

Original Research Article

Evaluation of the predisposing factors and cause of resistance which are associated with ART 1 failure and shifted to ART 2 regime

Narendra Singh^{1*}, R. K. Varma¹, Richa Giri¹, Punit Varma², Seema Dwivedi³, Lalit Kumar¹

¹Department of Medicine, KPS PG Institute of Medicine, GSVM Medical College, Kanpur, Uttar Pradesh, India

²Department of Community Medicine, GSVM Medical College, Kanpur, Uttar Pradesh, India

³Department of Obstetrics and Gynaecology, GSVM Medical College, Kanpur, Uttar Pradesh, India

Received: 10 March 2019

Revised: 25 April 2020

Accepted: 01 May 2020

*Correspondence:

Dr. Narendra Singh,

E-mail: narendrasingh0011@gmail.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Background: This study is to evaluate the predisposing factors and cause of resistance which are associated with ART1 failure and shifted to ART 2 regime.

Methods: This study was conducted in ART plus centre K.P.S. Post Graduate Institute of Medicine (G.S.V.M. Medical College, Kanpur, India) tertiary care teaching hospital (G.S.V.M. Medical College, Kanpur, India). It will be a clinical (assessment with investigation), continuous, longitudinal, prospective and retrospective, observational, single centre hospital-based study at ART Centre, Kanpur, India. All the subjects who were on 1st line ART regime, attended in our centre were screened for treatment failure of based on clinical, immunological and virological criteria as decided by SACEP. Duration of this study was DEC 2016 TO DEC 2018. This study was taking as regime ART2 as TLATV/R, ZLATV/R, TLLP/R and ZLLP/R.

Results: In this study there is PL HIV subjects that are considered for ART2 are mostly living in rural area and more are female having less adherence to ART1. Smoking, alcohol and tobacco chewing were also having less adherence to ART and cause resistance to ART1.

Conclusions: In this study subjects were having associated with predisposing factor as Alcoholic 53 (45%), Tobacco Chewing 8 (07%), SMOKING 13 (11%). Alcoholic, Tobacco Chewer and Smoker have significant association of predisposing factor for low adherence to ART1 and resistance to ART1 drugs. There is also concluded that females and rural areas subject are having low adherence and cause ART1 failure.

Keywords: A-Atazanavir, Antiretroviral therapy, Human immunodeficiency virus, L- Lamivudine, L-Lopinavir, R-Ritonavir, Sacep, T-Tenofovir, Z-Zaduvudine

INTRODUCTION

Reason of resistant of drug is due to mutation at the majority of M184 Or K103 Mutation that was most common NNRTI Mutation.

During treatment of HIV medicine some HIV mutation can develop and the treated regimen is not effective. Drug

resistance testing can identify the effective regimen. A good adherence to medication of HIV regimen reduces the drug resistance. It can also spread from person to person called as transmitted.

The chronic persistent form of the virus with high rate of replication has lead to mutant resulting into anti-retroviral drug resistance increasing report of resistance.

Resistance are mostly two type

- *Induced resistance*

During treatment of ART.

- *Primary resistance*

Resistance strain is infected to the patient.

Causes of resistance are as following

- Mutation that block the incorporation of nucleoside
- Lack of adherence of drugs and low level of adherence.
- Missing of drugs

When resistance testing could be done

- At the time of beginning of drug regimens.
- When viral load is not reduced during treatment
- When during treatment viral load again appeared. And during treatment low CD4 count reappeared

There are three type tests for detecting HIV drug resistance

- Genotypic
- Phenotypic
- Viral load

Genotypic testing

In this there is looking at specific genetic sequence in viral D.N.A and check any change in wild type virus and check any mutation.

Phenotypic test

In phenotypic test there is in vitro testing the inhibitory dose of different antiretroviral drugs

Viral load testing

In viral load testing there is indicator of viral replication in body and also indicator of drug effectiveness.

Smoking and chewing Tobacco have adverse effect on the CD4 count and decrease CD4 count alcohol drinker have some ART failure because alcohol drinker has less adherence to ART regimen and it also have some interaction with some ART medication.

