Antiretroviral Resistance in HIV/AIDS Patients

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Abstract. The higher prevalence of HIV drug resistance was observed in areas with greater ART coverage. The HIV resistance-associated mutations occur when people have inadequate levels of antiretroviral drugs as well as inadequate potency, inadequate adherence, and pre-existing resistance. The degree to drug cross-resistance is observed depends on the specific mutations and number of mutation accumulation. In the Southeast Asia region, the challenging of people with treatment failure is the availability and accessibility to subsequent new antiretroviral drugs to construct he second and salvage regimen. Genotypic resistance testing is a useful tool because it can identify the existing drug resistance-associated mutations under the selective drug pressure. Thus, understanding the basic interpretation of HIV drug resistance-associated mutation is useful in guiding clinical decisions for treatment-experienced people living with HIV.

In 2016, the World Health Organization (WHO) reported an estimated 36.7 million people were living with HIV worldwide and 3.5 millions of those were in the Southeast Asia region.[1] This figure is considered to be the second greatest burden of HIV infection after Africa region. Successful antiretroviral therapy (ART) scale-up has been mainly owing to the use of a public health approach to antiretroviral drug delivery supported by standardized protocols and simplified patient monitoring.[1] On the other hand, higher prevalence of HIV drug resistance was observed in areas with greater ART coverage.[2] Significant advances in antiretroviral treatment have been made since the introduction of zidovudine. Six classes of antiretroviral agents are currently approved to treat people living with HIV, including nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase inhibitors (INSTIs), fusion inhibitors (FIs), and chemokine receptor antagonists (CCR5 antagonists).[3] In the Southeast Asia region, NNRTI-based ART is recommended as a first-line regimen in ART-naïve people living with HIV and PI-based regimens are reserved as regimen in both ART- and toxicity- experienced people. However, people who experienced virologic failure were approximately twice as likely to have a major resistance-associated mutation if they failed NNRT-based first-line regimen compared to PI-based first-line regimen.[4] As we know that virologic failure diagnosis go unrecognized if viral load monitoring is not performing timely. In this scenario, the patient stays on a failing regimen for a prolonged period of time, during which time resistance-associated mutation may develop. There was a recent a multicenter cohort study undergoing genotypic resistance testing among 1926 patients from 36 countries with virologic failure from a first-line regimen containing tenofovir plus a cytosine analogue (lamivudine or emtricitabine) combined with either efavirenz or nevirapine between 1998 and 2015.[2] It revealed that prevalence of tenofovir resistance-associated mutation in people with treatment failure was highest in low-income and middle-income regions. The plausible explanation of geographic

differences in tenofovir resistance-associated mutation are probably due to the frequency of viral load monitoring with close patient follow-up and turn-around time of testing results.[2]

