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HIV Infected Soldier on Third Line HAART after Immunological and Virological Failure on First and Second Line Regimen

Samir Kumar Rama, Dipankar Chakraborty
Department of Infectious Diseases and ART, Assam Rifles Composite Hospital, Sukhovi, Dimapur, Nagaland, India.

Abstract:

Introduction: With universal access to first line antiretroviral therapy need for second and third line regimen are increasing. Non-adherence, drug resistance and independent factors like age at start of therapy, low education level and HIV RNA viral load contribute to the second line anti-retroviral therapy failure wherein third line drugs are needed to be started as salvage therapy. Protease inhibitors used in second line therapy can fail due to primary mutation which can be detected with the help of drug resistance testing. *Case Report:* 45 years old HIV infected soldier developed first line anti-retroviral therapy failure five years after the start of drugs due to common mutations to non-nucleoside and nucleoside reverse transcriptase inhibitor like K103N, M184V, M41L, D67N, V75M. Thereafter two years of start of second line anti-retroviral therapy consisting of boosted protease inhibitor (lopinavir/ ritonavir) he developed immunological and virologic failure with drug resistance testing showing primary mutation to protease inhibitor (lopinavir/ ritonavir) as L24I, L33F, V82S and M46I. Third line anti- retroviral therapy was started consisting of boosted darunavir, raltegravir with tenofovir and lamivudine as nucleoside reverse transcriptase inhibitor backbone. Three months post therapy his HIV RNA viral load have decreased from 4,81,879 copies/mL to 9,563 copies/mL. *Conclusion:* Emergence of protease inhibitor resistance during second line anti-retroviral therapy need to be monitored with the help of clinical and virologic monitoring and third line drugs should be used as salvage therapy if adequate viral suppression has not been achieved.

Key words: Drug Resistance, HIV infections, Lamivudine, Protease Inhibitors, Viral Load.

Introduction

Wide availability of HAART has increased the life expectancy among HIV infected population and reduced transmission of virus to HIV negative individuals. There is also reduction in number of new HIV infections from 24.8 to 11.4 per 1,00,000 persons between year 2000 to 2012 [1]. Universal access to first line HAART in national programs worldwide have also led to increase in number of people in need of second and third line regimens. In resource limited settings of developing world, percentage of individuals receiving second line regimen are 0.05%. As the number of individual on

Corresponding Author: Dr. S.K.Rama
Email: samdiprc@gmail.com
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second line regimen are increasing, need for third line regimen are also likely to increase in coming years.

Patients who are unable to tolerate first line regimen or have virologic failure are started on second line but they are more unlikely to adhere to the changed regimen due to dosing complication, high costs and requirement of special storage condition for drugs. Resorting to third line regimen or salvage therapy are more expensive and have higher profile of adverse effects. Limited drug availability and high cost of drugs in third line regimen is an important barrier in implementing the regimen at the global level. Also third line regimen consisting of ritonavir boosted darunavir, etravirine and raltegravir is 14 times more expensive than WHO recommended first line fixed dose combination [2].

Hence continued success of ART programmes will require understanding the emergence of HIV drug resistance patterns among individuals in whom the treatment have failed and managing ART from both of an individual and public health perspective. Optimising adherence, performing resistance surveillance and improving monitoring of treatment are important issues in prevention of drug resistance to different lines of ART.

We report a case of a HIV infected soldier on first line c-ART since 2007 with failure to both first and second line c-ART within five and two years of start of respective regimens and presently in immunologically recovered and viral suppressed state on third line c-ART.

Case Report

45 years old male soldier, detected to be of HIV positive status since 2007 was evaluated for chronic cough and diagnosed to have aspergilloma in the left upper lobe of the lung. He was on regular follow up with our Infectious disease and ART centre since May 2011 and was on first line c-ART consisting of AZT (zidovudine), 3TC (lamivudine) and NVP (nevirapine) with cotrimoxazole prophylaxis and itraconazole 200 mg once daily for aspergilloma.

His CD4 count in May 2011 was 47 cells/cumm and was found to have poor adherence to c-ART due to alcohol seeking behaviour. Regular counselling and de-addiction measures to alcohol was done but his CD4 count dropped serially to 64 cells/cumm in July 2011 and 34 cells/cumm in September 2011. Thereafter he was put under direct medical observation for improving adherence to prescribed first line c-ART but his CD4 consistently remained less than 100 cells/cumm.

