ORIGINAL ARTICLE

Viral suppression with antiretroviral therapy after single drug substitution of efavirenz with dolutegravir at an HIV Centre in Karachi, Pakistan

Saima Samad[1], Nazish Misbah[1], Sughand Memon Mir[1], Sadia Ishaque[1], Obaidullah Farooqui[2], Shehla Baqi[3]

[1]Shaheed Mohtarma Benazir Bhutto Institute of Trauma, Karachi Pakistan
[2]Pakistan Air Force Karachi Institute of Economics and Technology, Karachi Pakistan
[3]Bronxcare Health System, New York, United States of America

ABSTRACT

Background: AIDS was first reported in the 1980s. The HIV prevalence rate among Pakistani adults is 0.2%. The Sindh Center for AIDS Control Programs (SACP) was established in Karachi in 2006. In 2018, the SACP introduced the integrase chain transfer inhibitor dolutegravir (DTG) and lamivudine (3TC) and tenofovir diproxilfumarate (TDF). Patients who developed virological failure on Efavirenz, 3TC, and TDF were switched to DTG/3TC/TDF. As the two nucleoside reverse transcriptase inhibitors remained the same, EFV and DTG were effectively substituted as single agents. We assessed immunological, virological and clinical responses to DTG.

Material and Methods: A retrospective chart review was conducted at the SACP of adults with virological failure on EFV/3TC/TDF who were switched to DTG/3TC/TDF from April 2019 till November 2023.

Results: The 14 patients were switched after a mean of 28.2 months of prior antiretroviral therapy with mean CD4 of 116 cells/mm^3. Mean age was 28.4 years with 7 (50.0%) males.12 were adherent to the DTG regimen; 11 (92 %) achieved viral suppression. The Mean period of suppression was31 months. There was no clinical or immunological failure with upsurge of mean CD4 to 632cells/mm^3.

Conclusion: The patients with virological failure on an efavirenz-based regimen are likely to have viral suppression after switch to a dolutegravir-based routine even if they potentially have NRTI resistance. These results are relevant to HIV programs in resource poor settings where switches between regimens are often implemented without frequent viral load or resistance testing.

Keywords: HIV, Dolutegravir, Efavirenz, Tenofovir, Viral suppression, CD4 count

BACKGROUND

AIDS (Acquired Immune Deficiency Syndrome) was first reported in the 1980s and has affected more than 75 million people worldwide. In 2021, an estimated 3.4 million people worldwide are living with HIV. WHO has identified Pakistan as a country of concentrated epidemic. HIV prevalence among adults aged 15-49 is 0.2%, with the latest estimates of 270,000 adults living with HIV.[1]

As of June 2023, approximately 60,439 HIV cases were registered with the National AIDS Control Program (NACP), and 38,234 were receiving antiretroviral treatment (ART) at 74 HIV centers.[2] The group at the highest risk were the users of injected drugs, who represented 38% of the registered patients.[3,4] In addition, poor infection control practices in healthcare facilities and unsafe blood transfusions have been recognized as major risk factors for infectious diseases.[5] The Sindh AIDS Control Program Centre (SACP) was established at the Ruth KM Pfau Civil Hospital in Karachi in 2006.[6] In 2018, the SACP launched Dolutegravir, a new integrase strand transfer inhibitor (INSTI) that blocks the integration of the HIV genome into host DNA in a single-dose combination (FDC) with lamivudine (3TC) and tenofovir diproxilfumarate (TDF) for the newly diagnosed patients as well as for the treatment experienced patients. The latter included patients on efavirenz (EFV)-based regimens of EFV/3TC/TDF and those who were virologically suppressed, had side effects, or had virological failure.[7] These patients were changed to DTG/3TC/TDF. Since the 2 nucleoside reverse transcriptase inhibitors

Correspondence: Dr. Saima Samad, Infectious Diseases Fellow, Shaheed Mohtarma Benazir Bhutto Institute of Trauma, Karachi Pakistan

