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Research Article

Prevalence of virological failure amongst WHO- defined immunological failure HIV patients on first line of highly active antiretroviral therapy in a tertiary care hospital in Haryana, India

Manisha Rajian*, Paramjeet S. Gill, Uma Chaudhary

Department of Microbiology, Pt. B. D. Sharma PGIMS Rohtak, Haryana, India

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***Correspondence:**
Dr. Manisha Rajian,
E-mail: manisharajian@gmail.com

ABSTRACT

Background: In resource limited settings in India, monitoring of treatment in HIV patients taking highly active antiretroviral therapy is done by six monthly CD4 count instead of highly sensitive plasma viral load. Patients are subjected to viral load only when their CD4 count is low for the last 12 months. This protocol has a huge disadvantage as treatment failure is detected much later than it has actually occurred and switch over to second line therapy gets delayed by approximately one year.
Methods: Plasma viral load (pVL) of 50 WHO defined immunological failure cases was done using RT-PCR to detect virological failure (VF).
Results: Out of 50 WHO defined immunological failure cases, 16 percent had developed virological failure.
Conclusions: Nearly one-sixth of WHO defined immunological failure (IF) cases had developed virological failure. These patients required second line highly active antiretroviral therapy (HAART) therapy but due to following of current treatment monitoring protocol, treatment got delayed by one year. Thus, amendment in national policy for monitoring ART is required to diagnose treatment failure early so that there is no delay in switching to second line ART and morbidity and mortality in these patients can be reduced.

Keywords: VF, IF, CD4 count, pVL, HAART

INTRODUCTION

The primary goals of initiating highly active antiretroviral therapy (HAART) among HIV patients are to suppress HIV viral replication and to restore immune function. As the global experience has increased over last few years, there have been changes in timing of initiation of ART, which regimen to follow and monitoring mechanisms. The clinical decision to check whether such goals have been achieved is made through CD4 cell counting.[1]

Virological monitoring, though being the most sensitive tool, is not done routinely because of its high cost, advanced technological infrastructure requirement and limited access in most resource limited settings.[2,3] Therefore CD4 cell count becomes a crucial element in monitoring treatment response.

Due to the lack of routine pVL monitoring for HAART, the patient is designated as having treatment failure only after 6 – 12 months of failure of CD4 reconstitution, and is continued with the same ARVs with further delay in switching over to second-line therapy.

It has been well established that virological failure precedes Immunological failure which precedes clinical failure.[4]

The initiation of HAART generally leads to a rapid reduction in HIV-RNA plasma levels and to an increase in peripheral CD4 count.[5,6] However, some patients experience a discordant response, whereby the HIV-RNA plasma level is below the limit of detection but the CD4 cell count response is blunted. There are limited data on discordant responses in patients being treated in India.[7]

Four scenarios are expected during the antiretroviral treatment for HIV (as shown in Table 1).

A detectable plasma viral load (pVL) is among the earliest signs of treatment failure and continuing a failing regimen has been associated with increased morbidity and mortality as well as accumulation of drug-resistance mutations that further limit second-line options.[8-10] Therefore, routine virological monitoring is the standard of care in developed world.[11] However, because of cost and limited access to laboratory technology, routine pVL monitoring is not performed or recommended in resource-limited settings.[12] Instead, clinicians in these settings rely on defining treatment failure based on CD4 cell counts, clinical manifestations of disease progression, or both.[13]

Several studies from resource-limited settings have shown that lack of VL monitoring leads to frequent misclassification of failure and therefore, either premature switching to second-line regimen or a delay in change to second-line agents.[14-16]

Current protocol

In India, as per the NACO guidelines, the patients stable on first-line regimen are monitored every six-months, and treatment monitoring includes weight, haemoglobin, alanine aminotransferase (ALT) and CD4 count. Routine pVL monitoring is not available. Patients suspected of having treatment failure for WHO-defined immunologic and clinical criteria are referred to select government HIV treatment centres designated as centre for excellence for viral load testing.[17] If the patient is having virological failure (>10,000 copies/ml of HIV-RNA), he is switched to second-line regimen which is a combination of zidovudine or Tenofovir, lamivudine, and ritonavir-boosted atazanavir. The patients with low or undetectable viral load are continued with the same treatment.[13]

