

# Adverse reactions and cardiac arrhythmias related to antiretroviral use in patients with HIV/AIDS

## Abstract

**Introduction:** AIDS is an advanced clinical manifestation of human immunodeficiency virus (HIV) infection. These patients have improved with antiretroviral drugs; but there is an increased risk of toxicity and cardiac disease, including cardiac arrhythmias.

**Objective:** To clinically characterize patients with HIV/AIDS who presented adverse reactions due to the consumption of antiretroviral, as well as to estimate the prevalence ratio of cardiac arrhythmias.

**Method:** Descriptive and cross-sectional study, which made possible the clinical characterization and the relationship of ART with general adverse reactions, including cardiac arrhythmias, in the General Clinical-Surgical Teaching Hospital Dr. "Juan Bruno Zayas Alfonso" in the period 2018-2020.

**Results:** Adverse reactions related to oropharyngeal candidiasis were marked, representing 80%. Antiretroviral treatment was very unfavorable for Scheme I, with 66.6% of adverse reactions. Esophagus-gastritis and cardio toxicity marked the differences, with 28 (53.8%) and 14 (55.8%) respectively. The ratio between patients with cardiac arrhythmias versus those without arrhythmias is reasonably higher in those who consumed antiretroviral compared those who did not consume it.

**Conclusion:** Adverse reactions in patients with HIV/AIDS continue to be a health problem in our territory, demonstrating the relationship between adverse reactions and antiretroviral treatment with Cuban generics, especially due to gastrointestinal effects and cardiac arrhythmias. The drug-disease interaction results a complex but indisputably frequent process in patients with HIV/AIDS.

**Keywords:** AIDS, adverse reactions, antiretrovirals, arrhythmias

Volume 8 Issue 2 - 2022

Reinier Besse Diaz,<sup>1</sup> Liliana Martinez Cantillo,<sup>2</sup> C.Ventura Bridge Sani,<sup>3</sup> Est. Carmen Nathali Galera Fernandez<sup>4</sup>

<sup>1</sup>1st and 2nd Degree Specialist in Internal Medicine, Associate Researcher, Santiago de Cuba, Cuba

<sup>2</sup>1st Degree Specialist in Comprehensive General Medicine, Frank País García teaching polyclinic. Santiago de Cuba, Cuba

<sup>3</sup>Doctor of Pedagogical Sciences, 1st and 2nd Degree Specialist in Internal Medicine, Associate Researcher, Clinical-surgical Hospital Dr. Juan Bruno Zayas Alfonso, Santiago de Cuba, Cuba

<sup>4</sup>6th year student of the Medicine School, University of Medical Sciences, Santiago de Cuba, Cuba

**Correspondence:** Dr. Reinier Besse Diaz, 1st and 2nd Degree Specialist in Internal Medicine, Associate Researcher, Santiago de Cuba, Cuba, Email reinier.besse@infomed.sld.cu

**Received:** July 19, 2022 | **Published:** August 05, 2022

## Introduction

Acquired immunodeficiency syndrome (AIDS) is an advanced clinical manifestation of human immunodeficiency virus (HIV) infection. In this stage, immunodeficiency is severe, leading to infections and associated neoplasms that can cause death.<sup>1</sup> The human detriment caused by this scourge due to physiological, psychological and social disorders is incalculable, as well as the demographic change generated in some countries by deaths caused by the disease, all of which accounts for the sad reality to which the population is exposed today. Humanity, which is why it is considered a global epidemic and there is a need to increase information, education and communication, aimed at the general population and the most vulnerable populations.<sup>2,3</sup> Currently, the number of people with HIV/AIDS has increased, which is why it is considered a public health problem.<sup>1-3</sup> These patients have improved with highly active antiretroviral drugs (HAART) and combinations of therapies that help reduce virus transmission, increase survival expectancy and improve the quality of life of carriers. There is ample evidence that patients have revolutionized their horizons with this treatment.<sup>3</sup>

