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Pharmacovigilance of antiretroviral dolutegravir in the state of Paraná

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ABSTRACT. The aim of this study was to investigate adverse reactions to Dolutegravir, a drug recently made available by the Unified Health System (SUS) for treating HIV infections. The frequency, severity and sex distribution of adverse reactions to Dolutegravir were identified over the first 18 months of its availability in users in the state of Paraná. Information was obtained through the pharmacovigilance questionnaire prepared by the Ministry of Health, accessed through the Logistics Control System for Medicines (SICLOM). During the study period, dolutegravir was dispensed to 9,865 patients in the state. However, 9,207 users (93.3%) answered the pharmacovigilance questionnaire. Among them, 1.75% reported 279 adverse reactions. This population was composed mainly of male people (69.57%), in the ratio of 2.29 men for each woman, white (67.08%), aged between 20 and 29 years (26.71%), single (45.34%) and with education between 8 and 11 years of study (41.61%). Gastrointestinal (36.92%) and nervous system (14.34%) disorders were the most prevalent. 77.78% adverse reactions were considered non-serious by users. It can be concluded that dolutegravir had a low prevalence of adverse reactions in users in the state of Paraná, demonstrating to be safe for use by the population in therapy against HIV, in accordance with clinical trials.

Keywords: dolutegravir; HIV; Anti-retroviral agent; drug-related side effects; adverse reactions.

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Introduction

Pharmacovigilance is the practice of monitoring medications in use by the population to identify adverse reactions, especially rare and serious ones, which were not identified during the clinical development of medications. Although pharmacovigilance actions are aimed at all drugs, without distinction, those of continuous use attract greater attention due to the need for prolonged exposure. Among these drugs are antiretrovirals (Edwards, 2017; Alomar, Palaian, & Al-Tabakha, 2019).

In 1996, Brazil began making antiretroviral drugs available free of charge to the entire population infected with the human immunodeficiency virus (HIV). Since then, several of these drugs have been incorporated into the list and made available for the treatment of people with HIV (Brasil, 1996). The most recent antiretroviral drug approved by the Unified Health System (SUS) is dolutegravir (Brasil, 2015).

To treat the growing number of HIV-infected people, therapeutic options with fewer adverse reactions, greater effectiveness and simplified dosage are sought (Kandel & Walmsley, 2015). In this context, dolutegravir confers advantages over other drugs of the same class (integrase inhibitors), as it promotes a greater barrier to HIV resistance genetic mutations, a slow dissociation rate of the viral integrase enzyme (Llibre et al., 2015) and the need for only one oral daily dose (Shah, Schafer, & Desimone, 2014). Furthermore, there is evidence of greater safety compared to other antiretrovirals (Shah et al., 2014; Curtis et al., 2014; Patel et al., 2014). For these reasons, dolutegravir became part of the initial regimen of antiretroviral therapy prescribed for people newly diagnosed with HIV. In this regimen, dolutegravir is combined with Lamivudine and Tenofovir, antiretroviral drugs already available in Brazil (Brasil, 2018).

In order to identify adverse reactions to dolutegravir in the Brazilian population, the Ministry of Health instituted a specific pharmacovigilance protocol for dolutegravir. Upon dispensing, the computerized system

proposes a questionnaire to patients so that they can report their complaints to the pharmacist who works at the SUS medicine dispensing units, where antiretrovirals are exclusively dispensed (Brasil, 2017). The purpose of this study was, therefore, to identify adverse reactions to dolutegravir, their frequency and severity in the population using this antiretroviral, soon after its availability for the treatment of HIV infection in the state of Paraná.

Material and methods

This is a descriptive observational study, covering the period from July 2017 to December 2018, which corresponds to the first eighteen months of use of dolutegravir by the population starting antiretroviral therapy in the state of Paraná.

Secondary data on the use of dolutegravir, sociodemographic information and reported adverse reactions were obtained from reports generated by the Logistics Control System for Medicines (SICLOM) and patient registration forms. SICLOM is a system with access restricted to public service employees who work with pharmaceutical antiretroviral assistance. Information used in this study was accessed and provided by one of the authors, who is also an employee of the Paraná State Medicines Center (CEMEPAR) of the Paraná State Department of Health (SESA-PR).