METHODS

A total of 50 patients, all above 18 years of age and receiving first line HAART for more than 1year and having WHO defined immunological failure i.e., their last reading of CD4 count falling down to pre-therapy baseline or if there was 50% fall from the on-treatment peak value or persistent CD4 levels below 100 cells/µl, were included in the current study after taking their informed written consent.Whole blood specimen of 50 patients was collected in ethylene diamine tetra acetic acid (EDTA) vacutainer by phlebotomy under aseptic conditions and plasma viral load was done using Roche Diagnostics' RT-PCR Kit (COBAS® TaqMan® HIV-1 Test, version 2.0 (v2.0) with the high pure system as an in vitro nucleic acid amplification test).[18]

The patient was designated as virological failure depending upon the results of the plasma viral load. If the patient had high viral load (>10000 copies/ml), he was designated as having virological failure and if the viral load was low then he was designated as immunological failure. The prevalence of VF was calculated among WHO defined treatment failure cases.

RESULTS

Out of 50 cases, 30% were females and 70% were males; median age was 32.5 years; mean time on ART was 38.5months; mean baseline CD4 cell count was 139cells/mm^3. The commonest first-line ART regimens were: zidovudine/lamivudine/nevirapine (AZT/ZDV+ 3TC+NVP) (40%) followed by zidovudine/Lamivudine/Efavirenz (ZDV+3TC+EFV) (18%) and Stavudine/Lamivudine/Nevirapine (d4T30+3TC+NVP) (16%). On the basis of plasma viral load testing, 8 (16%) of the total cases had treatment failure and these were designated as virological failures while the remaining 42 (84%) were classified as immunological failures only. Study subjects had a mean viral load of 0.62 X 10^5 copies/ml at the time of study. The results of the study have been summarized in Table 2.

The Prevalence of virological failure among WHO defined immunological failure criteria was found to be 16%.

Some associated parameters in these 8 virological failure cases were analyzed. Out of the 8 cases, 6 belonged to age group 18-35 years and 2 belonged to 36-54 years' age group. Even though, in our study, the cases of VF were more in the younger age group, this finding was not found to be statistically significant (p value>0.05)

It was observed in our study that number of cases of VF was more when the pre HAART CD4 count was <200 cells/mm^3 (p value>0.05).

Among the patients with adherence more than 95%, only 4.9% cases had VF.

It was observed that poor adherence to treatment resulted in more cases of VF. This finding was found to be statistically significant (p value<0.05). The probability of developing virological failure was observed to be more, when the patient was co-infected with TB than when there was no HIV-TB co-infection. This observation was also found to be statistically significant (p value<0.05).

Table 1: Scenarios expected during the antiretroviral treatment for HIV.

	Viral load high (plasma viral load >10,000 copies/mL)	Viral load low
CD4 low (not improving)	VF and IF both	IF only
CD4 high (Improving)	VF only	Treatment successful

Table 2: Distribution of cases according to various parameters.

Parameters		WHO IF criteria based cases	Virological failure (VF)
Total		50	8
Gender	Females	14	2
	Males	36	6
Age (years)	18-35	29	6
	36-54	21	2
	>55	-	-
Pre HAART CD4 count (cells/mm^3)	<100	19	5
	100-200	17	1
	200-350	14	2
Adherence (%)	<80	6	4
	80-95	3	2
	>95	41	2
WHO Clinical Stage	I	20	1
	II	14	4
	III	14	3
	IV	2	-
Duration of HAART (in months)	12-36	29	1
	>36	21	7
Co-infection with TB	Yes	17	7
	No	33	1
HAART Regimen	Efavirenz based	16	3
	Nevirapine based	34	5

DISCUSSION

On the basis of plasma viral load testing, 8 (16%) of the total cases had treatment failure and these were designated as virological failures while the remaining 42(84%) were classified as immunological failures only. Study subjects had a mean viral load of 0.62X10^5 copies /ml at the time of study.

