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Research Article

DETERMINATION OF HIV-1 TROPISM. ROOSEVELT HOSPITAL, GUATEMALA

***Jessenia Sabrina Navas Castillo, Maria Cristina Quintana Galindo, Nydia Anaidé Orózco Morán, Mircea Lisbeth Romero Trujillo, Corilia Sucely García Porres, Diana Karina Baldizón Pernillo, Verónica Lucía Patzán Guamuch, Rodolfo Pinzón Meza and Ana Johanna Samayoa Bran**

Comprehensive Care Unit for HIV and Chronic Infections "Dr. Carlos Rodolfo Mejía Villatoro", Roosevelt Hospital, Guatemala

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Abstract

Objective: Establish the proportion of adult patients with multiple failures to antiretroviral therapy regimens who could benefit from the use of R5 antagonists by determining HIV-1 tropism. **Methodology:** Records of 42 HIV-1-positive adult patients treated at the "Dr. Carlos Rodolfo Mejía Villatoro" of the Roosevelt Hospital, who were instructed to perform a viral tropism test of the V3 hypervariable region of glycoprotein 120 by sequencing on the MiniSeq™ - Illumina system, using the DeepChek® v2.0 software, during the period from January 2018 to February 2021. **Results:** Of the 42 included records of patients for whom viral tropism testing was indicated, 50.0% were male. The median age at the time of the test request was 41 years (IQR 33.3, 45.8). 61.9% corresponded to co-receptor R5. **Conclusion:** The high proportion of R5 virus obtained by determining HIV-1 tropism in adult patients with multiple failures is similar to that reported in other studies. The performance of this test is necessary for a targeted and personalized treatment in which patients could benefit from the use of R5 antagonists.

Keywords: HIV-1, Multiple failure, Resistance, Viral tropism, Maraviroc.

INTRODUCTION

Tropism is defined as the affinity of the HIV-1 virus for the host tissue, using entry coreceptors that allow it to replicate in two cell lines: monocyte/macrophage and CD4+ T cells[1,2]. The former, together with memory CD4+ T cells, express the coreceptor CCR5 (R5) [3,4] and this is almost always associated with new HIV infections. While the coreceptor CXCR4 (X4) is expressed by naïve and memory CD4+ T cells, as well as by monocytes/macrophages at lower levels [2]. Furthermore, it has been identified that so-called dual/mixed (D/M) coreceptors express both of the aforementioned coreceptors [5]. The clinical importance of knowing the tropism of HIV-1 in patients with failure to multiple antiretroviral therapy regimens lies in assessing whether a patient is a candidate for including an R5 coreceptor antagonist within the combination of drugs that will constitute rescue therapy [6], therefore the determination of viral tropism is an essential requirement to be met prior to its use [7], Maraviroc being the first antagonist drug of this coreceptor to be approved by the Food and Drug Administration (FDA) [6]. In Guatemala, the use of Maraviroc was included in the Antiretroviral Treatment Guide in 2013 [8]; However, in the Comprehensive Care Unit for HIV and Chronic Infections "Dr. Carlos Rodolfo Mejía Villatoro" from Roosevelt Hospital, was included in the rescue therapy for patients failing multiple families of ART in May 2015. The tropism test was implemented in 2018; before that date, the samples for this determination were sent to a regional reference laboratory. The objective of the present investigation was toestablish the proportion of adult patients with multiple failures to antiretroviral therapy regimens who could benefit from the use of R5 antagonists by determining HIV-1 tropism.

Corresponding Author:** ***Jessenia Sabrina Navas Castillo,
Comprehensive Care Unit for HIV and Chronic Infections "Dr. Carlos Rodolfo Mejía Villatoro", Roosevelt Hospital, Guatemala.

METHODOLOGY

Population and sample

A descriptive cross-sectional investigation was carried out that included records of 42 HIV-1 positive adult patients with failure to multiple antiretroviral therapy regimens treated at the "Dr. Carlos Rodolfo Mejía Villatoro" from the Roosevelt Hospital, who were instructed to perform a viral tropism test, during the period from January 2018 to February 2021. The sampling method was non-probabilistic for consecutive cases.

Patient selection criteria

- Present at least two viral loads in plasma greater than 1000 copies/mL within a period of 4 to 12 weeks apart.
- Documented resistance to multiple families of ART: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTs), protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs).

