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Research Article

Antiretroviral Drug Resistance Transmitted in HIV-1 Newly Diagnosed Cuban Patients. April 2013-April 2014

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Submitted: 03 July 2020

Accepted: 01 September 2020

Published: 03 September 2020

Keywords

- HIV
- Cuba
- New diagnostic patients
- Drug resistance

Abstract

Background: High levels of acquired drug resistance have been reported in Cuban HIV-1 infected patients. The aim of this study is to determine the levels of primary HIV drug resistance in newly diagnosed Cuban´s patients.

Material and methods: Demographic, clinical and laboratory data were collected from 225 newly diagnosed HIV-1 patients from Cuba between April 2013 and April 2014. Sequences of 187 patients were analyzed. The HIV-1 pol gene was sequenced using Sanger sequencing. Drug resistance was interpreted according to the WHO surveillance drug-resistance mutations list, 2009. HIV-1 subtyping was performed using the Rega subtyping tool version 3.

Results: The mean age at sampling time was 33.5 years, 80.7% of the patients were men and the major transmission route was MSM (80.1%). The 27.2% of patients had HIV-1 chronic infection and 72.7% recent infection. The median viral load value was 60,300 RNA copies/mL (16,900 - 133,000), and median CD4+ count value was 359 cells/mm3 (263-558). In the 17.6% (33/187), of the studied viruses, transmitted resistance mutations were detected. Simple non-nucleoside mutants were the most common (1.1%), followed by double class resistance against to nucleoside reverse transcriptase inhibitors and non-nucleoside reverse transcriptase inhibitors (8.0%) and single mutants to the protease inhibitors (2.1%). From the 33 patients with transmitted drug resistances mutations, 22 (66.6%) were MSM, 26 (78.8%), were diagnosed with a recent HIV-1 infection, 13 (39.4%) were from Havana

Conclusions: This study highlights the need of further studies in order to elucidate the factors that influencing the high levels of resistance in newly diagnosed population, in order to take actions toward the possible causes. It also reinforces the need for drug resistance testing in patients that start therapy. It was shown that first-line therapy may not be effective, so in 2016 it is replaced by Atripla.

ABBREVIATIONS

ART: Antiretroviral Therapy; TDR: Transmitted Drug Resistance; SDRM: Surveillance Drug Resistance Mutations; NRTI: Nucleoside Reverse Transcriptase Inhibitor; NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor; PI: Protease Inhibitor; CPR: Calibrated Population Resistance; MSM: Men Having Sex With Men; HT: Heterosexual; CI: Chronic Infection; RI: Recent Infection; VL: Viral Load; LAC: Latin-Americans and the Caribbean Countries.

INTRODUCTION

The highly effective antiretroviral therapy has changed the natural history of human immunodeficiency virus ((HIV)/aids), delaying the disease progression and improving the life quality of the HIV patients. The introduction of antiretroviral therapy (ART), in Cuba has resulted in a remarkable improvement of the morbidity and mortality rates in patients infected with HIV type 1 (HIV-1) (Pérez et al. 2004). By the end of 2018 there were more than 34,000 people infected with HIV in Cuba, 86% of them had received ART. The wide access of ART for more than 20 years represents a major concern because of the emergence and spread of antiviral drug resistance, as they could be a threat to sustain the impact of the first-line therapies [1-3].

In HIV-1 Cuban population treated with ART, several factors contributed to high drug resistance levels, such as the prescription of suboptimal regimens containing non-boosted PI,

the prolonged exposure to failing therapies due to limited access to laboratory monitoring and the limited options of substitutions antiviral drug if required [4]. These conditions might also increase levels of transmitted drug resistance (TDR).

Previous studies performed in HIV Cuban untreated population have shown high levels of drug resistance (7-20%), although these studied population were not representative of the country and they were not classified in recent or chronic HIV infection [5,6]. In 2018, following the guidelines of the WHO, a new study is conducted that reflects TDR levels of 28.9%) [7].