A study conducted by Robbins et al showed that rate of VF was higher (42.5%) when the age of the patients was <40 years.[19] In our study as well, the chances of VF dropped as the age of the patients progressed. The explanation behind the above findings may be that older patients might be more adherent to treatment.

The results of our study were in agrrement with Bello et al where the the percentage of developing virological failure was more when the pre treatmnet CD4 count was below 200cells/mm^3.[20]

Findings of our study were consistent with those of Paterson et al and Low Beer et al as the rate of VF decreased with increasing adherence (p value<0.001).[21]

The findings of Bello et al with regard to occurrence of increased chances of VF in patients who are co-infected with tuberculosis are in congruence with our findings and the same are also corroborated by the studies by Bekker et al, von Reyn et al and Ahoua et al which also showed that the mycobacterial disease was a major contributor to HIV mortality and VF is associated with occurrence of TB coinfection.[20,22-24]

CONCLUSION

It could be seen that switch over to second line treatment would have been earlier, had there been early viral load testing, thus not wasting the precious time. It calls for the need to change the current treatment response monitoring protocol. It was also seen that factors like age, adherence, pre-HAART CD4 count and co infection with TB have greatly impacted the occurrence of virological failure and these can be used as predictors of virological failure in resource limited settings where routine plasma viral load monitoring is not possible.

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Ethical approval: The study was approved by the Institutional Ethical Committee

REFERENCES

1. Federal Ministry of Health (FMoH) website. Guideline for management of opportunistic infections andantiretroviral treatment in adolescents and adults in Ethiopia. Available: http://www.who.int/hiv/pub/guidelines/ethiopia_art.pdf. Accessed 2013 Nov 11.
2. Kanapathipillai R, McGuire M, Mogha R, Szumilin E, Heinzelmann A, et al. Benefit of viralload testing for confirmation of immunological failure in HIV patients treated in rural Malawi. Trop Med IntHealth. 2011;16:1495-500.
3. WHO website. Antiretroviral Therapy for HIV infection in Adults and Adolescents Recommendations fora public health approach 2010 revision. Available: http://wholibdoc.who.int/publications/ 2010/ 9789241599764_eng.pdf. Accessed 2013 Dec 9. 12/09/2013.
4. Deeks SG, Barbour JD, Martin JN, Sanson MS, Grant RM. Sustained CD4+ T cell response after

