Chapter 100

Mutation Profile And Tarv Resistance In People Living With Hiv Submitted To Genotyping Test In A Reference Laboratory In Belém Do Pará, Brazil

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ABSTRACT
To describe the presence of mutations and the ART resistance profile in PLHIV in Belém, Pará. Methods: This is a cross-sectional, descriptive and retrospective study, where 189 genotyping reports of individuals were included, regardless of age or sex and who were seen in the period from 2013 to 2015. Results: Most individuals had a high viral load (93%), low TCD4+ lymphocyte levels (97%) and the most prevalent HIV subtype was B (78%). We observed in this study a high presence of mutations in all classes of drugs used in ART with emphasis on M184V (ITRNN), K103N (ITRNN) and L63A/P/T/Q (PI), demonstrating that many mutations can contribute to the profile of viral resistance. Conclusion: The results presented show the importance of genotyping testing not only for choosing therapeutic and surveillance regimens, but also to contribute to patient adherence to antiretroviral treatment.

Keywords: PLHIV, Mutations, Resistance, ART.

1 INTRODUCTION

AIDS has promoted a major epidemiological impact worldwide. Over 40 years, about 77.3 million people became infected with HIV and 35.4 million died of AIDS (SEYLER L, et al., 2018). In Brazil the epidemiological picture is alarming, from 2007 to 2021 about 381,793 cases of HIV infection in the country were reported to the Sistema de informação de agravos de notificação (SINAN), with the southeast region having the highest prevalence (43.3%) and the central-west region the lowest (7.7%) (BRASIL, 2021).

Antiretroviral therapy (ART) is one of the ways employed in the control of the HIV epidemic, which aims to delay and prevent disease progression, thus improving patient survival. However, it requires rigorous monitoring, which encourages adherence to treatment and consequently prevents the appearance of drug resistance mutations used in this therapy. The monitoring of patients consists mainly in the analysis of CD4 + T lymphocyte levels and viral load (CV) that are essential parameters to assess the evolution of the disease, the treatment and possible virological failures, as well as the risks related to the onset of AIDS (MACEDO O, et al., 2011; SAAG MS, et al., 2018; BRASIL, 2018).

The advance of the drugs used in ART has allowed an increase in the quality of life of people living with HIV (PLHIV). This fact occurred thanks to the combination of the action mechanisms of the drugs available in the market. ART has allowed greater virologic suppression, corroborating for individual needs to be taken into consideration, such as aspects related to adherence, or changes in treatment regimens. Despite the undeniable advances of HAART in controlling HIV infection, the emergence of mutations and possible drug resistance has opened a new field of questions for the scientific community.

The appearance of mutations may be linked to a simple process of virus evolution since it is already known that HIV is responsible for the highest mutation rate ever known to science. The diversity of HIV mutations is great and its study, in its various forms, can cooperate for the monitoring and control of infection in various regions of the world. The emergence of mutations can also be linked to numerous responses to environmental pressures to which the virus is subjected. Such facts corroborate the emergence of mutations that may or may not contribute to a viral resistance profile (NOMAGUCHI M, et al., 2018).

The development of resistance is closely linked to the process of therapeutic failure, and the early detection of resistance is a crucial point for therapeutic response (SAAG MS, et al., 2018). Despite the efforts deployed in the fight against AIDS, HIV resistance to antiretroviral drugs is still a challenge, which in turn hinders the control of disease progression and quality of life of patients, besides causing additional expenses for the government. Thus, this study sought to understand the profile of genotypic mutations present in individuals using HAART and associate them with the drugs used in these treatments, thus contributing to the epidemiological monitoring of mutations in the northern region.

2 METHODS

2.1 STUDY TYPE AND LOCATION

The study was characterized as cross-sectional, descriptive, retrospective, which included PLHIV living in the State of Pará. We included 189 reports of individuals, regardless of sex and age, whose blood samples were sent to LACEN- PA to be forwarded to the Reference Laboratory of the Dr. Heitor Vieira Dourado Tropical Medicine Foundation, in Manaus, Amazonas State, to perform the HIV-1 genotyping test, in the period from January 2013 to December 2015, with information in the reports that could support this research.

During the period from October 2018 to April 2019, the reports of the genotyping results of PLHIV, which were archived in the custody of LACEN-PA, were analyzed. Data were collected through direct consultation of the reports and the Control System of Laboratory Tests of the National Network of CD4 Lymphocyte Counting^{+} /CD8^{+} and HIV Viral Load (SISCEL). Clinical information such as CD4 T lymphocyte count^{+} , viral load and HIV-1 subtype, treatment regimen, and the presence of mutations was collected. This information was stored in a database for analysis. The research was approved on June 11, 2018 by the Research Ethics Committee (CEP) of the Federal University of Pará - UFPA (CAAE 87122518.1.0000.0018), under opinion 2.704.658.

