Virological and Immunological Status of the People Living with HIV Undertaking Highly Active Antiretroviral Therapy

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ABSTRACT

Background

The major goal of antiretroviral therapy (ART) is immunological recovery and virological suppression. Immunological and virological response in People Living with HIV (PLHIV) undertaking ART has to be monitored to assess the treatment response, diagnosing treatment failure and switching antiretroviral therapy.

Objective

To assess the immunological and virological response to antiretroviral therapy among Human Immunodeficiency Virus (HIV) infected individuals.

Method

This is a cross-sectional study including people living with HIV (PLHIV) taking antiretroviral therapy for at least 6 months and was conducted in Dhulikhel Hospital in 2017. The socio-demographic profile, clinical characteristics, CD4 count and viral load were analyzed. Descriptive analysis of socio-demographic and other characteristics was done.

Result

Fifty-two patients undertaking antiretroviral therapy were included in the study with the mean age of 29.69±9.59 years at diagnosis. The majority of the patients were male (51.9%). Sexual transmission was the dominant mode of transmission (78.9%). The mean CD4 count at baseline was 244.08±214.32 cells/µL. Four patients (7.7%) had a virological failure. There was a discordance between immunological and virological response in patients taking antiretroviral therapy for more than 2 years' duration with four patients with a recent CD4 count of ≤250 cells/µL had virological suppression. The mean CD4 count at treatment increased from 229.65 cells/µL to 453.33 cells/µL after 1 year of commencement of antiretroviral therapy ($p<0.001$).

Conclusion

There are optimal CD4 recovery and virological suppression as expected with antiretroviral therapy use.

KEY WORDS

Antiretroviral therapy, CD4, Human immunodeficiency virus, Viral load

INTRODUCTION

Human Immunodeficiency Virus (HIV)/Acquired immunodeficiency syndrome (AIDS) was first known to mankind in 1981 which has now become the global disease.[1] The first case of HIV was reported in Nepal in 1988. Chander and Pahwa reported the presence of HIV-2 infection in Nepal in 2004.[2,3] The antiretroviral therapy (ART) has been available at free of cost in Nepal for all eligible people living with HIV(PLHIV) since 2004.[4]

According to the National consolidated guideline for treating and preventing HIV in Nepal, 2014, ART should be initiated in all individuals with HIV with CD4 count less than or equal to 500 cells/µL irrespective of World Health Organization (WHO) clinical stage but the guideline in 2017 recommends ART to all adults living with HIV, regardless of WHO clinical stage and CD4 cell count.[5,6] Viral load testing is the gold standard test for monitoring response to antiretroviral therapy. In addition to the viral load testing, CD4 count can be used to assess the progression of disease, to initiate and switch to second-line ART. If viral load testing is not accessible or unavailable, the clinical and immunological response should be used for diagnosing treatment failure.[5,7] The limited accessibility and unavailability of viral load testing and monitoring is an important cause for the lower rate of ART switch in developing countries.[8]

Though viral load monitoring has to be done at 6, 12 months and then every 12 months to evaluate the response to antiretroviral therapy, it is not readily available in all ART centers of Nepal. Immunological and virological response in PLHIV undertaking ART has to be monitored to assess the treatment response, diagnosing treatment failure and switching ART. Studies on immunological and virological outcomes have been conducted only in few ART centers of Nepal. Despite Dhulikhel Hospital being one of the small ART centers of Nepal, this study will provide insight on baseline information of the virological and immunological status of HIV infected patients taking ART for more than 6 months which will facilitate to overview the status of HIV treatment outcome in Nepal.

METHODS

This is a cross-sectional study including PLHIV taking antiretroviral therapy for at least 6 months and those who have done viral load test, from October to December 2017. The medical records of PLHIV were reviewed from records available at the ART clinic of Dhulikhel Hospital and information regarding the socio-demographic profile and clinical characteristics were recorded. The socio-demographic profile included age at diagnosis of HIV infection, gender, education. The clinical characteristics including mode of transmission, bodyweight, WHO clinical stage, CD4 count, recent viral load, ART regimen, duration of ART, switch of ART regimen were recorded from clinical records. Fifty two HIV infected patients who were taking ART for at least 6 months and meeting the study criteria were enrolled. The baseline CD4 count was defined as the CD4 measurement at the time of diagnosis, and CD4 at ART initiation as the CD4 count occurring closest to the date of starting ART, within a window of 6 months. The recent CD4 count was defined as the latest CD4 count available while the recent viral load was defined as the latest viral load available. The enumeration of CD4 count and viral load quantification were performed at the National Public Health Laboratory, Kathmandu under the Department of health services and Ministry of Health and Population of Nepal.

