ORIGINAL ARTICLE

A study on individualized regimen for north Indians living with human immunodeficiency virus-1 subtype C: A public health approach

Sushanta Kumar Barik[1], Avi Kumar Bansal[1],Ashwini Yadav[1],Srikanth Prasad Tripathy[2],Tej Pal Singh[3], Srikanta Jena[4],Shripad A Patil[1],KesharKunja Mohanty[1]*

[1]ICMR-National JALMA Institute for Leprosy and Other Mycobacterial Diseases, Agra-282004 (Uttar-Pradesh), India, [2]ICMR-National Institute for Research in Tuberculosis, Chetpet, Chennai-600031(Tamil Nadu), India, [3]Sarojini Naidu Medical College, Agra-282003 (Uttar-Pradesh), India, [4]Ravenshaw University, Cuttack-753003 (Odisha), India

Abstract

Background: The study analyses several first line and second line drugs, CD4 counts and viral load in patients experiencing treatment failure over a period of 1 to 6 years of first line antiretroviral therapy (ART). The study emphasizes the implementation of tailor-made regimen and the drug resistance testing in the national programme in India. *Aim and Objectives:* A study on the efficacy of the first line individualized regimen of HIV-1 subtype C infected North Indian population and recommendation of first line tailor made regimen after detection of Drug Resistance Mutations (DRM) associated with first line drugs. *Material and Methods:* The study of HIV-1 patients taking first line ART (period 2009-2016) was conducted at ART centre, S.N Medical College, Agra, India. The follow-up of fifty-seven patients were conducted after a confirmation of genotyping test. The primary data analysis was done on the data availability based on inclusion criteria to observe the correlation between the CD4 counts and viral loads (markers of the clinical outcome) of the individual North Indian patients infected with HIV-1 Subtype C. The DRM in individual patients were analysed through the drug resistance database, Stanford University, United States of America. The study design was based on the primary data analysis of the 57 patients' drug profiles which were associated with DRM during the first line ART. The data of the resistance associated drugs, CD4 counts, viral loads of the individual patient were compiled and the patterns of drug resistance profiles were statistically analysed using Microsoft Excel 2016 and SPSS Version 22. The normality of the data was checked by Shapiro-Wilk test ($p<0.05$). *Results:* Fifty-one patients were detected with DRM. Out of 57 first line ART failure patients, 45 patients were continuing with first line and second line ART in alive condition. Twelve patients died during the treatment of first line and second line ART. Twenty four patients whose complete data of CD4 counts and viral load were available, did not show difference in drug adherence. Despite being resistant to most of the first line drugs, CD4 count increased and viral load decreased in 12 patients. Both CD4 count and viral load increased in 3 patients. Both markers declined in 2 patients while 7 of them with decrease in CD4 counts showed increase in viral loads. Median duration of treatment was 41.84 months while median treatment adherence was 98.25%. Among the 24 patients, 16 patients were shifted on second line regimen. *Conclusion:* The study suggests the provision of a tailor-made first line and second line individualized regimen to each patient under a policy program of National AIDS Control Organization (NACO), Govt. of India. The implementation of drug resistance testing of first- and second-line therapy is very essential for changing the suitable regimen to increase CD4 counts and decrease viral load of individual patients.

Keywords: Acquired Immunodeficiency Syndrome, Genotyping, Human Immunodeficiency Virus, Nucleoside Reverse Transcriptase Inhibitors, Non-nucleoside Reverse Transcriptase Inhibitor

Introduction

Acquired immunodeficiency syndrome (AIDS) is caused by Human Immunodeficiency Virus (HIV). The use of various Antiretroviral Therapy (ART) is the only option for the treatment of HIV/AIDS. In India, in the year 2004, the first-line ART regimen was implemented at ART centres by National AIDS Control Organization (NACO), Govt. of India [1]. The first line ART comprises two Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and a Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI). The development of Drug Resistance Mutations (DRM) on first-line ART requires switching over to second line ART like Atazanavir, Ritonavir, etc. The clinical and immunological monitoring of CD4 count and viral load of first-line ART patients is completely guided at ART centres of India under national program [1-3]. The implementation of CD4 counts, viral load and genotyping to detect the DRM at an early stage in a national program is very important [4]. The harrowing time spent by patients with DRM without genotyping test can have a significant impact on the life of the patients [5]. Genotyping is the most common method of gene sequencing for the detection of HIV DRM [6]. Commercial and in-house methods are widely used for the genotypic test of HIV-1 drug resistance [7]. The continuation and strengthening ART of HIV infected individuals was implemented under National Program, Govt. of India [8].