The aim of this study was to determine the prevalence of TDR in a representative newly diagnosed HIV-1 population in Cuba, from April 2013 to April 2014.

MATERIALS AND METHODS

Study population and design

The number of samples was calculated considering the predicted number of new HIV-1 infection people in Cuba during 1 year (1,800), and the predicted prevalence of TDR. The predicted prevalence of TDR was 25%. Two hundred and twenty-five (225), patients were included in the study, distributed all over the country, from April 2013 to April 2014.

Patients were selected randomly. Epidemiological information was obtained from a questionnaire (including age, place of residence, gender, route of transmission, date of diagnosis and infection).

Sample collection

Three mL of plasma was collected from each patient and sent to the National Reference Laboratory for HIV/aids Diagnostic (LISIDA). The plasma was kept at -80°C until use. Viral load was also determined from 1mL of plasma, at the time of sampling.

We studied 225 samples taking in to consideration the inclusion and exclusion criteria.

Inclusion Criteria: Patient newly diagnosed with HIV infection (less than one year of HIV diagnosis) with viral load ≥ 1,000 RNA copies/mL.

Exclusion Criteria: plasma sample with hemolysis, viral load with less than 1000 RNA copies/mL, treated patients.

Samples (225), were processed in the laboratory of Sexually Transmitted Infections at the Institute of Tropical Medicine "Pedro Kourí" (IPK), and LISIDA laboratories.

Ethics

This research has been approved by the Ethical Committee of IPK, and conforms to the principles laid down in the Declaration of Helsinki [8]. Informed consent was included for every patient who agreed to participate in the study.

Viral load and CD4+ cell count

CD4+ cell count and viral loads were determined at the time of sampling collection. CD4+ cell counts were determined using a FAC Scan (Becton Dickinson, USA). Plasma HIV-1 viral loads were determined using COBAS TaqMan HIV-1 Test (Roche, Mannheim, Germany).

Genotypic drug resistance testing

One mL of plasma was centrifuged at 14,000 rpm for 1 hour; the pellet was resuspended in 140 uL of plasma. Viral RNA extraction was performed manually using the QIAamp Viral RNA Kit (QIAGEN, Hilden, Germany), following the manufacturer's protocol (www.qiagen.com, Cat No. /ID: 52906). HIV-1 reverse transcription, amplification and population-based bi-directional Sanger sequencing of pol fragments were carried out using a methodology previously described (Aleman et al., 2015). The sequences were edited and assembled using Sequencer, version 4.10 (Gene Codes Corporation, Ann Arbor, MI 48108, USA).

DATA ANALYSIS

HIV subtype was determined using BLAST (www.hiv.lanl.gov/) and confirmed by manual phylogenetic analysis, using CLUSTAL-X and the neighbor-joining method in MEGA version 4 (Kimura's 2-parameter correction, bootstrap 1000) [9]. Assignment of recombinant genetic forms was done using Simplot version 3.5.1. Tree topology reproducibility was evaluated by bootstrapping using 1000 replications. A phylogenetic group was defined as having a bootstrap value of P>70% [10].

The prevalence of genotypic drug resistance was analyzed using the Calibrated Population Resistance (CPR), tool version 6.0, based on the Surveillance Drug Resistance Mutation (SDRM) list from 2009 [11]. Drugs resistance levels were identified based upon the HIV Rega db genotypic resistance interpretation algorithm version 8.0.2 (http://sierra2.stanford.edu/sierra/servlet/JSierra?action=algSequenceInput).

Newly diagnosed patients could have a recent or a chronic infection. Recent infection was considered in those patients who were diagnosed as HIV positive on the year after the previous negative HIV serology result. Chronic infections were considered when the evidence of previous negative HIV-1 test was not available.