Viral tropism

Determination of viral tropism of the V3 hypervariable region of glycoprotein 120 was performed through sequencing on the MiniSeq™ - Illumina system using DeepChek® v2.0 software. Tropism is determined by the Geno2pheno algorithm from the Max Planck Institute, Germany and uses a false positive rate of 3.5% to assess the probability of falsely classifying an R5 virus as X4.

Data collection instrument and procedure

The database was generated in an Excel Office 2019 electronic sheet. The information was filled out in the pre-established

order of the fields. The variables sex and age were obtained from the database of the sequencing area of the laboratory of the Comprehensive Care Unit for HIV and Chronic Infections "Dr. Carlos Rodolfo Mejía Villatoro" from the Roosevelt Hospital. Viral tropism was transcribed from reports generated by DeepChek® software.

Analysis of data

It was carried out using the freely distributed statistical software Jamovi v2.3.26; the characteristics of the patients are described through frequencies and percentages, the quantitative variable in median and interquartile range. Viral tropismsare presented in percentage.

Ethical aspects

This research did not require informed consent, since no intervention was performed on the patients during the research, nor were any identifying data collected. The research protocol was subject to review and approval by the authorities of the Department of Internal Medicine, Comprehensive Care Unit for HIV and Chronic Infections "Dr. Carlos Rodolfo Mejía Villatoro" of the Roosevelt Hospital and the Department of Teaching and Research of the same hospital.

RESULTS

Of the 42 included records of patients for whom viral tropism testing was indicated, 50.0% were male. The median age at the time of requesting the test was 41 years (IQR 33.3, 45.8). 61.9% corresponds to co-receptor R5.

Table 1. HIV-1 tropism in patients with failure to multiple antiretroviral therapy regimens

			95% CI	
Tropism	Frequency	Proportion	Lower	Superior
D/M	14	33.3%	19.6%	49.5%
R5	26	61.9%	45.6%	76.4%
X4	2	4.85%	6.0%	16.2%

D/M: dual/mixed

Of the patients in whom tropism for the R5 co-receptor was identified, 34.6% (9/26) were on containment therapy with 3TC. At the time of this analysis, of the 42 patients, 13 had abandoned antiretroviral treatment, 4 died, And 3 were transferred to other HIV care centers. Of the 26 patients with CCR5 (R5) tropism, 7 received Maraviroc; however, only 3 were active (Table 3) (they had been using Maraviroc for 3 to 4 years) since one abandoned treatment, two died and another was transferred (Table 4).

Table 2. Antiretroviral therapy regimen of patients at the time of requesting the HIV-1 tropism test

	TROPISM							
ART	D/M [n (%)]		R5 [n (%)]		X4 [n (%)]		Total [n (%)]	
3TC	4	28.6	9	34.6	1	50.0	14	33.3
3TC + DTG + DRV/r	0	0.0	1	3.8	0	0.0	1	2.4
3TC + DTG + ETR	0	0.0	1	3.8	0	0.0	1	2.4
3TC + DTG + LPV/r	1	7.1	0	0.0	0	0.0	1	2.4
3TC + RAL + LPV/r	0	0.0	0	0.0	1	50.0	1	2.4
ABC + 3TC + EFV	1	7.1	0	0.0	0	0.0	1	2.4
ABC + 3TC + LPV/r	0	0.0	1	3.8	0	0.0	1	2.4
ABC + DTG + LPV/r	1	7.1	1	3.8	0	0.0	2	4.8
ABC + TDF + LPV/r	0	0.0	2	7.7	0	0.0	2	4.8
AZT + 3TC + DTG	1	7.1	2	7.7	0	0.0	3	7.2
AZT + 3TC + LPV/r	0	0.0	1	3.8	0	0.0	1	2.4
AZT + 3TC + RAL	0	0.0	1	3.8	0	0.0	1	2.4
AZT + TDF+ ETR	1	7.1	0	0.0	0	0.0	1	2.4
AZT + TDF + LPV/r	1	7.1	0	0.0	0	0.0	1	2.4
DTG + 3TC + DRV/r	0	0.0	1	3.8	0	0.0	1	2.4
FTC + TDF + LPV/r	0	0.0	2	7.7	0	0.0	2	4.8
EVG / COB / FTC / TAF	1	7.1	1	3.8	0	0.0	2	4.8
FTC + TDF + EFV	1	7.1	2	7.7	0	0.0	3	7.1
RAL + 3TC + DRV/r	1	7.1	0	0.0	0	0.0	1	2.4
TDF / 3TC / DTG	1	7.1	1	3.8	0	0.0	2	4.8
Total	14	100.0	26	100.0	2	100.0	42	100.0

ART: antiretroviral therapy. D/M: dual/mixed. 3TC: lamivudine, DTG dolultegravir, DRV: darunavir, r: ritonavir, ETR: etravirine, LPV: lopinavir, RAL: raltegravir, ABC: abacavir, EFV: efavirenz, TDF: tenofovir, EVG: elvitegravir, COB: cobicistat, FTC: emtricitabine, TAF: tenofovir alafenamide.

