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Community viral load of HIV in Brazil, 2007 – 2011: potential impact of highly active antiretroviral therapy (HAART) in reducing new infections

Carga viral comunitária do HIV no Brasil, 2007 – 2011: potencial impacto da terapia antirretroviral (HAART) na redução de novas infecções

Artur Iuri Alves de Sousa[I], Vitor Laerte Pinto Júnior[II]

ABSTRACT: ***Objectives:*** To estimate the human immunodeficiency virus (HIV) viral load in the Brazilian population and to assess the potential impact of highly active antiretroviral therapy (HAART) in reducing new infections to build evidences and to gather information to support health policies. ***Methods:*** Spatial analysis and modeling tools were used to describe the existing patterns of the viral load density, using the Kernel method. Data on viral load and treatment were retrieved from the databases Laboratory Tests Control System (SISCEL), which contains information on the individual's history of viral load, and Medication Logistics Control System (SICLOM), which controls the dispensing of drugs used for antiretroviral therapy. ***Results:*** It was observed that the community viral load (CVL) decreased progressively from 2007 to 2011, accompanied by a decrease of more than 32% in the mean CVL (CVL_M) — 22,900 copies/mL in 2007 *versus* 15,418 copies/mL in 2011. During this period, there was a reduction of CVL_M in all regions of Brazil, although North and Northeast showed, respectively, CVL_M 1.7 and 1.5 times higher than that in the Southeast region. A comparison between the individuals who underwent and who did not undergo HAART showed an increase of up to 3.9 times in 2011 in the viral load among those who did not undergo the therapy. ***Conclusion:*** The approach presented in this study indicates the existence of clusters with high concentrations. The use of Kernel in the identification of clusters proved to be a good tool for exploratory analysis, enabling the risk identification in certain geographic areas without the usual political and administrative divisions.

Keywords: Epidemiology, descriptive. Acquired immunodeficiency syndrome. Risk. Indicators. Viral load. Spatial analysis.

[I] *Universidade de Brasília,* School of Medicine,Tropical Medicine Center – Brasília (DF), Brazil.

[II] *Fundação Oswaldo Cruz,* Regional Directorate of Brasília – Brasília (DF), Brazil.

Corresponding author: Artur Iuri Alves de Sousa. Universidade de Brasília. Faculdade de Medicina. Núcleo de Medicina Tropical. Campus Universitário Darcy Ribeiro, sem número, Asa Norte, CEP: 70904-970, Brasília, DF, Brasil. E-mail: aia.desousa@gmail.com

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RESUMO: ***Objetivo:*** Estimar o volume de vírus circulante de HIV na população brasileira e avaliar o potencial impacto da terapia antirretroviral (HAART) na redução de novas infecções, com o propósito de construir evidências e informações para subsidiar a implementação de políticas de saúde. ***Métodos:*** Ferramentas de análise espacial foram utilizadas para descrever os padrões existentes na densidade da carga viral utilizando o método *Kernel* quártico. As informações da carga viral e tratamento são oriundas da base conjunta do Sistema de Controle de Exames Laboratoriais (Siscel), com informações do histórico da carga viral do indivíduo e do Sistema de Controle Logístico de Medicamentos (Siclom), que controla a dispensa dos medicamentos para a terapia antirretroviral. ***Resultados:*** Observou-se que a carga viral comunitária (CVC) apresentou redução progressiva no período de 2007 a 2011, acompanhada de uma redução da carga viral média (CVC_M) superior a 32% (22.900 cópias/mL em 2007 *versus* 15.418 cópias/mL em 2011). Nesse período, houve redução da CVC_M em todas as grandes regiões do Brasil, embora o Norte e Nordeste tenham apresentado, respectivamente, CVC_M 1,7 e 1,5 vezes a registrada no Sudeste. Em uma comparação entre os indivíduos que faziam ou não uso da HAART, observou-se aumento persistente da carga viral naqueles que não faziam uso da terapia de até 3,9 vezes em 2011. ***Conclusão:*** A abordagem apresentada neste estudo aponta a existência de aglomerados no espaço com altas concentrações. O uso do *Kernel* na identificação de aglomerados no espaço mostrou-se um bom instrumento para análise exploratória, possibilitando a visualização do risco em determinadas áreas geográficas sem as usuais divisões político-administrativas.