Therefore we proposed to conduct this study to assess the efficacy of NRTIs and NNRTIs over a period of six years among the HIV-1 subtype C patients attending ART centre at Sarojini Naidu Medical College, Agra, India. Our study findings may broaden the scale of implementation research for the use of the tailor-made suitable drugs after individualized genotyping test in the national program of NACO, Govt. of India.

Material and Methods

Study site and design

At ART centre, Sarojini Naidu Medical College, Agra, North India, 57 patients on the first line ART from December 2009 to November 2016 were tested for drug resistance by genotypic study. Patients were followed up till August 2019. All patients' information was collected using the patient information leaflet [9]. The study was designed based on the selection of patients for genotyping based on either CD4 counts (<350 cubic/mm), WHO clinical staging of HIV/AIDS or viral load ($\geqslant$ 1000 copies/ml). The patients whose duration of ART follow up was less than six months and those with leprosy, invasive cervical cancer, cryptococcosis, Kaposi's sarcoma, lymphoma, schizophrenia etc. were excluded from the study. The primary data of 57 patients' CD4 counts, viral loads and drug resistance patterns were analysed. Out of 57 patients, 51 were found to be drug resistant. Pre-treatment and study endpoint CD4 count, viral load and HIV drug resistance primary data were available for 24 patients while only starting CD4 counts with viral loads and study endpoint CD4 counts of 33 patients were available.

Ethics approval and informed consent

The HIV drug resistance study was approved by the Institute Human Ethics Committee of National JALMA Institute for Leprosy and Other Myco-bacterial Diseases, (Indian Council of Medical

Research), Dr. M. Miyazaki Marg, TajGanj, Agra-282004. Patients were recruited only after taking their written informed consent [10].

Genotyping

Viral load was estimated using the Abbott Molecular's automated m2000RT instrument. The genotyping was performed for first-line ART failure HIV/AIDS patients at the National Institute for Research in Tuberculosis, Chennai by using the WHO dried blood spot protocol 2010. The details of the DRM on first line antiretroviral therapy was reported [11].

Statistical analysis

After analysis of DRM in individual patients, the data of individuals were compiled and analysed using Microsoft Excel 2016 and SPSS Version 22. The normality of data was checked by Shapiro-Wilk test ($p<0.05$). It showed that CD4 counts and viral loads were not normally distributed. The frequency analysis was done when resistance was found in more than one first-line anti-retroviral drugs. The Wilcoxon signed rank test was used for hypothesis testing for CD4 counts and viral loads.

Results

All 57 HIV-1 infected patients were tested by genotyping and the DRM were analysed in individual patients. Fifty-one patients were detected with DRM associated with NRTIs and NNRTIs. The CD4 counts and viral loads were considered as prognostic markers to assess the treatment outcome. The patients received different regimens of the mentioned drugs as per their clinical profile and adverse drug events during the treatment duration. Data on pre-treatment and study endpoint CD4 counts, viral loads, and HIV drug resistance were available for 24 patients and all showed resistance to one or more than one first-line anti-retro viral drugs. Out of 24 patients, three patients died during the treatment. One of them had lower CD4 counts and viral loads while 2 patients had CD4 counts lower with higher viral load. In rest of the 21 patients, in the presence of drug resistance, both CD4 counts and viral load declined in two patients while CD4 count decreased and viral load increased in 7 patients. Both CD4 counts and viral load increased in 3 patients, whereas increased CD4 counts and decreased viral load was observed in 12 patients despite drug resistance.