The HIV resistance-associated mutations occur when people have inadequate levels of antiretroviral drugs as well as inadequate potency, inadequate adherence, and pre-existing resistance.[5] This review will focus on the resistance-associated mutations of NRTI and NNRTI drugs that most frequent prescribed in this region. The thymidine analogue mutations (TAMs) include M41L, D67N, K70R, L210W, T215F/Y and K219Q/E.[6] The degree to which cross-resistance is observed depends on the specific mutations and number of mutation accumulation. Although such resistance-associated mutations are selected only by zidovudine- and stavudine- containing regimens, the TAMs confer different magnitude of cross resistance to other NRTI drugs, i.e. tenofovir, abacavir and didanosine, except lamivudine and emtricitabine. The TAMs occur in dichotomous pathways but overlapping patterns that may occur in people receiving an initial zidovudine- or stavudine-containing regimen.[6] The first pathway includes M41L, L210W and T215Y and confer higher-level zidovudine resistance, more NRTI cross-resistance, and lesser effect of M184V when compared to another pathway.[7] The second TAM pathway with lesser magnitude of zidovudine resistance and NRTI cross-resistance includes D67N, K70R, T215F and K219Q/E.A reduce also occurs in the presence of 3 or more TAMs inclusive of either M41L or L210W. Beside TAMs, the remaining common mutations include M184V/I, K65R, K70E/G, L74V, and the Q151M complex of mutations. M184V is one of the most frequent mutation developed after lamivudine-containing NRTI backbone regimen failure. M184V/I cause high-level in vitro resistance to lamivudine and emtricitabine and low-level resistance to didanosine and abacavir.[8] However, M184V itself reduces viral fitness and may be associated with lowering plasma HIV-1 RNA levels than wild-type virus.[8,9] Therefore, it is not absolute contraindications to continued treatment with lamivudine and emtricitabine because they increase susceptibility to tenofovir, zidovudine and stavudine and are associated with clinically significant reductions in HIV-1 replication. K65R cause intermediate to high level resistance to tenofovir, didanosine, and stavudine and low to intermediate resistance to lamivudine and emtricitabine but this mutation increases susceptibility to zidovudine.[7] K70E/G cause low-level resistance to tenofovir, didanosine, and abacavir and possibly lamivudine and emtricitabine and it increase susceptibility to zidovudine. L74V/I cause high-level resistance to didanosine and intermediate resistance to abacavir. Q151M causes intermediate/high-level resistance to zidovudine, didanosine, stavudine and abacavir and low-level resistance to tenofovir, lamivudine and emtricitabine.[7] In combination with accessory mutations at positions 62, 75, 77, and 116, Q151M confers high-level resistance to zidovudine, didanosine, stavudine and abacavir and intermediate resistance to tenofovir, lamivudine and emtricitabine.

There are three commonly prescribed NNRTIs as first-line treatment in this region, include efavirenz, nevirapine, and rilpivirine. On the other hand, etravarine in another NNRTI drug that always be used in combination with other antiretroviral drugs in the salvage regimen for the treatment–experienced patient. There is a study showing that previously used dual-NRTI regimens, such as zidovudine and lamivudine with efavirenz, indicates that approximately 40% had NNRTI resistance, approximately 30% had lamivudine resistance, and approximately 20% to 25% had resistance to both with very little in the way of resistance to the other NRTIs.[10] Thymidine-analogue mutations emerge much more slowly and gradually over time. Thus, resistance is really limited to the first-generation NNRTIs and to lamivudine in the early detection of virologic failure.K103N is a non-polymorphic mutation and selected frequent by efavirenz. It causes high-level resistance to NVP by ~50-fold reduced susceptibility and EFV by ~20-fold reduced susceptibility but it confers low-level resistance to rilpivirine. There is no effect on etravirine susceptibility. Nevertheless, there is no evidence for the utility of rilpivirine in people failing nevirapine and efavirenz.[11] Y181C is selected in patients receiving nevirapine, etravirine and rilpivirine but not with efavirenz-containing regimens. It confers partial cross-resistance to etravirine, efavirenz and nevirapine. E138K is selected in patients receiving rilpivirine.[12,13] Alone it causes RPV resistance ~2 to 3-fold reduced susceptibility. As a consequence, there is no evidence for the utility of efavirenz, nevirapine, or rilpivirine in patients with

NNRTI resistance.[11] Etravirine may be effective against strains of HIV that have developed resistance to other NNRTIs. Nonetheless, etravirine's activity against resistant strains is strongly affected by the number of NNRTI mutations present, as well as by the specific mutations. Five mutations on three amino acid positions, i.e.L100I, K101P, Y181C/I/V, have a greatest impact on etravirine susceptibility.[14]

In the resource-limited setting, the challenging of people with treatment failure is the availability and accessibility to subsequent new antiretroviral drugs to construct he second and salvage regimen, fewer ARV choices arises when compared to the availability in resource-rich setting. Genotypic resistance testing provides essential information because it can indicate the existing drug resistance-associated mutations under the selective drug pressure and guide the optimal second-line regimen. Therefore, understanding the basic principles and interpretation of HIV drug resistance is useful in guiding clinical decisions.

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