Table 3. ART regimens based on the use of Maraviroc and reason for changing ART combinations among patients who are being monitored

No.	Sex	Age	Schemes with Maraviroc	Reason for change	Condition
1	M	83	FTC/TDF + DTG 50 mg c/12 + MVC 300 mg c/12	Shortage	Active
			TDF/3TC/DTG + MVC 300 mg c/12	Replenishment	
			TDF/3TC/DTG + MVC 300 mg c/12 + DTG	Shortage	
			TDF/3TC/DTG + AZT + DTG	Replenishment	
			TDF/3TC/DTG + MVC 300 mg c/12 + DTG	Current scheme	
2	F	50	ETR + MVC 150 mg c/12 + DTGc/12	Shortage	Active
			TDF/3TC/DTG + MRV 150 mg c/12	Shortage	
			TDF/3TC/DTG + DRV + RTV	Current scheme	
3	F	89	MVC 150 mg c/12 + DTG + LPV/r	Shortage	Active
			MVC 150 mg + TDFc/48 + 3TCc/24 + LPV/r	Replenishment, Simplification	
			MVC 150 mg c/12 + DTG + LPV/r	Current scheme	
			3TC	Various subsequent schema changes.	

M: male, F: female, mg: milligrams, c/12: every twelve hours, FTC: emtricitabine, TDF: tenofovir, DTG: dolutegravir, MVC: maraviroc, 3TC: lamivudine, AZT: zidovudine, ETR: etravirine, LPV: lopinavir, r: ritonavir, DRV: darunavir, RAL: raltegravir.

Table 4. ART regimens based on the use of Maraviroc and reason for changing ART combinations in patients according to their condition

No.	Sex	Age	Schemes with Maraviroc	Reason for change	Condition
1	F	42	FTC/TDF + MVC 150 mg c/12 + DRV/r	Unique scheme	Deceased
2	M	42	DTG + MVC 150 mg c/12 + LPV/r	Shortage	Abandonment
			RAL + 3TC + LPV/r	Virological failure	
			RAL + MVC + LPV/r	Virological failure	
			3TC	Virological failure	
			ETR + DTG c/12 + MVC 600 c/12	Unique scheme	
3	M	51	TDF + MVC 150 mg c/12 + LPV/r	Shortage	Transferred
			3TC	Virological failure	
			TDF/3TC/DTG + DRV/r + DTG		
4	F	42	TDF + DRV/r + MVC 150 mg c/12	Poor adhesion	Deceased
			3TC	Return to previous scheme	
			TDF + DRV/r + MVC 150 mg c/12	Abandonment	
			TDF + DRV/r + MVC 150 mg c/12	Interaction with antifimics and poor adherence	
			3TC	Virological failure	
			TDF + MVC 600 mg c/12 + DRV/r	Change due to interaction with Rifampicin. Latest scheme with MVC	
			3TC	Various subsequent schema changes.	

M: male, F: female, mg: milligrams, c/12: every twelve hours, FTC: emtricitabine, TDF: tenofovir, DTG: dolutegravir, MVC: maraviroc, 3TC: lamivudine, AZT: zidovudine, ETR: etravirine, LPV: lopinavir, r: ritonavir, DRV: darunavir, RAL: raltegravir.