In the context of the above, despite everything, the situation is favorable in our region, with official health statistics that place around 2,000 HIV cases reported each year in Cuba, a country that exhibits the lowest prevalence of HIV infection. In the Americas, with only 0.2%-0.3% of the population affected, which places it among the lowest in the world, as recognized by the World Health Organization (WHO). (However, given the growing access to effective prevention, diagnosis, treatment and care of the health-disease process, including opportunistic infections, this disease process has become a bearable

chronic health problem, which allows people living with the virus lead a long and healthy life.

From what concerns the theme that has been addressed and the preceding ideas, it is necessary to popularize that the management of people infected with HIV/AIDS with antiretroviral treatment is long-term and continues to strengthen its results. In most patients, prolonged medication intake causes treatment noncompliance and, consequently, therapy becomes inefficient, the virus becomes resistant, and the number of cases increases. To classify adherence to treatment as correct, the index must be greater than 95%, this means that the patient cannot stop taking (or do so late) more than five pills per month, or doses taken appropriately.<sup>4</sup>

In this sense, adherence, especially with individual drugs, has been difficult, but the annual appearance of 2 or 3 new antiviral agents since 1995 hallowed unprecedented advances in the treatment of this scourge and combined therapy has proven to be the most effective. The latter can increase viral suppression, prevent drug resistance, optimize drug exposure, and simplify dosing, but it is also not exempt from pharmacological antagonism, sub-therapeutic drug concentrations, and unexpected toxicity.<sup>4</sup>

Consistent with this holistic thinking, it is recognized that disease control requires permanent clinical follow-up and the continuous use of antiretroviral is effective but can also be quite deleterious. In accordance with this, people infected with HIV/AIDS, due to the long-term toxicity of antiretroviral drugs, increased age and the pro-inflammatory and immune-activated state caused by the virus, even in patients on antiretroviral therapy effective antiretroviral

treatment, suffer from an increasing number of comorbidities, such as cardiovascular disease, dyslipidemia, hypertension, diabetes, osteoporosis or kidney disease, this makes them susceptible to symptomatic complications derived from them and, in turn, to the drug interactions per se of the treatment, together with drugs for concomitant diseases.<sup>5,6</sup>

However, a drug interaction is accepted as clinically relevant when the efficacy or toxicity of a drug is significantly altered after the administration of other substances. The mechanism of interaction between drugs can be pharmacokinetic and pharmacodynamics. In any case, the interactions of antiretroviral with other drugs are complex and often subject to interindividual variations that also depend on genetic background and diet. Any drug, in its interaction with our organ system, can affect the ability to function and thereby produce pathological disorders and the cardiovascular system is one of them, thus cardiovascular risk (CVR) increases in patients infected with HIV/AIDS. This risk is due to intrinsic factors of the patient, such as the higher prevalence of classic cardiovascular risks and factors associated with the virus itself, such as immune activation, inflammation and immunodeficiency, others such as the components associated with antiretroviral therapy are markedly special, mainly due to its intrinsic metabolic alterations.<sup>5,7</sup>

Antiretroviral therapy is associated with an increased risk of heart disease and arrhythmias are very common in HIV/AIDS patients, although the mechanism is not yet fully understood. Each antiretroviral drug differs from the others in the way it contributes to increasing CVR, mainly by causing lipid and metabolic disorders, such as insulin resistance, affecting its bimolecular components. In accordance with this introductory topic, it is worth mentioning that diseases such as high blood pressure (HBP), torzade point, atrial fibrillation and other cardiovascular abnormalities have been described, including arrhythmias that can be very dangerous, with important repercussions for the patient, but not a serious investigation has been outlined, which clearly undertakes their frequency or their patterns of association with the specific consumption of antiretrovirals, this health situation being unknown by a representation of the medical union of our territory.<sup>8</sup>