The first line ART regimens in adults and adolescent are Tenofovir+Lamivudine+Efavirenz (TDF+3TC+EFV), Zidovudine + Lamivudine + Efavirenz (Nevirapine) (ZDV + 3TC/ + EFV (NVP)), Tenofovir + Lamivudine+Nevirapine (TDF + 3TC + NVP), Stavudine + Lamivudine + Nevirapine (d4T + 3TC + NVP), Stavudine + Lamivudine + Efavirenz (d4T + 3TC + EFV). Stavudine (d4T) has been phased out due to its toxicity. The second line regimens in adults and adolescent are Tenofovir + Lamivudine + Lopinavir/Ritonavir (TDF + 3TC + LVP/r) and Zidovudine + Lamivudine + Lopinavir/Ritonavir (ZDV + 3TC + LVP/r).[6,9]

This study was approved by the institutional review committee of Kathmandu University School of Medical Sciences. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) 20.0 software for windows. Descriptive analysis of socio-demographic and clinical characteristics data was done. Bivariate analysis was done with paired t-tests and the Mann Whitney test. The level of significance was considered at 5%.

RESULTS

Fifty-two patients undertaking ART were included in this study. The majority of the patients 88.5% were in the age group of 15-45 years at diagnosis of HIV infection with the mean age of 29.69±9.59 years. Most of the patients were male (51.9%) and 42.3% of the patients were illiterate in the study. Sexual transmission was the dominant mode of transmission (78.9%) followed by the parenteral route (15.4%) and MTCT (5.7%) respectively. Around 77% of the patients were diagnosed with HIV infection for more than 5 years duration whereas 61.6% of the patients were receiving ART for more than 5 years duration. The majority of the patients were in WHO stage III (40.4%). Eight patients had TB co-infection, 3 had HBV and 5 had HCV co-infection.

The mean CD4 count at baseline was 244.08±214.32 cells/µL and ranged from 11-947 cells/µL. The mean CD4 count at initiation of ART was 229.65±202.40 cells/µL. The majority of the patients (88.5%) had a well suppressed viral load of fewer than 400 copies following initiation of ART while 7.7% of the patients had a virological failure. AZT+3TC+NVP (44.2%) and AZT+3TC+EFV (17.3%) were commonly used initial ART regimens. Less than one third

Table 1. Sociodemographic characteristics of PLHIV (n=52)

Variable	n (%)
Age at diagnosis	
0-15	2(3.8)
15-30	24(46.2)
30-45	22(42.3)
45-60	4(7.7)
Gender	
Male	27(51.9)
Female	25(48.1)
Marital Status	
Married	45(86.5)
Single	3(5.8)
Divorced/Widowed	4(7.7)
Educational Status	
Literate	30(57.7)
Illiterate	22(42.3)
Occupation	
House maker	17(32.7)
Agriculture Workers	8 (15.4)
Business	10 (19.2)
Migrant Workers	4 (7.7)
Service	7(13.5)
Driver	2 (3.8)
Student	4 (7.7)
Residence (District)	
Kavre	40(76.9)
Others	12(23.1)

Table 2. Clinical characteristics of study participants (n=52)

Variable	n (%)
Mode of Transmission	
Sexual route	41(78.9)
Injecting drug use	8(15.4)
Mother to child transmission (MTCT)	3(5.7)
Duration of HIV diagnosis (years)	
<5	12(23.1)
5-10	28(53.8)
>10	12(23.1)
Treatment Duration (in years)	
<5	20(38.4)
5-10	24(46.2)
>10	8(15.4)
WHO clinical stage	
I	16(30.8)
II	9(17.3)
III	21(40.4)
IV	6(11.5)
History of Tuberculosis since diagnosis	
Yes	8 (15.4)
No	44 (84.6)
Hepatitis co infection	
Hepatitis B	3(3.8)
Hepatitis C	5(9.6)
Weight (kg)	
<40	5(9.6)
40-60	41(78.9)
>60	6(11.5)
Baseline CD4 count	
<200	29(55.8)
200-499	16(30.8)
>500	7(13.4)
CD4 count at ART initiation	
<200	29(55.8)
200-499	18(34.6)
>500	5(9.6)
Recent CD4	
<200	7(13.4)
200-499	16(30.8)
>500	29(55.8)
Recent Viral Load	
<400	46 (88.5)
400-1000	2 (3.8)
>1000	4(7.7)
Initial treatment regimen	
AZT+3TC+NVP	23(44.2)
d4T+3TC+NVP	3(5.8)
AZT+3TC+EFV	14(26.9)
TDF+3TC+NVP	3(5.8)
TDF+3TC+EFV	9(17.3)
Switch of ART	
Yes	15 (28.8)
No	37 (71.2)
Reason for ART switch	
Anemia	2(3.8)
Change of recommendation	3(5.8)
Treatment failure	4(7.7)
Tuberculosis	4(7.7)
Drug allergies	2(3.8)
Recent ART regimen	
First line regimen	47(90.4)
Second line regimen	5(9.6)

