Prevalence and patterns of HIV transmitted drug resistance in Guatemala

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ABSTRACT

Objective. *To assess human immunodeficiency virus (HIV) diversity and the prevalence of transmitted drug resistance (TDR) in Guatemala.*

Methods. *One hundred forty-five antiretroviral treatment-naïve patients referred to the Roosevelt Hospital in Guatemala City were enrolled from October 2010 to March 2011. Plasma HIV* pol *sequences were obtained and TDR was assessed with the Stanford algorithm and the World Health Organization (WHO) TDR surveillance mutation list.*

Results. *HIV subtype B was highly prevalent in Guatemala (96.6%, 140/145), and a 2.8% (4/145) prevalence of BF1 recombinants and 0.7% (1/145) prevalence of subtype C viruses were found. TDR prevalence for the study period was 8.3% (12/145) with the Stanford database algorithm (score > 15) and the WHO TDR surveillance mutation list. Most TDR cases were associated with non-nucleoside reverse transcriptase inhibitors (NNRTIs) (83.3%, 10/12); a low prevalence of nucleoside reverse transcriptase inhibitors and protease inhibitors was observed in the cohort (< 1% for both families). Low selection of antiretroviral drug resistance mutations was found, except for NNRTI-associated mutations. Major NNRTI mutations such as K101E, K103N, and E138K showed higher frequencies than expected in ART-naïve populations. Higher literacy was associated with a greater risk of TDR (odds ratio 4.14,* P = *0.0264).*

Conclusions. *This study represents one of the first efforts to describe HIV diversity and TDR prevalence and trends in Guatemala. TDR prevalence in Guatemala was at the intermediate level. Most TDR cases were associated with NNRTIs. Further and continuous TDR surveillance is necessary to gain more in-depth knowledge about TDR spread and trends in Guatemala and to optimize treatment outcomes in the country.*

Key words HIV; drug resistance, viral; molecular epidemiology; epidemiologic surveillance; Guatemala.

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Extensive use of antiretroviral (ARV) drugs has led to increasing transmission of human immunodeficiency virus (HIV) variants with drug resistance mutations that can be maintained in individuals before initiation of treatment (1–9), reducing the efficacy of first-line ARV therapy (ART) (10). In resource-limited countries with recent introduction of broad access to ART, a relatively low prevalence of

transmitted drug resistance (TDR) is expected, especially considering that most patients in this setting are starting on potent ART regimens (11). However, the lack of information on TDR prevalence and trends in many of these countries is alarming. In the past 5–10 years, most governments of Latin American and Caribbean countries have made efforts to implement programs to provide broad access to ART. As this strategy is cost–benefit advantageous and is the most visible among government responses to the epidemic, universal access to ART has become a priority goal in most countries in the region, while access to clinical attention, prevention programs, and laboratory monitoring of patients under treatment are neglected (12). TDR surveillance will generate important information to guide first-line ART selection, support education and prevention programs, and promote the rational use of ARV drugs by clinicians and policy makers (11, 13–15).

This study reports the first results of a large collaborative effort between Mexico and the countries of Central America to assess HIV TDR and viral diversity in the Mesoamerican region, focusing on Guatemala. ART was introduced in Guatemala by 2001 in hospitals managed by the Ministry of Public Health. From the 60 000 individuals in the country expected to live with HIV, more than 10 360 are reported to be receiving ART and 24 000 more are in need of ART according to World Health Organization (WHO) 2010 guidelines (16). Approximately 25% of patients using ART are treated in the Roosevelt Hospital in Guatemala City, a third-level, university hospital receiving patients from all over the country. From 2001 to 2007, first-line ART regimens were composed of zidovudine or stavudine + lamivudine + efavirenz (EFV) or nevirapine (NVP). From 2007, first-line ART regimens were changed to tenofovir disoproxil fumarate + emtricitabine + EFV or NVP. The use of protease inhibitors is reserved for second-line regimens and for pregnant women. Additionally, from all the patients using ART, 83% were reported to remain under ART after 12 months in 2009 (16). Considering this scenario, TDR prevalence and patterns in Guatemala are not known. This study reports TDR data on 145 ARV drug-naïve patients enrolled in 2010 and 2011.