Then, based on a hypothetical Bayesian thought, arrhythmias in patients with HIV/AIDS may be related to various factors and, taking as a premise everything that has been said so far, the consumption of antiretroviral drugs may be one of them. This scientific presumption, as it has been glimpsed in the present investigation, has not been outlined or demonstrated through tangible evidence and there are few inquiries about it, so it would be wise then to ask: What are the adverse reactions and the clinical characteristics present in the studied conglomerate? What will be the ratio of prevalence of cardiac arrhythmias in patients who consume nationally produced antiretroviral versus non-consumers? Taking into account and for all that has been foreseen so far, it is imperative to clinically characterize patients with HIV/AIDS with opportunistic diseases who presented adverse reactions due to the consumption of nationally produced antiretrovirals and to identify the reason for the prevalence of cardiac arrhythmias in this patient. Cluster of patients.

## Method

The research was carried out in the city of Santiago de Cuba, through a study design that, depending on the scope and the theme to be investigated, is of a descriptive and cross-sectional type, which made possible the clinical characterization, as well as the relationship of ART with Cuban generics with general adverse reactions and the presence of cardiac arrhythmias, found in the sick population with

opportunistic diseases, belonging to the 28 de September polyclinic, in the period 2019-2021. The study population consisted of 84 cases, all with opportunistic diseases who had or were not taking nationally produced antiretrovirals. Some of the variables studied were chosen according to the national strategic program for the prevention and control of STIs and HIV-AIDS.<sup>6</sup>

## Statistical processing

To achieve the contrast and verification of the results, an exhaustive review of the clinical records of the patients was carried out. Quantitative and qualitative summary measures were used and percentages were estimated as summary measures.

The 95% confidence interval (95% CI) was calculated for the proportion of patients with HIV-AIDS and adverse reactions to antiretroviral therapy, for the entire period of analysis. The  $\chi^2$  test of independence was used to identify a statistically significant association between the criteria of interest. A significance level of  $\alpha = 0.05$  was selected. The statistical hypotheses to test were:

H0: There is population independence between the different selected criteria.

H1: There is no population independence between the criteria of interest.

Test Statistician

$\chi^2$

$$\chi^2 = \sum_{l=1}^L \sum_{j=1}^J (O_{ij} - E_{ij})^2 / E_{ij} \rightarrow \chi^2, \text{ with } (rows - 1) *$$

$l = 1, j = 1$

H0 was rejected when the probability of obtaining results as extreme or more extreme than those obtained with the sample data, if H0 were true, was less than the predetermined level of significance ( $\alpha$ ).

## Association between variables

The association between the consumption of nationally produced antiretrovirals and the appearance of cardiac arrhythmias was evaluated, estimated for cross-sectional studies, using the prevalence ratio of cardiac arrhythmias in patients receiving antiretroviral therapy who presented adverse reactions related to the cardiovascular system and patients who did not consume antiretrovirals. antiretrovirals, through the following equation:  $(a/a+b)/(c/c+d)$ , in addition to its OR, through  $(a/b)/(c/d)$ , as a measure of effect, with their respective confidence intervals (95% CI).

**Ethical considerations:** Ethical aspects raised in the Declaration of Helsinki were taken into consideration and the anonymity of the patients was guaranteed, with a view to protecting the privacy of the participants.

## Results

Table 1 shows a marked predominance of adverse reactions linked to patients with opportunistic diseases such as oropharyngeal candidiasis with 25 patients, which represents 80%, followed by neurotoxoplasmosis with 65%.

Table 2 Related to antiretroviral treatment with Cuban generics, schedule I was the most harmful, representing 66.6 of the adverse reactions presented by this group of patients, followed by schedule II (64.3%), with schedule V not being negligible.