2.2 STATISTICAL ANALYSIS

The statistical analysis of the data was performed using the Graphpad Prism statistical program, version 5 3.0.1. The Chi-square test was used for comparison of frequencies and the correlation was based on Friedman's correlation test. The significance level adopted in all tests was 5% (p-value 0.05).

3 RESULTS

In the present study our group evaluated the levels of CD4 T lymphocytes^{+} (LTCD4^{+}) and HIV-1 viral load. Of these, most of the study population had a high treatment failure profile, with only 1% having an undetectable viral load as shown in table 1. Only 6% had no information in their medical records. Regarding the HIV subtype, subtype B was the most prevalent (76.5%), followed by subtype F1 (13%). The subtypes A1 and C both had a prevalence of 0.5%. In addition, 9% of the individuals had no information regarding the subtype in their genotyping reports (Table 1).

Table 1 - Levels of CD4 T lymphocytes^{+} , viral load and HIV-1 subtype in PLHIV who underwent HIV genotyping test in the state of Pará, in the years 2013 to 2015.

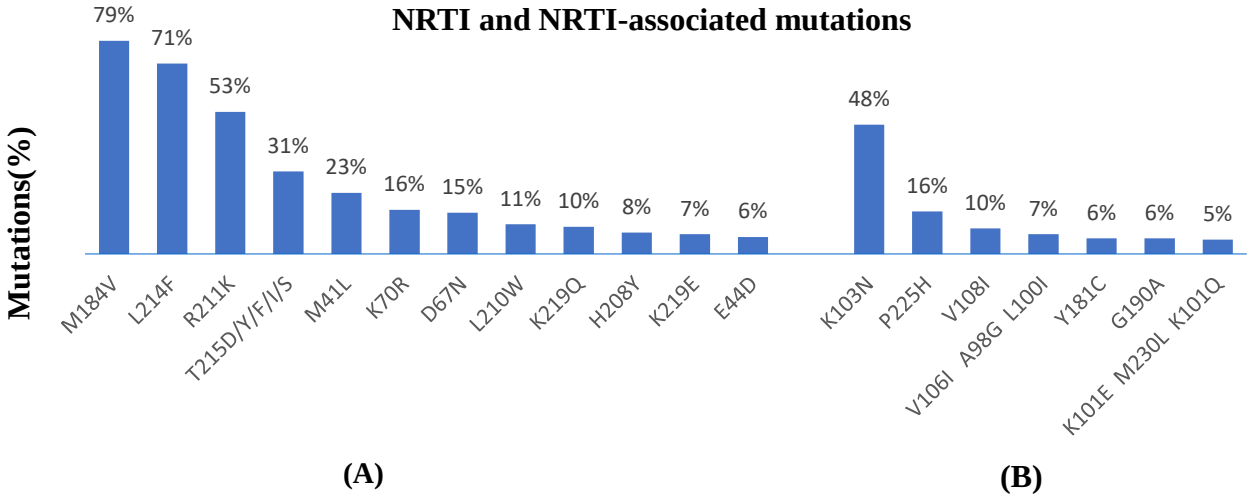
	Patients (N= 189)	%
LTCD4^{+} (Cells/mm^{3})	256 ± 263,2	97,4
Viral load (log)	2,2 ± 1,4	92,6
HIV subtype		
A1	1	0,5
B	145	76,5
C	2	0,5
F1	24	13
Not Informed	17	9

Source: Bentaberry-Rosa AA, et al., 2022; data extracted from LACEN-PA.

Based on the findings regarding therapeutic failure, the hypothesis related to the presence of mutations was established. Thus, 44 mutations were identified for the class of Nucleoside Reverse Transcriptase Inhibitors (NRTIs). The M184V mutation was the most prevalent in the study (79%), followed by L214F (71%), R211K (53%), T215D/Y/F/I/S (31%), M41L (23%). In addition, 25 mutations were identified in the class of Non-nucleoside Reverse Transcriptase Inhibitors (NRTIs). The K103N

mutation was the most prevalent (48%), followed by P225H (16%), V108I (10%) and the others as shown in Figure 1. However, mutations that were less than 5% prevalent for both classes were not presented in this paper.