Adverse reactions were identified and grouped into different categories. For this, we followed the organizational model proposed by the Monitoring Center in Uppsala (Sweden), a collaborating center of the World Health Organization (WHO) for the worldwide monitoring of medicines (van De Ven et al., 2019). By accessing its database called VigiAccess (vigiaccess.org), it was possible to identify the following categories for grouping adverse reactions: gastrointestinal; nervous system; cutaneous and subcutaneous tissues, psychiatric; musculoskeletal and connective tissue; ear and labyrinth; general reactions and conditions of the site of administration; metabolism and nutrition; respiratory, thoracic and mediastinal; cardiac; vascular; hepatobiliary; eye reactions, among others and under investigation.

In the analysis of the results, descriptive statistics calculations were used, such as absolute and relative frequencies, means, standard deviation and confidence interval. To compare the proportions of adverse reactions between genders, Fisher's exact test was used. Variations with $p \leqslant 0.05$ were considered significant. To monitor the evolution of adverse drug reaction reports over the eighteen months of this study (1^{st} to 6^{th} trimester), the estimated percentage change of adverse reactions to dolutegravir was calculated with a 95% confidence interval. The statistical package used was Stata 14®. The figure was created using GraphPad Prism® software.

This study was approved by the Research Ethics Committee of the Federal University of Paraná - Health Sciences Sector - SCS/UFPR (CAAE: 82936318.3.0000.0102), and by the Paraná State Ethics Committee - Hospital do Trabalhador/SES/PR (CAAE: 82936318.3.3001.5225).

Results

Between July 2017 and December 2018, dolutegravir was dispensed to 9,865 people living with HIV in the state of Paraná. However, 9,207 users (93.3%) responded to the questionnaire for notification of adverse reactions to dolutegravir, proposed by the Ministry of Health on return for the acquisition of this drug in antiretroviral dispensing units. Among users who responded, 161 (1.75%) reported adverse reactions, resulting in an estimated rate of 17.5 patients with adverse reactions for every thousand drug users in the state.

In this population of 161 users, males (69.57%) prevailed, with a ratio of 2.29 men for each woman, white (67.08%), aged between 20 and 29 years (26.71%), single (45.34%) and with schooling between 8 and 11 years of study (41.61%) (Table 1).

The 161 patients reported 279 adverse reactions, resulting in an average of 1.55 reactions for each user who reported adverse reactions to dolutegravir. However, the majority (59.63%) reported only one complaint in the period (Table 1).

The 279 reported reactions were grouped into 15 categories (Table 2). The category of gastrointestinal disorders was the most prevalent, with 36.92% reported reactions. Within this category, there are reactions such as diarrhea (41 reports) and nausea (34 reports), respectively the first and second most reported reactions in the population using dolutegravir in the state of Paraná. The second most prevalent category of adverse reactions was nervous system disorders (14.34%), in which headache predominates, with 29 reports, which corresponds to the third most prevalent reaction in the study population.

Table 1. Sociodemographic data of patients who reported adverse reactions to DOLUTEGRAVIR in the state of Paraná and number of reported reactions.

Variables		Sex	
	Total n (%)	Men n (%)	Women n (%)
Age group (years)			
15 to 19	2 (1.24)	1 (0.89)	1 (2.04)
20 to 29	43 (26.71)	37 (33.04)	5 (12.24)
30 to 39	36 (22.36)	24 (25.00)	8 (16.33)
40 to 49	40 (24.84)	20 (20.54)	16 (34.69)
50 to 59	21 (13.04)	11 (11.61)	8 (16.33)
⩾ 60	19 (11.80)	10 (8.93)	5 (18.37)
Race			
Yellow	2 (1.24)	1 (0.89)	1 (2.04)
White	108 (67.08)	75 (66.96)	33 (67.35)
Brown	33 (20.50)	24 (21.43)	9 (18.37)
Black	7 (4.35)	5 (4.46)	2 (4.08)
Not informed	11 (6.83)	7 (6.25)	4 (8.16)
Marital status			
Single	73 (45.34)	60 (53.57)	13 (26.53)
Married	16 (9.94)	9 (8.04)	7 (14.29)
Widowed	5 (3.11)	3 (2.68)	2 (4.08)
Separated*	14 (8.69)	9 (8.04)	5 (10.2)
Stable union	16 (9.94)	7 (6.25)	9 (18.37)
Not informed	37 (22.98)	24 (21.43)	13 (26.53)
Education			
From 1 to 3 years	11 (6.83)	4 (3.57)	7 (14.29)
From 4 to 7 years	37 (22.98)	22 (19.64)	15 (30.51)
From 8 to 11 years	67 (41.61)	53 (47.32)	14 (28.57)
From 12 to over	24 (14.91)	20 (17.86)	4 (8.16)
None	2 (1.24)	1 (0.89)	1 (2.04)
Not informed	20 (12.42)	12 (10.71)	8 (16.33)
	Number of reported reactions		
1	96 (59.63)	65 (58.04)	31 (63.27)
2	33 (20.50)	24 (21.43)	9 (18.37)
3	19 (11.80)	14 (12.50)	5 (10.20)
4	9 (5.59)	7 (6.25)	2 (4.08)
5	1 (0.62)	1 (0.89)	0 (0.00)
6	2 (1.24)	1 (0.84)	1 (2.04)
7	1 (0.62)	0 (0.00)	1 (2.04)
	161	112 (69.57)	49 (30.42)