All provinces were grouped by regions, with exception of Havana Province that was analyzed apart, because there is more than the half of the HIV patients in this province. Thus, we included in the Western region the provinces: Pinar del Río, Isla de la Juventud, Mayabeque, Artemisa and Matanzas; Central region: Cienfuegos, Villa Clara, Sancti Spiritus, Ciego de Avila and Camagüey and Eastern region: Las Tunas, Holguín, Granma, Santiago de Cuba and Guantánamo.

The characteristics of each patient were analyzed using mean, median, interquartile range (IQR) and frequencies (%). Univariate logistic regression was used to determine the factors associated with TDR. The odds ratio (OR) and its 95% confidence interval (CI) were calculated, p-value ≤ 0.05 was considered significant. All statistical analysis was performed using the SPSS statistical software version 18 (SPSS Inc., Chicago, USA).

RESULTS

Patient's characteristics

Two hundred and twenty five newly diagnosed patients were included in the study. From the 225 processed samples, 187 were successfully sequenced (84.3%). The non-sequenced samples

(16.8%), could be related with the viral load level (close to the cut off value of 1000 RNA copies/mL) and freezing and thawing during the transportation.

The mean age of the patients was 33.5 years old (values ranging from 17 to 74 years old). The 80.7% were male and 80.1% of them were men who have sex with men (MSM), 27.2% were diagnosed as chronic infection and 72.7% as recent infection. Seventy two resided in Havana (38.5%), 28 (14.9%) in the Western Region (excluding Havana), 32 (17.1%) in the Central region and 55 (29.4%) in the Eastern region. The median viral load was 60, 400 RNA copies/ml and the median CD4+ lymphocyte count was 359 cells/mm^3 (Table 1).

Patients with RI were four times more likely to be within 15-30 years old compared with patients with chronic infection (79/136 vs 13/51, OR=4.051, IC=1.980-8.290, p=0.000), in contrast patients with CI were three times more likely to have 46-61 years old (15/51 vs 15/136, OR=3.361, IC=1.500-7.530, p=0.002, Table 1).

Viral load values over 100,000 copies/mL were more frequently detected in men (57/64 vs 94/123, OR=2.512, CI=1.033-6.109, p=0.05, Table 2), than in women.

Western region was associated with the age ranges 15-30 (20/92 vs 8/95, OR= 3.021, CI= 1.256-7.264, p=0.013); while Havana province was associated with the age range of 46 to 61 years (19/30 vs 53/157, OR = 3.389, CI: 1.503-7.641, p = 0.004).

As expected, HIV viral load (VL) over than 100,000 copies/mL was associated with CD4+ cells counts below 200 cells/mm^3 (16/29 vs 48/158, OR = 2.821, CI= 1.259-6.318, p=0.018).

Subtype distribution

BG recombinants (CRF20_BG, CRF23_BG, CRF24_BG), were the HIV-1 strains more frequently identified (27.8%), followed by subtype B (23.5%), CRF19_cpx (19.5%), unique recombinant forms (URF) (11.2%), and CRF18_cpx (9.6%). Other subtypes like G (4.2%), C (2.1%), H (1.0%), and CRF01_AE (0.5 %) were less frequently detected.

HIV-1 drug resistance

The prevalence of any TDR was 17.6% (33/187). TDR was classified as: 1.1% to reverse transcriptase inhibitor (NRTI) (2/187), 8.0% to non-reverse transcriptase inhibitor (NNRTI) (15/187), 2.1% to protease inhibitor (PI) (4/187), 4.8% double mutants to NRTI+NNRTI (9/187), and 1.6% triple mutants (NRTI+NNRTI+IP) (3/187, table 3).

The NRTI mutations most frequently selected were: M184V (4.2%), T215Y (2.1%), K219Q (2.1%), D67N (1.0%) and L74V (1.0%). The NNRTI mutations resistance more frequently selected were K103N (8.0%), Y181C (5.3%) and G190 (1.6%) and to PI, D30N (1.0%, table3).