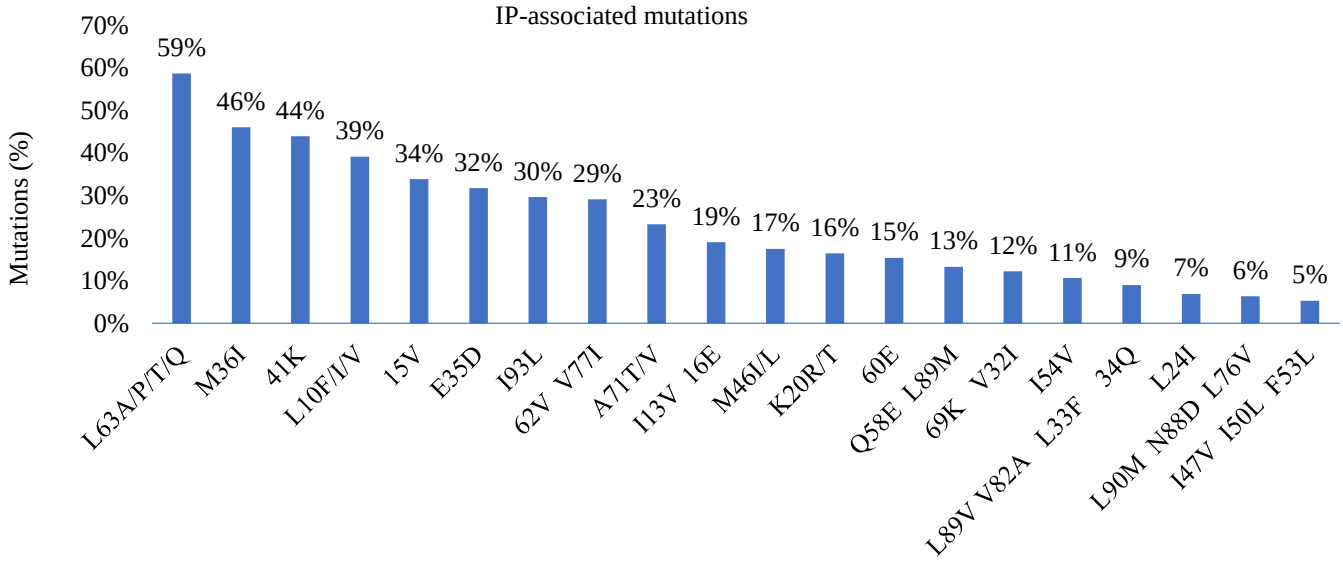
Figure 1 - Frequency of distribution of genotypic resistance mutations associated with Nucleoside Reverse Transcriptase Inhibitors (A) and Non-Nucleoside Inhibitors (B) found in PLHIV submitted to genotyping test in the state of Pará, from 2013 to 2015.



Source: Bentaberry-Rosa AA, et al., 2022; data extracted from LACEN-PA.

Regarding protease inhibitors, 70 mutations were identified. The L63A/P/T/Q mutation was the most prevalent (59%), followed by M36I (46%), 41K (44%), L10F/I/V (39%), 15V (34%), E35D (32%) as shown in Figure 2. The other mutations that had a prevalence of less than 5% were not shown.

Figure 2 - Frequency of distribution of genotypic resistance mutations associated with Protease Inhibitors (PI) found in PLHIV submitted to genotyping test in the state of Pará, from 2013 to 2015.