* Separated corresponds to civil status divorced and legal separation.

Table 2. Adverse reactions to dolutegravir, frequency and sex distribution

Adverse Reaction Categories	Total n (%)	Men n (%)	Women n (%)	p
Gastrointestinal	103 (36.92)	81 (41.75)	22 (25.88)	0.027*
Nervous system	40 (14.34)	26 (13.40)	14 (16.47)	0.844
Cutaneous and subcutaneous tissues	31 (11.11)	22 (12.34)	9 (10.59)	1.000
Psychiatric	28 (10.04)	20 (10.31)	8 (9.41)	0.811
Musculoskeletal and connective tissue	19 (6.81)	11 (5.67)	8 (9.41)	0.570
Ear and labyrinth	18 (6.55)	16 (8.25)	2 (2.35)	0.098
General reactions and conditions of the site of administration	15 (5.38)	9 (4.64)	6 (7.06)	0.514
Others#	6 (2.15)	3 (1.55)	3 (3.53)	0.639
Metabolism and nutrition	5 (1.79)	3 (1.55)	2 (2.35)	0.639
Respiratory, thoracic and mediastinal	5 (1.79)	1 (0.52)	4 (4.71)	0.083
Investigations##	3 (1.08)	0 (0.00)	3 (3.53)	0.027*
Cardiac	2 (0.72)	0 (0.00)	2 (2.35)	0.091
Vascular	2 (0.72)	1 (0.52)	1 (1.18)	0.516
Hepatobiliary	1 (0.36)	1 (0.52)	0 (0.00)	1.000
Eye	1 (0.36)	0 (0.00)	1 (1.18)	0.303
TOTAL	279 (100.0)	194 (69.53)	85 (30.47)	0.0001*

#Includes: Allergy, allergy to animals, voice change, allergic reaction and bitter taste. ## reactions detected from laboratory or anthropometric tests, such as elevated cholesterol and albuminuria. * Significant p-values (p ⩽ 0.05). Statistical test used: Fisher's exact.

There was a statistically significant predominance of males in the frequency of records of adverse reactions to dolutegravir, especially in the category of gastrointestinal disorders (p = 0.027). In the Investigations category, which includes reactions detected from laboratory or anthropometric tests, such as elevated cholesterol and albuminuria, there was a predominance of females (p = 0.027). However, this corresponded to only 1.08% patients with complaints.

Of the reported reactions, 77.78% were considered non-serious by users. However, 6.45% of the reactions motivated the hospitalization of patients and 1.08% caused risk to life, according to the users' reports. These results are similar to those of other studies (Kandel & Walmsley, 2015).

The evolution in the number of patients, records and number of reactions notified was analyzed quarterly (Figure 1). In the period considered, the total number of patients using dolutegravir in Paraná increased by 65%, from 3,441 in the first quarter to 9,865 in the last, considering in this calculation all people using the drug, including those who did not respond to the pharmacovigilance questionnaire of dolutegravir. In the same period, the number of notifications decreased sharply (46.7%), as well as the number of notified reactions (55.1%), which ranged from 25.0% to 73.2% in the period. The monthly average of the number of notifications was 13.83. Throughout the period considered, the rate of adverse reactions reported by patients using dolutegravir in the state of Paraná dropped from 3.40 to 0.52 (Figure 1).

