

Adverse effects of using dolutegravir HIV in pregnant women and their newborn

Abstract

Introduction: The adverse effects of dolutegravir on the mother and the fetus not yet have been widely studied; the integrate inhibitor antiretroviral drug was to prevent vertical transmission of HIV.

Objective: To identify the adverse effects of the use of dolutegravir That Have occurred in HIV-positive pregnant women and their children.

Methodology: A scoping review we performed in the Medline, Cochrane Library and EBSCO databases, with the MeSH terms dolutegravir and pregnancy.

Eligibility criteria: Clinical trials and observational studies conducted in pregnant women with HIV Were Treated with dolutegravir included. The search was limited to articles in Inglés and Spanish and published Until September 1 2018.

Results: The bibliographic search obtained seven investigations. Two studies report mild adverse effects in the mother. Six studies related to pregnancy outcomes described and delivery, with preterm delivery and small for age stational being the MOST reported. Four cases of neural tube defects in four studies we reported.

Discussion: There is not enough scientific evidence to associate the use of dolutegravir with the appearance of adverse effects on the mother and her children.

Keywords: dolutegravir, pregnancy, adverse effects, newborn

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Abbreviations: APRI, antiretroviral pregnancy registry International; EMA, European medicines agency; FDA, food and drug administration; CEEC, patient exposure, comparison and results; MeSH, medical subject headings; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ART, antiretroviral therapy

Introduction

The dolutegravir is a drug belonging to the family of integrase inhibitors, used in the treatment of disease by HIV. HIV¹ has been used by a large proportion of patients with HIV that has been administered to pregnant women in order to prevent vertical transmission.²

Being part of a relatively new drug family, performing blunt studies detailing the pharmacokinetics of this drug in pregnancy² and describing the adverse effects presented in the mother and children born to HIV positive mothers are not evidence, for therefore this research aims to contribute to reducing the knowledge gap about the use of that drug.

HIV infection itself does not increase the risk of congenital malformations.^{3,4} The risk of congenital malformations of antiretrovirals has been described in observational studies and a collaborative record of women exposed to antiretroviral therapy, the Antiretroviral Pregnancy Registry International (APRI), with data from over 5,000 patients exposed to ART between 1989 and 2007 is a 2.6% prevalence of birth defects per 100 live births among patients receiving ART at any time during pregnancy.^{4,5}

Major health agencies worldwide recognition as the WHO, the

European Medicines Agency (EMA) and the Federal Agency for Food and Drug Administration (FDA) issued statements in May this year on precaution of using dolutegravir⁶ in pregnant women with HIV, because the results of a study that found 4 cases of children born with neural tube defects such as spina bifida in children of mothers who took dolutegravir during pregnancy.⁷

Because of the impact that could cause the use of this medicine in breast population with possible consequences for their children, it is important to do this review to identify adverse effects that could occur in both the expectant mother and the newborn, in order to establish precautions in the use of dolutegravir.

Therefore a review of the literature arises with the aim of identifying the adverse effects that have occurred in both HIV-positive pregnant women and their children, associated with use of dolutegravir.

Methodology

Search strategy guide was followed to conduct a scoping review in order to ensure a standard and quality in the presentation of the results of the review.

A search was conducted in the scientific literature following the scheme of Patient Exposure, Comparison and Results (CEEC). Participants were pregnant women with HIV and their children. The exhibition was the use of dolutegravir. The primary outcome was the occurrence of adverse events associated with administration of dolutegravir during pregnancy. The main objective was to determine the occurrence of adverse events in pregnant women with HIV, such

as depression, mental disorder, gastrointestinal effects, among others; and their children, as the presence of congenital malformations.

The search was conducted in the databases Medline, EBSCO and Cochrane library, using the terms of the Medical Subject Headings (MeSH) dolutegravir and pregnancy. The search was limited to humans, no restrictions on sample size were presented; there were restrictions on language to English and Spanish, and included studies published until 1 September 2018.

Inclusion criteria

Clinical trials, observational studies and summaries of work that included pregnant women with HIV who led dolutegravir treatment, and the children of HIV-infected women during pregnancy took dolutegravir were included.

As a source of information for gray literature, it took into account: congresses, symposia, thematic experts, abstracts and list of references.

Two researchers reviewed the titles and abstracts of retrieved studies to assess eligibility criteria. After reviewing the titles and abstracts, articles were reviewed in full text to determine eligibility criteria. Differences in Articles were resolved by discussion and consensus. If they persisted differences were a result of a third researcher.

