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Review article

# A retrospective study on comparison of effects of older art regimen against Dolutegravir based art in PL-HIV

**B S B Mallika[1], Silla Jyothi Prakash[1], Kaniganti Sri Rahitya[1], Pilla S Surya Durga Devi*[1], K V SivaPrasad[2]**

[1] Rangaraya medical college, Kakinada, Andhra Pradesh, India

[2] Department of Pharmacology, Government Medical College, Rajamahendravaram, Andhra Pradesh, India

**Corresponding author:** Pilla S Surya Durga Devi ✉ sreesuryadurgadevi@gmail.com, **Orcid Id**: https://orcid.org/0000-0002-9875-5326
Rangaraya medical college, Kakinada, Andhra Pradesh, India



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## ABSTRACT

According to the WHO guidelines 2020, Dolutegravir-based antiretroviral treatment (ART) is a preferred first-line ART regimen for people living with HIV (PLHIV) because of its efficacy, tolerance, high barrier to resistance, and minimal drug interactions. The main aim of this study is to assess the safety and efficacy of a Dolutegravir based antiretroviral therapy regimen to that of older regimens. A retrospective observational study was conducted among the people who visited the ART center on an Out-Patient basis. One to One interview was taken with the patients who met the inclusion criteria and all the information was noted down in the demographic form. Adverse Drug Reactions were noted in the Suspected Adverse Drug Reaction (ADR) Form and then we assessed causality, severity, and Prevent-ability. All the data was entered into an excel sheet and analyzed using SPSS21 software. Out of the study population of 100, 63% are females and 36% are males. The paired T-test sampling statistics revealed a significant difference between an increase in CD4 count after transitioning to a Dolutegravir-based regimen in comparison with the older regimens ($p<0.001$). 34 ADRs are reported before the transition and 54 ADRs are reported after the transition to Dolutegravir. The most common ADR found was rashes before the transition and blurred vision after the transition respectively. The comparison with various parameters like CD4 count, and viral load, proves that the Dolutegravir-based drug regimen is quite more effective in reducing HIV load. So proper counseling and regular screening are advised to prevent the risks of the newer drug regimens.

**Keywords:** Antiretroviral therapy, Dolutegravir, Dolutegravir transition, Adverse Drug Reactions.

## INTRODUCTION

Highly Active Anti-Retroviral Therapy (HAART) has made a significant change in the lives of people living with HIV (PLHIV) in decreasing AIDS-related deaths and improving quality of life [1]. Treatment majorly focuses on the direct toxic effects of HIV on host cells, mainly CD4 T lymphocytes. The goal of the therapy is to suppress virus replication as much as possible as far as possible [2]. The treatment efficacy of the anti-retroviral medicines are monitored by checking plasma HIV RNA loads and CD4 lymphocyte count for regular intervals [3]. The preferred initial regimen issued by World Health Organization (WHO) for treating HIV infection consist of two nucleoside reverse transcriptase inhibitors (NRTI) combined with non-nucleoside reverse transcriptase inhibitors (NNRTI) [4].

This Fixed Drug Combination (FDC) was given as a single tablet once daily with doses of Tenofovir 300mg, Lamivudine 300mg and Efavirenz 600 mg [5]. Efavirenz which was used previously as first line drug, has presented with various side effects like headache, rashes, dizziness, insomnia and neuropsychiatric symptoms and Resistance to Efavirenz develops rapidly due to point mutation of the enzyme [2,6]. Recently in 2020, WHO has recommended Dolutegravir based drug regimens for both newly diagnosed and for people who are already using a first line ART regimen.

This FDC was given as a single tablet once daily with doses of Tenofovir 300mg, Lamivudine 300mg and Dolutegravir 50mg [5].

Dolutegravir is an alternative second generation viral integrase inhibitor which is active against the strains of HIV and also with no cross resistance with other antiretroviral drugs [7]. Due to high efficacy, tolerability and convenience, high barrier to resistance and minimal drug interactions, it is increasing popular as a starting agent in treatment naive HIV infected patients in high income countries [4,8].