Email: dr.saima_samad@yahoo.com

This article can be cited as: Samad S, Misbah N, Mir SM, Ishaque S, Farooqui O, Baqi S. Viral suppression with antiretroviral therapy after single drug substitution of efavirenz with dolutegravir at an HIV Centre in Karachi, Pakistan. Infect Dis J Pak. 2024; 33(1): 24-30.
DOI: https://doi.org/10.61529/idjp.v33i1.277

Receiving date: **06 Dec 2023** Acceptance Date: **27 Feb 2024**
Revision date: **14 Feb 2024** Publication Date: **30 Mar 2024**

remained the same, this switch amounted to essentially a single drug substitution from EFV to DTG.

However, one of the steadfast principles of antiretroviral therapy has always been that single drug substitution must be avoided as it can lead to the emergence of drug resistance. Resistance testing to guide management is also strongly recommended.[8] Common mutations include development of M184V in a lamivudine and emtricitabine based regimen leading to decreased susceptibility to these agents, although when options are limited, HIV care providers have continued lamivudine or emtricitabine despite the presence of M184V in order to select for a less fit virus.[9] The mutation K65R leads to resistance to tenofovir. The guidelines state that second line ART regimen should have a new drug class or drug to which individuals have been exposed but with no evidence of cross-resistance and must include two or three active ingredients. The guidelines have repeatedly warned that adding only one active agent to a weak regimen is the same as monotherapy and there is a risk of failure.

The Genotypic resistance testing is not routinely available in resource limited settings such as the SACP. Empiric first line regimens initiated by SACP are based on WHO guidelines which have advised HIV programs to utilize a DTG based regimen as preferred first line treatment.[10,11]

Dolutegravir has been shown to be equivalent or superior to current treatment regimens in experienced and naïve patients, including patients who have previously failed raltegravir or elvitegravir.[12] Dolutegravir has a high genetic barrier to resistance and its use in ART regimens has been associated with sustained viral suppression and immunological recovery.[13] In addition to first line therapy, dolutegravir is also recommended as second line therapy, although the efficacy is uncertain when dolutegravir is given with NRTIs that are predicted to be compromised by resistance.[11] Therefore, WHO guidelines recommend changing one of the NRTIs from tenofovir to zidovudine when switching to second line therapy.[11]

However, these principles and guidelines were challenged in the RCT NADIA study conducted in seven sub-Saharan African sites, where tenofovir was continued in the second line regimen and found to be superior than switching to zidovudine in terms of achieving viral suppression, reducing viral rebound, increasing CD4 cell count and diminishing the risk of high level dolutegravir resistance.[14] The NADIA trial also provided evidence that patients, even if they have extensive NRTI resistance, are likely to have viral suppression after a switch to dolutegravir.[14]

A prospective interventional study conducted in Cape Town South Africa evaluated the recycling of tenofovir and lamivudine/emtricitabine with dolutegravir in second line ART and demonstrated that a high proportion of participants achieved viral suppression. [15]

The data about changing ART in this manner as second line treatment in Pakistan is almost absent. We therefore carried this study so as to see the effects in our HIV center where patients failing to an EFV containing regimen were switched to a DTG containing regimen with two NRTIs not changed. This switch was performed without the benefit of earlier genotypic determination of NRTI resistance. Implementing WHO's recommendation of TDF switch to zidovudine is also not possible as that drug was also not in stock. Therefore, we felt that the focus should be on these patients who completely stopped efavirenz intake and started dolutegravir as a single drug substitution.

MATERIAL AND METHODS

This descriptive retrospective cross-sectional study was conducted at The Sindh AIDS Control Program (SACP) center at the Ruth KM Pfau Civil Hospital in Karachi, Sindh, Pakistan.