Study selection

Search databases yielded 72 records; after removing duplicates, 69 were selected to review the title and summary. Of these, 62 were excluded and reviewed in full text 4. In the search for references and products presented at scientific events additional 3 studies were included.⁷ work finally met the eligibility criteria for the review (Figure 1).

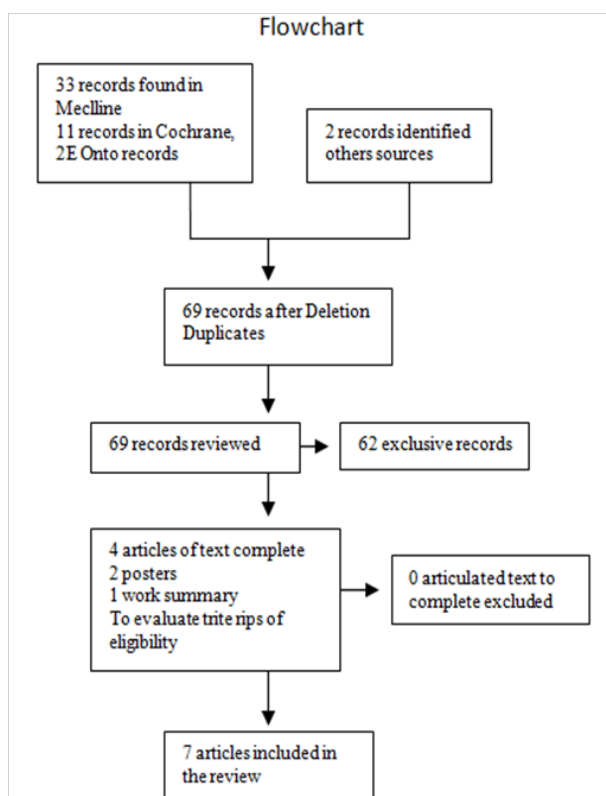


Figure 1 Flow chart.

The most frequent reasons for rejecting the investigations were:

- a. Pregnant women without condition
- b. Patients with no treatment dolutegravir
- c. 2 posters included any of the scarce information about the population extracted with cases according to the outcome in the newborn and the mother and related pregnancy and childbirth.

Data extraction

The item information was extracted by three reviewers, using an established format containing the following variables: lead author, year of publication, geographic location, population, study design, dose dolutegravir, outcomes in pregnant women, pregnancy-related and delivery, and outcomes in the newborn.

Synthesis of information

Qualitative analysis of each of the articles was performed, considering the characteristics of the studies, the population level of exposure and outcomes or adverse events experienced.

Results

The literature search yielded 7 Research. The studies were published between 2016- 2018, and were carried out in Botswana,⁸ United States,^{9,10} Sweden,¹¹ England,¹² and a cohort of European countries,¹³ composed of Belgium, Italy, Ireland, UK, Germany, Holland, Switzerland and Spain. 100% of the studies were published in English.

Of the studies found, the adverse effects were classified according to the outcome in the mother outcome in the newborn and outcomes related to pregnancy and childbirth (Table 1).

Denouement in the mother

The study reported Borhnedé 6 cases (16%) with moderate increase of liver enzymes such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and a case of pre-eclampsia (2.7%). eleven

US Mulligan reported 3 maternal (14.2%) who had anemia, 2 patients with preeclampsia (9.5%), a headache patient (4.7%), a case with proteinuria (4.7%) and a mother who presented blurred vision (4.7%).¹⁴

Of the 7 studies found none reported depression and mental disorders in the mother (Table 1).

Outcomes in the newborn

Congenital malformations in 4 studies reported:

Zash Bostwana reported in 4 patients (0.9%) of neural tube defects in 426 live births.¹⁵

Thorne reported study of 81 children studied four congenital malformations: a case of congenital heart malformation (1.2%), one with a history of hexadactilia parent equal status (1.2%) a case dorsal case hyperpigmentation (1.2%) a case ankyloglossia (1.2%).¹³

Grayhack in the United States reported 2 cases; a child with fetal hydrops (1.7%) and a case of cardiac malformation (1.7%)(17). And in the United States, Mulligan 10 children studied reported 4 cases with congenital malformations; a case of pulmonary vein abnormalities (10%), a case of kidney abnormalities, polycystic kidney disease, and cystic fibrosis (10%), a case of tremor congenital chin (10%) and a case of terminal fibrolipoma phylum (10%)¹⁹ (Table 1).

