but are close to those in Lomé, the capital city. Lowering the rates of drug resistance represents a challenge for the country. The first goals will be to identify factors associated with drug resistance.

| Patient code | Months on ART | NNRTI mutations | NRTI mutations | Subtype/CRF | Accession |
|--------------|---------------|------------------|----------------|-------------|-----------|
| KO148        | 24            | K103N            | M184V          | CRF02_AG    | KO047817  |
| KO150        | 24            | K103N,Y181C      | M184V          | CRF02_AG    | KO047818  |
| KO158        | 24            | A98AG,K101E,Y181C| D67N,K70R,M184V,T215F,K219E | URF       | KO047819  |
| KO193        | 24            | K103N            | M184V          | CRF02_AG    | KO047820  |
| KO195        | 24            | Y181CY           | –              | CRF02_AG    | KO047821  |
| KO197        | 24            | V001,V179I,G190A | M184V          | A3          | KO047822  |
| KO200        | 24            | E138EG           | –              | URF         | KO047823  |
| KO203        | 24            | Y181C,H221Y      | M184V,T215T    | CRF02_AG    | KO047825  |
| KP202        | 24            | Y181C,H221Y      | M184V,T215T    | CRF02_AG    | KO047826  |
| KP210        | 24            | G190S            | M184V          | CRF02_AG    | KO047827  |
| KP213        | 24            | K103N            | M184V,T215T    | CRF02_AG    | KO047828  |
| KP221        | 24            | A98AS,K103N,E138Q | M41L,V75I,M184V,T215F | URF       | KO047830  |
| KP223        | 24            | K103N,Y181C,H221Y| M41L,D67N,K70R,V75I,M184V,T215F,K219E | CRF02_AG    | KO047831  |
| KP234        | 24            | K103N            | M41L,M184V     | CRF02_AG    | KO047832  |
| KP235        | 24            | V001,A98AG,E138Q,V179T | M184V          | CRF02_AG    | KO047833  |
| KP241        | 24            | Y181V,H221Y      | M41L,M184V,L210W,T215F | CRF02_AG    | KO047834  |
| KP243        | 24            | K101E,G190A      | M41L,D67N,M184V,L210W,T215F | URF       | KO047835  |
| KP253        | 24            | K103N            | M184V          | CRF02_AG    | KO047836  |
Authors’ contributions

AK and NV carried out the viral load assays, genotypic drug resistance testing and interpretation, and drafted the manuscript. PK, DK, PK, TN, DN, enrolled patients and collected data on patient history. AD, MS, AP, MPD, ED and MP conceived the study, participated in its design and coordination and wrote the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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