Standard combination of antiretroviral regimens is two NRTI together with an NNRTI, Protease Inhibitor (PI) or Integrase Inhibitor. Starting regime of Integrase Inhibitor. This regimen should be monitored for resistant testing. If resistant testing is not available then PI in second line regimens are preferable.¹

Monitoring of efficacy during art treatment²

A base line viral load should be measured prior to initiating treatment. Viral load should be repeated 4 to 8 weeks after starting a new regimen when the count should show at least a tenfold decrease. After six month of ART The viral load should be suppressed defined as below the detection of the assay (usually less than 50 copies/ml).

WHO defined immunological failure as fall in CD4 COUNT to base line or a 50% fall from peak on ART or persistent count below 100cell/mm.³

Failure of art is defined as viral load become detectable after suppression typically more than 400 or more than 1000 copies/ml.⁴

First time ART should consist of two Nucleoside reverse transcriptase inhibitor (NRTI) + Non-nucleoside reverse transcriptase.

India ranks third among the countries having most number of HIV - infected patients and HIV related deaths in the world. In India, ART at public sector hospital is provided free of charge under the National AIDS Control Organization (NACO). The second line ART regimens comprised of Zidovudine (ZDV), Lamivudine (3TC), Tenofovir (TDF), and boosted Lopinavir/Ritonavir (LPV/r) have been introduced recently in a phase wise manner at limited centres.

The criteria to switch on second line ART includes clinical and/or immunological and/or virological failure in a patient who had received 6 months or more of standard first-line ART. The patient qualify for second line ART if they demonstrate CD4 decline to pre-ART values, CD4 drop to less than 50% of peak on-treatment value, failure to achieve CD4 greater than 100 c/mm³ (immunologic failure), or develop a new WHO stage III/IV AIDS-defining illness (clinical failure) or those with HIV RNA 10,000 c/ml or greater (virological failure).

The Second line treatment programme is still relatively new with little experience in India population. Without resistance testing and 6 monthly virological monitoring the consequences of second line therapy outcomes are unclear.

It is therefore, critical to assess the clinical, virological and immunological effectiveness and treatment outcome over the first year of follow-up in the patients switched to second line therapy at public sector tertiary care centre.

Aims and objective of this study was to Evaluation of the predisposing factors and cause of resistance which are associated with ART1 failure and shifted to ART2 regime.¹

METHODS

This study was conducted in ART plus centre K.P.S. Post Graduate Institute of Medicine (G.S.V.M. Medical College, Kanpur, India) tertiary care teaching hospital (G.S.V.M. Medical College, Kanpur, India)

Type of study Single centre hospital-based study. Study period is Dec 2016 to Dec 2018.

Study design this was clinical (assessment with investigation) continuous longitudinal, prospective and retrospective, observational, single centre hospital-based study at ART Centre, Kanpur, India.

Study subject all the on-1st line ART treating attending in our centre will be screen for treatment failure of based on clinical, immunological and virological criteria as decided by SACEP.

Inclusion criteria

Patient over the age of 18 years at pre-inclusion and monitored under outpatient condition.

Documented HIV-1 (group m) infection regardless of clinical stage and CD4 lymphocyte-count (taken in 6 months).

Patient with treatment failure after first-line antiretroviral treatment with a combination including a non-nucleoside reverse transcriptase inhibitor and two nucleoside reverse transcriptase inhibitors, failure.

Adherence (>80%) to first-line antiretroviral treatment (questionnaire) at pre inclusion.

Patient agrees not to take any concomitant medication during the trial without informing the investigator.

Informed consent

For women in childbearing age: negative pregnancy test at inclusion, with no plan of pregnancy in the coming 12 months and agreeing to use mechanical contraception (with or without hormonal contraception) during the study.

Exclusion criteria

Infection with HIV-2 or HIV-1 groups O or N or HIV 1+2.

Adherence (<80%) to first-line Antiretroviral treatment at pre inclusion.

Participation in any other clinical trial.

Presence of an uncontrolled, ongoing opportunistic infection or of any severe of progressive disease.

First-time treatment with a protease inhibitor, Abacavir.