Table 1 Characteristics of included studies

Author, Country, Year	Kind of study	n	Exposition	Outcome in the mother		Links related to pregnancy and stop		Links in the newborn		Risk					
				n	%	n	%	n	%						
Borhede, Sweden, Stockholm 2014-2 017 (20)	Cohort retrospective	36	Dolutegravir 50mg/día	Controlled preclampsia	1	2,70%	Live births	30	80,30%	They did not report Congenital malformations	0	0%			
							Caesarean section	17	56,60%						
							Vaginal delivery	13	43,30%						
							Early Miscarriage (> week 12)	3	8,30%						
							Miscarriage (sem 19)	1	2,70%						
							Elevación ALT-AST	6	16,00%						
							Abortion (SEM 19)	1	2,70%						
Lost tracking	1	2,70%													
C Thorne Europe: Belgium To Germany Italy Holland Spain Switzerland Ireland and UK 2017 (22)	Cohort	101	Dolutegravir 50mg/día	No effect adverse	0	0%	Live births	81		80.10% Cardiac malformation congenital	1	1,20%			
							Spontaneous abortion	1	0,99%	Hexadactyly (father with same condition)	1	1,20%			
							Induced abortion	1	0,99%	Dorsal hyperpigmentation	1	1,20%			
							Fetus birth <22 weeks	1	0,99%						
							Short stature for gestational age	24	29,60%	Ankyloglossia	1	1,20%			
							Preterm Birth	11	13,50%						
													Congenital abnormalities:(4,9%, 95% CI 1,4, 12,2%)		
Grayhack 2015-2018 (17)	Cohort	66	Dolutegravir 50mg/día	No effect adverse	0	0%	Live births	57	86,36%	Fetal dropsy	1	1,70%			
							Preterm Birth	18	31,60%						
							Short stature for gestational age	9	15,80%	Cardiac malformation	1	1,70%			
Mulligan United States 2016 (19)	Learn to pronounce Test clinical	21	Dolutegravir 50mg/día	eclampsia	2	9,50%	Preterm delivery (<37 serms)	4	14%	Pulmonary venous abnormalities	1	10%			
							Anemia	3	14,20%	Low weight (<2500 grams)	4	14%	Abnormalities of the kidney, kidney polycystic and fibrosis cystic	1	10%
							Proteinuria	1	4,70%	Short stature for gestational age	5	17%	Chin tremor congenital	1	10%
							Blurry vision	1	4,70%	Very low weight (<1500 grams)	2	7%	Fibrolipoma	1	10%
							Headache	1	4,70%						

Table Continues...

Author, Country, Year	Kind of study	n	Exposition	Outcome in the mother	n	%	Links related to pregnancy and stop	n	%	Links in the newborn	n	%	Risk
Mounce United States 2007-2015 (18)	Cohort retrospective	21	50mg/día		0	0%	Do not report	0	0%	Do not report adverse effects	0	0%	
Simons. Inglaterra 2016 (21)	Cohort	9	Dolutegravir 50mg/día	No effect adverse	0	0%	Preterm birth at 28.2 weeks (Pre-existing HTA)	1	11,11%	Do not report adverse effect	0	0%	
								n %	RRa (IC 95%)				
							Preterm birth (<37 weeks)	309 (18%)	0,98 (0,87- 1,11)				RRa 0.95 effects birth CI (0.8-1.3)
							Preterm birth (<32 weeks)	66 (3,8%)	1,09 (0,82- 1,45)				
Zash R. Africa. Bostwana 2014-2017 (23)	Cohort prospective	845	Dolutegravir 50mg/día	No effect adverse	0	0%	Small for the gestational age (<10th percentile)	297 (17,4%)	0,94 (0,83- 1,06)	Neural tube defects	4	0,90%	
							Small for the gestational age (<percentile 3)	104 (6,1%)	0,91 (0,74- ,				RRa 0.94 serious eecos CI (0, 81-1, 11)
							Birth of a child	39 (2,3%)	0,99 (0,69-				
							Neonatal Merte	21 (1,2%)	0,96 (0,58- 1,57)				

Outcomes related to pregnancy and childbirth

6 studies describing outcomes related to pregnancy and childbirth, where most events reported were preterm birth and small for gestational age were found. In 3 studies¹⁵⁻¹⁷ the highest number of cases of preterm birth and small for gestational age was observed.

Zash described in Bostwana 401 cases small for gestational age of which 297 (17.4%) were in the 10th percentile RRa (0.94) 95% (0.83 to 1.06), and 104 (6.1%), in the 3rd percentile RRa (0.91) 95% (0.74-1.13). In addition 375 parts of pre terms which 309 (18%) were before 37 weeks RRa (0.98) 95% (0.87 to 1.11) and 66 (3.8%) before 32 weeks RRa (0.91) 95% (0.82-1.45) as not being statistically significant dolutegravir not represent risk factor for an adverse event or a serious outcome.⁷

Thorne study reported in 24 (29.6%) cases of low height for gestational age and 11 parts pre terms (13.5%). In 13 of 18 cases Grayhack (31.6%) of preterm labor and 9 cases (15.8%) of low height for gestational age were presented.