Palavras-chave: Epidemiologia descritiva. Síndrome da imunodeficiência adquirida. Risco. Indicadores. Carga viral. Análise espacial.

INTRODUCTION

Progress has been achieved in combating acquired immune deficiency syndrome (AIDS) in the last 30 years, especially with the discovery and improvement of highly active antiretroviral therapy (HAART). HAART was the most important factor impacting disease prognosis and epidemiology[1,2]. Since the beginning of the AIDS pandemic in Brazil, the disease surveillance has undergone revisions in its case definition and has incorporated new prevention practices[3,4]. In this context, the analysis of the epidemiological situation turned out to be of major importance to defining and conducting surveillance activities to enable the implementation of new treatment protocols and prevention.

The first case definition of AIDS in the world was issued by the Centers for Disease Control and Prevention (CDC) in the United States of America. The Ministry of Health (MH) of Brazil, in 1987, adopted its first definition restricted to individuals aged 15 years and over. This definition was based on that developed by the CDC in 1985 and was named CDC-Modified Criteria. This was based on laboratory evidence of infection with human immunodeficiency virus (HIV) and at least one diagnosis of a disease indicative of AIDS. Since then, the definition of AIDS cases in adults in Brazil underwent several revisions that had the adequacy of the criteria for laboratory diagnostic conditions and for the morbidity profile in the country as the main objective. The latest revision made in 2004 established as criteria for AIDS case definition the adapted CDC,

the Rio de Janeiro / Caracas (only for individuals aged 13 years and over) and the exceptional death criterion[5].

The individual diagnosed as seropositive for HIV in Brazil is subjected to the initial laboratory evaluation to measure their clinical and immunological status and the magnitude of viral multiplication. CD4+ and CD8+ T-lymphocyte counts, quantification of HIV RNA [viral load (VL)], and a full clinical and laboratory evaluation are requested. Regular visits are carried out to monitor the clinical course of patients by means of these tests, which are repeated 3–4 times a year, as recommended by the MS[6]. The medical monitoring of HIV infection is essential, both for those who do not have symptoms, and for those who already show signs of the disease[6].

The MS, in 2002, implemented a system for monitoring the immune status of the individual with HIV, both for CD4 and VL, named Laboratory Tests Control System (SISCEL). Concomitantly, the MS launched a system for monitoring of individuals undergoing treatment, named Medication Logistics Control System (SICLOM). As studies show that the VL is associated with HIV transmission[7], monitoring the VL with an appropriate intervention method may be one of the strategies for breaking the chain of transmission[8,9]. Knowing the magnitude, the distribution as for the location, and the exposure and transmission of HIV means may contribute to targeting actions and policies to the general population. In Brazil, few studies aiming at knowing the magnitude and distribution of the HIV were conducted to date.

The concept of community viral load (CVL) was introduced to quantify the amount of virus circulating in the population and assess the potential impact of antiretroviral therapy in reducing new infections[10]. Under these circumstances, CVC can be used as an indicator of HIV transmission level; consequently, its reduction may be associated with a decreased incidence of virus transmission[11].

Given that both SISCEL and SICLOM can be used to study the VL distribution in Brazil, associated with the use of HAART or not, the proposal was to map the HIV VL to assess the potential level of transmission and contribute to the improvement of policies for breaking the chain of transmission.

Accordingly, this study aimed at estimating the volume of circulating HIV in the population and evaluating the HAART potential impact on reducing new infections, with the purpose of building evidence and information to support the implementation of health policies in Brazil.

METHODS

A retrospective analytical study of the VL distribution in the population, by the municipality of residence, was conducted from 2007 to 2011. Individuals aged 13 years and over, who were included in the combined registration database of SISCEL (laboratory monitoring) and SICLOM [monitoring the use of antiretroviral (ARV) drugs], were studied.

