EXPERIENCE WITH DOLUTEGRAVIR IN HIV PATIENTS AT A PUBLIC SECTOR HOSPITAL IN KARACHI, PAKISTAN

Farzana Batool, Sohaima Manzoor, Azizullah Khan Dhiloo*, Humera Muhammad Ismail, Shah Muhammad Shaikh, Shehla Baqai**

Shaheed Mohtarma Benazir Bhutto Institute of Trauma & Civil Hospital, Karachi Pakistan, *Dow University of Health Sciences, Karachi Pakistan, **Civil Hospital, Karachi Pakistan

ABSTRACT

Objective: To study the tolerability and efficacy of dolutegravir in naïve and experienced patients, their management and outcome.

Study Design: Cross sectional study.

Place and Duration of Study: Ruth KM Pfau Civil Hospital, Karachi Pakistan, from Apr 2018 to Apr 2020.

Methodology: In this study all treatment-naïve and experienced HIV infected patients were included and started on integrase strand-transfer inhibitor dolutegravir (DTG) containing fixed dose combination at Sindh AIDS Control Program (SACP) was conducted. We documented virological suppression, defined as a viral load of <1000 copies/ml, immunological and clinical outcomes.

***Results*:** Eighty-two patients, of whom 53 (64.6%) were Antiretroviral Therapy naïve and 29 (35.4%) experienced, were started on DTG. Fifty-six (68.3%) were males. The median age was 31.6 ± 9. Of 82, 61 returned for their first follow-up visit for assessment and viral load determination. Of 61, adverse effects to DTG were reported in 12 (19.6%), including 9 with pruritis. Of 35 naive patients, 30 achieved virological suppression by 3.3 ± 0.7 months and 1 at 8 months. All 26 experienced patients achieved virological suppression by 4.5 ± 0.9 months. Overall, of 61 patients, 57 (93.4%) achieved virological suppression, of whom 1 had immunelogical failure and none had clinical failure after 6 months of DTG. Three (3.6%) patients died within the first two months of initiating DTG.

Conclusion: Dolutegravir has good tolerability, with virological suppression achieved in the majority, including in highly ARV experienced patients.

Keywords: Antiretroviral therapy, Dolutegravir, Efficacy, HIV, Integrase Inhibitor, Outcome, Pakistan, Tolerability.

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INTRODUCTION

According to WHO, Pakistan has a prevalence of HIV of <1% with an estimated 150,000 cases and the highest incidence of HIV in the region with 21,000 new cases registered annually.[1] The Sindh AIDS Control Program (SACP) introduced the integrase strand-transfer inhibitor dolutegravir (DTG) with lamivudine (3TC) and tenofovir fumurate (TDF) in fixed dose combination (DLT) in April 2018. According to WHO, the lower income countries with pre-treatment resistance to EFV or neviraprine at or above 10% should revise their first line regimen. DTG is now the preferred first line regimen in adults.[2] These guidelines were adopted by our National Guidelines for the prevention and treatment of HIV.[3]

Cruciani and Parisi in 2019 in a meta-analysis of 7 randomized clinical trials in naïve patients demonstrated that dolutegravir containing antiretroviral therapy (ART) have an increased likelihood of achieving viral suppression.[4] DTG is also known to have a high genetic barrier to resistance.[5,6]

Our aim was to study the tolerability and efficacy of dolutegravir in naïve and experienced patients, their management and outcome. There is no such data from Pakistan, to our knowledge. We also wanted to assess compliance by SACP with National HIV Guidelines in the management of patients started on a DTG containing regimen with the objective of improving patient care and outcomes, and ensuring that this newly introduced antiretroviral drug is appropriately utilized.

METHODOLOGY

We conducted a cross sectional, descriptive study at the SACP centre after approval from Ethical Review Committee (ERC#000002/SMBBIT) and permission from Manager of SACP, from Apr 2018 to Apr 2020.

Inclusion Criteria: All the treatment-naïve and experienced HIV infected patients registered at the SACP and started on a DTG containing regimen.

Correspondence: Dr Farzana Batool, Fellow Infectious Disease, SMBBIT & CH, Karachi Pakistan

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Exclusion Criteria: The pregnant women and ≤12 years of age.

Based on a previous estimate of HIV viral load suppression found in (63.9%) 8 of patients on dolutegravir with margin of error 11% and 95% confidence level, a sample size of 74 with allowance of attrition rate of 10%, a total of 82 patients were required for this study, using OpenEpi calculator. The last date of patient enrollment was October 31, 2019, thus allowing for at least 6 months of follow-up and viral load determination.