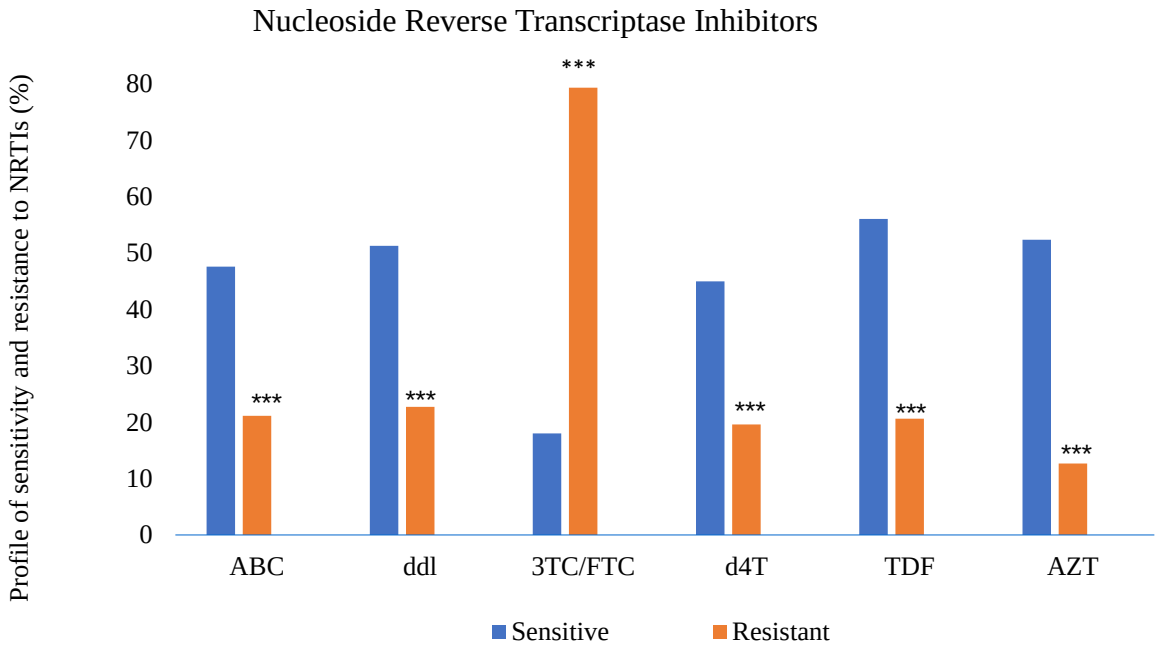


Source: Bentaberry-Rosa AA, et al., 2022; data extracted from LACEN-PA.

Once the mutations were identified, the resistance profile for the three pharmacological classes was evaluated based on the results of the genotyping tests and classified as sensitive (S) and resistant (R). The association between 3TC +FTC showed a high (79%) and statistically significant ($p<0.001$) resistance

profile when compared to the sensitivity profile of this pharmacological association. All drugs except for the 3TC + FTC association, ABC and d4T showed a sensitivity profile above 50%: TDF (56%), AZT (52%) and ddI (51%). Between 0.5% (ABC, ddI, d4T, TDF and AZT) and 1.6% (3TC/FTC) of absence of drug-related information in the reports was found (Figure 3).

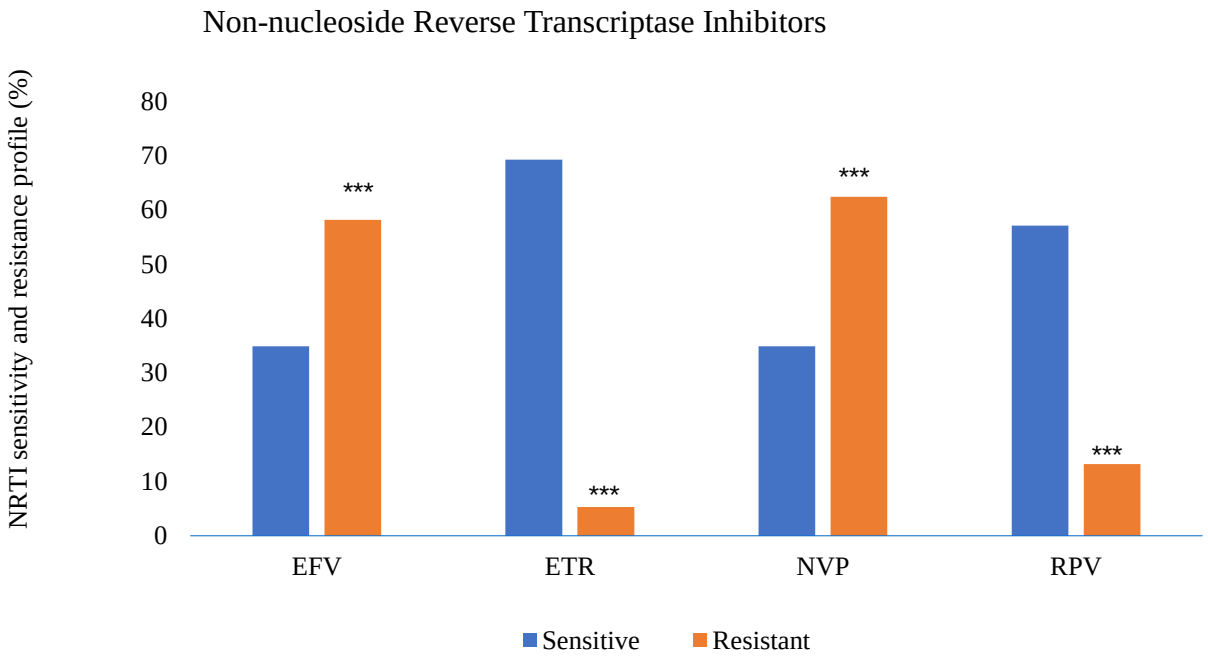
Figure 3 - Resistance profile to Reverse Transcriptase Inhibitors (RNTI) found in PLHIV submitted to genotyping test in the state of Pará, in the period from 2013 to 2015.



Source: Bentaberry-Rosa AA, et al., 2022; data extracted from LACEN-PA.

In the findings regarding NRTIs, the NVP drug showed the highest resistance rate (62%), followed by EFV (58%). The drugs that showed the best sensitivity profile were ETR (69%) and RPV (57%). In addition, between 0.5% (EFV, NVP), 1.6% (ETR) and 20.6% (RPV) of absence of drug-related information was found in the reports (Figure 4).