Out of 24 patients, 16 patients were shifted on a second-line regimen after the detection of first-line HIV DRM in them. Abacavir + Lamivudine/ Atazanavir/Ritonavir, (AL/ATV/RTV) were started in one patient. But the patient died during the course of treatment. There was a decline in both CD4 counts and viral loads. Stavudine Lamivudine + Atazanavir/Ritonavir, (SL/ATV/RTV) were started in two patients, Tenofovir + Lamivudine + Atazanavir/Ritonavir (TL/ATV/RTV) in 8 patients and Zidovudine + Lamivudine + Atazanavir/ Ritonavir, (ZL/ATV/RT) in 5 patients. There was no significant difference between starting and endpoint CD4 count ('p' value 0.391) as well as viral load ('p' value 0.616).

Viral load data at study end point was not available for 33 patients. It showed that although CD4 counts were improved in 24 patients, 5 of them died. Two patients on TLE regimen who died during treatment, did not show resistance to any ART drug. Eighteen patients were alive with improved CD4 counts (11 patients had less than

300/mm^3 and 7 patients had ⩾ 300/mm^3). Five patients were shifted on second-line regimen out of which one died during the treatment. There was no significant difference between starting and endpoint median CD4 count ('p' value 0. 189) of these 33 patients.

Median duration between diagnosis and initiation of treatment was 8 weeks (Range: 1 to 460 weeks). Median duration of treatment was 41.5 months (range 10.3 to 86.6 months) and treatment adherence was 97.34% (range 82.21% to 99.7%). When the drug resistance patterns of these patients were studied, Efavirenz and Nevirapine resistance were observed in most of these patients followed by Lamivudine and Zidovudine. Few patients were resistant to Tenofovir, Stavudine and Abacavir. Thus, resistance to NNRTIs was observed more frequently than NRTIs.

Discussion

Treatment failure was assessed by an immunological and virological measure. The establishment of the measurement of RNA copies was a surrogate marker for HIV disease progression [12]. The low-level RNA copies predict virologic failure. However, the high RNA copy number was a risk of treatment failure [13]. The successful antiretroviral treatment was specifically defined as viral suppression in People Living with HIV (PLHIV) [14]. Few patients in the present study had higher endpoint viral loads than baseline in the presence of resistance to the first line drugs.

CD4 counts of individual patients after therapy confirms, the risk of the progression of AIDS or death of patients [15]. But in present study, decline in CD4 count was observed irrespective of drug resistance status. Few patients died during treatment although their CD4 count was increased.

The clinical goal for each patient requires an effective, active, tolerable, and minimal side effects regimen to achieve maximal clinical benefits to avoid treatment failure. In this study, drug resistance was found to various first-line drugs such as Zidovudine, Lamivudine, Tenofovir, Stavudine, Efavirenz and Nevirapine. HIV drug resistance has been monitored by affordable HIV drug resistance testing in Sub-Saharan Africa [16]. From the multi-centric study in India, it was concluded that Nevirapine therapy is reasonable alternative for Efavirenz [17]. In this study, resistance to Nevirapine and Efavirenz was mainly observed.

Tenofovir is an important drug included in the first-line ART. Tenofovir based virological monitoring predicted treatment failure for patients [18]. In this study, 18 patients were found to be resistant to Tenofovir [19], ensured the monitoring of the genotypic resistance to Zidovudine. In this study, Lamivudine resistance was found in 35 patients while Zidovudine resistance was found in 23 patients. Similar findings were observed in a study in Zidovudine and Lamivudine combination therapy, both Zidovudine and Lamivudine therapy failure were marked in HIV-1 infected patients [20].

Stavudine exhibits antiretroviral activity as a monotherapy or combination therapy to manage the adults with HIV infection [21]. The rate of treatment failure for Stavudine/Lamivudine/Nevirapine was determined in Asian region [22]. In this study, out of 11 patients on SLE/SLN

combination therapy, 9 developed resistance to Stavudine. Abacavir is a suitable antiretroviral drug with lamivudine for treatment of HIV patients [23]. One patient was treated with ALN regimen and Abacavir treatment failure was observed in one patient. The management of HIV resistance differs in lower middle-income countries compared to high income countries. HIV drug resistance testing is like a point of care test [24]. This study utilized WHO dried blood spot protocol 2010 polymerase chain reaction and sequencing primers. Thermal conditions are useful in genotyping test which can reduce the cost of the test.