Even it was proven efficacious in various parts of the world; it was reported with various unnecessary Adverse Drug Reactions (ADRs). In India, the studies based on this newer drug regimen are significantly very low in number. Hence, it is imperative to study the efficacy and its ADRs observed in long course of treatment and its preventive strategies and any other newer things that are needed to be explained to all across the world. The main aim of this study is to assess the effectiveness and safety of Dolutegravir linked antiretroviral regimen to that of older antiretroviral regimen.

## MATERIALSAND METHODS

A Retrospective Observational study was conducted for two months (October 2022- November 2022) in Antiretroviral Therapy (ART) Centre at a Tertiary Health care teaching hospital. After approval from Ethics Committee informed consent was taken from People Living with HIV (PLHIV), who visited the ART center for follow-up during the period of two months. One to One interview was taken with the patients and all the information was entered into an excel sheet. We maintained confidentiality by using a unique ID system (ART Number). The details of the patients who met the inclusion criteria were taken. The Inclusion criteria include Adults above 18 years of both genders who are willing to participate in this study; Patients receiving the treatment with standard older drug regimens and Dolutegravir linked regimen for at least one year and attending the hospital for regular follow-up; HIV patients with Tuberculosis (TB), Acute Respiratory Infections (ARI), and other Opportunistic infections(OI). The pregnant and lactating women; Patients on ART for <1 year; Records with incomplete data; Patients who are unwilling to participate in the study were excluded from the study. The demographic details, the regimen and their efficacy profile, and any other prophylactic measures like Cotrimoxazole, Isoniazid Preventive Therapy (IPT) prophylaxis, CD4 count, and viral load values of the patient were recorded in the demographic/record form. Adverse Drug Reactions are noted in the Suspected Adverse Drug Reaction Form [9] and then assessed their causality, severity, and preventability using respective scales [10]. All the data was entered into an excel sheet and was analyzed using SPSS21 software. $P<0.05$ was considered to be statistically significant.

## RESULTS AND DISCUSSION

Out of study population of 100, where the maximum age is 80 years and the minimum age is 15 years, and the mean age is 43 years. It is observed that 46% of the study population belong to the age group 41-50 years, 26% of the study population belong to age group 31-40 years, 11% of the study population belong to age group 51-60 years, 6% of the study population belong to age group 21-30 years, 5% of study population belong to age group 15-20 years, 4% of the study population belong to age group 61-70 years, and 2% of the study population belongs to the age group 71–80 years of age. The majority of participants in the current study were women (63%) followed by men (36%) and transgender people (1%). The majority of those in the study population (93%) contracted HIV through heterosexual relationships. 5% of the participants in the research had contracted the illness by vertical transmission (Mother to Child). 1% of the study participants had contracted the illness from female sex workers, and a further 1% had done so through transgender people. This is shown in table 1.

**Table 1:** Base line parameters of the study population

| Base line Parameters | Study population (N:100) | Percentage (%) |
|---|---|---|
| Age group | | |
| 15-20 | 5 | 5 |
| 21-30 | 6 | 6 |
| 31-40 | 26 | 26 |
| 41-50 | 46 | 46 |
| 51-60 | 11 | 11 |
| 61-70 | 4 | 4 |
| 71-80 | 2 | 2 |
| **Gender** | **Study population (N:100)** | **Percentage (%)** |
| Male | 36 | 36 |
| Female | 63 | 63 |
| Transgender | 1 | 1 |
| Typology | | |
| Heterosexual | 93 | 93 |
| Mother to child | 5 | 5 |
| Female sex worker | 1 | 1 |

The study population were on various regimens before the transition to a Dolutegravir-based regimen. 70% of the study population were on Tenofovir, Lamivudine, Efavirenz (TLE) regimen followed by Zidovudine, Lamivudine and Nevirapine (ZLN) (22%), Tenofovir, Lamivudine and Azatanavir/Ritonavir combination (TLAR) (4%), Abacavir, Lamivudine, Efavirenz (ALE) (2%). Various regimens used by the study population after transition to Dolutegravir based regimen were observed. 93% of the study population are on Tenofovir, Lamivudine and Dolutegravir (TLD) regimen. 4% are on Tenofovir, Lamivudine, Dolutegravir and Azatanavir/Ritonavir regimen (TLD + ATV/R). This was explained in Table 2.