Not interested to participate in study.

Severe hepatic insufficiency.

Creatinine clearance calculated by Cockcroft-Gault formula <50 ml/min.

Hb≤8 g/dl

Platelets <50,000 cells / mm³

Neutrophils <500 cells / mm³

Pregnancy or lactation.

Blood sample collection

On admission, 10 ml of peripheral venous blood was collected from the antecubital vein by an autoclaved syringe using 20 gauge needles. The blood was allowed to clot at room temperature for at least half an hour.

The glass tube with clotted blood was centrifuged at 2000 rpm for 20 minutes and the centrifugation was repeated once more to remove the red cells completely. The supernatant serum, devoid of cellular elements, was separated from the clot and placed in two acid cleaned small test tubes.

Viral load testing

Patient of HIV suspecting first line ART failure send to BHU Varanasi, Department of Microbiology, IMS BHU Banaras. For estimation of viral load

In BHU viral load is tested quantitatively real time PCR from HIV RNA by PCR machine.

Measuring

Viral load is typically reported as copies of HIV in a millilitre (ml) of blood. Changes in viral load are usually reported as a log change (in powers of 10).

For example, a three-log increase in viral load (3 Log₁₀) is an increase of 10³ or 1000 times the previously reported level, while a drop from 500,000 to 500 copies would be a three-log-drop (also 3 Log₁₀).

CD4 count

CD4 count is done by BD facts flow machine by kit and report is analysed and given same day.

RESULTS

This study was conducted in ART plus centre. K.P.S. Post Graduate Institute of Medicine (G.S.V.M medical college Kanpur, India). This study is on the patients of first line ART failure and started ART 2. In this study total number of patients was taken as 118 in which 47 was male and 71 was female as male was 40% and female was 60% (Table 1).

The patient who was failure of ART1 were belong 65 from rural area that was 55% and 53 from urban areas that was 45% (Table 2). This study also shows that 53 (45%) patient are taking alcohol, 8 (7%) patient was taking tobacco and smoking was done by 13 (11%) (patients. (Table 3)

In this study regime was taken as ART 1 that was failure was as TLE regime 47 (76%) patient and ZLN REGIME was taken 28 (23%) patient 9 (Table 4). 74 (63%) Patient are treated with ART 2 the Regime are TLATV/R Tenofovir + Lamivudine + Atazanavir + Ritonovir, 35 (30%) patients are taken ZLATV/R- Ziduvudine + Lamivudine + Atazanavir + Ritonovir, 5 (4%) patients are taken TLLPR- Tenofovir + Lamivudine + Lopinavir + Ritonavir and 4 (3%) patients are taken ZLLP/R- Ziduvudine + Lamivudine + Lopinavir + Ritonavir (Table 5).

Distribution of study subject on the basis of sex. In our study there is male was und 40% and female was found 60% this show female patient is more involve in HIV infection (Table 1).

Table 1: Tabular representation of Sex distribution in ART1 failure.

Sex	No. of subjects	%
Male	47	40%
Female	71	60%

Distribution of study subject on the basis of residence. This study show that rural subject is more involve that is 55% (Table 2).

Table 2: Tabular representation of Geographical distributions of ART 1 failure and started ART 2.

Area	No. of subjects	%
Rural	65	55%
Urban	53	45%

This study shows there is seen that in ART1 failure subject having 45% alcohol drinker, 10% have Tobacco chewer 6% are having smoking (Table 3).

In this study there is ART 1 regime is taking as TLE and ZLN in which 76% is taking TLE and ZLN regime is taking 23% (Table 4).

Table 3: Tabular representation of predisposing factor in ART 1 failure.

Predisposing factor	No. of subjects	%
Alcohol	53	45%
Tobacco	8	7%
Smoking	13	11%
No Alcohol/Smoking/ Tobacco	61	39%

Table 4: Tabular representation of regime of treatment of ART 1.