Information on data collection for the VL test, date of ARV dispensing and the individual municipality of residence, which were part of the records on SISCEL/SICLOM, were used. In the analyzed period, the MS applied different methodologies to quantify the VL — the Nucleic Acid Sequence-Based Amplification (NASBA) and b-DNA (recombinant). Each of the methodologies presented different detection limits, both upper and lower. For this study, in an attempt to standardize the detection limits, a VL of 50 copies/mL was assigned to individuals who presented values below the test detection limit, and a VL of 500,000 copies/mL was assigned to those who presented values above the test detection limit.

Given the possibility that an individual has been recorded more than once in the systems (SISCEL and SICLOM) and aiming at obtaining a database without duplication of records, probabilistic procedures were applied[12] using Reclink application, in which, with established probabilities of duplicated records, common fields such as the patient's name, the patient's mother's name, and date of birth were compared[13,14]. After the identification of duplications, a single database was compiled with the merge of the entire history of laboratory tests and medications dispensing under the same record.

After gathering the history of tests and drugs dispensing of the individuals, VL indicators for the years 2007, 2009, and 2011 were calculated. The first indicator was CVL, which is the sum of the VL of all individuals in the period and year of collection of biological material for the examination, according to Equation 1:

$$\text{Community Viral Load (CVL) in year t} = \sum_{i=1}^{n} CV_i \quad (1)$$

Where:
n is the number of subjects.

The second indicator was the mean CVL (CVL_M), which is the sum of the VL of all individuals by year of collection of biological material for the examination, divided by the total number of individuals being monitored in the same year, according to Equation 2:

$$\text{Mean Community Viral Load } (CVL_M) \text{ in year t} = \frac{\Sigma_{i=1}^{n} CV_i}{n} \quad (2)$$

Where:
n is the number of individuals.

Spatial analysis was performed with CVC_M, including the strata of undergoing treatment or not, searching for the identification of density patterns by means of Kernel interpolation and smoothing, with adaptive radius of influence[15,16]. This method enables estimating the concentration of events in space, indicating clusters in a spatial distribution so that the events are weighted according to proximity to other events, in which the closest "neighbors" receive higher weights[15,17].

For the areas density classification, the gradient between lowest and highest density was used. Light green was adopted for areas with the lowest density, and red was adopted for those with higher density. Smoothing function with adaptive radius was carried out by the quartic kernel.

IBM® SPSS® version 18.0 was used for the descriptive analysis, whereas TerraView® software version 4.2.2 was applied for the analysis of spatial data. Linkage of the databases was carried out by the RecLink® version 3.0.

This study was approved by the Ethics Committee of the School of Health Sciences of the *Universidade de Brasília* (CEP/FS-UNB) and the by Department of STD, AIDS and Viral hepatitis (DDAHV) of the Secretariat of Health Surveillance, Ministry of Health, under opinion No 379.170 of August 30, 2013.

RESULTS

The study included 300,596 subjects aged 13 years and over, whose CVL showed progressive reduction in the period of 2007 – 2011, concomitant with the reduction of CVL_M of over 32% in the same period. Table 1 shows the values for CVL and CVL_M stratified by individuals treated with HAART.

Table 2 presented the evolution of the CVL and CVL_M stratified by variables on the individual characteristics in the studied period. There was a reduction in CVL_M in all regions of Brazil comparing 2007 – 2011, which ranged from 21.3% (the lowest reduction in the Northeast region) to 37.3% (the largest reduction in the Southeast). The smallest CVL_M was observed in 2011 in the Southeast (13,187 copies/mL). North and Northeast regions had CVL_M 1.7 and 1.5 times higher, respectively, when comparing with the average in Southeast, whereas the South and Midwest showed CVL_M 1.2 and 1.3 times higher than the Southeast, respectively. In relation to gender, there was a reduction of 32% in CVL_M for both the genders, although the CVL_M among men have shown persistently lower decrease when compared to women, being approximately 1.2 times higher in 2007 and 2011.