(28.8%) of patients were switched to other treatment regimens due to treatment failure (7.7%), tuberculosis (7.7%), change of recommendation (5.8%) and others. Five patients were receiving a second-line regimen following the switch of ART.

The mean CD4 count at diagnosis for WHO clinical stage I was 405.69 cells/µL while it was 190.11, 165.9 and 167.67 cells/µL for stage II, III and IV respectively. The difference in

Table 4. Discordance between Immunological and Virological response in PLHIV taking ART for more than 2 years with recent CD4 count ≤ 250 cells/µL and Viral load > 1000 copies/ml

Case	Duration of treatment (in years)	Baseline CD4 count (cells/µL)	Recent CD4 count (cells/µL)	Recent Viral Load (copies/mL)
A	8	147	177	<20
B	6	112	238	429
C	6	56	207	<20
D	2	175	134	<20
E	6	148	147	191000
F	4	108	128	9830
G	5	244	450	1930
H	3	109	563	13000

average baseline CD4 counts between stage III and IV and stage I and II was significant (p <0.05). A majority (91.11%) of patients with CD4 ≥ 200 cells/µL had a viral load of < 400 copies/ml. Table 4 shows that there was a discordance between immunological and virological responses in patients taking ART for more than 2 years duration. Four patients with a recent CD4 count of ≤ 250 cells/µL had virological suppression. Two patients with a better CD4 response had a virological failure while 2 patients with a CD4 count of ≤ 250 cells/µL had virological failure. There was good CD4 recovery following the initiation of ART. The mean CD4 count at initiation of ART increased from 229.65 cells/µL to 453.33 cells/µL after 1 year of commencement of ART (p<0.001), while it increased to 485.97 cells/µL after 5 years of treatment.

DISCUSSION

The study showed 15-45 years age category which is the sexually active and economically productive age group as the common age group for the acquisition of HIV i.e. 88.5% which is similar to the HIV estimates in Nepal, 2017. The adult HIV prevalence (15-49 years) was 0.17% in 2016.[3,6] Sexual transmission was the dominant mode of transmission (79%) followed by parenteral route (15%). The major mode of transmission in south and south east Asia is heterosexual transmission.[10]

The WHO clinical staging system for HIV/AIDS is used where there is unavailability or limited access of CD4 count and viral load testing, and the clinical staging highlights the use of clinical parameters for the management of HIV/AIDS patients.[11] In the study, the mean CD4 count of patients in WHO clinical stage I was 405.69 cells/µL. The mean CD4 count was 190.11 cells/µL, 165.9 cells/µL and 167.67 cells/µL for stage II, III and IV respectively. The mean CD4 counts in all the 4 clinical stages were less than 500 cells/µL. The difference in average baseline CD4 counts between stage III and IV and stage I and II was significant which suggest that the baseline mean CD4 count was low with severity

Table 3. Comparison of mean CD4 counts between the various WHO clinical stages

WHO clinical stage	Baseline CD4 (Md±IQR)	p-value
Stage III&IV	147±157 cells/µL	0.015
Stage I&II	269±394 cells/µL	