Of the 17.6% (33/187) of patients showing HIV-1 TDR mutations, 13.7% (7/51) had CI, and 19.1% (26/136) RI, (p≥ 0.05) (Table 3).

In our study, the presence of TDR associated mutation (ARVs), were associated with 100,000 RNA copies/mL or higher (17/64 vs 16/123, OR=2.419, IC: 1.127-5.193, p=0.02). The presence of TDR associated mutation to each (NRTI, NNRTI, and PI) or double and triple drug family mutants were not associated with any other variables studied (type of infection, sex, route of transmission, region of residence, VL or CD4 + cell count).

ARV resistance

The 2.2% of the analyzed viruses were resistant to NRTI, 9.8% NNRTI and 0.3% PI. The highest resistance levels were observed

Table 1: General characteristics of newly diagnosed HIV-1 patients. April 2013- April 2014.

Characteristics	Total[a] N (%)	Chronic infection (CI)[b] N (%)	Recent infection (RI)[c] N (%)
Sequenced samples n (%)	187 (100)	51 (27.2)	136 (72.7)
Age (years)			
15-30 **31-45** **46-61** **62-77**	92 (49.1) 63 (33.6) 30 (16.0) 2 (1.0)	13 (25.4) 22 (43.1) 15 (29.4) 1 (1.9)	79 (58.0) 41 (30.1) 15 (11.0) 1 (0.7)
Male gender	151 (80.7)	40 (78.4)	111 (8.6)
Route of transmission MSM*	121 (80.1)	29 (56.8%)	92 (67.6%)
Region			
Havana City	72 (38.5)	21 (41.1)	51 (37.5)
Western region	28 (14.9))	3 (5.8)	25 (18.3)
Central region	32 (17.1))	8 (15.6)	24 (17.6)
Eastern region	55 (29.4))	19 (37.2)	36 (26.4)
CD4 cell count at sampling (cells/mm^3, median (IQR))	359 (260-560)	370 (262-572)	358 (261.5-558)
HIV-1 viral load at sampling (RNA copies/ml, median (IQR))	60,400 (17,425-132,500)	83,600 (24,200-175,000)	58,150 (16,200-128,750)

[a]Newly diagnosed: patients diagnosed with HIV infection during the last year.
[b]Chronic infection: newly diagnosed patients with no evidence with HIV negative test for HIV-1 infection.
[c]Recent infection: newly diagnosed patient with evidence of a previous negative test HIV-1 infection.
MSM: Men who have sex with men
HT: Heterosexual
*MSM was determined based in the total number of men (151)

Table 2: Relation between CD4+ cell count and HIV viral load with others variables.

Total 187 (100%)*	Age year old at diagnosis N (%)				Gender N (%)		Route of transmission N (%)		Region N (%)			
	15-30	31-45	46-61	62-77	M	F	MSM	HT	Havana City	Western region	Central region	Eastern region
	92 (49.1)	63 (33.6)	30 (16.0)	2 (1.0)	151 (80.7)	36 (19.2)	121 (64.7)	66 (35.2)	72 (38.5)	28 (14.9)	32 (17.1)	55 (29.4)
CD4+ cell (cells/mm^3)**												
<200	10 (10.8)	17 (26.9)	2 (6.6)	0 (0)	24 (15.8)	5 (13.8)	20 (16.5)	9 13.6)	13 (18.0)	5 (17.8)	3 (9.3)	8 (14.5)
200-350	27 (29.3)	15 (23.8)	8 (26.6)	0 (0)	39 (25.8)	11 (30.5)	28 (23.1)	22 (33.3)	17 (23.6)	8 (28.5)	10 (31.2)	15 (27.2)
351-500	18 (19.5)	13 (20.6)	9 (30.0)	0 (0)	34 (22.5)	7 (19.4)	28 (23.1)	13 (19.6)	14 (19.4)	5 (17.8)	8 (25.0)	14 (25.4)
>500	26 (28.2)	15 (23.8)	10 (33.3)	1 (50.0)	43 28.4)	9 (25.0)	36 (29.7)	16 24.2)	19 (26.3)	6 (21.4)	9 (28.1)	18 (32.7)
HIV-1 viral load RNA copies/ml)												
1,000-10,000	19 (20.6)	7 (11.1)	2 (6.6)	0 (0)	20 (13.2)	8 (22.2)	18 (14.8)	10 15.1)	7 (9.7)	6 (21.4)	2 (6.2)	13 (23.6)
10,001-100,000	48 (52.1)	33 52.3)	14 (46.6)	0 (0)	74 (49.0)	21 (58.3)	58 (47.9)	37 56.0)	36 (50.0)	12 (42.8)	25 (78.1)	22 (40.0)
>100,000	25 (27.1)	23 (36.5)	14 (46.6)	2 (100)	57 (37.7)	7 (19.4)	45 (37.1)	19 28.7)	29 (40.2)	10 (35.7)	5 (15.6)	20 (36.3)