Only 2 studies report cases of spontaneous abortions and volunteers. Stockholm (Sweden) A retrospective study was conducted

during the years 2014-2017 that included 36 pregnant women, where abortions were 3 spontaneous preterm (8%) and a miscarriage.¹¹ Only one study, Mounce reported no adverse effects on the mother or the newborn.⁹

Discussion

There is not enough scientific evidence to demonstrate the severe adverse reactions dolutegravir use in pregnant women with HIV. Only 7 studies were found and these adverse events were assessed different, so the results are very different in each study.

One study reported six cases of elevated liver enzymes¹¹ and another study reported a case of headache¹⁴ corresponding with that described in the literature on the adverse effects of dolutegravir; 2 studios to be alone with these results more epidemiological studies to assess the adverse effects of dolutegravir on the mother and newborn are needed.

Stunting for gestational age is a result of poor maternal environment, intrinsic fetal abnormalities, congenital infections or other forms of fetal malnutrition¹⁴; Preterm birth is a complex disorder with factors

of various risk include a history of preterm birth before, uterine abnormalities, multiple gestation, maternal medical complications, low rate of pre-pregnancy body mass, gestational bleeding, low socioeconomic status, minority racial origin, behavioral habits such as smoking, alcohol, drug abuse, stressful events, limited or no prenatal care, periodontal disease and infections.^{15,16,18} This makes it difficult to associate small for gestational age with the use of dolutegravir.

Adverse effects to antiretroviral therapy (ART) are common, some may be manageable and others can be serious. 18 According to a Swiss study, there is a high incidence of toxic effects associated with the administration of antiretroviral drugs; In this study, 1160 patients 47% of subjects showed clinical symptoms such as fatigue and headache; Gastrointestinal effects such as nausea diarrhea and vomiting, nephrolithiasis associated with indinavir, lipodystrophy associated with stavudine, disturbances of mood and sleep-related lamivudine and efavirenz, and 27% adverse effects observed in laboratory tests as increased levels lipid, bilirubin, alkaline phosphatase and related anemia zidovudine.¹⁴

Among the adverse effects associated with the use of dolutegravir they have been reported impaired liver function tests, sleep disturbances, headache and nausea, neuropsychiatric symptoms such as depression.^{19–22}

Methodological aspects of the included studies

The number of studies have been performed is reduced. Furthermore, the sample size of the included studies was varied from 2 to 845 pregnant patients, so it is considered insufficient to show the correlation between adverse effects such as congenital malformations and using dolutegravir during pregnancy.

Limitations of the review

The main limitation of this review is that it does not provide sufficient evidence to answer the research question. In addition the limited published information 2 poster so I can not access the document was obtained in full text were included.

Advantages of the review

The main advantage of the study is a comprehensive literature search was conducted to find all published studies. Furthermore, not only the outcome was evaluated in the mother but also in the newborn. It is also considered that due to the absence of literature, this is the first review of this topic, which would be one of the great advantages of this review. Using a systematic review because using it can collect and analyze the evidence that is available to all.

Implications for research

It is important that more intervention studies are conducted with better inclusion and exclusion criteria to have scientific evidence and to relate the association between the use of dolutegravir during pregnancy and adverse effects on the mother and child.

Implications for medical practice

According to these results could not implement protocols or management guidelines where indicated whether it is appropriate to initiate antiretroviral therapy dolutegravir women in gestation or use in women of childbearing age who may be in a state of pregnancy is contraindicated, or women with antiretroviral therapy dolutegravir remaining in a state of pregnancy and should make suspension and change it.

Conclusion

To conclude there is insufficient scientific evidence to associate the use of dolutegravir with the occurrence of adverse effects on the mother and her children.

Author contributions

Search, selection of articles was made by Lorena Paredes and Isabel Vargas, evaluation and extraction of information by Diana Cabrera, Isabel Vargas and analysis was conducted by Isabel Vargas and Lorena Paredes Eduardo Mahecha reviewed the proposed work and the revision of the article; Jorge Ramos was responsible for searching, selecting items, monitor the preparation and review of the proposal, analysis, drafting and revising the manuscript.

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Conflicts of interest

The authors declare no conflicts of interest.

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