In March 2012, CD4 count was 55 cells/cumm and 30 cells/cumm in October 2012 despite adherence improving to more than 95%. His viral load was 92,104 copies/mL and he was started on second line c-ART in view of immunological and virological failure on first line drugs. HIV genotype drug resistance showed high level resistance to all NNRTI with K103N mutation. High resistance was seen to 3TC/ FTC (emtricitabine)/ d4T (stavudine)/ AZT due to NRTI mutations of M41L, D67N, V75M, M184V. He was started on second line c-ART consisting of TDF, IND/ RTV, 3TC with cotrimoxazole and MAC prophylaxis with macrolide weekly.

Thereafter his follow-up CD4 count in January 2013 was 54 cells/cumm and 31 cells/cumm in October 2013. Adherence to c-ART remained an issue to the individual due to increased pill count and adverse effects of indinavir. His PI was changed to boosted lopinavir and continued c-ART but his CD4 count in March 2014 was 44 cells/cumm and 27 cells/cumm in November 2014 despite adherence to HAART >95%. His viral load was 2,83,458 copies/mL in November 2014 which increased to 4,81,879 copies/mL in February 2015. Protease inhibitor resistance typing was

done which showed resistance mutation to boosted lopinavir and indinavir due to primary mutations of L24I, L33F, V82S and M46I.

Thereafter he was started on third line c-ART in March 2015 consisting of boosted darunavir, raltegravir, tenofovir, lamivudine along with cotrimoxzole and macrolide prophylaxis. In June 2015, his viral load have decreased to 9,563 copies/mL and CD4 increased to 186 cells/cumm.

Discussion

In 2010, prevalence of HIV drug resistance at time of first line c-ART failure was systematically reviewed. The threshold of HIV RNA load for genotyping has been >1000 copies/mL for the vast majority of resistance surveillance work inducted to data in resource limited settings [3]. In systemic review by Barth *et al*. prevalence of HIV suppression was 78% after 6 months of treatment, 76% after 12 months and 67% after 24 months. Most common mutations were M184V mutation found in 65% patients and K103N mutation in 52% patients. Thymidine analogue mutations (TAMs) were found less common ranging from 5%-20% of patients and K65R mutation in 5% patients [4].

In our case, the individual came to attention with resistance to first line c-ART after four years of start of treatment because of lost to follow-up with our ART centre in initial four years due to continuing alcohol abuse and poor adherence to HAART. There was no immune recovery in the individual and he had virological failure with viral load of 92,104 copies/mL despite de-addiction measures to alcohol and improved adherence post counselling >95% due to mutations M184V, K103N and TAMs. He was started on second line c-ART consisting of boosted PI with 3TC and TDF as NRTI backbone in the regimen due to use of AZT before in first line.

Second line c-ART accounts for less than 5% of total anti-retroviral treatment in resource limited settings. This is a small proportion of the total number in whom treatment is failing and receiving second line therapy. Detection of failure due to clinical and immunological monitoring in cases leads to accumulation of more complex mutations that renders second line NRTI backbone less effective as found in our case also. Outcomes of second line ART have been satisfactory in different settings. In low income and middle income countries, second line therapy failed in 21.8% at 6 months, 23.1% at 12 months, 26.7% at 24 months and 38% at 36 months [5]. In our case, the individual have shown no immunological recovery with virologic failure on second line therapy within 24 months despite adherence >95%.

Patients who are initiated second line c-ART with detectable HIV RNA, age and level of education were independently associated with hazard of second line failure [6]. A protective pattern was found for older age when compared to younger age (< 30 years) and for higher education compared to those with less number years of education for second line c-ART failure [6].

In our case, the individual was 45 years old at the start of second line c-ART with primary school education only. Also, HIV RNA level was 10,000-1,00,000 copies/mL when second line c-ART was started which was seen to have high hazard of failure to second line therapy [6]. Indeed HIV RNA >1,00,000 copies/mL is well known to be associated with higher rise of first line c-ART virologic failure [7-9] and second line c-ART failure [10,11].

Only small studies have evaluated PI resistance at time of second line failure and PI resistance mutants are present in approximately 18% of genotyped virus [5]. 67% of second line failure cases have wild type viruses underscoring

non-adherence as cause of treatment failure [5]. Emergence of PI resistance at the time of virologic failure is very uncommon in PI naïve patients and mutation in gag gene have been known to contribute to viral fitness in presence of PI mutations [12]. It is not known whether mutation in gag gene only contribute to the sizeable portion of patients with unexplained PI failure [13]. However in the study of Cardoso *et al*. one primary PI mutation was identified in 75% of patients using an un-boosted PI c-ART based regimen (D30N, 150L, 46V) and 10 % among those using PI-r c-ART regimen (47V, 82A and 90M) [6]. In our case primary mutation to r-PI found was L24I, L33F, V82S and M46I leading to failure of lopinavir/ritonavir (r-PI) used in second line c-ART.