**Table 1** Opportunistic diseases linked to patients with adverse reactions

Opportunistic diseases	Adverse reactions		
	Total patients	Nope	%
Tuberculosis	4	1	25
Neurotoxoplasmosis	20	13	65
Oropharyngeal Candidiasis	25	20	80

Percentage calculated based on the total number of patients according to opportunistic disease and adverse reactions

Font: Medical records and specialized consultation control card

**Table 2** Adverse reactions according to treatment scheme with Cuban generics

Antiretroviral treatment	Total	Adverse reactions	%
Scheme I	24	16	66.6
Scheme II	14	9	64.3
Scheme III	5	4	80
Scheme IV	4	3	75
Scheme V	5	2	40
Total	52	3.4	65.4

Percentage calculated based on the total number of patients according to treatment schemes.

95% CI: [51.4;79.2].

Font: Medical records and specialized consultation control card.

**Table 3** Types of adverse reactions associated with sex recorded in sick patients

Adverse reactions	Patients	%	Females	%	Masculine	%
Cardio-toxicity	14	26.9	9	17.3	5	9.6
Lipodystrophy	1	1.9	0	0	1	1.9
Hepato-toxicity	3	5.8	1	1.9	2	3.9
Nephro-toxicity	1	1.9	0	0	1	1.9
Esophagus-Gastritis	28	53.8	12	23.1	16	30.7
Peripheral neuropathy	3	5.8	1	1.9	2	3.9
Dyslipidemia	2	3.9	0	0	2	3.9
CNS neurotoxicity	0	0	0	0	0	0
Total	52	100	23	44.2	29	5.8

Font: Medical records and specialized consultation control card

**Table 4** Cardiac arrhythmias and their association with the consumption of antiretrovirals according to the type of regimen used

Antiretrovirals	Cardiac arrhythmias					
	Consumption	Present (n=13)	%	Absent (n=29)	%	OR
Scheme I	5	33.3	19	34.5	3,460	2,929
Scheme II	7	46.7	7	12.7	13,157	7,042
Scheme IV	1	6.7	3	5.4	4,381	3,521
I dnt consume	2	13.3	26	42.3		
Total	15	100	55	100		

OR of prevalence of cardiac arrhythmias versus patients without antiretroviral use with their 95% CI: [1.232; 4.897]-[12.421; 15.021]-[12.421; 15.021]. Prevalence ratio of cardiac arrhythmias versus patients without antiretroviral use with 95% CI: [1.387; 3.896]-[6.421; 8.079]-[2.231; 4.669].

Font: Medical records and specialized consultation control card.

Table 3 shows the type of adverse reaction presented by the patients and its relation to biological sex. There was a higher frequency of adverse reactions associated with patients with esophageal gastritis with 28, for 53.8%, followed by cardio toxicity with 14 patients from the total sample, with male participation being more frequent (55.8%).

Table 4 shows the prevalence ratio between the variables studied and it has been found that the ratio between patients with cardiac arrhythmias versus those without arrhythmias is 3.460; 13,157; and 4,381 times higher in patients who consumed antiretrovirals compared to patients who did not consume them, with statistical significance being observed, but more pronounced for Scheme II.

## Discussion

In the surveillance of a pharmacological product, the main problem is related to the participation of a restricted number of people in the initial stage of the trial and to the ideal conditions in which the study is conceived, for which only a small number of effects are detected. adverse; however, when the product is consumed by more people, the possibility of observing other adverse reactions that were not described in the first stage of development of the new drug in question increases.<sup>6-8</sup>

Most of the adverse reactions to antiretrovirals related to the presence of opportunistic diseases in our series of cases were nuanced by oropharyngeal candidiasis, an opportunistic disease that unquestionably affects the digestive tract, making the patient more vulnerable when consuming the drugs. A similar study<sup>6</sup> indicates that the most predominant adverse effects were those related to the digestive system, although they do not specify which one, a result that partially coincides with our series, while in the case series of Szlejfetel<sup>7</sup> the pharmacy staff mentioned Oropharyngeal candidiasis as a deleterious marker of the gastrointestinal system.