METHODS

Patients

Newly diagnosed and follow-up ART-naïve HIV patients were enrolled in an observational study from October 2010 to March 2011 at the Roosevelt Hospital in Guatemala City. No exclusion criteria were applied except for known exposure to ARV drugs. Being a reference health center, the Roosevelt Hospital receives nearly 40% of patients from places outside Guatemala City, mainly from the southern Pacific Coast and the western regions of the country, including the departments of Escuintla, Santa Rosa, Suchitepequez, Retalhuleu, and San Marcos. After giving written, informed consent, patients donated a single peripheral blood sample, collected in vacuum tubes with ethylenediaminetetraacetic acid (BD, San Jose, California, United States of America) for molecular assays and in Cyto-Chex BCT tubes (Streck, Omaha, Nebraska, United States) for immunophenotypic flow-cytometry assays. Demographic data were collected through direct application of a questionnaire before sample donation. All blood samples were sent via air courier and processed at the National Institute of Respiratory Diseases in Mexico City within 48 hours after collection. Plasma viral load assays, $CD4^+$ T cell counts, HIV genotyping, and TDR analyses were performed for each patient. Results were sent to the Roosevelt Hospital for patient clinical follow-up. This study was revised and accepted by the Ethics Committees of the National Institute of Respiratory Diseases and the Roosevelt Hospital and was conducted according to the principles of the Declaration of Helsinki.

HIV sequencing and genotypic drug resistance testing

A fragment of the viral *pol* gene including the whole protease and 334 codons of the reverse transcriptase was bulk-sequenced from plasma HIV RNA, using a ViroSeq HIV-1 genotyping system (Celera Diagnostics, Alameda, California, United States), according to the manufacturer's specifications. Sequences were obtained with a model 3730 genetic analyzer (Applied Biosystems, Foster City, California, United States), assembled, and manually edited with ViroSeq v2.8 software.

Genotypic drug resistance analyses were carried out with the Stanford HIV drug resistance database algorithm, using the HIVdb program (17, 18). The presence of resistance was defined according to Stanford score (SS) ranges as follows: 0–9, susceptible; 10–14, potential low-level resistance; 15–29, low-level resistance; 30–59, intermediate resistance; 60 or higher, high-level resistance. All samples were analyzed at the same time using the last program update available (v6.0.11). Additionally, genotypic drug resistance was assessed by using the drug resistance mutation list for HIV TDR surveillance proposed and periodically updated by WHO (19). The combination of these two genotypic resistance interpretation systems provides a sound understanding of ARV drug resistance in the epidemiological setting of HIV TDR.

HIV subtyping and phylogenetic analyses

HIV subtyping was performed with the REGA subtyping tool v2.0 (20, 21), available online. Neighbor joining and maximum likelihood trees were built to confirm subtyping, using the software Mega 5.0, and recombination was confirmed with the RIP HIV recombination identification program (22), available online.

Statistical analyses

Chi-square or Fisher's exact tests were used to determine associations among patients' demographic variables and TDR risk. Odds ratios were calculated for each variable. Student's *t* tests were used to compare clinical variables and age in the TDR and susceptible groups.

RESULTS

TDR prevalence and patterns in 145 ART-naïve HIV-infected Guatemalan individuals, predominantly from Guatemala City, the southern Pacific Coast, and western regions of the country, were prospectively assessed. The protease/reverse transcriptase HIV region was amplified successfully for all participating individuals. The Guatemalan cohort presented a median $CD4^+$ T cell count of

TABLE 1. Demographic and clinical variables of individuals with and without TDR in Guatemalan cohort, 2010–2011

