Evaluation of HIV-1 evolution and its role in development of antiretroviral drug resistance in Nairobi Cohort

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ABSTRACT

The treatment of HIV-1 infection with antiretroviral drugs has greatly improved the survival of those who are infected. However, HIV-1 diversity and drug resistance are major challenges in patient management, disease control and surveillance especially in resource-poor countries.

In this study, 188 blood samples were collected from Nairobi cohort and peripheral mononuclear cells (PBMCs) separated. Total proviral DNA was used in nested polymerase chain reaction to amplify 450*bp* HIV *env* C2V3, 288*bp* Integrase and env gp41 regions and directly sequenced . Generated sequences were aligned and phylogenetically analysed using known reference subtypes sequences and drug resistance mutations and substitutions determined.

Phylogenetic analysis based on env C2V3 region revealed A1 (59.6%), C (18.1%), D (10.6%), B (2.1%), G (2.1%), CRF02_AG (3.2%) and the rest of 6.9% were CRFs. In HIV-1 co-receptor switch showed R5 tropism (69.6%) while X4 (30.4%). In addition, 2.4% T97A that is associated with reduced susceptibility to Raltegravir and 26.2% had secondary mutations associated with resistance to intergrase inhibitors. In fusion inhibitors, the following mutations were detected; A316T/I323V (2.6%) combination, A316T (63%), I323V (1.1%) for Maraviroc, (10%) K305R, (3.2%) G321E, (35.1%) R315Q, (4.5%) K305R/R315Q, (62.8%) T320R for Vicriviroc and (1.6%) A316T+ K305R+ R315Q, (12.7%) A316T+R315Q, (3.2%) R3I5Q+A316T+I323V, (0.5%) R315+A316T+G321E for Maraviroc and Vicriviroc combinations. In addition, 4.2% intermediate resistance associated to Enfuvirtide was detected. The point mutations at;

N42S was detected in 16.7% of all the samples, while N42D was detected in 4.2%, S138L /T 3.1%, L44M 2.1% and 1% each for in the following mutations; N43I and L45V drug resistance mutations. In evolutionary rate; 12.5% had dNdS ration 1>, 88.5% dNdS ration < 1 and in those with dNdS ration ≠1.

The results indicate that HIV-1 subtypes in Nairobi cohort like the rest of the country, is predominated by HIV-1 subtype A1, though there could be possibity of an increase proportion of HIV-1 subtype C prevalences. Existence of diverse HIV-1 recombinants indicated viral mixing among the population, possibly as a result of dual infections. Evolutionary rate of the virus showed natural selection with high proportions of R5 strains suggestive of feasibility of use of maraviroc (CCR5 antagonists) in Kenya. However, multiple drug resistance mutations observed in the newly classes of drug-prior to their introduction, there is a need for constant monitoring of HIV-1 genetic diversity and drug resistance. Drug resistance seen to common drugs was minimal (2 %), indicating that we need to continue to prescribe the current used drugs. In addition, the new classes of entry, fusion and integrase inhibitors are feasible as firstline and thirdline drugs respectively. In addition, it was realised that it is not necessary to carry out resistance testing at baseline unless there is strong evidence of virological failure.