The frequency of these effects in patients with HIV/AIDS who have an opportunistic disease is variable and depends on the stage of HIV infection. In our case, according to expert criteria, most patients have digestive system disorders. After discontinuation of the drug, the reactions are usually reversible, although in some cases corrective measures are necessary.<sup>8</sup> One aspect to take into account in our research is that most of our cases could be exposed to external factors such as alcohol consumption, a substance that increases the risk of adverse reactions and greater tissue damage, with multisystem involvement, obviously due to the results of the consumption of this substance. The addition of drugs in each therapy with these drugs increases the risk of adverse events by 10%.<sup>9</sup> despite the risk of adverse reactions associated with polypharmacy, this strategy is essential in HIV-infected patients.

Following this idea, the first line of initial treatment with nationally produced drugs usually includes two or more drugs. This almost always germinal medication is made up of zidovudine (AZT), lamivudine (3TC) and nevirapine, which are related to digestive disorders and drug rejection, an aspect that in turn reduces the possibility of raising CD4 levels and therefore therefore, it entails an increase in the viral load, which induces an increase in the frequency of appearance of opportunistic diseases, relating the latter to potentially dangerous adverse reactions.<sup>9,10</sup> Recently, international drugs have been introduced to the market that are not part of the national scheme, which, although they have been combined, have not yet become mandatory guidelines for access by all AIDS cases requiring treatment. But indisputably, where opportunistic infections or comorbidities are present, polypharmacy is mandatory.

Undoubtedly, adverse reactions are always present in consumers of antiretrovirals, Gil del Valle, in his study refers that the metabolic alterations with antiretrovirals is one of the conditions to change treatment regimens and manifest as hepatotoxicity, cardio toxicity, hyperlipidemia, hyperglycemia, and hematological type, each class of drug is associated with specific toxicities, which are enhanced by the interaction between antiretroviral agents, which is expressed in additional toxicity, all this is related to our research where scheme I prevailed, the largest number of patients who presented adverse reactions.<sup>10,11</sup>

In this series by Gil del Valle, it was found that patients who used the drugs that make up Scheme I, although apparently effective in their casuistry, presented the highest frequency of reported adverse reactions and, paradoxically, they are the ones with the highest associated toxicity.<sup>11</sup> But they are also the cheapest and the ones used in the generalization of the therapy in Cuba because they are generics of national production. In the management of these therapeutic combinations with antiretrovirals, the appearance of adverse drug reactions (ADRs) and interactions is an important aspect to take into account since they can cause a decrease in the efficacy of the treatment. These drawbacks mainly affect the patient's quality of life, and may favor therapeutic noncompliance and the induction of viral resistance to the different drugs.<sup>11-13</sup> The fact that these drugs are relatively recently used makes it convenient to establish drug-monitoring programs that make it possible to know the exact results of long-term toxicity and thus try to optimize their therapeutic management.<sup>12,13</sup>

The search for possible interactions is variable, so Marzolini. prospectively collected information on possible interactions between treatments from participants in the Swiss HIV Cohort Study over 10 months to determine the effect of drug use and age on the appearance of possible drug interactions. It was evident that the most important risk factors were with the use of protease inhibitors (PI), a group

of antiretrovirals used in the production scheme and used in our casuistry.<sup>12-14</sup>

According to Moore et al.<sup>14</sup> adverse reactions to nucleoside reverse transcriptase inhibitor drugs (drugs from the first and second schemes with Cuban generics) occur frequently, and even if favorable clinical responses are obtained, they force the withdrawal of the drug involved, an aspect that coincides with our casuistry.

Metabolic alterations constitute one of the most worrisome adverse effects of antiretroviral treatment. Early initiation of antiretroviral therapy and the use of medications with a higher safety profile have made it possible to reduce the risk of dyslipidemia and cardiovascular risk.<sup>15,16</sup> Our investigation showed an important group of patients with esophagus-gastritis and cardiac arrhythmias, although with relative coincidence with other studies, it could be due to casuistic differences in the referred investigations.