MSM: Men who have sex with men; HT: Heterosexual

* All percentages were calculated on basis to the total number of samples (187)

** Sixteen patients had not CD4+ cell value, 11 in 15-30 years group, 3 in 31-45 years group, 1 in 45-61 years and 1 in > 61 years group.

Table 3: Characteristics of the patients with HIV-1 transmitted drug resistance.

Infection	Age	Region of residence	HIV-1 subtype	Sex	Route of transmission	TDR mutations		
						NRTI	NNRTI	PI
Chronic[a]	26	Eastern region	B	F	HT		K103N	
Recent[b]	20	Western region	CRF24_BG	F	HT		G190A	N83D
Recent	51	Havana	CRF19_cpx	M	MSM	M41L, M184V, T 215CY	K103N	
Chronic	30	Havana	CRF20_BG	F	HT		K103N	
Recent	31	Havana	Unique Recombinant Form	M	HT		K103N	
Recent	23	Western region	Unique Recombinant Form	M	HT			L23I
Chronic	56	Central region	CRF18_cpx	F	HT		K103N	
Recent	28	Eastern region	B	M	MSM	D67N, M184V	K103N	
Recent	39	Western region	CRF23_BG	M	MSM	D67N, M184V, K219N	Y181C	
Recent	58	Havana	CRF19_cpx	M	MSM		K103N	
Chronic	45	Havana	CRF18_cpx	M	MSM		K103N	
Recent	23	Havana	Unique Recombinant Form	M	MSM		K101E	
Recent	23	Havana	CRF19_cpx	M	MSM	K219N	Y181C	
Recent	25	Havana	B	M	MSM	L74V, M184V	K103N	
Recent	24	Central region	CRF24_BG	M	MSM	L210W, T215Y	K103N, Y181C	
Recent	20	Havana	CRF19_cpx	M	MSM			I47V
Recent	31	Western region	CRF20_BG	F	HT	M184V	Y181C	

Recent	22	Central region	CRF18_cpx	M	MSM		K101E, G190A	
Recent	37	Central region	G	M	MSM		Y181C	
Recent	19	Central region	CRF19_cpx	M	MSM	M41L, L74V, M184V, T215SY	K103N	D30N
Recent	57	Western region	CRF19_cpx	M	MSM	L74V, M184V, T215Y	K103N	D30N, N88D
Chronic	17	Eastern region	CRF20_BG	F	HT	M184V	K101E, K103N, G190A	
Recent	29	Central region	B	M	MSM		K103N	
Recent	37	Havana	CRF18_cpx	M	MSM			L90M
Recent	19	Eastern region	B	F	HT		Y181C	
Recent	44	Eastern region	Unique Recombinant Form	M	MSM	K219Q	Y181C	
Recent	22	Havana	CRF19_cpx	M	HT		Y181C	
Recent	49	Central region	CRF20_BG	M	MSM		G190A	
Recent	39	Eastern region	G	F	HT		K103N	
Chronic	42	Eastern region	CRF19_cpx	M	MSM	F77L		
Recent	40	Havana	B	M	MSM	K219Q		
Chronic	59	Havana	CRF19_cpx	M	MSM		Y181C	
Recent	23	Western region	Unique Recombinant Form	M	MSM			F53L