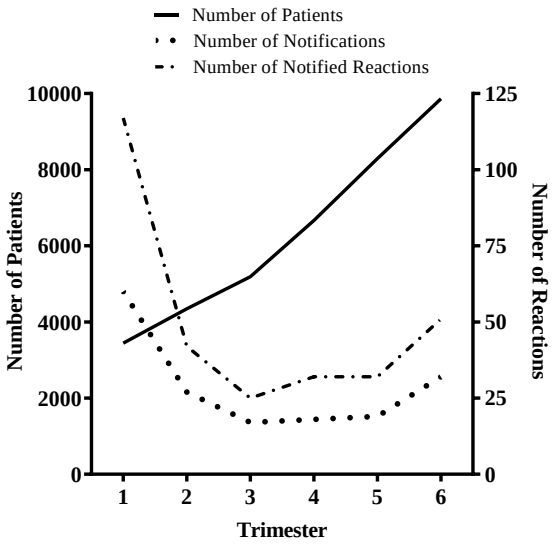

Figure 1. Quarterly evolution of the number of patients, notifications and notified reactions to dolutegravir in the state of Paraná.

Discussion

Adverse reactions are defined by the World Health Organization as harmful and unintentional responses caused by drugs used in doses normally administered in humans. Pharmacovigilance, through notifications carried out mainly by health professionals, identifies these adverse reactions caused by medications available on the market. The growing use by a population with varied characteristics (e.g. people with comorbidities, polymedicated, elderly, pregnant women and children), different from those of the subjects of clinical research, raises the possibility of rare, serious or fatal adverse reactions not observed in the previous stages of the development. These reactions need to be identified, notified and investigated to enable the safe use of the drug in question. Therefore, pharmacovigilance contributes to the provision of safe and effective pharmacological therapies for the population, being crucial to the maintenance of the supply of the investigated drugs or even to their exclusion from the market, according to the risks and damages caused to users (Pitts, Louet, Moride, & Conti, 2016).

In Brazil, the availability of antiretroviral drugs to the entire HIV-positive population has been foreseen in a SUS health policy since 1996 (Brasil, 1996). Since then, new antiretroviral drugs have been made available after evaluating the pharmacological profile and economic feasibility. This was the case of dolutegravir, the most recent antiretroviral drug incorporated into the SUS. Clinical studies have demonstrated pharmacological and toxicological advantages over other antiretrovirals, including those in the same

pharmacological class of integrase inhibitors like Raltegravir and Elvitegravir. Dolutegravir showed greater efficacy, excellent tolerability, both in patients at the beginning of treatment, and in those multi-experienced patients undergoing antiretroviral rescue therapies. Infrequent interactions with other drugs make dolutegravir suitable to compose different antiretroviral regimens, generally consisting of at least three drugs (Kandel & Walmsley, 2015).

Despite the existing clinical evidence, the Ministry of Health implemented a pharmacovigilance tool exclusive to dolutegravir, aiming to obtain greater knowledge about its effectiveness and safety in the Brazilian population, for which the drug is now widely available (Brasil, 2017).

In this study, reports of adverse reactions from 9,207 users of dolutegravir in the state of Paraná were evaluated. Their sociodemographic profile matches the epidemiological data of HIV infection in the state (Paraná, 2015), with small variations in the level of education and in the ratio between the sexes. The predominance of males in the notifications can be explained by their higher prevalence of infection, as well as by the restrictions on the use of dolutegravir by women of childbearing age who do not use effective contraceptive measures. This recommendation came from the World Health Organization after identifying four cases of defects in neural tube formation in a population of 426 women treated with dolutegravir in Botswana. The 0.9% rate of this malformation attributed to dolutegravir is higher than the 0.1% attributed to other antiretrovirals (van De Ven et al., 2019).

Gastrointestinal disorders (diarrhea and nausea) were the most prevalent adverse reactions in the state of Paraná, followed by nervous system disorders (headache). These same adverse reactions were reported as the most prevalent in other studies (Curtis et al., 2014; Llibre et al., 2015; Taha, Das, & Das, 2015; Kandel & Walmsley, 2015).

In clinical studies of dolutegravir, reactions described as uncommon (occurring between 0.1 and 1% drug users) include hypersensitivity reactions, reconstitution syndrome, impaired renal function, hepatitis and suicidal thoughts or suicide attempts, these latter reported by patients with a history of depression or pre-existing psychiatric disorders (Taha et al., 2015; Kandel & Walmsley, 2015). In the present study, altered kidney function was the only unusual reaction reported by one of the users of dolutegravir in the state of Paraná.

Some studies highlight neuropsychiatric reactions and confirm the occurrence of a high rate of insomnia during the use of dolutegravir (Taha et al., 2015; Fettiplace et al., 2017). In the population studied here, the percentage of reports of insomnia among reactions was 3.94%, and it is the fourth most reported reaction by patients using the drug in the state.

