Virologic Response Following a Switch to Dolutegravir-based Regimen in People Living with HIV/AIDS at a Tertiary Care Center in Nepal

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ABSTRACT

Background

The dolutegravir-based antiretroviral regimen is the preferred first-line regimen for the management of people living with human immunodeficiency virus in Nepal recently. It is considered safe to transition to a dolutegravir-based regimen for children and adults on Nevirapine and Efavirenz-based regimens.

Objective

To determine the virologic response following the transition to a Dolutegravir-based regimen in people living with human immunodeficiency virus previously taking Nevirapine and Efavirenz-based regimen.

Method

This is a retrospective cohort study including people living with human immunodeficiency virus/ acquired immunodeficiency syndrome (HIV/AIDS) who were transitioned to Tenofovir/Lamivudine/Dolutegravir previously on other antiretroviral therapy regimens for at least 6 months and who had their viral load test done before transition. The medical records of patients were reviewed from records available at the antiretroviral therapy clinic of Dhulikhel Hospital. The viral load done at least 3 months after switching to the Dolutegravir-based regimen was recorded. Descriptive analysis of socio-demographic and clinical characteristics data was done.

Result

Fifty-seven people living with human immunodeficiency virus/ acquired immunodeficiency syndrome who transitioned to a Dolutegravir-based regimen previously on other antiretroviral therapy regimens for at least 6 months were included in this study. Tenofovir/Lamivudine/Efavirenz (47.4%), Zidovudine/ Lamivudine/Nevirapine (22.8%) and Zidovudine/Lamivudine/Efavirenz (17.5%) were the most common antiretroviral regimens before transition. The majority of the patients (86%) had suppressed viral load of fewer than 40 copies/mL before the switch. Following the transition, 96.5% of the patients had suppressed viral load of fewer than 40 copies/mL.

Conclusion

Dolutegravir-based antiretroviral regimen led to untransmittable viral load following a switch from Nevirapine and Efavirenz-based regimen.

KEY WORDS

Antiretroviral therapy, Dolutegravir, Human immunodeficiency virus, Viral load

INTRODUCTION

The first human immunodeficiency virus (HIV) case was detected in Nepal in 1988. Antiretroviral therapy (ART) has been available free of cost in Nepal for all eligible people living with HIV/AIDS (PLHA) since 2004.[1] According to earlier reports in 2016, 11089 HIV-infected patients were undertaking ART in Nepal. Among them, 8003 patients were on first-line therapy and 142 patients were taking second-line antiretroviral therapy. The total PLHA currently taking ART increased to 20,883 in 2021.[1,2]

Dolutegravir (DTG) a recently approved integrase inhibitor has become an effective treatment for patients who are on other antiretroviral regimens in addition to treatment-naïve patients.[3] HIV-2 infections which are naturally resistant to Efavirenz are also susceptible to DTG. Rapid and sustained viral load suppression in addition to lesser chances of developing drug resistance is achieved with the use of a fixed-dose combination at a lower cost has made DTG a preferred first-line ART regimen.[4,5] Nepal published national HIV testing and treatment guidelines in May 2020 regarding the transition to a DTG-containing regimen as first-line ART as the results from the national HIV pre-treatment drug resistance conducted in 2016 revealed more than 10% resistance to non-nucleoside reverse transcriptase inhibitor (NNRTI). Routine viral load (VL) testing is required for switching to the optimal regimen if the VL report is older than 12 months otherwise VL testing is not a requirement for transitioning.[4] The DTG-based regimen was introduced recently in Nepal and a study regarding the virological response to the DTG-based regimen has not been commenced in Nepal.

METHODS

This is a retrospective cohort study including PLHA who transitioned to Tenofovir/Lamivudine/Dolutegravir (TLD) previously on other ART regimens for at least 6 months and who had their viral load test done before transitioning to TLD, from March to August 2021. The medical records of PLHA were reviewed from records available at the antiretroviral therapy clinic of Dhulikhel Hospital. Information regarding the socio-demographic profile and clinical characteristics were recorded. The socio-demographic profile like age at diagnosis of HIV infection, gender, and the clinical characteristics including risk exposure, CD4 count, viral load before the commencement of TLD, ART regimen, and duration of ART was recorded from the clinical records. The viral load done at least 3 months after switching to TLD was recorded. PLHA who were not tested for viral load after transitioning to TLD, treatment failure patients, and newly diagnosed PLHA commenced directly on TLD were excluded. Fifty-seven 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.

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) 25.0 software for windows. Descriptive analysis of socio-demographic and clinical characteristics data was done. Bivariate analysis was done with paired t-test. The tests were considered statistically significant when the p value < 0.05.