This study included HIV infected patients who were registered at the SACP and were above the age of 18 years, were not virally suppressed on EFV/3TC/TDF for last six months and were switched to DTG/3TC/TDF for salvage therapy. They were further required to have a minimum of 6 months of follow-up at the SACP center and at least two viral load determinations documented after start of the DTG regimen in order to be included.

Definitions according to the National AIDS Control Program, Pakistan.[15]

Virological failure: Plasma VL above 1000 copies/ml (based on two consecutive viral load measurements within a 3-month interval, with adherence support following the first viral load test, and after at least six months of starting a new ARV regimen.

Immunological failure: CD4 count not rising above 250 cells/mm^3 following clinical failure or persistent CD4 cell count below 100 cells/mm^3.

Clinical failure: New or recurrent clinical event indicating severe immunodeficiency (WHO clinical

stage 4 condition) after six months of effective treatment.

Viral Suppression: Viral load less than 500 copies/ml.

Adherence: Documentation of >95% of scheduled clinic visits and doses as determined by pill counts and self-reports at each visit.

All patients who had been on Dolutegravir treatment from the time the SACP started DTG in 2018 were identified from the records. A chart review of these patients was conducted using manual reviewing and the reason why they changed from a prior ART to DTG containing regimen was taken note of. These patients who met the inclusion criteria of our study also went the additional analysis and their medical charts were reviewed from the time DTG was given till their last visit documented. The period of our study was from the month of April 2019 when the first patient who was not responding to therapy was started on a DTG-based regimen to the month of November 2023, where the data were collected, analysed and the results were represented.

The features of patients, laboratory results, clinical events and the outcome were recorded. The laboratory tests indicated by HIV RNA PCR level, CD4 cell count and complete blood count, as well as liver function tests, were documented twice during the study: at the point of the switch from EFV to DTG and then the last values documented in the study. The progress notes by the HIV care providers in charts were assessed to see if the patients were taking their HIV medication well without side effects, any new disease that developed or whether they had any weight gain or loss. The primary outcomes of the study on the patients that use DTG containing protocol include virological failure, viral suppression, immunological failure or recovery, clinical response or new HIV related clinical event, and death. Other outcomes were patients lost-to-care-or-transfer. The Patients who met the inclusion criteria were identified and data was entered into Microsoft office Excel 2013. The descriptive statistics were calculated for quantitative variables. The distribution of patients by socio-demographic characteristics and other relevant variables in the study were described using descriptive analysis and were presented as mean or grouped into ranges for determination of percentages. The two main variables, CD4 count and viral loads, were studied and their time series was plotted through MS excel using scatter plot to observe the overall trends of the values over time.

RESULTS

33 patients were recognized who were switched from EFV/3TC/TDF to DTG/3TC/TDF. The indications for the switch were in order to comply with new WHO guidelines in 2 (6.06%) patients, due to adverse effects to efavirenz in 16 (48.4%), and virological failure in 15 (45.4%).

Of 15 patients with virological failure, 14 met the study inclusion criteria since one patient was excluded as he was lost to follow-up after only 4 months of starting the new regimen and had only one viral load determination documented. He did, however, achieve viral suppression and was undetectable at 4 months.

Of 14, the mean age was 28.4 years; there were 7 (50.0%) males. Most patients were from Karachi. Of 14, 6 (42.8%) and 2 (14.3%) patients were classified as WHO HIV Clinical Stages III and IV, respectively. The 14 patients had already been on antiretroviral therapy for an average duration of 28.2 months prior to the switch. The mean CD4 was 116 cells/mm^3 prior to the switch to DTG/3TC/TDF regimen.