Table 1. Total and mean community viral load, with and without antiretroviral therapy, of individuals aged 13 years and over, according to the last count of viral load per year of data collection. Brazil, 2007, 2009, and 2011.

Variável	2007	2009	2011
CVL (Community Viral Load)*	4,886,438,747	5,000,824,351	4,634,632,707
CVL_M (Community Viral Load Average)**	22,900	19,502	15,418
With HAART	12,573	11,080	8,679
Without HAART	29,737	37,043	33,604

*Sum of viral load of all individuals monitored during the year; ** Sum of viral load of all individuals divided by total of individuals being monitored during the year; HAART: highly active antiretroviral therapy.

Table 2. Total and mean community viral load of monitored individuals aged 13 years and over, presented by different sociodemoghraphic characteristics, according to the last count of viral load per year of data collection. Brazil, 2007, 2009, and 2011.

	2007		2009		2011	
	CVL	CVL_M	CVL	CVL_M	CVL	CVL_M
Brazil	4,886,438,747	22,900	5,000,824,351	19,502	4,634,632,707	15,418
Region						
North	231,907,979	29,576	312,399,773	26,215	357,173,748	22,065
Northeast	662,589,503	25,740	843,231,330	23,542	908,457,372	20,268
Southeast	2,520,798,151	21,044	2,401,870,642	17,436	2,059,270,800	13,187
South	1,147,653,365	24,134	1,122,831,924	20,022	1,004,489,684	15,244
Mid-West	323,489,749	25,962	320,490,682	21,564	305,241,103	17,409
Gender*						
Male	1,942,331,346	20,954	1,950,449,736	17,511	1,794,707,087	13,915
Female	2,943,958,112	24,394	3,044,986,856	21,012	2,837,715,506	16,546
Age range (years)						
13 – 19	104,127,097	25,928	109,918,772	19,431	121,221,617	15,770
20 – 24	289,791,051	30,750	315,101,556	28,938	324,634,067	24,243
25 – 29	679,548,123	29,469	709,339,848	28,160	618,412,344	22,831
30 – 34	920,033,885	26,528	920,184,162	23,714	818,165,650	19,464
35 – 39	970,395,594	23,669	919,165,533	20,392	817,201,431	16,648
40 – 49	1,364,426,809	20,596	1,364,700,521	16,692	1,294,470,784	13,511
50 – 59	429,829,287	16,370	517,009,887	14,145	487,404,402	10,154
60 and over	128,286,901	14,749	145,404,072	11,627	153,122,412	8,749
Race/color of skin						
White	1,613,000,300	20,383	1,749,364,302	18,154	1,507,994,288	13,504
Black	287,423,311	22,082	324,702,559	19,859	299,357,915	15,500
Yellow	17,951,791	21,655	20,103,256	18,965	17,310,076	14,073
Brown	857,973,795	21,400	1,006,323,010	19,608	974,805,418	15,843
Indigenous	13,528,172	31,171	12,951,765	30,619	4,509,712	17,018
Not available**	2,096,561,378	26,290	1,887,379,459	20,791	1,830,655,298	17,209

*131 individuals with not available gender information; **106,587 not available race/color of skin information; CVL: total community viral load; CVL_M: mean community viral load.

In the analysis of CVL_M by age, a decrease in mean CVL was observed in all groups. Despite the decrease, the intensity of CVL_M was different among age groups, and the highest average was observed in the range equivalent to 20 – 34 years of age in all studied years (Table 2). Older age groups (34 years old and over) had CVL_M systematically lower when compared to those individuals aged 20 – 34 years. With regard to the ethnicity/color of skin, there was also a persistent reduction in CVL_M for all groups in the period analyzed (Table 2).