RESULTS

Fifty-seven PLHA who transitioned to TLD previously on other ART regimens for at least 6 months were included in this study. The majority of the patients 73.7% were in the age group of 20-40 years at diagnosis of HIV infection with a mean age of 33.77 ± 9.41 years. Most of the patients were male (50.9%). Migrants (26.3%), Spouse/Partners of migrants (22.8%), and Persons who inject drugs (PWID) (17.5%) were the commonest risk exposure in such patients. The mean CD4 count at baseline was 261.13 ± 233.86 cells/µL and ranged from 11-1057 cells/µL. Around 72% of the patients were diagnosed with HIV infection for more than 5 years duration whereas 65% of the patients were receiving ART for more than 5 years duration. TLE (47.4%), ZLN (22.8%), and ZLE (17.5%) were the most common ART regimens before patients were transitioned to the TLD regimen.

The majority of the patients (86%) had suppressed viral load of fewer than 40 copies/mL. Four patients had a viral load of 40 - 1000 copies/mL and 4 patients had a viral load of more than 1000 copies/mL before switching to TLD. Following the transition to TLD, 96.5% of the patients had suppressed viral load of fewer than 40 copies/mL whereas only 2 patients had a viral load of 40-1000 copies/mL. Table 2 shows the changes in viral load of individual patients following the switch to TLD in different ART regimens. Eight patients who had a viral load of more than 40 copies/mL had viral suppression of fewer than 40 copies/mL following the transition whereas 2 patients with viral load suppression developed viral load > 100 copies/mL following the switch to TLD. There was no significant change in serum creatinine and ALT level following the switch to the TLD regimen.

DISCUSSION

TLE (47.4%), ZLN (22.8%), and ZLE (17.5%) were the most common ART regimens before patients were transitioned to the TLD regimen. The National HIV and testing guidelines in 2017 recommended the initiation of ART in all adults and adolescent HIV-infected patients irrespective of CD4 count or clinical stage, as soon as found positive. TLE was the preferred first-line regimen, and ZLE/ZLN/TLN/TLD were considered alternative first-line regimens. Later in 2020, Nepal adopted DTG containing regimen as a preferred first-line regimen for adults, adolescents, and pregnant or

Table 1. Sociodemographic and clinical characteristics of PLHA (n=57)

Variable	n (%)
Age at diagnosis(n=57)	
< 20	3(5.3)
20-40	42(73.7)
40-60	11(19.3)
> 60	1(1.7)
Gender(n=57)	
Male	29(50.9)
Female	28(49.1)
Risk exposure(n=57)	
Migrants	15(26.3)
Spouse/Partner of migrants	13(22.8)
PWID	10(17.5)
Vertical transmission	3(5.3)
Client of sex worker	2(3.5)
MSM	1(1.8)
Others	13(22.8)
Baseline CD4 count (n=51)	
< 200	25(49.0)
200-350	16(31.4)
350-500	3(5.9)
> 500	7(13.7)
Duration of HIV diagnosis (years) (n=57)	
< 5	16(28.1)
5-10	12(21.0)
10-15	25(43.9)
> 15	4(7.0)
Treatment duration (years)(n=57)	
< 5	20(35.1)
5-10	18(31.6)
10-15	16(28.0)
> 15	3(5.3)
ART before the switch to TLD (n=57)	
Tenofovir/Lamivudine/Efavirenz (TLE)	27(47.4)
Zidovudine/Lamivudine/Nevirapine (ZLN)	13(22.8)
Zidovudine/Lamivudine/Efavirenz (ZLE)	10(17.5)
Tenofovir/Lamivudine/Nevirapine (TLN)	7(12.3)
Viral load before the switch to TLD (n=57)	
< 40	49(86.0)
40-1000	4(7.0)
> 1000	4(7.0)
Viral load following the switch to TLD	
< 40	55(96.5)
40-1000	2(3.5)

breastfeeding women and has also considered transitioning to DTG based regimen for children and adults who were on Nevirapine (NVP) and Efavirenz (EFV) based regimens.[4,6] It

Table 2. Individual cases with changes in viral load following the switch to TLD in different ART regimens

Case	ART regimen before the switch	Viral load before switching to TLD	Viral load following the switch to TLD
A	TLE	48000	<40
B	TLE	33579	<40
C	TLE	383	<40
D	TLE	65	<40
E	TLE	63	<40
F	ZLE	14335	<40
G	ZLE	183	<40
H	TLN	1824	<40
I	TLE	<40	113
J	TLE	<40	102

Table 3. Laboratory parameters before and after the switch to TLD

Lab parameter	Before TLD	After TLD	p value
Creatinine	0.74±0.17	0.78±0.22	0.218
ALT	34.96±20.55	41.46±49.02	0.230

can be considered from these results that ART centers are strictly following the National guidelines for managing HIV patients in Nepal. In this study, the majority of the patients (86%) had suppressed viral load of fewer than 40 copies/mL. Four patients (7%) in this study had a viral load of more than 1000 copies/mL before transitioning to TLD among which two patients were in the TLE regimen and 1 patient in each ZLE and TLN regimen. A descriptive cross-sectional study done in Nepal in 2015 in HIV-1 seropositive individuals undertaking ART for at least 6 months revealed that 9.92% had a virological failure (viral load > 1000 copies/mL) and TLE was the most frequently used ART regimen followed by TLN and ZLN. Virological failure with the use of ZLE and TLE was 11.76% and 11.34% respectively.[7]