Clinical/demographic variable	Total		Susceptible		TDR (SS ≥ 15)		Odds ratio
	No.	%	No.	%	No.	%	
Number of patients	145	. . .	133	. . .	12	. . .	. . .
Mean age, years	37.3	. . .	37.4	. . .	35.8	. . .	. . .
Median viral load, RNA copies per mL	50 038	. . .	50 984	. . .	60 115	. . .	. . .
Median CD4+ T cell count, cells/µL	302.6	. . .	224	. . .	115	. . .	. . .
Female	64	44.1	59	44.4	5	41.7	1.12
HIV transmission risk factor							
Heterosexual	127	87.6	118	88.7	9	75.0	
MSM	12	6.9	10	7.5	2	16.7	2.62
Other/unknown[a]	6	4.1	4	3.0	1	8.3	
Literacy[b]							
Cannot read or write/none	28	19.3	27	20.3	1	8.3	4.14
Primary school	63	43.4	60	45.1	3	25.0	($P < 0.05$)
Secondary school/technician	42	29.0	36	19.5	6	50.0	
Prep school							
Degree	3	2.1	2	1.5	1	8.3	
Unknown[a]	5	3.4	4	3.0	1	8.3	
	4	2.8	4	3.0	0	0.0	
Marital status[c]							
Married	39	26.9	34	25.6	5	41.7	0.71
Single	55	37.9	52	39.1	3	25.0	
Free union	41	28.3	40	30.1	1	8.3	
Divorced	3	2.1	2	1.5	1	8.3	
Widowed	5	3.4	3	2.3	2	16.7	
Unknown[a]	2	1.4	2	1.5	0	0.0	
Employment[d]							
Unemployed	48	33.1	43	32.3	5	41.7	0.66
Employed	48	33.1	45	33.8	3	25.0	
Housewife	21	14.5	21	15.8	0	0.0	
Self-employed	8	5.5	7	5.3	1	8.3	
Unknown[a]	20	13.8	17	12.8	3	25.0	

Note: TDR: transmitted drug resistance, SS: Stanford score, . . . : not applicable, MSM: men who have sex with men.
[a] Unknown cases were omitted from odds ratio estimations.
[b] Odds ratio for the literacy category was calculated between the primary or none and the secondary or higher groups.
[c] Odds ratio for the marital status category was calculated between the married/free union/widowed and single/divorced groups.
[d] Odds ratio for the employment category was calculated between the unemployed and the employed/self-employed groups.

TABLE 2. TDR prevalence in a cohort of 145 ART-naïve Guatemalan individuals, 2010–2011

Drug class	TDR level									
	SS ≥ 10		SS ≥ 15		SS ≥ 30		SS ≥ 60		WHO[a]	
	No.	%	No.	%	No.	%	No.	%	No.	%
Any ARV drug	22	15.0	12	8.3	10	6.9	4	2.8	12	8.3
NNRTI	13	9.0	10	6.9	10	6.9	4	2.8	10	6.9
Protease inhibitor	4	2.8	1	0.7	0	0.0	0	0.0	1	0.7
NRTI	2	1.4	1	0.7	0	0.0	0	0.0	1	0.7