In India, after the detection of HIV positive status, ART is introduced in any CD4 count without drug resistance testing. This might be the main cause of mortality among HIV patients. This study assessing the relationship between DRM and their effect on treatment outcome are limited. An insight into HIV drug resistance pattern and its effect on prognosis of AIDS in individual patients is important. It can also enable the health care providers to monitor HIV drug resistance over the period of treatment. However, utility of such a test at the level of national health program needs to be studied in detail before formulation of policy.

Conclusion

To support evidence-based policy decision, determinants of HIV drug resistance and its effect on ART outcome need to be explored further in a structured manner in North Indian population. The introduction of molecular drug resistance testing in the program may lead to proper management of healthcare resources for drug resistance management in HIV-1 patients. The highly active ART based on individualized genotyping test in North Indian population proved an effective intervention study of drug efficacy with clinical outcomes in a planned manner through a primary data analysis.

Funding

Indian Council of Medical Research, Govt. of India funded this project titled “Characterization of drug resistant HIV-1 mutants of Agra region, India by genomic and proteomic approaches” for senior research fellowship of Mr. Sushanta Kumar Barik (File No. 80/990/2015-ECD-I).

Acknowledgements

We thank the staff members of ICMR-NIRT, Chennai for their assistance in the viral load and genotyping study in HIV-1 patients' samples.