The percentage of people whose baseline CD4 count is less than 350 cells/$mm^3$ are 71%, and CD4 count is in between 350-500

cells/mm$^3$ are 14% and more than 500 cells/mm$^3$ are 15%. The average CD4 Count is 301 cells/mm$^3$. The maximum is 1120 cells/mm$^3$ and minimum is 2 cells/mm$^3$.

**Table 2:** Regimen used by study population before and after transition to Dolutegravir

| Regimen before transition | Number of patients on the regimen (n-100) | Percentage (%) |
|---|---|---|
| TLE | 70 | 70 |
| ZLN | 22 | 22 |
| TLAR | 4 | 4 |
| ALE | 2 | 2 |
| TLN | 1 | 1 |
| ZLE | 1 | 1 |
| **Regimen after transition** | **Number of patients on the regimen (n-100)** | **Percentage (%)** |
| TLD | 93 | 93 |
| TLD+ATV/R | 4 | 4 |
| ALD | 1 | 1 |
| ZLD | 1 | 1 |
| DTG+ATV/R | 1 | 1 |

In older regimen 54% of the study population have CD4 cell count greater than 500 cells/mm$^3$. 26% of the study population have CD4 cell count between 350-500 cells/mm$^3$. 20% of the study population have CD4 cell count less than 350 cells/mm$^3$. The average CD4 count is 583 cells/mm$^3$ with maximum count of 1868 cells/mm$^3$ and minimum count of 42 cells/mm$^3$.

Dolutegravir based regimen 79% of the study population have CD4 cell count greater than 500 cells/mm$^3$. 6% of the study population have CD4 cell count between 350-500 cells/mm$^3$. 15% of the study population have CD4 cell count less than 350 cells/mm$^3$.The maximum is 1445 cells/mm$^3$ and minimum is 92 cells/mm$^3$. There is a significant growth in CD4 cell count from baseline to Pre-Dolutegravir regimen, but there is a greater growth after getting transition to Dolutegravir linked regimen. It is explained in figure 1 (Table 3).

**Figure: 1:** Comparative evaluation of CD4 count at baseline, before and after transition to Dolutegravir

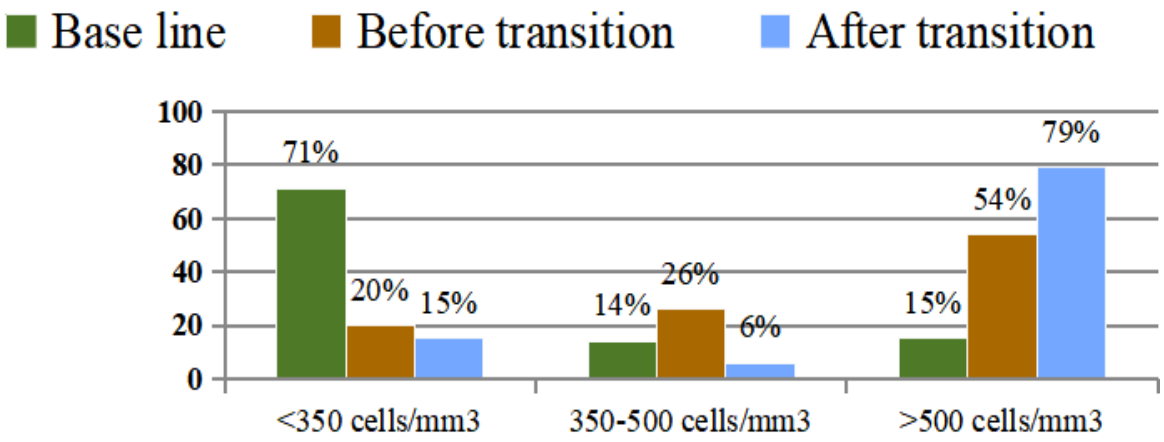


**Table 3:** Paired T-test sampling statistics

| Paired T-test sampling statistics | Older regimen | Dolutegravir linked regimen |
|---|---|---|
| Number of samples | 100 | 100 |
| Mean CD4 count | 583.50 | 694.24 |
| Standard deviation | 313.70 | 303.27 |
| **Pair 1 Older regimen- Dolutegravir linked regimen** | | |
| Mean | -110.74 | |
| Std. Deviation | 247.03 | |
| 95% Confidence Interval of the difference- lower | -166.44 | |
| 95% Confidence Interval of the difference- upper | -55.04 | |
| T | -3.959 | |
| Significance (2- tailed) | <0.001 | |