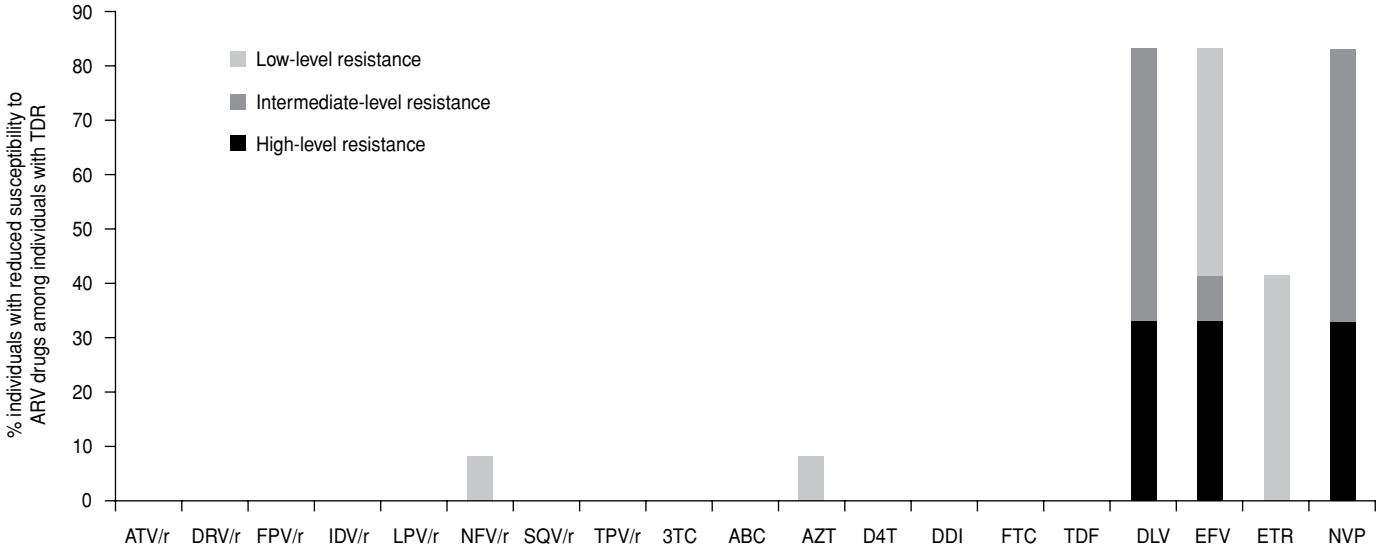
Note: TDR: transmitted drug resistance, ART: antiretroviral therapy, SS: Stanford score, WHO: World Health Organization, ARV: antiretroviral, NNRTI: non-nucleoside reverse transcriptase inhibitor, NRTI: nucleoside reverse transcriptase inhibitor.
[a] ARV drug resistance defined according to presence or absence of mutations included in WHO TDR surveillance list (19).

303 cells per µL of blood (Table 1) with 46.2% (67/145) of patients diagnosed with CD4+ T cell counts < 200 cells per µL and 11.7% (17/145) with < 50 cells per µL. More than 44% of patients enrolled were female and the mean age at enrolment was 37.3 years (Table 1). Self-reported men who have sex with men (MSM) represented 14.8% (12/81) of the males enrolled.

Of the 145 HIV sequences analyzed, 140 (96.6%) belonged to subtype B. The remaining sequences (4/145, 2.8%) corresponded to BF1 recombinant forms and subtype C viruses (1/145, 0.7%). All non-B viruses were associated with heterosexual transmission.

A global TDR prevalence of 8.3% (12/145) to any ARV drug was found for the study period, based on SS values with a threshold of 15 (at least low-level ARV drug resistance). This definition of TDR was comparable to the one based on the WHO TDR surveillance mutation list (19), applicable for TDR surveillance (Table 2). The use of these two resistance definitions is informative as the Stanford algorithm considers polymorphic and minor mutations that, if accumulated, can result in some

FIGURE 1. Antiretroviral (ARV) drug resistance levels among individuals with transmitted drug resistance, Guatemala, 2010–2011. Levels of ARV drug resistance in 12 of 145 individuals with transmitted drug resistance (TDR) in Guatemalan cohort are shown. Low-level resistance corresponds to a Stanford score (SS) of 15–29, intermediate-level resistance to a SS of 30–59, and high-level resistance to a SS ≥ 60



Note: ATV/r: atazanavir with ritonavir, DRV/r: darunavir with ritonavir, FPV/r: fosamprenavir with ritonavir, IDV/r: indinavir with ritonavir, LPV/r: lopinavir with ritonavir, NFV/r: nelfinavir with ritonavir, SQV/r: saquinavir with ritonavir, TPV/r: tipranavir with ritonavir, 3TC: lamivudine, ABC: abacavir, AZT: zidovudine, D4T: stavudine, DDI: didanosine, FTC: emtricitabine, TDF: tenofovir disoproxil fumarate, DLV: delavirdine, EFV: efavirenz, ETR: etravirine, NVP: nevirapine.

degree of ARV drug resistance, and the WHO mutation list provides a universal system for ARV drug resistance surveillance. Also, the Stanford algorithm would detect viruses (SS 10–14) that, although they are likely to be fully susceptible to ARV drugs, may contain mutations that could indicate previous exposure to the ARV class of the drug (23) (Table 2).