References

1. National guidelines for implementation of antiretroviral therapy, New Delhi: NACO; 2004:1-151.
2. Ministry of Health and Family Welfare of India NACO. Guidelines for Prevention and Management of Common Opportunistic Infections/ Malignancies among HIV-Infected Adult and Adolescent.2007 1-85.
3. Ministry of Health and Family welfare of India NACO. Antiretroviral Therapy Guidelines for HIV-Infected Adults and Adolescents. 2013: 40–45.
4. Karade S, Chaturbhuj DN, Sen S, Joshi RK, Kulkarni SS, Shankar S, *et al*. HIV drug resistance following a decade of the free antiretroviral therapy programme in India: A review. *Int J Infect Dis* 2018;66:33-41.
5. Van Vaerenbergh K. Study of the impact of HIV genotypic drug resistance testing on therapy efficacy. *Verh K Acad Geneeskd Belg* 2001;63(5):447-473.
6. Shafer RW. Genotypic testing for human immunodeficiency virus type 1 drug resistance. *Clin Microbiol Rev* 2002; 15(2):247-277.
7. Chaturbhuj DN, Nirmalkar AP, Paranjape RS, Tripathy SP. Evaluation of a cost-effective in-house method for HIV-1 drug resistance genotyping using plasma samples. *PloS One* 2014;9(2):e87441.
8. Ghate M, Zirpe S, Shidhaye P, Gurav S, Rao A, Verma V, *et al*. A retrospective study of characteristics of HIV infected individuals opting out from antiretroviral treatment under national programme. *J Krishna Inst Med Sci Univ* 2019;8(3): 19-26.
9. Barik SK, Tomar S, Tandon R, Mohanty KK, Joshi B. Practical challenges in implementing a simplified leaflet for HIV patients in resource poor settings: the practice towards public health. *J Gen Pract* 2018;6(347): 1-3.
10. National ethical guidelines for biomedical research involving human participants. *Indian Counc Med Res* 2017: 1-141.
11. Barik SK, Bansal AK, Mohanty PS, Tripathy SP, Hanna LE, Karunaianantham R, *et al*. Detection of drug resistance mutations in the reverse transcriptase gene of HIV-1-infected North Indian population failing first-line antiretroviral therapy "a follow-up cohort study". *AIDS Res Hum Retrovir* 2021;37(10):796-805.
12. Haubrich RH, Currier JS, Forthal DN, Beall G, Kemper CA, Johnson D, *et al*. A randomized study of the utility of human immunodeficiency virus RNA measurement for the management of antiretroviral therapy. *Clin Infect Dis* 2001; 33(7): 1060-1068.
13. Kiweewa F, Esber A, Musingye E, Reed D, Crowell TA, Cham F, Semwogerere M, Namagembe R, Nambuya A, Kafeero C, Tindikahwa A. HIV virologic failure and its predictors among HIV-infected adults on antiretroviral therapy in the African cohort study. *PLoS One* 2019; 14 (2):1-16.
14. Karade SK, Kulkarni SS, Ghate MV, Patil AA, Londhe R, Salvi SP, *et al*. Antiretroviral resistance following immunological monitoring in a resource-limited setting of Western India: A cross-sectional study. *PLoS One* 2017; 12: 1-11.
15. Opportunistic infections project team of the collaboration of observational HIV epidemiological research in Europe (COHERE) in EuroCoord. CD4 cell count and the risk of AIDS or death in HIV-infected adults on combination antiretroviral therapy with a suppressed viral load: a longitudinal cohort study from COHERE. *PLoS Med* 2012: 9.
16. Inzaule SC, Ondoa P, Peter T, Mugyenyi PN, Stevens WS, de Wit TF, *et al*. Affordable HIV drug-resistance testing for monitoring of antiretroviral therapy in sub-Saharan Africa. *Lancet Infect Dis* 2016; 16: e267–e275.
17. Sinha S, Gupta K, Tripathy S, Dhooria S, Ranjan S, Pandey RM. Nevirapine-versus Efavirenz-based antiretroviral therapy regimens in antiretroviral-naive patients with HIV and tuberculosis infections in India: A multi-centre study. *BMC Infect Dis* 2017:17(1):1-8.
18. Shet A, Neogi U, Kumarasamy N, DeCosta A, Shastri S, Rewari BB. Virological efficacy with first-line antiretroviral treatment in India: predictors of viral failure and evidence of viral resuppression. *Trop Med Int Health* 2015; 20(11): 1462-1472.
19. Zazzi M, Catucci M, De Milito A, Romano L, Venturi G, Valensin PE, *et al*. Zidovudine resistance mutations and human immunodeficiency virus type 1 DNA burden: longitudinal evaluation of six patients under treatment. *Infection* 1996; 24(6): 419–425.
20. Miller V, Phillips A, Rottmann C, Staszewski S, Pauwels R, Hertogs K, *et al*. Dual resistance to zidovudine and lamivudine in patients treated with zidovudine-lamivudine combination therapy: association with therapy failure. *J Infect Dis* 1998; 177(6): 1521–1532.
21. Moyle GJ. Stavudine: pharmacology, clinical use and future role. Expert opinion on investigational drugs. *Expert Opin Investig Drugs* 1997 6(2): 191–200.

22. Zhou J, Paton NI, Ditangco R, Chen YM, Kamarulzaman A, Kumarasamy N, *et al*. Experience with the use of a first-line regimen of stavudine, lamivudine and nevirapine in patients in the TREAT Asia HIV Observational Database. *HIV Med* 2007 8(1): 8-16.
23. Achenbach CJ, Scarsi KK, Murphy RL. Abacavir/ lamivudine fixed-dose combination antiretroviral therapy for the treatment of HIV. *Adv Ther* 2010 27(1):1-16.
24. Noguera-Julian M. HIV drug resistance testing–The quest for point-of-care. *E Bio Medicine* 2019; 50: 11–12.

Author for Correspondence:
Dr Keshar Kunja Mohanty (Scientist-F), National JALMA Institute for Leprosy and Other Mycobacterial Diseases, Taj-Ganj, Agra, Uttar-Pradesh
Email: keshar63@yahoo.com, mohanty.kk@icmr.gov.in
Phone: +919412255180

How to cite this article:
Barik SK, Bansal AK, Yadav A, Tripathy SP, Singh TP, Jena S, Patil SA, Mohanty KK. A study on individualized regimen for north Indians living with human immunodeficiency virus-1 subtype C: A public health approach. *J Krishna Inst Med Sci Univ* 2023; 12(1):17-23

Submitted: *27-Sep-2022* ***Accepted:*** *30-Nov-2022* ***Published:*** *01-Jan-2023*