The frequency of adverse reactions varied significantly between genders, with a predominance of reports by males ($p = 0.0001$). Similar data were reported by Chauhan, Shah, Desai, and Shah (2018). According to the scientific literature, this difference is possibly due to hormonal effects on drug metabolism, body mass, genetic constitution, in addition to the higher incidence of infection in males (Patel et al., 2015; Waal et al., 2018). It is important to mention that adverse reactions are determining factors for the greater abandonment of antiretroviral therapy at the beginning of treatment, which occurs more frequently in males (Waal et al, 2018).

Dolutegravir was introduced in Brazil as an alternative to Efavirenz, a drug of the class of non-nucleoside reverse transcriptase enzyme inhibitors, which has known adverse reactions, mainly neuropsychiatric, which interfere with routines of patients using it (Gaida et al., 2016). This replacement was supported by effectiveness and safety studies. Since then, dolutegravir has been dispensed with as initial therapy, in the first line of HIV treatment, as was the case with Efavirenz, as well as in rescue therapies (Meireles, Pascom, Duarte, & McFarland, 2019).

Several pharmacological advantages are attributed to dolutegravir over other antiretroviral drugs. Among them, once daily dose, absence of cross-resistance with other integrase inhibitors and high barrier to resistance. For these reasons, it is considered the drug of choice for people starting treatment, but it does not exclude patients using other therapeutic options that may benefit from dolutegravir (Kandel & Walmsley, 2015).

A multicenter clinical study has shown that adverse reactions to dolutegravir occur in approximately 90% people undergoing treatment, but are not usually a reason for substitution (Kandel & Walmsley, 2015). In this study, patients who experienced adverse reactions classified about 78% reactions as non-serious, in line with previous studies (Bailly & Cotelle, 2015). However, as reported by dolutegravir users in this study, 1.08% adverse reactions were life-threatening. This number is close to that observed by Kandel & Walmsley (2015), where only 1% adverse reactions caused by dolutegravir were considered severe.

Despite the progressive increase in new users of dolutegravir in Brazil, the number of notifications of adverse reactions has drastically reduced after the first three quarters of use of the drug by people undergoing

HIV treatment in the state of Paraná. Among the justifications, adaptation to the medication stands out, which usually occurs in the first six months of therapy. During this period, acute and transient adverse reactions are expected, which are more noticeable to the patient, and this is a moment of attention with the possibility of abandoning the therapy. After this period, chronic reactions appear, with less evident signs and symptoms (Kandel & Walmsley, 2015).

As dolutegravir was prescribed, a proportional increase in the number of notifications of adverse reactions was expected, as new users who had never before been exposed to this drug joined. During the period considered in the study, the number of new users of dolutegravir increased every quarter, but the number of reported adverse reactions, as well as the number of notifications, did not increase in the same proportion. Therefore, the possibility of the occurrence of underreporting is considered, motivated by the growing demand in the antiretroviral dispensing units, aggravated by the shortage of employees. On the other hand, it is considered that the transience and low severity of adverse reactions to dolutegravir have discouraged notifications (Montané & Santesmases, 2019).

Poor adherence to antiretroviral drugs and discontinuation of therapy negatively impact individual and collective health, as they make it difficult to control the viral load, increase the potential for transmission of HIV to other people, and also predispose to complications of the disease and progression to the acquired immunodeficiency syndrome (Aids) (Chauhan et al., 2018). Knowledge of adverse reactions to dolutegravir favors better therapy management and greater adherence, which is reflected in infection control, better quality of life for users and less financial impact on the health system.

Conclusion

Of all dolutegravir users in the state of Paraná, 93.3% answered the pharmacovigilance questionnaire proposed by the Ministry of Health. Of these, only 1.75% reported adverse reactions. This proportion is very low and differs from those obtained in clinical trials (90%) and in a population of dolutegravir users (43%) (Walmsley et al., 2013; Kandel & Walmsley, 2015). Nevertheless, in all cases, mild, transient adverse reactions and considered non-serious by users predominated. In the state of Paraná, gastrointestinal disorders (diarrhea and nausea) were the most prevalent adverse reactions, followed by nervous system disorders (headache). No adverse reactions other than those reported in clinical trials have been identified. The results obtained reinforce the safety of dolutegravir for use by people on antiretroviral treatment.

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