The sample statistics i.e. Mean CD4 count and Standard Deviation for both older regimen and Dolutegravir linked regimen were shown in **Table 3**. Statistics conducted using the paired T test show that this is statistically significant (p 0.05) because the significance value is less than 0.001. This demonstrates that the paired T-test revealed a significant difference between an increase in CD4 count and the switch to a regimen based on dolutegravir.

The viral load statistics of the study Population before and after transition are denoted here. The patients whose viral loads were not done are 6 in older regimen and 23 in Dolutegravir based regimen. TND (Traces Not Detected) were seen in 44 patients in older regimen and 38 in a dolutegravir-based regimen. 7% before the transition and 8% after the transition of the study population had a viral load less than 20 copies. 13% before the transition and 17% after the transition had fewer than 1000 copies. Finally, 30% before transition and 14% after transition had greater than 1000 copies of viral load.

61% of the study population had received Isoniazid Prophylactic Therapy (IPT) prophylaxis and 39% of study population did not receive this prophylaxis. About 60% of the study population were taken Cotrimoxazole, which is the combination of Trimethoprim and Sulfamethoxazole. Remaining 40% did not take this combination.

34 ADRs are reported before transition and 54 ADRs are reported after transition to Dolutegravir. The most common ADR

found was rashes before transition and blurred vision after transition respectively. The adverse drug reactions were tabulated in table 4. It was explained that these ADRs are 100% possible by causality scale. 99% mildly severe by severity scale and 100% definitely preventable by preventability scale.

**Table 4 Adverse Drug Reactions before and after transition to Dolutegravir regimen**

| Before transition to Dolutegravir regimen | | | After transition to Dolutegravir regimen | | |
|---|---|---|---|---|---|
| **Name of ADR** | **Number of patients** | **Percentage of study population (%)** | **Name of ADR** | **Number of patients** | **Percentage of study population (%)** |
| Rashes | 5 | 15 | Blurred vision | 16 | 29.5 |
| Fatigue and sleep disturbances | 4 | 11 | Polyuria | 5 | 9 |
| Fatigue | 3 | 9 | Weight gain | 4 | 7 |
| Diarrhoea | 2 | 5 | Diabetes | 3 | 5.5 |
| Headache | 2 | 5 | Nausea | 3 | 5.5 |
| Sleep disturbances | 2 | 5 | Blurred vision and polyuria | 3 | 5.5 |
| Anemia | 1 | 3.1 | Increased appetite | 2 | 4 |
| Hemiparesis | 1 | 3.1 | Blurred vision and bilateral leg and knee pain | 1 | 1.8 |
| Neuropathy | 1 | 3.1 | Blurred vision and eye strain | 1 | 1.8 |
| Tremors and difficulty in walking | 1 | 3.1 | Blurred vision and gastritis | 1 | 1.8 |
| Delusions and throat pain | 1 | 3.1 | Blurred vision and peripheral neuropathy | 1 | 1.8 |
| Jaundice and Dysmenorrhea | 1 | 3.1 | Chest pain | 1 | 1.8 |
| Cellulitis | 1 | 3.1 | Fatigue | 1 | 1.8 |
| Hair loss and mental disturbances | 1 | 3.1 | Fatigue, blurred vision and polyuria | 1 | 1.8 |
| Insomnia | 1 | 3.1 | Gastritis | 1 | 1.8 |
| Weakness and Dizziness | 1 | 3.1 | Headache and increased appetite | 1 | 1.8 |
| Meningioma | 1 | 3.1 | Itching | 1 | 1.8 |
| Increased appetite | 1 | 3.1 | Diarrhoea | 1 | 1.8 |
| Nausea | 1 | 3.1 | Nausea and indigestion | 1 | 1.8 |
| Renal problems | 1 | 3.1 | Polydipsia, polyuria and blurred vision | 1 | 1.8 |
| Decreased sleep and constipation | 1 | 3.1 | Polyuria and weight gain | 1 | 1.8 |
| Dizziness | 1 | 3.1 | Sleep disturbances | 1 | 1.8 |
| | | | URTI | 1 | 1.8 |
| | | | Hemiparesis | 1 | 1.8 |
| | | | Increased appetite and weight gain | 1 | 1.8 |
| **Total** | **34** | | **Total** | **54** | |

