Dolutegravir and Treatment Non-Compliance

Mulubwa Chilambe[1], Nyambe Lyoko[1], Makomani Siyanga[1], Billy Chabalenge[1]

[1]Zambia Medicines Regulatory Authority, Lusaka, Zambia

Introduction

Dolutegravir-based antiretroviral regimens for the treatment of HIV have reported high levels of effectiveness and acceptability[1]. It is currently recommended as a part of the first- or second -line treatment for HIV and has the potential to benefit up to 38 million patients worldwide. However, there are concerns about poor adherence to the treatment regimen, which could affect its effectiveness[2]. Experiencing side Effects may result in poor adherence[3]. Poor adherence to HIV treatment can be multifactorial with patient related and system of care components[4]. We identified cases of reported treatment non-compliance in combination with dolutegravir containing medications and how they compared with other anti-HIV medications.

Figure 1. Countries with reports for dolutegravir and poor adherence (PT)

Methods

A search of VigiBase, the WHO global database of individual case safety reports, was performed on 29 April 2024. Cases were identified when they reported both a reaction by the Preferred Term (PT) "Treatment noncompliance"; and dolutegravir -containing products in the WHODrug Standardised Drug Grouping (SDG) "Drugs for treatment of HIV infections". Disproportionality measures, using the Information Component (IC) values, were calculated for the combination of the PT and dolutegravir-containing products. An IC_{025} of greater than 0 indicates positive disproportionate reporting with statistical significance[5].

vigiPoint[6] was used to compare reporting for medications containing dolutegravir with medications that do not contain dolutegravir in the WHODrug SDG "Drugs for treatment of HIV infections". The positive lower end of the 99% credibility interval for the calculated shrinkage log odds ratio (SLOR) highlights variables with an overrepresentation among the dolutegravir subset. A threshold of greater than 0.5 for the lower end of the 99% credibility interval ($SLOR_{005}$) highlights substantial deviation.

Results

For all dolutegravir-containing active ingredients, a total of 389 reports were identified in VigiBase. The countries that contributed the largest number of reports were USA (n=110, 28.3%) and Italy (n=63, 16.2%) with reports received from 25 countries (see Figure 1). The WHO regions represented being AFR, AMR, EUR, SEAR and WPR. The IC_{025} value for this combination was 3.0, indicating statistically significant disproportionate reporting for this combination. The PT "Treatment noncompliance" had two Low Level Terms (LLT): Treatment noncompliance (n=322, 82.8%) and Treatment nonadherence (n=67, 17.2%). There were 319 co-reported PTs, mostly side effects (n=232, 72.7%). The most common co-reported PTs were virologic failure (n=191, 49.1%), pathogen and drug resistance (n=113, 29%) and viral mutation identified (n=96, 24.7%). The results of the vigiPoint analysis are shown in Table 1, with Preferred Terms related to treatment noncompliance.

Conclusions

This potential signal warrants further investigation. Initial results indicates that treatment noncompliance may be associated with side effects and may result in treatment ineffectiveness and drug resistance. Treatment adherence programs should incorporate monitoring and management of side effects.

Table 1. vigiPoint results for MedDRA Preferred Terms related to treatment non-compliance when comparing dolutegravir-containing HIV treatment to non-dolutegravir containing HIV treatments. Total case count for DTG: 31,554; for all anti-HIV excluding DTG: 360,691.
Abbreviations: DTG – dolutegravir; SLOR – Shrinkage Log Odds Ratio; $SLOR_{005}$ refers to the lower end of the 99% credibility interval.

MedDRA Level	Term	DTG % (N Reports)	Non-DTG % (N Reports)	$SLOR_{005}$
High Level Term	Medication errors, product use errors and issues NEC	1.1% (827)	0.5% (4,657)	0.53
High Level Term	Product administration errors and issues	2.8% (2,066)	0.8% (7,382)	1.13
High Level Term	Therapeutic and nontherapeutic responses	2.3% (1,680)	1.7% (15,069)	0.34
High Level Term	Virus identification and serology	1.3% (976)	0.6% (5,457)	0.58
Preferred Term	Treatment noncompliance	0.5% (389)	0.1% (1,205)	0.46
Preferred Term	Product dose omission issue	2.4% (1,790)	0.3% (2,955)	1.44
Preferred Term	Virologic failure	0.9% (698)	0.4% (3,518)	0.53
Preferred Term	Pathogen resistance	0.4% (304)	0.1% (873)	0.39
Preferred Term	Treatment failure	0.2% (147)	0.2% (1,381)	0.07
Preferred Term	Drug ineffective	0.5% (379)	0.6% (5,044)	-0.02
Preferred Term	Drug resistance	0.2% (153)	0.2% (2,027)	-0.01

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National Pharmacovigilance Unit
Zambia Medicines Regulatory Authority
Email: npvu@zamra.co.zm