DISCUSSION

The correct phenotypic classification of HIV-1 tropism is of utmost importance in the pathogenesis and in the study of disease progression [(1)]. Determining the tropism of the virus is essential to prescribe Maraviroc (a powerful alternative with little resistance); the most frequently used methods facilitate reliable prediction in clinical practice, with a false positive rate of approximately 5% [(9)]. Maraviroc is an antiretroviral antagonist of the CCR5 co-receptor of CD4, indicated in combination with other antiretroviral drugs for the treatment of pretreated adult patients infected with HIV-1 and with R5 tropism [(10)]. In Guatemala, its use was included in the 2013 regulations [(8)], although in practice it was used for the first time in 2015 to treat patients with multiple failures in the NRTI, NNRTI, IP families and/or INSTI with R5 tropism. It was found that 61.9% (95% CI 45.6 – 76.4%) of the patients included in the present study had R5 tropism (table 1). This data is similar to the 64.9% (153/437) of R5 tropism reported by Fuentes (2015) in patients with failure to highly active antiretroviral treatment (HAART) from 27 states of Mexico[(11)]. The high proportion of R5 viruses may be due to the route of transmission; R5 viruses predominate in patients who acquire the infection sexually, and although it has been described that R5 is predominant in the initial stages of the infection, it can remain unchanged over time, in multi-treated patients[(5,9)]. The pharmacological approach to patients who have failed multiple ART regimens is usually complex since it is essential to take into account the drug history and thus decide the best combination with Maraviroc. Of the patients in whom R5 co-receptor tropism was identified, 34.6% (9/26) were on containment therapy with 3TC (table 2), suggesting that the patients had exhausted the available therapeutic options and were awaiting the result of the tropism test to make an appropriate pharmacological decision. The accumulation of resistance to multiple classes of ARTs limits options for effective therapy, which can lead to disease progression and death. The results show that 28.3% (13/42) of the patients dropped out of ART after the determination of viral tropism, only one of them was receiving Maraviroc at the time of dropping out; adherence to antiretroviral treatment determines the success or failure of therapy [(12)]. Less adherence represents greater development of resistance and compromise of the immune system, which is reflected in these patients who needed more than one change in antiretroviral regimen due to the accumulation of resistance and 4 of them died as a consequence of immune suppression, even though two were using Maraviroc. In Guatemala, the tropism test has been carried out locally only in the Comprehensive Care Unit for HIV and Chronic Infections "Dr. Carlos Rodolfo Mejía Villatoro" from the Roosevelt Hospital, from 2018 to 2021 but not continuously. Prior to this period, tropism determinations were carried out outside the country with restrictions on the number of tests available. Maraviroc, which has been available since 2015, had periods of shortage, as well as other ARTs used in combination, which has been reflected in the change of drugs and readjustment of doses at the individual level, and therefore it was necessary to evaluate combinations with the available ARTs (table 3 and 4). Since 2018, administrative procedures have been implemented to ensure the supply of Maraviroc through two entities of the Ministry of Public Health and Social Assistance: the National STI and HIV/AIDS Program, which is responsible for the supply of ARVs at the national level, and the hospital. Roosevelt, which allocated part of its budget for the purchase of Maraviroc, which has achieved relative stability; however, the inclusion of this drug for a greater number of patients than is considered still remains a challenge, as well as ensuring long-term supply, mainly due to costs outline. The D/M tropism was found in 33.3% of the patients and CXCR4 (X4) tropism was showed in 4.8% (table 1). It is possible that there is a change in tropism over time, mainly in patients treated with multiple therapies, which makes the use of Maraviroc impossible and considerably reduces therapeutic options. In these patients, an individualized drug combination is sought with the available drugs, since in Guatemala there is no experience in the use of monoclonal antibodies specifically to treat multiple resistances, which in other countries are already in the study phase[(13)].

On the other hand, since there is no previous data on tropism in patients without previous exposure to ARTs, there is no evidence to say that patients with X4 tropism or DM could have changed to one of the latter over time. However, it is possible that there are reservoirs with a low percentage of X4 tropic virus and that when under pharmacological pressure with Maraviroc these populations emerge or are expressed, so that while Maraviroc suppresses the replication of R5 tropic viruses, the X4 viral population will continue to replicate and consequently the reduction of viral load will not be achieved[(14)]. Therefore, it is important to take into account

three considerations related to the use of Maraviroc: 1) the antiretroviral drugs to which patients have been previously exposed, since Maraviroc is indicated in combination with other ARTs, and history of failure to multiple regimens; 2) adherence to antiretroviral treatment and 3) access to tropism testing and availability of Maraviroc, as well as the importance of determining and monitoring viral tropism in patients with a recent diagnosis or those with multiplex failure.

Conclusion

The high proportion of R5 virus obtained by determining HIV-1 tropism in adult patients with multiple failure is similar to that reported in other studies. Carrying out this test is necessary to make a targeted and personalized treatment where patients could benefit from the use of R5 antagonists.

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