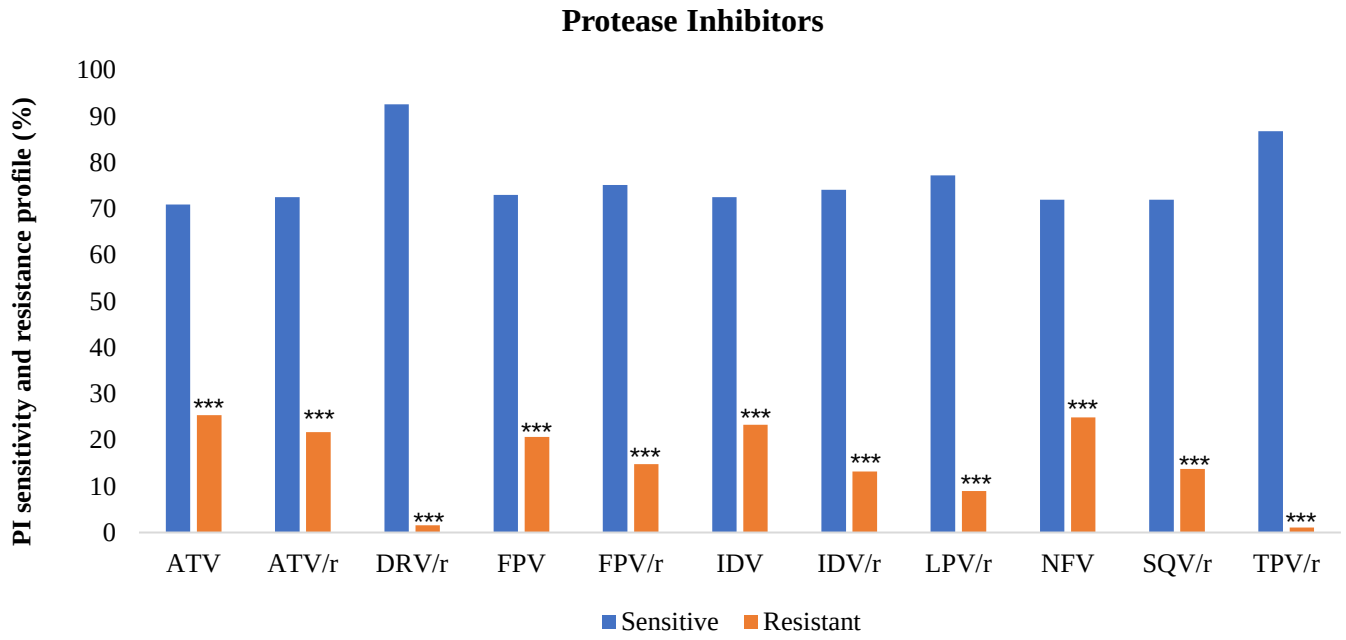
Figure 4 - Resistance profile to non-nucleoside Reverse Transcriptase Inhibitors (NRTIs) found in PLHIV submitted to genotyping test in the state of Pará, in the period from 2013 to 2015.



Source: Bentaberry-Rosa AA, et al., 2022; data extracted from LACEN-PA.

In the PI class, 4 drugs alone and 7 drugs associated with ritonavir(/r) were evaluated. The drug ATV showed the highest resistance rate with 25.4%, followed by NFV (24.9%), IDV (23%), FPV (21%). In general, the drugs associated with ritonavir showed a lower resistance profile when compared to those administered alone. The first association with the highest sensitivity was attributed to DRV/r with 93% sensitivity, in addition, it showed low frequencies of resistance (1.6%). It was observed that 1.6% of the records evaluated had no information related to administration of drugs alone or associated ATV, DRV/r, FPV, IDV, LPV/r, NFV, TPV/r) up to 2.1% (ATV/r, FPV/r IDV/r) (Figure 5).

Figure 5 - Profile of resistance to Protease Inhibitors (PI) found in PLHIV submitted to genotyping test in the state of Pará, in the period from 2013 to 2015.



Source: Bentaberry-Rosa AA, et al., 2022; data extracted from LACEN-PA.