With the Stanford algorithm, the prevalence of TDR resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs) was the most prevalent (10/145, 6.9%), while TDR to nucleoside reverse transcriptase inhibitors (NRTIs) and protease inhibitors was low (each at 1/145, 0.7%) (Table 2). High-level ARV drug resistance (SS ≥ 60) was observed only for NNRTIs (4/145, 2.8%) (Table 2, Figure 1). TDR to multiple drug classes was not observed in the Guatemalan cohort.

Overall, the presence of ARV drug resistance-associated mutations in the Guatemalan cohort was low (Table 3). TDR cases occurred almost exclusively for NNRTIs, with a third of the individuals with TDR showing high-level resistance to delavirdine, EFV, and NVP (Figure 1).

It was not possible to apply the WHO TDR threshold method for TDR surveillance (11, 24) because of the small numbers of patients under 25 years of age required for this analysis. Further TDR surveillance will allow the enrolment of adequate numbers of patients who fulfil the inclusion criteria required for this estimation.

Most NNRTI high-level TDR cases were associated with the presence of the reverse transcriptase K103N mutation (3/4), while most intermediate-level TDR cases presented a combination of the K101E and E138K/Q mutations (4/6) (Table 4). The single TDR cases found for the NRTI and protease inhibitor families were related to the presence of the reverse transcriptase K219K/Q and the protease L23I mutations, respectively (Table 4).

Univariate analyses showed no differences in age or clinical variables (i.e., viral load and $CD4^+$ T cell counts) between subjects with and without TDR (Table 1). Interestingly, a greater probability of presenting TDR was found for individuals with higher literacy (primary school or none versus secondary school or higher; odds ratio 4.14, P = 0.0264) (Table 1). However, this result should be interpreted with care, as possible selection bias may exist with a larger proportion of individuals living in Guatemala City represented in the cohort. No differences associated with HIV transmission risk factor, marital status, or employment situation were found for TDR risk in the Guatemalan cohort.

DISCUSSION

This study presents the first results of a large collaborative effort between Mexico and Central American countries to describe HIV diversity and TDR prevalence in the Mesoamerican region, focusing on Guatemala. A cohort of ART-naïve, HIV-infected Guatemalan individuals referred to the Roosevelt Hospital was formed. The cohort reflected the previously observed male focalization of the infection and late presentation of HIV patients to medical care in the Guatemalan setting (16, 25). Nevertheless, a large proportion of females was observed in the study cohort, which most likely can be explained by an enrolment bias, as active HIV screening in the Gyneco-Obstetrics Service of the Roosevelt Hospital has been in place since 2002 for ambulatory patients and since 2006 in the emergency room (26). Interestingly, heterosexual transmission was the dominant risk factor for HIV infection, with only 14.8% of men identi-

TABLE 3. Prevalence of transmitted ARV drug resistance mutations in a cohort of 145 Guatemalan individuals, 2010–2011