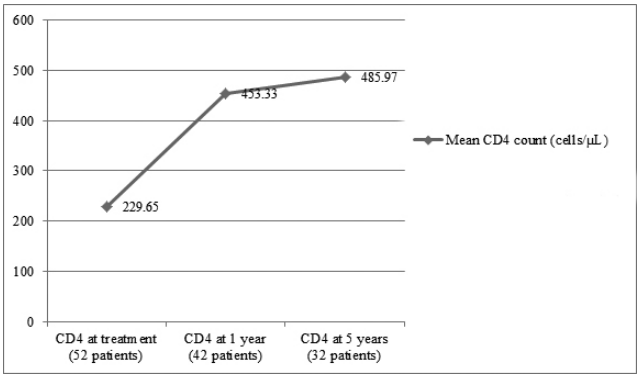

Figure 1. Progression of mean CD4 cell count after initiation of ART of patients who had recorded CD4 data

of clinical stage (p=0.015). The results are comparable to other studies carried out by Edathodu et al. in Saudi Arabia and Ilovi et al. in Kenya.[12,13] Like CD4 count, the clinical findings included in WHO clinical staging can be used in resource limited settings as a guide for the management of HIV patients.

Achieving virological suppression and CD4 recovery is the main goal of ART. The current recommendation for Nepal states that if viral load is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure. The patients can be misclassified into treatment failure despite virological suppression if immunological failure is only considered and the patients are at risk of unnecessary switch to second-lineregimen.[6,8] In this study also there was discordance between immunological and virological response in patients taking ART for more than 2 years duration. Four patients with a recent CD4 count of ≤ 250 cells/µL had virological suppression. Two patients with better CD4 responses had a virological failure. A study done by Prabhakar et al. in India among 251 individuals on ART with immunological failure revealed 28 patients with discordant virological response who had plasma level of HIV below the limit of detection but the CD4 + cell count response was blunted.[14] Another study done in India among 50 WHO defined immunological failure cases, 16% had virological failure.[15] Thus patients with poor immunological response still can have virological suppression. Hence, both immunological and virological response has to be monitored to declare treatment failure and switch to second line ART.

There is a CD4 response with increased CD4 count during the first year of ART. After that CD4 count plateaus and then continues to increase again during the second year of treatment.[5] The mean CD4 count at ART initiation

increased from 229.65 cells/µL to 453.33cells/µL after 1 year of commencement of ART (p<0.001), while it increased to 485.97 cells/µL after 5 years of treatment. The significant increment of mean CD4 count is similar to the study conducted in Nepal by Tiwari et al. which showed significant CD4 response after six months of ART.[16] The finding on long term CD4 response appear to agree to a collaborative analysis of prospective studies on long term immunologic response to ART in low-income countries.[17] A study done by Montarroyos et al. found the factors affecting the kinetics of CD4 response which included patient's age, smoking, use of illicit drugs, hospital treatment, changing doctors and the use of ART.[18]

Viral load above 1000 copies/mL based on two consecutive viral load measurements in 3 months, with adherence support following the first viral load test is defined as Virological failure.[6] In this study, 4 patients (7.7%) who were taking ART for more than 2 years had viral load more than 1000 copies/mL, hence they were considered as virological failure while 91.11% of patients with CD4 ≥ 200 cells/µL had viral load of < 400 copies/ml. The virological failure is comparable to the study done in Nepal (9.92%).[7] Another study done in the National Public Health Laboratory had shown virological failure rate in Nepal fall drastically from 35.9% in 2009 to 10.2% in 2015 with increasing viral load testing coverage.[19] The result is almost similar to targeted by UNAIDS globally in 2014 which highlighted that 90% of all people accessing antiretroviral therapy are virally suppressed by the year 2020, and Nepal is also committed to working on 90-90-90 strategy and achieving the targets.[6,20] Wang et al. had shown Injecting drug use as a route of HIV transmission, higher CD4 count at baseline and non adherence to treatment as important risk factors for virological failure.[21] A study done in Ghana had shown strong evidence of association between having CD4 count < 350 cells/µL after 6 months on ART and having a diagnosis of tuberculosis since HIV diagnosis and viral load > 1000 copies/ml after 6 months on ART.[22]

There are limitations to the study. The number of enrolled PLHIV is low. The viral load testing is not easily accessible because of the limited resource. The failure rates were determined based on a single point testing of the viral load because of which the exact proportion of virological failure couldn't be determined. The CD4 count reports within a window of 6 months were taken into consideration. Despite these limitations, this study will certainly provide an overview of treatment outcomes in ART centers outside the Kathmandu valley.

CONCLUSION

There are optimal CD4 recovery and virological suppression as expected in this study. Both immunological and virological monitoring has to be done to assess the treatment response, diagnosing treatment failure and switching to second-line ART regimen.

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