Treatment regimen	No. of patients	%
TLE	90	76%
ZLN	28	23%

This study is taking as regime as ART2 as TLATV/R – Tenofovir + Lamivudine + Atazanavir + Ritonovir is taking by 65% ZLATV/R- Ziduvudine + Lamivudine + Atazanavir + Ritonovir is taking by 30% TLLP/R – Tenofovir + Lamivudine + Lopinavir + Ritonavir is taking by 4% ZLLP/R- Ziduvudine + Lamivudine + Lopinavir + Ritonavir is taking by 3% (Table 5).

Table 5: Tabular representation of regime of second line ART in study subjects.

Regime	No. of subjects	%
TLATV/R	74	63%
ZLATV/R	35	30%
TLLP/R	5	4%
ZLLP/R	4	3%

In this study there is adherence to the ART medication 84% before start of ART 2, but during start of ART 2 there is 93% adherence to ART2 medication but after 6 months of start of start of ART is 95% (Table 6).

Table 6: tabular representation of adherence of ART.

Before art 2 start	Time of start of art 2	After 6 month of start art 2
84%	93%	95%

DISCUSSION

In this study there was 35 subjects is taking Tenofovir + Lamivudine + Lopinavir/Ritonovir regime, 74 subjects is taking Zidovudine + Lamivudine + Atazanovir/Ritonovir regime, 5 subjects was taking Tenofovir + Lamivudine + Atazanavir/Ritonovir and 4 subjects was taking Zidovudine + Lamivudine + Lopinavir/Ritonovir regime The regime considered in study that also have less chance of resistance development. Oldfield V, Plosker 1- This study take Lopinavir /Ritonavir base antiretroviral therapy is generally well tolerated and has shown durable virological efficacy in clinical trial in ART failure in

naive and patient with virological failure. It has less interaction so it have more chance of adherence

Subjects were having associated with predisposing factor such as alcoholic 53 (45%), tobacco chewing 8 (10%), smoking 13 (39%) and no smoking, alcoholic, tobacco chewer. Subject have significance association of predisposing factor for alcoholic and increase in infection of HIV adherence of ART1 regime is disturbed patient does not take art1 treatment properly in time because alcohol have some adverse reactions with antiretroviral medications and patient was avoiding taking ART1 treatment. Kyser M, Buchacz K.² In this study 528 patient taking antiretroviral s enrolled from March 2004 to June 2006. This study show that patient taking more indulge to alcohol have less adherence to antiretroviral therapy. Smoking and tobacco produce some cytokines that have decrease effectiveness of ART 2. Jonathan Shuter, Steven L Bernstein 3. This Study taken 64 patient and 57 reported ever having smoked this show adherence rate to smoker was less than than non-smoker.

This study shows that female (71) were more ART1 failure than male (47).

In this study patients were treated ART 1 higher from rural (65out of 118) area that outreach of ART 1 medicine is low because of this adherence of ART medicine decrease with proper counselling adherence is improve further in ART 1.

This study there was 35 subjects is taking Tenofovir + Lamivudine + Lopinavir/Retinovir regime, 74 subjects is taking Zidovudine + Lamivudine + Atazanavir / Retinovir regime, 5 subjects was taking Tenofovir + Lamivudine + Atazanavir/Retinovir and 4 subjects was taking Zidovudine + Lamivudine + Lopinavir/Retinovir regime. Shuter JS, Sarlo J, Kanmaz TJ, et al.⁴ This study was taking 64 subjects and 975 recieved Lopinavir/Rotinavir and virlogical supspression were obserbed in less adherence Patel D. et al.⁵ Overall outcome of Out of 126 patients, 82 received regimen V [Zidovudine (ZDV) + Lamivudine (3TC) + Tenofovir (TDF) + boosted Lopinavir (LPV/r)] and 44 received regimen Va [3TC + TDF + LPV/r. This study also shows that association of alcoholism with more probability of ART1 failure.

Matthew P FOX, Gilles VAN CUTSEM, Janet Giddy, Mhairi Maskew, Olivia Keiser, Hans Prozesky, Robin Wood, Miguel A. Hernán, Jonathan AC Sterne, Matthias Egger, and Andrew Boule- this study measure rate of failure of ART1 and shifted to second line ART.⁶

Tsegaye AT, Wubshet M, Awoke T, et al.⁷ This study was consider 356 adult patient and in which 198 was male and individuals who were on second line ART for at least 6 month of treatment .and concluded treatment failure was at 12 month and stage 4 of WHO and also

CD4 count less than 100. This study have also failure ahen symptom appear and CD4 count decrease.