The spatial analysis of the distribution of CVL_M density showed changes in the circulating virus concentration in the country in the period analyzed. In 2007, the highest average concentration (Figure 1A) occurred on the route between Natal and João Pessoa, São Paulo

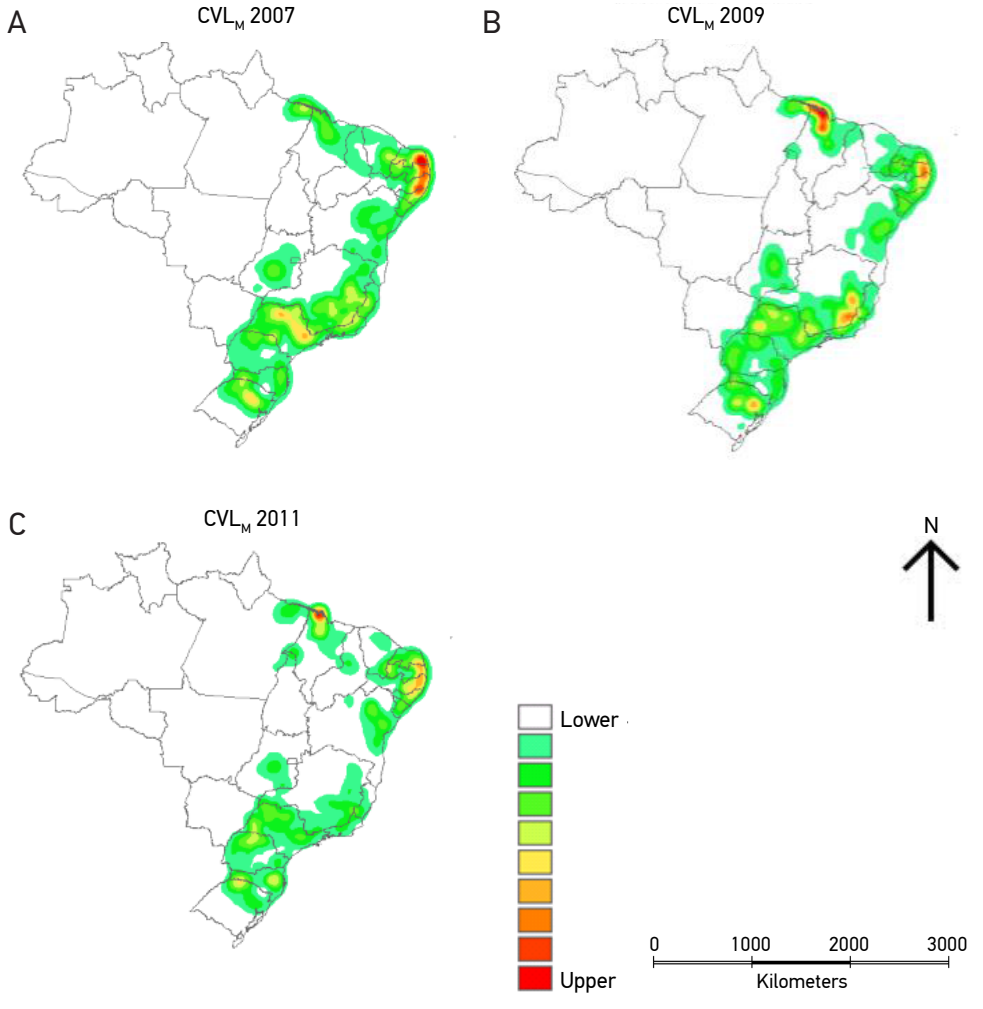

Figure 1. Surface density of mean community viral load (CVL_M) of individuals with AIDS aged 13 years and over, monitored by surveillance systems in Brazil, Kernel method (assigning 50 copies/mL for individuals with undetectable viral load). Brazil, (A) 2007, (B) 2009, and (C) 2011.

and countryside area, and region of Porto Alegre. Moderate concentration (green color) stood out in coastal cities such as São Luís, in Maranhão State, in the south of Brazil, showing its predominance in municipalities of the São Paulo, Paraná, and Santa Catarina States, and in the inner cities of Bahia and Minas Gerais (Figure 1B). In the year 2011, a reduction of concentration in several areas was observed when compared to the beginning of the period analyzed (Figure 1C).