Protease inhibitor			Nucleoside reverse transcriptase inhibitor			Non-nucleoside reverse transcriptase inhibitor		
	Frequency in cohort			Frequency in cohort			Frequency in cohort	
Mutation	No.	%	Mutation	No.	%	Mutation	No.	%
L10/V	17	11.7	M41L	0	0.0	A98G	0	0.0
L10F	0	0.0	M41R	0	0.0	L100I	0	0.0
V11I	0	0.0	E44D	0	0.0	K101Q	2	1.4
L23I	1	0.7	A62V	1	0.7	K101N	0	0.0
L24I	0	0.0	K65R	0	0.0	K101E	5	3.5
D30N	0	0.0	D67T	0	0.0	K103N/S	3	2.1
V32I	0	0.0	D67H	0	0.0	K103R	6	4.1
L33F	1	0.7	D67N/G	0	0.0	V106A	0	0.0
E35G	0	0.0	D67E	0	0.0	V106M	1	0.7
K43T	0	0.0	T69A	1	0.7	V108I	2	1.4
M46/L	0	0.0	T69D	0	0.0	E138K/Q	4	2.8
I47A	0	0.0	T69ins	0	0.0	E138G/A	3	2.1
I47V	0	0.0	T69N	1	0.7	V179A/T	0	0.0
G48V/M	0	0.0	T69C	0	0.0	V179D	3	2.1
I50L	0	0.0	T69I	0	0.0	V179E	1	0.7
I50V	0	0.0	T69G	0	0.0	V179F	0	0.0
F53L	0	0.0	T69S	1	0.7	Y181/V	0	0.0
F53Y	0	0.0	K70G	0	0.0	Y181C	0	0.0
I54V/A	0	0.0	K70N	0	0.0	Y188L	0	0.0
I54L	0	0.0	K70R	0	0.0	Y188H	1	0.7
I54M	0	0.0	K70E	0	0.0	Y188C	0	0.0
I54S/T	0	0.0	L74I	0	0.0	G190S	0	0.0
Q58E	3	2.1	L74V	0	0.0	G190A	0	0.0
A71I/V/T	20	13.8	V75L	0	0.0	G190E	0	0.0
G73C/S/T/A	0	0.0	V75A	0	0.0	G190C	0	0.0
T74S	0	0.0	V75T	0	0.0	P225H	0	0.0
L76V	0	0.0	V75S	0	0.0	F227L	0	0.0
V82A	0	0.0	V75M	0	0.0	M230L	0	0.0
V82F	0	0.0	F77L	0	0.0	K238T	0	0.0
V82T	0	0.0	Y115F	0	0.0	Y318F	0	0.0
V82S	0	0.0	F116Y	0	0.0			
V82M	0	0.0	V118I	7	4.8			
V82C	0	0.0	Q151M	0	0.0			
V82L	0	0.0	M184V/I	0	0.0			
N83D	0	0.0	L210W	0	0.0			
I84V/A/C	0	0.0	T215Y	0	0.0			
I85V	0	0.0	T215F	0	0.0			
N88D	0	0.0	T215C/D/E/S/I/V	0	0.0			
N88S	0	0.0	K219Q/E/N	1	0.7			
L90M	0	0.0	K219R	0	0.0			
			G333D	1	0.7			
			G333E	5	3.5			

Note: ARV: antiretroviral.

fying themselves as MSM. This observation could reflect the highly prevalent stigmatization of the infection and the characteristic *machismo* of many Latin American countries (27).

Remarkably, nearly 3% and 1% of the circulating viruses were subtyped as BF1 recombinant forms and subtype C viruses, respectively. This result is interesting, as recent observations in neighboring Mexico by this study group have shown a prevalence of < 0.15% of non-B viruses (unpublished data). These contrasting observations could reflect the existence of unique patterns of HIV transmission in Guatemala, which, further addressed, could yield important information on HIV epidemiological history in the country and provide HIV transmission and phylogenetic clustering information useful for HIV prevention and management in the country.

An intermediate global TDR level was found for the Guatemalan cohort. This TDR level is comparable to the one observed in some industrialized countries (1, 4, 6, 28). Analyses showed that more than 80% of TDR cases were associated with NNRTIs, with a very low prevalence of TDR to NRTIs and protease inhibitors (< 1% in both cases). This observation is consistent with the broad use of EFV/NVP-containing ARV regimens since 2001 in Guatemala. Moreover, this study showed evidence of low levels of selection of resistance mutations by ARV drugs in the study cohort, except for the case of NNRTI-associated mutations (Table 3). Remarkably, the K101E mutation was observed in 3.5% of Guatemalan patients, while the expected prevalence in ART-naïve populations is 0.2% (23). Similarly, the K103N, K103R, and E138K mutations, observed in 2.1%, 4.1%, and 2.8% of Guatemalan patients, respectively, are expected to be present in 0.8%, 2.0%, and 0.1% of ART-naïve populations (23). However, it is important to keep in mind that late detection of HIV disease is characteristic in most Latin American countries. As nearly half of the individuals enrolled in this study were diagnosed with < 200 $CD4^+$ T cells per µL of blood, these results reflect TDR levels characteristic of individuals infected a few years in the past. Although high levels of adherence to ART have been reported for the Guatemalan setting (29), the differentially higher prevalence of NNRTI TDR in the Guatemalan cohort compared with TDR in other ARV drug families strongly suggests the existence of ARV drug selective pressure and will have to be taken into account in HIV management in order to improve treatment outcomes by supplying information to support education and prevention programs and to promote the rational use of ARV drugs by clinicians and policy makers in the country.