Manual chart review was conducted for patient demographics, clinical, radiological and laboratory data. Baseline viral loads are not performed for naïve patients, but were available for experienced patients.

Patient drug compliance with ART was assessed based on the regularity of collection of ART and pill counting at the centre. In addition, clinical response was also gauged by the patient weight documented at each clinical visit.

As per National Guidelines, the first viral load after initiating ART should be performed at 3 months interval. If undetectable, the next VL is scheduled after 6 months whereas if detectable, VL must be repeated within 3 months for confirmation of failure. CD4 cell count determinations are recommended at baseline and then 6 monthly if less than 350 cells/mm^3.

We documented outcome in terms of clinical, immunological, virological suppression and failure as defined by our National Guidelines.[3] Virological suppression was defined as a viral load of <1000 copies/ ml achieved by the first or second viral load determination on unchanged ART. 3 Virological failure was defined as a viral load >1000 copies/ml (based on two consecutive viral load measurements within a 3 month interval, with adherence support) after at least six months on unchanged ART. Three immunological failure was defined as a CD4 count persistently <100 cells/ul or decline below the base line level. 3 Clinical failure was defined as a new or recurrent clinical event indicating severe immunodeficiency after 6 months of effective treatment.[3]

Patient transfer to another HIV treatment facility, lost to follow up, or death were recorded.

Data was analyzed by using SPSS-24. Descriptive analysis was done; qualitative variables were presented as frequencies and percentages. Quantitative variables were either presented as mean and standard deviation or were grouped into ranges for determination of frequency and percentages for each range.

RESULTS

At the end of the enrollment period, of 1183 patients receiving ARV at the SACP centre, 82 (7%) patients were on a DTG containing regimen. Fifty six (68.3%) were males, 24 were females (29.3%) and 2 were transgender (2.4%). The mean age was 31.6 ± 9 years. Of 82, 76 (93%) belonged to the province of Sindh. The route of HIV transmission was sexual in 42 (51.2%), injecting drug use in 19 (23.2%) and blood products in 17 (20.7%) (Table-I).

Table-I: Baseline characteristics of HIV Infected patients started on dolutegravir (n=82).

Baseline Parameter	n (%)
Age (years)	31.6 ± 9
Gender	
Male	56 (68.3)
Female	24 (29.3)
Transgender	2 (2.4)
Occupation	
Employed	52 (63.4)
Unemployed	11 (13.4)
House wife	18 (22)
Student	1 (1.2)
Education	
Illiterate	41 (50)
Primary	23 (28)
Secondary	9 (11)
College	9 (11)
Risk Factor for HIV Exposure	
Heterosexual contact (not spouse)	25 (30.4)
HIV infected spouse	15 (18.2)
Male homosexual contact	2 (2.4)
Injecting drug use	19 (23.2)
Blood products	17 (20.7)
Unknown	4 (4.9)
Co-Infections	
Anti-HCV positive	12 (14.6)
HBsAg positive	17 (20.7)
Co-morbidities	8 (9.7)
Thalassemia	2 (25.0)
Chronic Kidney Disease	1 (12.5)
Chronic Liver Disease	3 (37.5)
Tuberculosis (active)	2 (25.0)
Baseline CD4 (cells/mm^3)	
n (Mean ± SD)	60 (308 ± 230.7)
ARV Naive	
n (Mean ± SD)	36 (254.3 ± 223.3)
ARV Experienced	
n (Mean ± SD)	24 (388.7 ± 222)

Of 82, 18 patients were lost to follow-up, transferred or died before their first scheduled follow-up visit. Of the remaining 64 patients, medications were

collected regularly either by the patients themselves in 61 (95.5%), or by their social mobilizers in 3 (4.5%). Of 64, 61 (95.3%) returned for clinical assessment and first VL determination (VL1) whereas 3 (4.6%) patients did not come for follow-up, averaging 8 months since DTG regimen initiated, though receiving ARVs. Therefore, tolerability, clinical and virological response could only be assessed in 61 patients. Of 61 patients, adverse effects attributed to DTG were seen in 12 (19.7%) and included gastrointestinal in 1 (1.6%), non- pruritic rash in 1 (1.6%), depression in 1 (1.6%) and pruritus in 9 (14.7%). Of 82, 53 (64.6%) were ARV naïve and 29 (35.4%) were experienced.