When the analysis of CVL_M among individuals who were or were not undergoing treatment was performed, there was greater VL magnitude among those not treated (Figure 2A and B). Spatially, high concentrations of circulating viruses among untreated individuals in Northeastern areas were found, and less intensity was identified in the Mid-South of the country.

DISCUSSION

The results show that the spatial distribution of CVL in Brazil progressively decreased over time. However, it is spatially concentrated, evidencing permanently areas of greatest risk of HIV transmission. CVL was consistently lower with the use of HAART, being 70% lower when compared to the stratum of those who did not use the therapy.

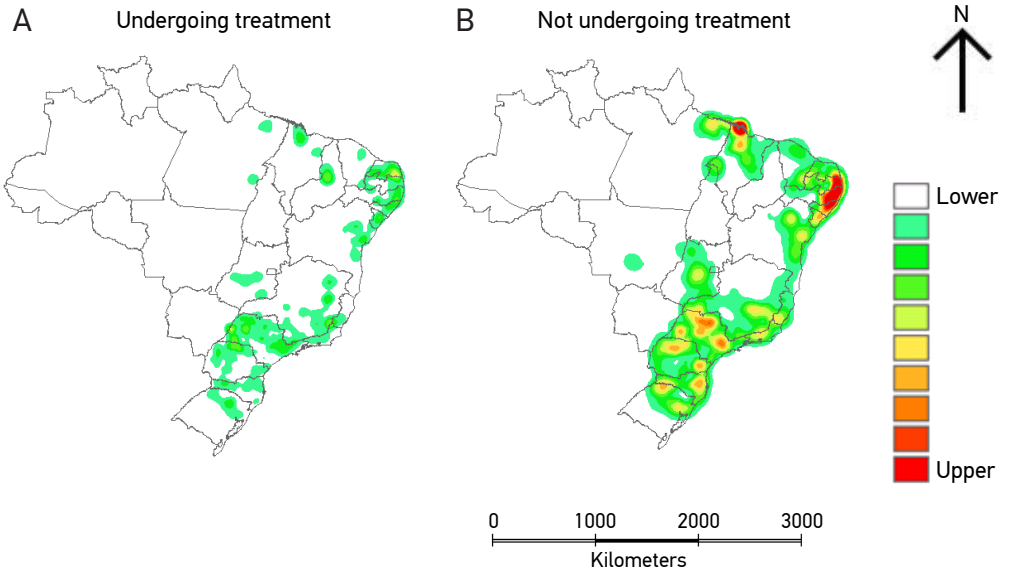

Figure 2. Surface density of mean community viral load (CVL_M) of individuals aged 13 years and over, monitored by Unified Health System, according to the treatment status: (A) undergoing treatment or (B) not undergoing treatment, Kernel method (assigning 50 copies/mL for individuals with undetectable viral load). Brazil, 2007, 2009, and 2011.

The increased incidence of HIV has been strongly associated with the level of circulating virus concentration[7]. High levels of VL is significantly associated with new cases of HIV, and the reduction of CVL would tend to reduce new infections[7]. A cohort study in HIV-positive adults showed that individuals in treatment had a reduction in the transmission rate of approximately 92% compared with those who were not in treatment[9]. With regard to the concentration of VL, the study showed that the transmission ratio was zero when subjects had undetectable VL levels or presented less than 1,500 copies/mL[8].

Geographical differences observed between the periods analyzed showed that the CVL_M among individuals who were not in treatment was consistently higher when compared to those who were in treatment, being 3.9 times higher in 2011. This analysis reinforces the evidence that ARV treatment administered to HIV-infected individuals, which aims at achieving and maintaining viral suppression in undetectable levels, would tend to prevent HIV transmission[18,19]. The association between growth in the use of the therapy, decreased CVL, and decrease in new HIV cases was observed in a study conducted in Canada[20].