Of 14 patients, 12 were adherent to their new DTG regimen. Of the two patients that were non-adherent, one was lost to follow-up and one died. For purposes of evaluation of response to the new DTG regimen, we followed only the 12 adherent patients for an average of 31 months. Of 12, 11 (92 %) achieved viral suppression whereas one patient had virological failure. He was suppressed for 20 months and then became detectable. He was switched to Atazanavir/ ritonavir (ATV/r) based regimen when repeat VL at 23 months was still high, but he also failed the protease inhibitor regimen despite documentation of adherence to ART. Mean duration of suppression for 12 patients on DTG regimen was 31 months (range of 20-38). There was no documentation of immunological or clinical failure (Table-II). A steady increase in CD4 cell counts over time on the DTG regimen was documented (Figure-I). Of 11 patients who achieved viral suppression, 9 were reported as undetectable at < 20cps/ml (Figure-II).

Table-I: Baseline characteristics of HIV Infected patients with virological failure on EFV/3TC/TDF (n=14).

Demographic Characteristics	**n (%)**
Mean Age (Years)	28.42 (20-40)
Gender	
Male	7 (50.0)
Female	5 (35.7)
Transgender	2 (14.2)
Occupation	
Housewife	4 (28.5)
Driver	1 (7.1)
Dancer	2 (14.2)
Unskilled worker	3 (21.4)
Hairdresser	1 (7.1)
Office worker/ shopkeeper	2 (14.3)
Domestic Staff	1 (7.1)
City of Residence in Sindh	
Karachi	13 (92.8)
Thatta	1 (7.1)
HIV Stage as per WHO Classification	
Stage I (Asymptomatic)	1 (7.1)
Stage II (Mild Symptoms)	5 (35.7)
Stage III (Advanced Symptoms)	6 (42.8)
Stage IV (Severe Symptoms)	2 (14.3)
Mean Duration of ART months	28.2 (11-70)
Mean CD4 cells/mm3	116
Clinic Disposition	
In HIV Care at SACP	12 (85.7)
Non-adherent and Lost to Care	01 (7.1)
Non-adherent and Died	01 (7.1)

Table-II: Laboratory Parameters and Outcome of 12 Patients Adherent to DTG/3TC/TDF Regimen

Laboratory Parameters	**Baseline (prior to switch)**	**Most recent values on record (after switch)**
MeanCD4 count (cells/mm3)	125	632
Mean HIV RNA PCR (cps/ml)	475157.3	<500 (n=11) 18100 (n =1)
Mean Hemoglobin (g/dL)	8.25 (5-11)	10.91 (7-13)
Mean Creatinine (mg/dl)	0.80 (0.6-1)	0.85 (0.7-1)
Mean AST (u/l)	18.25 (8-28)	15.83 (8-35)
Mean ALT (u/l)	24.25 (10-53)	19.5 (8-35)
Mean Weight(kg)	50 (32-62)	61 (48-79)
Mean Duration of DTG/3TC/TDF (months)	31 months (20– 38)	
Outcome	**n (%)**	
Viral Suppression	11 (91.63)	
Virological Failure	1 (8.3)	
Mean Duration of Sustained Suppression in Months	31 (range 20-38)	
Immunological failure	None	
Clinical Failure	None	
In HIV Care at SACP	12	

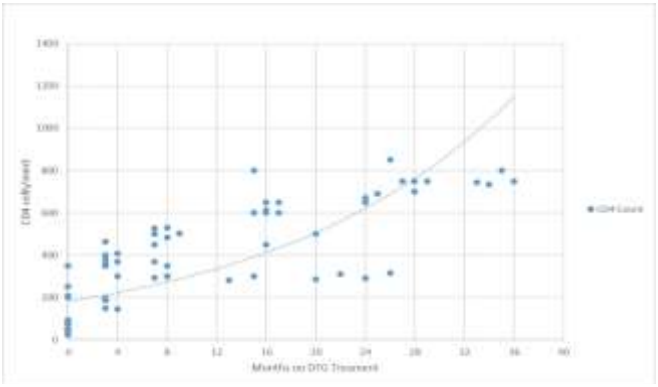

Figure-I: CD4 cell counts in 12 patients adherent to new DTG/3TC/TDF regimen.