One hundred PLHIV, who are currently receiving dolutegravir treatment are included in this study. Overall, 63% are female and the mean age was 43 years. We found that there is a surge in the CD4 cell count of the study population after the transition to the newer regimen. In our study, Ninety-two follow-up CD4 counts are available (before and after transition respectively). Immunological effectiveness is defined as no significant fall in CD4 counts (>30%). In our study the immunological effectiveness rates were 95.65% and five individuals had a >30% fall in CD4 count after the transition to dolutegravir at follow-up. Sanjay Pujari et.al, who have taken 62 people as their study population showed immunological effectiveness of 92% and only one individual had a >30% fall in CD4 count at the follow-up.

In our study, 7% reported weight gain, 5.5% with Diabetes, and 4% with increased appetite. In a descriptive cross-sectional qualitative study which was done in Uganda [14], Out of 25 WLHIV (Women Living with HIV) participants, 36% reported weight gain, 16% reported complaints of increased appetite and 8% reported Diabetes. These broad variations of results are due to less sample size of the research done in Uganda which is four times lesser than our sample. When it comes to tolerance, dolutegravir was well tolerated by the study population without any significant grade 3-4 clinical adverse events. In contrary to Sanjay pujari et.a l[13], only one patient

was affected with somnolence, a grade 3 adverse event after the transition to Dolutegravir-based regimen. According to the WHO causality assessment scale, all Adverse Drug Reactions are possibly related to ART due to Fixed Drug Combination. Most ADRs are 99% mild and 1% moderate in severity. One percent is due to Tenofovir-induced renal toxicity. All ADRs have a known treatment, so all are preventable according to the Schumock and Thornton criteria [12,13].

Viral load measurements could not be performed for all individuals. So we couldn't be able to compare the efficacy through viral loads. We could not able to assess the baseline INSTI resistance in our sample population. Differentiation of HIV 1 and 2 wasn't done so it hampered our results in terms of explaining which serotype is more effective for this newer regimen. Limited follow-up time i.e. 2 months and small sample size, i.e. 100.

This represents a significant effort to study the efficacy of the Dolutegravir-based antiretroviral therapy regimen to that of the previous antiretroviral drug regimen. In our study, we found that there is a surge in the CD4 cell count of the study population after the transition to the newer regimen. The majority of the study population has admitted that the newer regimen is quite acceptable and more compliant due to its lower pill burden (single tablet) and doesn't affect their daily lifestyle compared to the previous drug regimens which have more than one tablet. There are some considerable chronic side effects like hyper glycaemia proceeding to Diabetes in the majority of the study group who are complaining of polyuria, polydipsia, and polyphagia. These Adverse effects even if they affect the person, they are not severe and can be easily preventable. This proves that newer drug is more efficacious than the older drug.

## CONCLUSION

Dolutegravir-based regimen was effective for the management of PLHIV in this retrospective study. Dolutegravir-based ART is an excellent option for the management of individuals with HIV infection. Though we have more ADRs due to Dolutegravir based regimen, it might be due to insufficient data on ADRs with an older regimen.

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## ETHICS STATEMENT

An approval from the Institutional Ethical Committee (REG.NO: IEC/RMC/2022/009/UG) was taken before initiating the study. Informed consent was taken from all the participants, and full confidentiality will be maintained. The patient was assured that his/her replies are in no way going to prejudice the treatment given.

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