Conclusion

C-ART irrespective of whether it is first line or subsequent treatment regimen should achieve sustained viral suppression as its objective. Also emergence of PI resistance during second line c-ART use needs to be monitored with the help of clinical and virologic end-points and to be started on third line c-ART if accessible. PI resistance emergence at the time of virologic failure need consideration when second line c-ART is not causing viral suppression and drug resistance typing can detect primary PI mutations.

References

1. Malaysia Ministry of Health. Guidelines for the management of adult HIV infection with antiretroviral therapy. December 2013. Available from: http://www.moh.gov.my/images/gallery/Garispanduan/HIVGUIDELINES.pdf. Accessed on July 19, 2015.
2. Parienti JJ, Massari V, Descamps D, Vabret A, Bouvet E, *et al*. Predictors of virologic failure and resistance in HIV-infected patients treated with nevirapine- or efavirenz-based antiretroviral therapy. Clin Infect Dis. 2004;38:1311-1316.
3. Mackie NE, Phillips AN, Kaye S, Booth C, Geretti AM. Antiretroviral drug resistance in HIV-1 infected patients with low- level viremia. J Infect Dis. 2010;201:1303-1307.
4. Barth RE, Vanderloeff MF, Schuurman R, Hopelman AI, Wensing AM. Virological follow up of adult patients in antiretroviral treatment programmes in Sub-Saharan Africa: a systematic review. Lancet Infect Dis. 2010;10:155-166.
5. Ajose O, Mookherjee S, Mills EJ, Boulle A, Ford N. Treatment outcomes of patients on second-line antiretroviral therapy in resource-limited settings: a systematic review and meta-analysis. AIDS. 2012;26:929-938.
6. Cardoso SW, Luz PM, Velasque L, Torres TS, Tavares IC, Ribeiro SR, *et al*. Outcomes of second line combination antiretroviral therapy for HIV infected patients: a cohort study from Rio de Janerio, Brazil. BMC Infectious diseases. 2014;14:699.
7. van Leth F, Andrews S, Grinsztejn B, Wilkins E, Lazanas MK, Lange JM, Montaner J, Group NNs. The effect of baseline CD4 cell count and HIV-1 viral load on the efficacy and safety of nevirapine or efavirenz-based first-line HAART. AIDS. 2005;19(5):463-471.
8. Taiwo B, Zheng L, Gallien S, Matining RM, Kuritzkes DR, Wilson CC, *et al*. Efficacy of a nucleoside sparing regimen of darunavir/ritonavir plus raltegravir in treatment-naïve HIV-1-infected patients (ACTG A5262). AIDS. 2011;25(17):2113-2122.
9. Brinson C. Potential Implications of Baseline Viral Load on the Relative Potency of First-line. NNRTI-Based Antiretroviral Therapy. 2012;1:542.
10. Waters L, Bansi L, Asboe D, Pozniak A, Smith E, Orkin C, *et al*. UK CHIC Study, UK HIV Drug Resistance Database. Second-line protease inhibitor-based antiretroviral therapy after non-nucleoside reverse transcriptase inhibitor failure: the effect of a nucleoside backbone.

Antivir Ther. 2013;18(2):213-219.
11. Koulla-Shiro S, Ciaffi L, Le Moing V, Ndour CT, Sawadogo A, Eymard-Duvernay S, *et al*. Randomized Comparison of Three Second Line ART Regimens in Africa: the 2 Lady Study. *In*: Conference on Retroviruses and Opportunistic Infections: 2014. Boston; 2014.
12. Hosseinipour MC, Gupta RK, Van Zyl G, Eron JJ, Nachega JB. Emergence of HIV Drug Resistance During First and Second-Line Antiretroviral Therapy in Resource-Limited Settings. The Journal of Infectious Diseases. 2013;207(Suppl 2):S49-S56.
13. Fun A, Wensing AMJ, Verheyen, Nijhuis M. Human Immunodeficiency Virus gag and protease: partners in resistance. Retrovirology. 2012;9:63.