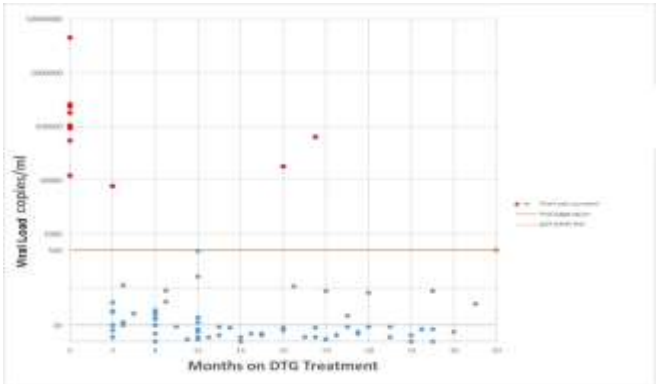

Figure-II: HIV RNA PCR in 12 patients adherent to new DTG/3TC/TDF regimen.

DISCUSSION

Our research revealed that, single drug substitution from efavirenz to dolutegravir while retaining the same two NRTIs among patients with virological failure led to sustained virological suppression in all patients with the exception of one. The regimen using DTG as the backbone was just as successful although the nucleosides coupled to DTG were predicted to lack activity because of drug mutation. Further, the WHO recommendation of using zidovudine instead of tenofovir was disregarded. These results are consistent with the NADIA study which recommends dolutegravir in combination with NRTIs as a treatment for HIV-1 infection, even in those patients with extensive NRTI resistance upon whom no NRTIs are predicted to be active.[14] The reason for preserved NRTI activity is uncertain but it may be due to impairment of viral replicative capacity by NRTI resistance mutations.[16]

Out of 12 patients, we reported that only 1 had virological failure in the DTG based treatment and or the ATV/r-based treatment. He is eligible for resistance screening, but unfortunately this is not offered at the SACP. Dolutegravir resistance is thought to be scarce in the case the drug is co administered with fully potent NRTIs. Reports from the NADIA study of intermediate-to high-level dolutegravir resistance among four patients within 48 weeks present a challenge to public health intervention, particularly in poor settings where frequent viral load monitoring is not permissible and integrase resistance testing is not available or is expensive.[14] The 2023 study, on the other hand, was promising as it evaluated the effectiveness and safety of using only two drugs, dolutegravir/ lamivudine (DTG/3TC), and it showed that most participants had sustained viral suppression, no treatment-emergent resistance, and good safety for more than 48 weeks.[17]

This study demonstrated a substantial immunological response as documented by different studies elsewhere.[18,19] Adverse event to the DTG-based treatment were not reported in our study.

In the context of comparing performance of dolutegravir based second-line treatment vs dolutegravir based treatment as a first regimen, virological suppression percentages are comparable. A 2020 study by Calamy A *et al* comparing dolutegravir based with low-dose efavirenz based regimen as first line treatments for HIV-1 infection found that at week 96 dolutegravir regimen was non-inferior and no dolutegravir resistance had emerged thus making it appropriate for use as first-line antiretroviral regimen. Suppression of viral load was achieved earlier in the dolutegravir trial patients and overweight was more pronounced in this group.[20] A more recent 2023 study conducted in India by Mahale PR *et al* in treatment naïve patients found that viral load suppression was achieved in 55.71% of clients in an efavirenz based treatment group after six months of ART whereas 88.57% of clients achieved viral suppression in the dolutegravir based treatment group, which was highly significant.[18]

The study from India by Mahale *et al* also documented significantly more weight gain at 12 months (mean +6.15 kg) as compared to the EFV-based regimen (mean +1.85 kg).[18] The findings from India are similar to ours where we proved that there was statistically significant weight gain which was a marker of the patients' return to health. However, a study by Brennan *et al* from South Africa disputed in the sense that the benefit of weight increases with dolutegravir and other integrase strand inhibitors should not be obvious in the light of the on-

going increasing obesity rates all over the world which in turn increase the risk of metabolic and cardiovascular diseases.[21]