In 53 ARV naïve patients, baseline viral loads had not been performed. After start of DTG regimen, VL1 could not be performed in those transferred (4), lost to follow (10) or died (1) due to CKD. Three patients had not returned for evaluation and testing, though receiving ARV. Therefore, VL1 was performed in 35 (66%) out of 53 naïve patients at an average of 3.3 ± 0.7 months. Of 35, 31 (88.6%) had virological suppression. Of these, 30 achieved VL suppression at VL1 with sustained virological suppression demonstrated 6 months later in 2, and 1 achieved suppression at the second VL determination (VL2) at 8 months. Of 35, 4 (11.4%) patients had detectable VL1. In 1, virological failure was confirmed. In 3 patients, virological failure for VL1 values of 2650 cps/ml, 5060 cps/ml and 85,000 cps/ml was not confirmed by a repeat VL. Of 53 patients, a baseline CD4 cell count was available in 36 with a mean of 254.3 ± 223.3. Of 36, 4 patients had CD4 cell count determination after DTG initiation with an increase from a baseline mean of 295.5 ± 181 to 472.0 ± 123 at an average of 6 months since the start of DTG. Of 31 patients with virological suppression on DTG, none had clinical failure by 6 months. Their average weight at baseline was 48.5 ± 9.8 with an increase to 52.3 ± 9.66 at 3.3 ± 0.7 months.

In 29 ARV experienced patients, they were switched to DTG containing regimen due to side effects in 12 (41.4%), suspected resistance in 11 (38%), non-availability of RAL in 4 (13.7%) and adoption of new guidelines in 2 (6.9%). (Table-II) Baseline VL was available in all 29, of whom 11 (38%) were suspected of resistance to efavirenz, lamivudine and tenofovir (ELT) regimen due to high VL of a mean of 97122 ± 86540 cps/ml. Of 29, VL1 could not be performed in 3 patients as one was transferred and 2 had died due to HIV related causes, whereas 26 patients achieved virological suppression at an average of 4.5 ± 0.9 months. Of 29, baseline CD4 cell count was available in 24 at a mean of 388.7 ± 222. Repeat CD4 cell count was available in 5 virally suppressed patients with increase from a mean of 278 ± 109 to 307.3 ± 182. Of 26 virally suppressed patients, none had clinical failure after 6 months of DTG. Their baseline weights averaged 55.2 ± 11.8 kg before DTG with repeat weights after DTG in 19 patients showing gain from 57.7 ± kg to 61.3 ± 12.4 by 4.5 ± 0.9 months. Overall, in 82 naive and experienced patients on DTG, 61 patients had viral load determinations, of whom 57 (93.4%) achieved virological suppression within the study period.

Assessment of the SACP centre's compliance with National HIV Guidelines in patient management revealed that DTG regimen was started promptly after registration in naïve patients. In experienced patients who reported significant side effects to prior regimen, or in case of non-availability of RAL, switch to DTG was also timely. However, in 11 patients with suspected resistance with confirmed virological failure, switch to DTG containing regimen was not initiated till an average of 3.3 ± 2.9 months later. Moreover, the ELT regimen was switched to DLT, thus substituting a single drug in a failing regimen. Of 82 patients, 2 with active tuberculosis were placed on treatment whereas 80 received isoniazid. Patients with CD4 cell count <350 cells/mm^3 or <50 cells/mm^3 were on PCP and MAC prophylaxis respectively. There was regular follow-up of patients who were collecting their ARV drugs themselves. Baseline CD4 determinations were not available in 22 (26.8%) of 82 patients. Follow up CD4 determinations after start of DTG was performed in 9 of 27 (33.3%) eligible patients, at an average of 6 months. VL1 was performed at an average of 3.9 ± 1.0 months in all eligible patients. However, VL2 was performed in only 3 of 25 (12%) eligible patients. In 2 patients,

Table-II: Anti-Retroviral therapy in experienced patients (n=29).

Variable	n (%)
Prior ART Regimen	
NNRTI	22 (75.8)
PI	3 (10.3)
INSTI (Raltegravir)	4 (13.7)
Main Reason for Switching ARV	
Suspected resistance	11 (37.9)
Side effects to efavirenz	12 (41.3)
Rash	2 (16.7)
Gynecomastia	7 (58.3)
Depression	3 (25.0)
Non-availability of raltegravir	4 (13.7)
Adoption of new guidelines	2 (6.9)

virological failure was not confirmed within the recommended interval.