Alexander bilioux Gertrude Nakigozi and Steven J Renolds.⁸ This study was consider 1841 participant initiating antiretroviral therapy in Rakai health science program between June 2005 and June 2011 were followed with viral load monitoring every 24 weeks after good counselling for adherence and viral load monitoring there is suppression of viral load in our study patient considered and monitored on the basis of viral load monitoring and good counselling to adherence to ART 2 treatment viral load suppression resulted.

Davidson principle's and practice of medicine, 22nd Edition.⁹ 1,2,3 and 4 in introduction the stated the regime that can take for PL. HIV treatment. Monitoring of efficacy during ART 2 treatment, Immunological failure and failure of ART.

CONCLUSION

Second line ART is most effective in treatment of subject treated after treatment failure of first line ART.

CD 4 count increase and viral load decrease clinical feature improve after treatment of ART 2.

Subject are having associated with predisposing factor such as alcoholic 53 (45%), tobacco chewing 8(10%), smoking 13(39%) and no smoking, alcoholic, tobacco chewer Subject have significance association of predisposing factor for alcoholic and increase in infection of HIV. subjects having low adherence to medications during treatment if ART 1 Low adherence to medication develop resistance to ART medication so durinking. This should most important to counselling of patient continuously. Patient is also routinely check viral load and CD4 count. At time of starting ART Genotypic and phenotypic testing should be taken routinely where resistance rate is very high.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee G.S.V.M Medical College Kanpur, India

REFERENCES

1. Oldfield V, Plosker GL. Lopinavir/ritonavir. A review of its use in the management of HIV infection. *Drugs.* 2006;66:1275-99.
2. Kyser M, Buchacz K, Bush TJ, Conley LJ, Hammer J, Henry K, et al. Factors associated with non-adherence to antiretroviral therapy in the SUN study. *AIDS care.* 2011 May 1;23(5):601-11.
3. Shuter J, Bernstein SL. Cigaret smoking is an independant predictor of nonadharance in HIV-infected individuals receiving highly active

- antiretroviral therapy. *Nicotine Tob Res.* 2008 Apr;10(4):731-6.
4. Shuter J, Sarlo JA, Kanmaz TJ, Rode RA, Zingman BS. HIV-infected patients receiving lopinavir/ritonavir-based antiretroviral therapy achieve high rates of virologic suppression despite adherence rates less than 95%. *JAIDS.* 2007;45(1):4-8.
 5. Patel D, Desai M, Shah AN, Dikshit RL. Early outcome of second line antiretroviral therapy in treatment-experienced human immunodeficiency virus positive patients. *Perspect Clin Res.* 2013 Oct-Dec; 4(4):215-20.
 6. Fox MP, Van Cutsem G, Giddy J, Maskew M, Keiser O, Prozesky H, et al. Rates and predictors of failure of first-line antiretroviral therapy and switch to second-line ART in South Africa. *Journal of acquired immune deficiency syndromes (1999).* 2012 Aug 1;60(4):428.
 7. Tsegaye AT, Wubshet M, Awoke T, Alene KA. Predictors of treatment failure on second-line antiretroviral therapy among adults in northwest Ethiopia: a multicentre retrospective follow-up study. *BMJ open.* 2016;6(12):e012537.
 8. Billieux A, Nakigozi G, Newell K, Chang LW, Quinn TC, Gray RH, et al. Durable suppression of HIV-1 after virologic monitoring-based antiretroviral adherence counseling in Rakai, Uganda. *PLoS One.* 2015;10(5).
 9. Davidson principle's and practice of medicine, 22nd Edition; 2014.

Cite this article as: Singh N, Varma RK, Giri G, Varma P, Dwivedi S, Kumar L. Evaluation of the predisposing factors and cause of resistance which are associated with ART 1 failure and shifted to ART 2 regime. *Int J Adv Med* 2020;7:977-82.