4 DISCUSSION

Low levels of CD4 T lymphocytes were observed in the PLHIV included in the present study[+] , consistent with results also observed by other authors in studies of HIV-1 genetic diversity and drug resistance mutations (MACEDO O, et al., 2012; MACHADO LFA, et al., 2017; IRIAS SDF, et al., 2018). These individuals also presented detectable HIV-1 viral load (>500 copies/mL) in the last two CV tests, results that were already expected since this is one of the prerequisites for the genotyping test, because when the individual presents at least two detectable CV tests in less than 6 months one can characterize a picture of virologic failure (BRASIL, 2018). In addition, high viral load values may be related to pharmacological non-adherence profiles (WHO, 2020). The findings related to HIV-1 subtyping in this study corroborate with previous studies, which indicate that subtype B is the most prevalent in all geographic regions, followed by subtype F and C (BAHLS LD, et al., 2019; BBOSA N, et al., 2019). The low frequency of subtype C can be explained by the fact that it is more common in Africa and India (BAHLS LD, et al., 2019; BBOSA N, et al., 2019; MBANGE AE, et al., 2018; RIEDEL M, et al., 2016). However, it is worth noting that in the southern region of Brazil the C subtype is the most prevalent (GRAAF T, et al., 2011).

In the present study, the M184V mutation was the most prevalent in the NRTI class (59%) very similar to what was also demonstrated by Macedo O, et al. (2011). Other works such as the one conducted in China, in which researchers found a prevalence of 56% for this same mutation, are also concordant with our data (SHU Z, et al., 2018). The M184V mutation is associated with early virologic failure in regimens where lamivudine (3TC) is used, a fact that may explain the findings described in Figure 3. This fact may contribute to a decrease in the susceptibility of the virus to this drug and may also be related to a reduction

in its half-life (HARZKE AJ, et al., 2018; RAMOS CG, et al., 2016). The presence of M184V in therapeutic regimens associating 3TC/FTC, as well as in the presence of dolutegravir or raltegravir has been associated with therapeutic failure (MUNHOZ LSR, 2011). However M184V is known as a "good mutation" which is able to contribute to increased sensitivity to zidovudine (AZT), stavudine (d4T) and tenofovir (TDF) which is supported by our findings (Figure 3) (Gallant JE., 2006; Hung M, et al.,2019).

The L214F and R211K mutations have been described as mutations capable of affecting the AZT resistance profile (HARZKE AJ, et al., 2018). Whereas the association between the M41L, T215Y mutations and their interaction with the L210W mutation are often associated with resistance to ABC, TFD, ddI and AZT which would justify the resistance profile found in our study (SAHLOFF EG, et al., 2019). Macedo O, et al. (2011) described the prevalence of resistance mutations in PLHIV in the states of Pará and Amazonas, the data obtained by the authors showed a significant percentage of mutations in positions 184, 41, 210 and 215 partially differing from the data found in the present study, where the positions most frequently found were 184, 214, 211 and 215. The class of NRTIs, with the exception of the 3TC/FTC association, mostly presented a low resistance profile.

P225H occurs in the presence of K103N and both are related to EFV use (SANTOS-PEREIRA A, et al., 2021). In addition, the contribution to the EFV resistance profile of the V108I and V106I mutations have also been described (GATANAGA H, et al., 2010). Such facts contribute to a resistance profile found in EFV, which corroborates with our findings as shown in figure 4. An interesting factor is that a Spanish study described that V106I detection was not associated with clinical, demographic or even virological characteristics in PLHIV (GUERRERO-BELTRAN C, et al., 2020). The K103N mutation in the presence of the L100I mutation also contributes to Rilpivirine (RPV) and Nevirapine (NVP) resistance a fact that is corroborated by the data found in our work (ARGHESE V, et al., 2009; CECCHINI DM, et al., 2015; ARRAIS CRA, et al., 2021)

It is worth noting that currently the NVP is no longer used as a first-line drug in Brazil, being usually made the association of two NRTI/ITRNt - lamivudine (3TC) and tenofovir (TDF) - associated with the integrase inhibitor (INI) - dolutegravir (DTG) (BRASIL, 2018). However, the Brazilian Ministry of Health established first-line therapy with two NRTI/ITRNt associated with one NRTI, besides determining that NVP could be administered in this association in cases of intolerance to EFV, which can then justify our results regarding NVP, and the absence of data on dolutegravir, since the patients in the present study followed the protocols in force in previous years (BRASIL, 2013). Other studies have indicated that resistance profiles are associated with the presence of the K103N mutation in patients in China (ZHAO J, et al., 2020), Democratic Republic of Congo (KWON EH, et al., 2020) and Brazil (FERREIRA AC, et al., 2017). This resistance profile can be considered common because of the selective pressure caused by ART.

In the protease inhibitor class, some studies have demonstrated a high prevalence of the first mutations found in our study: L63A/P/T/Q and M36I, L89M, A71V, 69K in addition to their contribution to protease inhibitor resistance profiles (UDEZE, et al.; 2020; LAMBERT-NICLOT S, et al., 2018). It is

important to emphasize the need for the presence of a high amount of mutations for the emergence of a major impact on the virological response facing associations with the presence of ritonavir (WENSING AM, et al., 2019). Such a fact could explain the high sensitivity rate found in our study. Another interesting factor to our knowledge is that mutations in positions: 41K and 15V have not been, to date, described in the literature. In general, the drugs associated with ritonavir showed a lower resistance profile when compared to the drugs administered alone.