DISCUSSION

This is the first retrospective analysis of clinical experience with DTG in Pakistan, which was the second HIV integrase inhibitor to be made available nationally. Overall, 93.4% of our patients achieved viral suppression while 88% efficacy was reported in the single clinical trial.[7] However in another efficacy study from Ireland, virological suppression was achieved in 63.9% of patients in 3 months.[8] A study from India demonstrated 82.9% viral suppression after 6 months.[9] A study from Hamburg Germany showed that at 3 months, viral suppression was recorded in 73% in treatment naïve and in 86% of treatment-experienced patients. A study from the UK demonstrated viral suppression as early as 1 month in 73% of naïve patients.[10,11]

Sustained virological suppression was demonstrated in 63.9% at 12 months in a study from Ireland 8 and in 92% in treatment naïve and 90% in treatment experienced at 12 months in a study from Germany.[10] However, we were unable to demonstrate sustained suppression since virological monitoring was not optimally performed in our patient population.

Four patients in our study that were undetectable on raltegravir, did not show virological rebound after switch to dolutegravir.[12]

In our study, naïve patients had a mean CD4 cell count of 234 cells/mm^3 at registration at SACP whereas when compared to a 2010 study reported from the same center, baseline CD4 at registration was 130 cells /mm^3 suggesting that patients are now being detected earlier a decade later, which is encouraging.[13]

This study demonstrated a more robust immunological response to DTG in naïve as compared to experienced patients. This was also reported by Todd *et al*, whereby baseline CD4 cell count increased from 435 cells/mm^3 to 590 cells/mm^3 in naïve patients whereas it remained unchanged at 490 cells/mm^3 in experienced switch patients at week.[12] In another study of DTG, in naïve patients baseline CD4 cell count increased from a mean of 225 cells/mm to 336 cells/mm after 3 month and to 463 cells/mm after 12 months, while in experienced increase was from a mean of 424 cells/mm^3 to 478 cells/mm^3 after 3 month and to 536 cells/mm^3 after 12 months. A meta-analysis reported a greater increase in CD4 cell count with DTG as compared to efavirenz, which was the first line ARV prior to DTG prescribed by our centre.[10,11,14]

We found patient compliance with collection of medications to be excellent, as was also seen in the earlier 2010 study of SACP. Overall, clinical response was good in both naïve and experienced patients in our study with no opportunistic infections documented beyond 3 months. We report early mortality of 3.6% within the first 2 months of starting DTG. When compared with mortality data reported from the 2010 study from the same centre, our mortality is much lower than the 23.3% HIV related deaths reported then.[13] This is likely related to earlier detection of patients with HIV at present and higher efficacy of Integrase Strand Transfer Inhibitor (INSTI) containing ART.

We reported adverse effects attributed to DTG in 19.7%, whereas in other studies adverse effects in 35%, 39% and 42.2% of patients have been reported.[8,11,15] Discontinuation rates due to neuropsychiatric effects were reported in 5.6% of patients by Hoffman *et al*, and in 6.9% by Cid-Silva *et al*, whereas only 1 patient reported depression after starting DTG which did not lead to discontinuation in this study.[16,17]

SACP centre demonstrated prompt initiation of ARV and maintained a steady supply of ARVs. However, SACP must ensure that baseline CD4 cell counts with subsequent monitoring is performed, which is essential for prophylaxis and its discontinuation. Follow-up of patients with close VL monitoring is essential for early detection of virological failure and prevention of drug resistance, in case of which switch to effective regimen must be prompt. Most crucially, substitution of a single drug in a failing regimen must never be allowed since the development of resistance is a major concern, and drug resistance testing is not widely available in resource poor settings such as ours.[18]

Our study has demonstrated excellent efficacy of DTG in both naïve and experienced patients, good tolerability and outcomes and therefore appears to be a better option for our patient population than an non-nucleoside reverse transcriptase inhibitors (NNRTI) based regimen. However, further studies will be required to determine superiority.

LIMITATION OF STUDY

Limitations of this study include a retrospective study design with missing information. It is a single center study with a small sample size. However, it has provided valuable information regarding the acceptability and outcome of a DTG containing regimen in our patient population.

CONCLUSION

DTG is well tolerated by patients, with virological suppression being achieved in the majority of patients, including in highly ARV experienced patients.

Conflict of Interest: None.

Authors' Contribution

FB: Conception and frame work, SM: Drafting, AKD: Data analysis & collection, HMI: Data collection, SMS: Drafting, SB: Critical reviw.

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