However, studies such as "The Danish HIV Cohort Study" and "The Copenhagen General Population Study"<sup>17</sup> with 3,251 patients with HIV infection and 13,004 controls adjusted for age and gender, showed an increased risk of AMI and cardiovascular arrhythmias in patients HIV smokers compared to the general population, attributing approximately three out of four AMIs that cause arrhythmias in patients with HIV infection, are associated with smoking, compared to one out of four in the control population. The authors conclude that quitting smoking could potentially prevent more than 40% of these cardiac abnormalities.<sup>16,17</sup> To reduce the appearance of these disorders, it is advisable to gradually increase the dose of medication on a daily basis, until the desired value is reached. Drug withdrawal due to these gastrointestinal effects has occurred on some occasions, but in general they are not considered serious reactions.<sup>18</sup>

This research confirmed that adverse reactions, especially those of cardiovascular origin, could be linked to the intake of antiretrovirals and particularly those derived from protease inhibitors. In the registry of clinical cases of the Veterans Health Administration in the USA, the association between different antiretroviral regimens and the risk of cardiovascular events such as AMI, arrhythmias and cerebrovascular events was sought. We analyzed 24,510 HIV-infected patients from 1996 to December 2009, finding that exposure to abacavir, efavirenz, lamivudine, and zidovudine was associated with increased risk of cardiovascular events with OR (odds ratio) ranging from 1.4-1.53. The EFV/AZT/3TC scheme was associated with an increased risk of cardiovascular events OR 1.6; 95% CI: 1.25-2.04 (54).<sup>19</sup> The EFV/AZT/3TC scheme was associated with an increased risk of cardiovascular events OR 1.6; 95% CI: 1.25-2.04.<sup>19</sup>

Our series coincides in aspects such as the use of antiretrovirals such as AZT and 3TC, which could explain the frequency of arrhythmias, facts such as knowledge of this phenomenon implies making therapeutic readjustments for a better comprehensive therapeutic approach. However, Hunt et al.<sup>20</sup> in a review of the literature published in MEDLINE and EMBASE up to August 2011, conclude that the use of protease inhibitors (PI) does not seem to be an independent predictor of QT interval prolongation as dangerous arrhythmias. And others that are not described as frequently.

This discrepancy may be due in part to various factors, including the diversity of samples with which we worked and other associated factors such as the presence of comorbidities, including heart disease, arterial hypertension, and phenomena that increase the potential of the drugs consumed on cardiovascular functions. Despite these evaluations carried out in our casuistry, it has had certain limitations; the detection of adverse reactions was carried out from a sample



of patients who came with their medication from the health areas, an aspect that limits the applicability of the results to the general population, especially in patients treated at other levels of care. An individual clinical evaluation of the risks and benefits of the therapy was not performed.

Although the study was not designed to investigate the clinical impact of the different therapies, it can be seen that the conclusions, although limited, are relevant for patients with HIV/AIDS, especially to point out the groups most vulnerable to antiretroviral medication and a particularity about certain casuistry in relation to cardiac arrhythmias, which undoubtedly is very likely to correspond to some antiretrovirals. As a climax It can be said that HIV/AIDS infection-disease continues to be a health problem in our territory, demonstrating the relationship between adverse reactions and antiretroviral treatment with Cuban generics, being visible in cardiac arrhythmias versus without arrhythmias, which was reasonably higher in those who used antiretrovirals. The drug-disease interaction is a complex but indisputably common process in some of these patients.

### Originality

This manuscript is an original and unpublished work, it has not been published in whole or in part, nor is it being evaluated by another journal or any other means of dissemination.

### Acknowledgements

None

### Conflict of interests

The authors declare that they have no conflict of interest.