The present study had a limitation, since, as of 2016, the genotyping tests of the Ministry of Health network were performed by another laboratory, which made it unfeasible to access the reports for the continuity of the research. Within this context, new studies that show sociodemographic, molecular, and clinical data, such as the study conducted by Lima, et al. (2021), are necessary for the monitoring and updating of these data in the state of Pará, thus contributing to a better epidemiological surveillance on the emergence of mutations and HIV-1 resistance to ART in the region.

5 CONCLUSION

In this study we observed that PLHIV who underwent genotyping test in the study period had low levels of CD4 T lymphocytes^{+} and detectable HIV-1 viral load with high prevalence of subtype B and the presence of mutations capable of contributing to the resistance profile found in pharmacological classes used in antiretroviral therapy. In addition, it is worth mentioning the presence of secondary mutations, which alone are not able to promote resistance, but may contribute in a cumulative manner. Thus, this study demonstrates the importance of genotyping test not only for the choice of the most appropriate therapy, but also for the adoption of strategies that seek to improve adherence of PLHIV to treatment with antiretroviral drugs.

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REFERENCES

Andrade Arrais CR, et al. HIV-1 subtypes and drug resistance in children duringantiretroviraltherapy in Brazil. Journal of Medical Virology, 2021; (8):4908-4914.

Arghese V, et al. Minority variants associated with transmitted and acquired HIV-1 nonnucleoside reverse transcriptase inhibitor resistance: implications for the use of second-generation nonnucleoside reverse transcriptase inhibitors. Journal of Acquired Immune Deficiency Syndromes, 2009; 52: 309-15.

Bbosa N, et al. HIV subtype diversity worldwide. *Current opinion* in *HIV* and *AIDS*, 2019;14;153–160.

Bahls LD, et al. Moderate prevalence of HIV-1 transmitted drug resistance mutations in southern Brazil. AIDS Research and Therapy, 2019;16: 4.

BRASIL. Protocolo Clínico e Diretrizes Terapêuticas para Manejo da Infecção pelo HIV em adultos. 2018. Disponível em: http://www.aids.gov.br. Acessado em: 11 de maio de 2022.

BRASIL. Boletim Epidemiológico HIV/Aids. 2021. Disponível em: *http://www.aids.gov.br. Acessado em:* 11 de maio de 2020.

Cecchini DM, et al. Rilpivirine resistance associated mutations in HIV-1 infected pregnant women . Enfermedades Infecciosas y Microbiología Clínica, 2015; 33 (7): 498-9.

Ferreira ACG, et al. Transmitted drug resistance in patients with acute/recent HIV infection in Brazil. Brazilian Journal of Infectious Disease, 2017;21(4):396–401.

Gallant JE. The M184V Mutation: What It Does, How to Prevent It,and What to Do With It When It's There . AIDS Reasearch, 2006; (10): 556-9.

Gatanaga H, et al. Combination of V106I and V179D polymorphic mutations in human immunodeficiency virus type 1 reverse transcriptase confers resistance to efavirenz and nevirapine but not etravirine.*Antimicrobial Agents* and *Chemotherapy*, 2010;54(4):1596–1602.

Gräf T, , et al. HIV-1 genetic diversity and drug resistance among treatment naïve patients from Southern Brazil: An association of HIV-1 subtypes with exposure categories. *Journal of Clinical Virology*, 2011; 51: 186–191.

Guerrero-Beltrán C, et al. The algorithm used for the interpretation of doravirine transmitted drug resistance strongly influences clinical practice and guideline recommendations. Journal of Antimicrobial Chemotherapy, 2020; 75: 1294–1300.

Harzke AJ et al. Substituting Generic Lamivudine for Emtricitabine in Virologically Suppressed HIV-Infected Patients. Journal of Correctional Health Care, 2018; 24(4):371–381.

Hung M, et al. Elucidating molecular interactions of L-nucleotides with HIV-1 reverse transcriptase and mechanism of M184V-caused drug resistance. Communications Biology, 2019;(2) 469.

Irias SDF, et al. Low HIV-1 subtypes diversity based on the pol gene and transmitted drug resistance in antiretroviral-naive patients from Belém, Pará, Amazon region of Brazil. *International Journal of Microbiology Research*, 2018; 10: 1406–1410.

Kwon EH, et al. HIV-1 subtypes and drug resistance mutations among female sex workers varied in different cities and regions of the Democratic Republic of Congo. PLoS One, 2020;15(2):1–14.