virologic failure of protease inhibitor-based regimens in patients with human immunodeficiency virus. J Infect Dis. 2000;181:946-53.
5. Gulick RM, Mellors JW, Havlir D, Eron JJ, Gonzalez C, McMahon D, et al. Treatment with indinavir, zidovudine, and lamivudine in adults with human immunodeficiency virus infection and prior antiretroviral therapy. N Engl J Med. 1997;337:734-9.
6. Hammer SM, Squires KE, Hughes MD, Grimes JM, Demeter LM, Currier JS, et al. A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. AIDS Clinical Trials Group 320 Study Team. N Engl J Med.1997;337:725-33.
7. Prabhakar B, Banu A, Pavithra B, Chandrashekhra P, Sasthri S, et al. Immunological failure despite virological suppression in HIV seropositive individuals on antiretroviral therapy. Indian J Sex Transm Dis. 2011;32(2):94-8.
8. Haubrich RH, Currier JS, Forthall 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: 1060-8.
9. Petersen ML, van der Laan MJ, Sonia N, Eron JJ, Moore RG, Deeks SG. Long-term consequences of the delay between virologic failure of highly active antiretroviral therapy and regimen modification. AIDS. 2008;22:2097-106.
10. Hatano H, Hunt P, Weidler P, Coakley E, Hoh R, Liegler T, et al. Rate of viral evolution and risk of losing future drug options in heavily pretreated, HIV-infected patients who continue to receive a stable, partially suppressive regimen. Clin Infect Dis. 2006;43:1329-36.
11. Panel on Antiretroviral Guidelines for Adults and Adolescents. Department of Health and Human Services; Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. [cited 2013 Nov 10]. Available from: http://www.aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf.
12. World Health Organization. Geneva, Switzerland: WHO; 2010. Antiretroviral therapy for HIV infection in adults and adolescents. Recommendations for a public health approach [2010 revision] [cited 2013 Nov 10]. Available from: http://whqlibdoc.who.int/ publications/ 2010/9789241599764_eng.pdf.
13. Vallabhaneni S, Chandy S, Heylen E, Ekstrand ML, et al. Evaluation of WHO immunologic criteria for treatment failure: implications for detection of virologic failure, evolution of drug resistance and choice of second-line therapy. J Int AIDS Soc. 2013;16(1):18449.
14. Mee P, Fielding KL, Charalambous S, Churchyard GJ, Grant AD. Evaluation of the WHO criteria for antiretroviral treatment failure among adults in South Africa. AIDS. 2008;22:1971-7.
15. Kantor R, Diero L, Delong A, Kamle L, Muyonga S, Mambo F, et al. Misclassification of first-line antiretroviral treatment failure based on immunological monitoring of HIV infection in resource-limited settings. Clin Infect Dis. 2009;49:454-62.
16. Rewari BB, Bachani D, Rajasekaran S, Deshpande A, Chan PL, Srikantiah P. Evaluating patients for second-line antiretroviral therapy in India: the role of targeted viral load testing. J Acquir Immune Defic Syndr. 2010;55:610-4.
17. National AIDS Control Organization. Antiretroviral therapy guidelines for HIV infected adults and adolescents including postexposure-2007. [cited 2013 Nov 7]. Available from:http://nacoonline.org/upload/Policies%20&%20Guidelines/1.%20Antiretroviral%20Therapy%20Guidelines%20for%20HIVInfected%20Adults%20and%20Adolescents%20Including%20Post-exposure.pdf.
18. Plasma viral load measurement by COBAS® TaqMan® HIV-1 Test, version 2.0 For Use with The High Pure System. Roche Molecular Systems. 11/2012; 05923573001-03 Doc Rev. 3.0.
19. Robbins GK, Daniels B, Zheng H, Chueh H,Meigs JB,Freedberg KA, et al. Predictors of Antiretroviral Treatment Failure in an Urban HIV Clinic. J Acquir Immune Defic Syndr. 2007;44(1):30-7.
20. Bello EJM, Correia AF, Marin JRP, Merchan-Hamm E, Kanzaki LIB. Predictors of virologic failure in HIV/AIDS treated with highly active antiretroviral therapy in Brasilia, Brazil during 2002-2008. Drug Targets Insights. 2011;5:33-41.
21. Low-Beer S, Yip B, O'Shaughnessy MV, Hogg RS, MontanerJS, et al. Adherence to triple therapy and viral load response. J Acquir Immune Defic Syndr. 2000;23:360-1.
22. Bekker LG, Orrel C, Reader L, Matoti K, Cohen K, Martell R. Antiretroviral therapy in a community clinic – early lessons from a pilot project. A Afr Med J. 2003;93(6):458-62.
23. Von Reyn CF, Kimambo S, Mtei L, et al. Disseminated tuberculosis in human immunodeficiency virus infection: ineffective immunity, polyclonal disease and high mortality. Int J Tuberc Lung Dis. 2011;15(8):1087-92.
24. Ahoua L, Guenther G, Pinoges L, Anguzu P, Chaix ML, Tiec CL, et al. Risk factors for virological failure and subtherapeutic antiretroviral drug concentrations in HIV-positive adults treated in rural northwestern Uganda. BMC Infectious Diseases. 2009;9:81.

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