Although number of patients were small, this study is the first significant analysis of practical experience of a single drug substitution in Pakistan. The findings of the study are useful not only to programs of this sort but also to other existing HIV programs situated in resource-deprived settings where switches are often performed in the absence of viral load testing and resistance testing. A resistance test for those patients who had achieved virological suppression or with virological failure in case of such patient's availability would have been defined as a future study direction. Globally, HIV care providers are switching to universal dolutegravir treatment, a combination that will be used by all patients. Those who are on second and third-line drug regimens and are NRTI-resistant are also likely to have viral suppression after the switch to dolutegravir. Some limitations of the research method employed in this study include the use of retrospective study. It is a single center study with a rather small sample size. This study demonstrated that the switch from efavirenz based treatment to dolutegravir based with single drug replacement was successful.

CONCLUSION

This study shows that patients with virological failure on efavirenz therapy experience virologic suppression after switching to dolutegravir-based therapy, even with high NRTI resistance. These findings are relevant to other HIV programs in low-resource settings where switching regimens without viral load testing or resistance testing is used. The results support a global trend of HIV patients switching to dolutegravir-based treatment.

CONFLICT OF INTEREST

None

GRANT SUPPORT & FINANCIAL DISCLOSURE

Declared none

AUTHOR CONTRIBUTION

Samia Samad: Conception and frame work, Drafting,
Nazish Misbah: Literature search
Sughand Memon Mir: Data collection
Sadia Ishaque: Review of manuscript
Obaidullah Farooqui: Data analysis, data interpretation
Shehla Baqi: Critical review, final approval of the article, study design

REFERENCES

1. www.unaids.org/en/regionscountries/countries/pakistan
2. https://www.cmu.gov.pk/nacp-national-aids-control-programme/nacp-national-aids-control-programmed-treatmzet/
3. Pakistan Country Snapshot 2023 | HIV/AIDS Data Hub for theAsia-PacificRegionpak-snapshot-2023.pdf (aidsdatahub.org)
4. https://www.unaids.org/sites/default/files/country/documents/PAK_2020_countryreport.pdf
5. Mir F, Nathwani AA, Simms V, Abidi SH, Siddiqui AR, Hotwani A, *et al*. Factors associated with HIV infection among children in Larkana District, Pakistan: A matched case-control study. Lancet HIV. 2021; 8(6): e342-e52. DOI: https://doi.org/10.1016/S2352-3018(21)00049-7
6. Baqi S, Abro AG, Salahuddin N, Memon MA, Qamar Abbas S, Baig-Ansari N. Four years of experience with antiretroviral therapy in adult patients in Karachi, Sindh, Pakistan. Int Health. 2012; 4(4): 260-7. DOI: https://doi.org/10.1016/j.inhe.2012.07.002
7. Batool FMS, Dhiloo AU, Ismail HM, Shaikh SM, Baqi S. Experience with dolutegravir in HIV patients at a public sector hospital in Karachi, Pakistan. Pak Armed Forces Med J. 2021;2021; 71(5): 1661-5. DOI: https://doi.org/10.51253/pafmj.v71i5.6288
8. McCluskey SM, Siedner MJ, Marconi VC. Management of virologic failure and HIV drug resistance. Infect Dis Clin North Am. 2019; 33(3): 707-42. DOI: https://doi.org/10.1016/j.idc.2019.05.004
9. World Health Organization. HIV Drug Resistance Report. Geneva: World Health Organization; 2017
10. World Health Organization. Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach. 2nd ed. Geneva: World Health Organization; 2016
11. Update of recommendations on first- and second-line antiretroviral regimens. Geneva: World Health Organization, July 2019 (https://apps.who.int/iris/bitstream/handle/10665/325892/WHO-CDS-HIV-19.15-eng.pdf?ua=1.
12. Kandel CE, Walmsley SL. Dolutegravir - a review of the pharmacology, efficacy, and safety in the treatment of HIV. Drug Des Devel Ther. 2015; 9: 3547-55. DOI: https://doi.org/10.2147/DDDT.S84850
13. Rusconi S, Adorni F, Tau P, Borghi V, Pecorari M, Maserati R, *et al*. Dolutegravir (DTG)-containing regimens after receiving raltegravir (RAL) or elvitegravir (EVG): Durability and virological response in a large Italian HIV drug resistance network (ARCA). J Clin Virol. 2018; 105: 112-7. DOI: https://doi.org/10.1016/j.jcv.2018.06.012
14. Paton NI, Musaazi J, Kityo C, Walimbwa S, Hoppe A, Balyegisawa A, *et al*. Efficacy and safety of dolutegravir or darunavir in combination with lamivudine plus either zidovudine or tenofovir for second-line treatment of HIV infection (NADIA): week 96 results from a prospective, multicentre, open-label, factorial, randomised, non-inferiority trial. Lancet HIV. 2022; 9(6): e381-93. DOI: https://doi.org/10.1016/S2352-3018(22)00092-3
15. Keene CM, Griesel R, Zhao Y, Gcwabe Z, Sayed K, Hill A, *et al*. Virologic efficacy of tenofovir, lamivudine and