Lambert-Niclot S, et al. Emerging resistance mutations in PI-naive patients failing an atazanavir-based regimen (ANRS multicentre observational study). Journal of Antimicrobial Chemotherapy, 2018; 73: 2147-2151.

Lima ACR, Bentaberry-Rosa AA, Costa MAO, Dantas REC, Silva ANMR, Monteiro JC, et al. Importância do teste de genotipagem em pessoas vivendo com HIV no Estado do Pará, Brasil. Research, Society and Development, 2021;10: 12.

Macêdo O, et al. Genotipagem da resistência genotípica secundária aos antirretrovirais em pacientes com aids nos Estados do Pará e Amazonas, Brasil : 2002 a 2006. Revista Pan-Amazônica em Saúde, 2011; 2 :27–34.

Macêdo O, et al. Distribution of HIV-1 subtypes in patients with HAART therapeutic failure in the States of Pará and Amazonas, Brazil: 2002 to 2006. Revista Pan-Amazônica em Saúde, 2012; 3(2):11–16.

Machado LFA, et al. Lower genetic variability of HIV-1 and antiretroviral drug resistance in pregnant women from the state of Pará, Brazil. BMC Infectious Disease, 2017; 17:1–8.

Mbange AE, et al. Surveillance of transmitted HIV-1 antiretroviral drug resistance in the context of decentralized HIV care in Senegal and the Ebola outbreak in Guinea. *BMC Research Notes*, 2018; 11: 723.

Ministério da Saúde (BR). Secretaria de Vigilância em Saúde. Protocolo Clínico e Diretrizes Terapêuticas para Manejo da Infecção pelo HIV em Adultos [Internet]. Brasília : Ministério da Saúde; 2013 [citado 2022 mai 11]. Disponível em: *http://www.aids.gov.br*

Munhoz LSR. Perfil de resistência genotípica do HIV-1 em pacientes com falha na terapia antirretroviral atendidos pela Rede Nacional de Genotipagem (RENAGENO) na região de Botucatu, SP – Brasil. [Dissertação]. São Paulo (SP):Universidade Federal Paulista, Faculdade de Medicina de Botucatu; 2011. 116 p.

Myer L, et al. Antiretroviral adherence, elevated viral load, and drug resistance mutations in human immunodeficiency virus-infected women initiating treatment in Pregnancy: A nested case-control study. Clinical *Infectious Diseases*, 2020; 70(3):501–508.

Nomaguchi M, et al. HIV-1 mutates to adapt in fluxing environments. Microbes and Infection, 2018; 20: 610-614.

Ramos CG. Mutações de resistência transmitida do vírus da imunodeficiência humana aos antirretrovirais : Prevalência e impacto no desfecho virológico [Tese]. Porto Alegre(RS): Universidade Federal do Rio Grande do Sul; 2016. 70 p.

Riedel M, Ribas JLC, Prevalência de subtipos de HIV-1 no Brasil: Uma revisão. Cadernos de Saúde e Desenvolvimento, 2016; 7: 91–103.

Saag MS, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2018 recommendations of the international antiviral society-USA panel. Journal American Medical Association, 2018; 320; 379-396.

Santos-Pereira A, et al. Nationwide study of drug resistance mutations in hiv-1 infected individuals under antiretroviral therapy in Brazil. *International Journal of Molecular* Sciences, 2021;22(10):5304.

Sahloff EG, Duggan JM. Clinical Outcomes Associated With Once-Daily Ritonavir-Boosted Darunavir Plus Tenofovir/Emtricitabine in HIV-Infected Patients Harboring at Minimum a M184V/I Resistance

Mutation. Annals of Pharmacotherapy, 2019; 53(1):50–55.

Seyler L, et al. Current challenges in the treatment of HIV. *Polish* Archives of *Internal* Medicine, 2018; 128: 609–616.

Shu Z, et al. Surveillance of HIV-1 drug resistance in Xinjiang: high prevalence of K103N in treatment-naïve individuals. Archives of Virology, 2018; 163(8):2111–2119.

World Health Organization. Consolidated HIV strategic information guidelines: driving impact through programme monitoring and management. 2020. Disponível em: https://apps.who.int/iris/handle/10665/331697. Acessado em: 22 de maio de 2022.

Wensing AM, Calvez V, Ceccherini-Silberstein F, Charpentier C, Günthard HF, Paredes R, Shafer RW, Richman DD. 2019 update of the drug resistance mutations in HIV-1. Top Antivir Med. 2019; 27: 111-121.

Zhao J, et al. HIV-1 molecular epidemiology and drug resistance-associated mutations among treatment-naïve blood donors in China. *Scientific Reports,* 2020; 10(1):7571.