### References

- Barrera, Richar W, Gómez Gonzales, Girón Vargas, et al. Factors associated with non-adherence to antiretroviral treatment in people with HIV/AIDS. *Horizon Med.* 2021;21(4):1498.
- Carvalho PP, Barroso SM, Coelho HC, et al. Factors associated with antiretroviral therapy adherence in adults: an integrative review of literature. *Cien Saude Colet.* 2019;24(7):2543–2555.
- Artimez-Jon, Artimez-Puente, Soler-Rodriguez. HIV/AIDS prevention education for adolescents with community intervention in the health area. *Teacher and Society.* 2021;18(1):64–77.
- Lamillar E. Adherence to antiretroviral treatment in patients of the program for the control of sexually transmitted infections and AIDS of the “Hipólito Unanue” National Hospital, Lima, Peru. *Horizon Med.* 2021;18(1):64–77.
- Cuba. Ministry of public health. National strategic plan for the prevention and control of STIs, HIV and hepatitis 2019–2023 Havana. MINSAP. 2022.
- Mendo Neity, Mesa Eduardo, Neyra Barrios, et al. Adverse reactions to antiretroviral drugs in patients with human immunodeficiency virus. *Medisan.* 2019;22(8):674–682.
- Betancourt J. Adherence to antiretroviral treatment in seropositive patients. *Cuban Journal of Comprehensive General Medicine.* 2019;34(3):0–1.
- Espinosa A, Avila M, Gibert Lamadrid. An updated conception of adherence to antiretroviral treatment. *Cuban Journal of Nursing.* 2018;34(1).
- Barrera RW, Gómez WE, Girón A, et al. Factors associated with non-adherence to antiretroviral treatment in people with HIV/AIDS. *Horiz Med.* 2021;21(4):1498.
- Tarragó Saday, Gravier Rosario, Gil Lizette. Pharmacovigilance in Cuba and under reporting of adverse drug reactions. *Horizon healthcare.* 2019;18(1):7–15.
- Morales M, García AJ. Serious preventable adverse reactions to antivirals. Cuban pharmacovigilance system. 2008-2017. *Horizonte Sanitario.* 2018;18(1).
- M J Lozano, M J Gómez, M. Miguel. Antiretroviral Therapy: Detection of adverse drug reactions from the diagnosis of hospital admission. *Farm Hosp.* 1999;23(6):337–342.
- Moore RD. Adverse events from drug therapy for human immunodeficiency virus disease. *Am J Med.* 1996;101:34–40.
- Fifteen Badillo, Barrera LK, Arias G, et al. Incidence of problems related to antiretroviral drugs for the treatment of HIV infection in hospitalized patients at the Santa Clara Hospital in Bogotá. *Biomedical.* 2019;39(3):561–575.
- Valderrama B, Gualtero S, Quiroga C, et al. Evaluation and management of cardiovascular risk in HIV infection. ACIN expert consensus. *Infectio.* 2019;23(1):73–91.
- Rasmussen LD, Helleberg M, May MT, et al. Myocardial infarction among danish HIV-infected individuals: Population-attributable fractions associated with smoking. *Clin Infect Dis.* 2015;60(9):1415–1423.
- Osorio T, Rivera C, Pino-Marín, et al. Clinical relevance of drug interactions in patients infected with the human immunodeficiency virus: update 2015-2017. *Rev. chil. infectol.* 2019;36(4):475–489.
- Sandra Liliana, Sandra Milena, Camilo, et al. Evaluation and management of cardiovascular risk in HIV infection. ACIN expert consensus. *Valderrama Beltran.* 2019;23(1).
- Oumar AA, Dakouo M, Tchiboza A, et al. Antiretroviral-induced adverse drug reactions in HIV-infected patients in Mali: aresource-limited setting experience. *Int J Basic Clin Pharmacol.* 2019;8(5):831–836.