Following the transition to TLD, 96.5% of the patients had suppressed viral load of fewer than 40 copies/mL whereas only 2 patients had a viral load of 40-1000 copies/mL in this study. A systemic review and meta-analysis of randomized controlled trials comparing dolutegravir-containing ART to non-dolutegravir-containing ART in HIV-infected treatment-naive patients showed suppression of VL < 50 copies/ml at 48 weeks was higher in the dolutegravir group compared to the alternative agents in the overall comparison, in the subgroups of patients with high or low baseline VL (< or >100 copies/mL).[8] In a retrospective cohort study utilizing programmatic data from the Brazilian HIV Program from 2014 to 2017 including 107647 ART-naive patients who were initiated on either TLE (71.5%) or TLD (10.5%), 90.5% of patients in the TLD group achieved viral load suppression of < 50 copies/mL whereas 84% of patients in the TLE group achieved similar VL suppression.[9] Similarly, a retrospective descriptive study done in Nigeria showed Dolutegravir-

based regimen had superior virologic suppression in transitioned Key population (TLE to TLD) at 3 months compared to key populations on TLE for 6 months. At 3 months post TLD, 88% of transitioned participants achieved untransmittable viral load suppression level (< 200 copies/ml) compared to 76.3% while on TLE.[10] However, there were no studies regarding viral load suppression following the switch to the TLD regimen in Nepal. In the TANGO study, DTG/ Lamivudine (3TC) fixed-dose combination was non-inferior to remaining on a Tenofovir-based regimen through week 48 in virologically suppressed adults with no prior history of virologic failure or known major resistance mutations to NRTIs or integrase inhibitors. The findings of that study support the use of DTG/3TC as a switch option for HIV-infected patients with viral suppression on a 3 or 4 drug regimen.[11]

Most of the patients achieved a viral load of < 50 copies/mL with the initiation of ART within three to six months. There may be the transient elevation of VL to detectable levels up to a maximum of 500 copies/mL, before decreasing to undetectable levels known as viral blips. In this study, eight patients who had a viral load of more than 40 copies/mL had viral suppression of fewer than 40 copies/mL following the transition to TLD whereas 2 patients with viral load suppression developed viral load >100 copies/mL following the switch to TLD. However, all the patients who transitioned to TLD achieved untransmittable viral load suppression levels (< 200 copies/mL). A retrospective study which was done in Sweden in HIV-1-infected ART naïve adults who were commenced on suppressive ART for at least 6 months showed that 10.3% of 736 patients had viral blips with viral load ranging from 56-138 copies/mL. In that study, they also found a higher baseline viral load in subjects with a viral blip and there was a subsequent risk of virological failure with viral blips.[12]

There was no significant change in serum creatinine and alanine aminotransferase (ALT) levels following the switch to the TLD regimen. Lu et al. have shown DTG-containing therapeutic regimens presented with higher serum creatinine elevation and decreased estimated glomerular filtration rate (eGFR) with a significant decrease of eGFR at 4 weeks with no further decline after 4 weeks.[13] Dolutegravir has been shown to inhibit tubular secretion of serum creatinine by organic cation transporters leading to an increase in serum creatinine and decreased eGFR or creatinine clearance (CrCl) without changing true GFR. There is a non-progressive decline in estimated CrCl during the first 2-3 weeks of treatment however true occurrence of true renal adverse actions has not been reported.[14] ART naïve and initial antiretrovirals experienced HIV-1 infected patients are usually associated with liver enzyme elevation.[15] Dolutegravir can be associated with ALT elevations with 2-5% of patients having elevations greater than 3 times the upper limit of normal, however, this elevated ALT was not different from those in comparator groups receiving matched background optimized antiretroviral therapy without dolutegravir.[16] DTG combined with two NRTIs is the preferred first-line regimen in Nepal. The DTG-based regimens have a faster rate of viral suppression, higher viral suppression (88% vs 81% with EFV), higher gains in CD4 count (267 cells vs 208 cells) at 48 weeks after ART initiation, fewer adverse events, lower risk of discontinuing treatment, fewer drug interactions and fewer chances of developing drug resistance compared with EFV-based regimens among treatment-naive adults.[4]

There are limitations to the study. The number of enrolled PLHA who were switched to TLD is less in number. Most of the patients enrolled in the study had suppressed viral load before switching to TLD. It would have given a clear idea if patients with a viral load of more than 1000 copies/mL were enrolled. However, it was not possible due to the minimum number of patients. Nevertheless, this study will give an overview of the virological response to Dolutegravir-based regimens in the Nepalese population.

CONCLUSION

In conclusion, switching from initial antiretroviral therapy to a dolutegravir-based antiretroviral regimen led to an untransmittable viral load in the studied population. Dolutegravir-based regimens can be considered safe for transition in PLHA who are on Nevirapine (NVP) and Efavirenz (EFV) based regimens.

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