Analysis by regions showed reduction in CVL_M in all major regions of Brazil, evidencing a gradual reduction of this risk over time in Brazil, as a result of ARV therapy. However, Southeast and South regions presented permanently CVL with higher levels of viral concentration, showing they are more exposed to the risk of HIV transmission.

Gender differences were also observed even with a 32% reduction in CVL_M for both the genders. CVL_M among men was consistently higher when compared to women, being 1.2 times higher in the analyzed years (2007, 2009, and 2011). To consider studying the CVL in subpopulations for HIV infection in Brazil such as men who have sex with men (MSM), which indicates differentiated magnitude of risk[21] and identifies areas with high levels of VL concentration, would possibly support the decision-making process for better planning of prevention actions and control of epidemic, with specific interventions in space because of the identification of the population subgroups which are more exposed to risks.

A study conducted by Krentz in Brazil with HIV-positive individuals showed that newly diagnosed HIV patients presented a higher VL concentration compared with those undergoing treatment. The newly diagnosed patients (6.6% of cases) contributed with 37.5% to the CVL, while those who were undergoing treatment (79.0% of cases) contributed with 29.5% to the CVL[10]. Additionally, Krentz highlighted that the loss of follow-up of HIV-positive individuals may not decrease the CVL, thus not reducing new cases of HIV in the population with increased coverage of HAART. High mobility in and out of specialized centers that monitors the individuals with HIV may disrupt the care provided to patients[22].

Early diagnosis of HIV infection has important clinical and public health implications. Early initiation of HAART may be considered to reduce the progression of serious opportunistic diseases. In this context, global initiatives, including Brazil[23], have been implemented as a strategy to break the transmission of HIV, although this strategy remains controversial because it involves ethical challenges, mainly by

differences in public health systems worldwide and because of the vulnerability affecting people living with HIV[24,25].

In Brazil, incidence rate for AIDS is the indicator used to establish the degree of risk of occurrence of HIV transmission[26]. To consider indicators that constituted the VL can additionally contribute to identifying areas that are at higher risks (hot areas)[27]. This identification may support targeting surveillance and health care actions.

The main limitation of this study is related to the patients diagnosed with HIV. This is due to the nonintegration of monitoring information held in the public system (SUS) with the monitoring of HIV cases carried out by the private system. This may lead to the underestimation of risks. In 2014, MS added HIV / AIDS disease to the compulsory notification list, which will allow assessing risk more accurately in the near future.

Another limitation of the study is monitoring of disease dynamics and individual behaviors over time at the municipal level, which requires careful consideration as the monitoring of the individuals can be performed in cities that are different from their residences. Analyzes that consider the relationship between the occurrence of events in the neighboring municipality can better explain the dynamics of the disease. Some authors suggest that the distance between the cities may be a factor that explains the increase in the cases of AIDS[28]. It is worth mentioning that Kernel analysis is subjective as there is no standard set of parameters to classify the risk, consequently depending on previous knowledge of the subject studied[27].

The intensification of HAART as a key component for combined prevention strategies[29] for HIV transmission break in Brazil now has an important relevance, considering that the country provides, complimentarily and universally, medications to treat HIV / AIDS. The challenge includes the incorporation of a medical monitoring system, integrating laboratory and pharmaceutical components to health care[30], and the increase of the population who know their HIV status.

CONCLUSION

The results of this study highlight the importance in identifying areas under higher risk (hot areas) in the country, estimating the relationship of distribution of CVL density with HIV transmission in space, encompassing the institutionalization of monitoring[31] of epidemiological information to support decision-making, aiming at the planning of actions for preventing and controlling the epidemic, with specific interventions in space due the higher risks.

CONTRIBUTION OF AUTHORS

Sousa AIA: participated in the conception and design of the study, analysis and interpretation of data, writing and critical review of the intellectual content and approved the

final version of the manuscript. Pinto Jr. VL: participated in the conception and design of the study, interpretation of data, writing and critical review of the intellectual content and approved the final version of the manuscript. All authors declare being responsible for all aspects of the work, ensuring its accuracy and completeness.

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