[a]: Recent infection: newly diagnosed patient with a previous negative HIV-1 test (less than 1 year after negative HIV-1 serology result).
[b]: Chronic infection: newly diagnosed patient with no previous negative HIV-1 test.
MSM: Men who have sex with men; HT: Heterosexual; M: Male; F: Female.

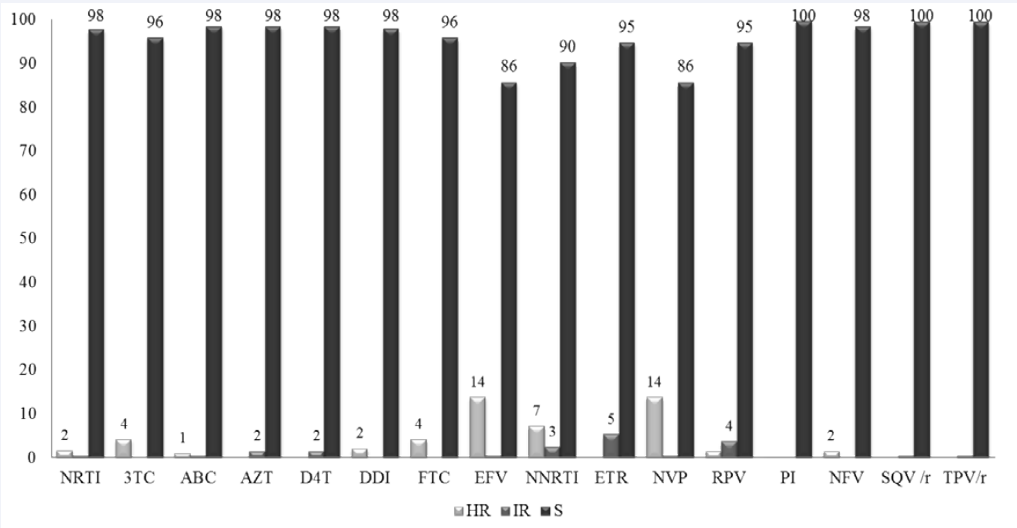

Figure 1 Drug resistance levels to antiviral drugs.

for nevirapine (NPV), efavirenz (EFV) (13.8%, respectively), and 3TC (4.2%, Figure 1).

CONCLUSIONS

This study confirmed that HIV-1 infection in Cuba is mainly present in males (MSM), who live in Havana city or Western Region. The majority of patients in Cuba are diagnosed during the early stages of HIV-1 infection. We confirmed the high genetic diversity of HIV-1 in the studied samples. The high incidence of TDR in Cuban patients with a recent diagnosis of HIV-1 infection, jeopardize the first-line therapies used in our country. The results confirm the necessity to performance the genotype drug resistances tests in newly diagnosed HIV-1 patients in Cuba.

Acknowledgements: The researchers thank all the patients who agreed to participate in the study, the heads of programs from all over the country who contributed to its successful

completion, and the epidemiology department of MINSAP for their support in carrying out the study. This work was supported by the Global Fund to Fight AIDS, Tuberculosis and Malaria.

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Cite this article

Pérez L, Machado LY, Pintos Y, Díaz HM, Kourí V, et al. (2020) Antiretroviral Drug Resistance Transmitted in HIV-1 Newly Diagnosed Cuban Patients. April 2013-April 2014. Clin Res HIV/AIDS 7(1): 1050.