dolutegravir as second-line antiretroviral therapy in adults failing a tenofovir-based first-line regimen. AIDS. 2021; 35(9): 1423-32.
DOI: https://doi.org/10.1097/QAD.0000000000002936

16. Ross L, Parkin N, Lanier R. Short communication: The number of HIV major NRTI mutations correlates directly with other antiretroviral-associated mutations and indirectly with replicative capacity and reduced drug susceptibility. AIDS Res Human Retroviruses. 2008; 24(4): 617-20.
DOI: https://doi.org/10.1089/aid.2007.0188
17. Rolle CP, Berhe M, Singh T, Ortiz R, Wurapa A, Ramgopal M, *et al*. Sustained virologic suppression with dolutegravir/ lamivudine in a test-and-treat setting through 48 weeks. Open Forum Infect Dis. 2023; 10(3): ofad101. DOI: https://doi.org/10.1093/ofid/ofad101
18. Mahale PR, Patel BS, Kasmani N. Treatment outcomes of dolutegravir- versus efavirenz-based highly active antiretroviral therapy regimens among treatment-naive people living with HIV. Cureus. 2023; 15(6): e40139. DOI: https://doi.org/10.7759/cureus.40139
19. Ayal MA, Berha AB. Comparative safety and changes in immunologic and virologic parameters of dolutegravir versus efavirenz-based antiretroviral therapies among HIV Patients: A retrospective cohort study. HIV AIDS (Auckl). 2023; 15: 173-90.
DOI: https://doi.org/10.2147/HIV.S396420
20. Calmy A, Tovar Sanchez T, Kouanfack C, Mpoudi-Etame M, Leroy S, Perrineau S, *et al*. Dolutegravir-based and low-dose efavirenz-based regimen for the initial treatment of HIV-1 infection (NAMSAL): week 96 results from a two-group, multicenter, randomized, open label, phase 3 non-inferiority trial in Cameroon. Lancet HIV. 2020;7(10): e677-e87.
DOI: https://doi.org/10.1016/S2352-3018(20)30238-1
21. Brennan AT, Nattey C, Kileel EM, Rosen S, Maskew M, Stokes AC, *et al*. Change in body weight and risk of hypertension after switching from efavirenz to dolutegravir adults living with HIV: Evidence from routine care in Johannesburg, South Africa. EClinicalMedicine. 2023; 57: 101836.
DOI: https://doi.org/10.1016/j.eclinm.2023.101836