Higher literacy levels were associated with higher risk of TDR in the study cohort. Whether this observation reflects a selection bias in the Guatemalan cohort or a possible behavioral trend needs to be assessed further. Nevertheless, it is possible that this observation reflects a tendency of the MSM group to present higher literacy levels than the heterosexual population that attends the Roosevelt Hospital. Also, although the Roosevelt Hospital receives individuals

TABLE 4. Clinical and demographic characteristics of individuals with TDR in Guatemalan cohort,[a] 2010–2011

Patient	Age, years	Gender	Marital status	Literacy	Employment	HIV transmission risk factor	HIV diagnosis	Date of reception[b]	Viral load, copies/mL	$CD4^+$ T cells, cells/μL	HIV subtype	TDR mutations in protease[c]	TDR mutations in RT[c]
3439-10	39	F	Married	Technician	Unemployed	Heterosexual	Oct 2010	26 Oct 2010	304	561	B		K101E, E138K
3461-10	46	F	Divorced	Prep school	Employed	Heterosexual	Oct 2010	26 Oct 2010	530 574	59	B		V118I, K219Q, K103R
3451-10	40	M	Married	Technician	Self-employed	MSM	Oct 2010	5 Nov 2010	83 398	18	B		K101E, E138K
1080-08	26	F	Married	Secondary	Unemployed	Heterosexual	Mar 2008	18 Nov 2010	60 115	568	B		Y188H
3835-10	37	F	Widow	None	NA	Heterosexual	Nov 2010	16 Dec 2010	621 905	15	B	A71T	K103N
1902-09	26	F	Married	Technician	Unemployed	NA	May 2009	16 Dec 2010	4,384	544	B		K101E, E138K
3914-10	44	M	Married	Secondary	NA	Heterosexual	Dec 2010	16 Dec 2010	81 322	16	B		V106M, V179D
132-11	29	M	Single	Degree	Employed	MSM	Jan 2011	20 Jan 2011	258	466	B	L10I, A71V	V118I. K103N
080-11	26	M	Widow	Secondary	Unemployed	Heterosexual	Jan 2011	20 Jan 2011	31 637	239	B		K101E, E138K
197-11	49	M	Single	Primary	Employed	Heterosexual	Jan 2011	3 Feb 2011	316 862	115	B	L10I	K101E, K103R
425-11	35	M	Free union	Primary	NA	Heterosexual	Feb 2010	18 Feb 2011	227 318	39	B	L23I	
528-11	32	M	Single	Primary	Unemployed	Heterosexual	Feb 2011	4 Mar 2011	6 182	53	B		K103N

Note: TDR: transmitted drug resistance, RT: reverse transcriptase, F: female, M: male, NA: not available.

[a] Transmitted drug resistance defined as having a Stanford score ≥ 15 for any antiretroviral drug.

[b] All blood samples were sent to and processed at the National Institute of Respiratory Diseases 48–72 hours after collection.

[c] Only mutations associated with antiretroviral drug resistance are shown.

from all over the country, more than half are known to reside in Guatemala City (26). These individuals usually have better access to education and also higher exposure to HIV and ART. Associations of other demographic and clinical variables cannot be discarded and need to be assessed further with larger cohorts.

This study represents one of the first efforts to describe HIV diversity and TDR prevalence and trends in Guatemala. It shows the existence of intermediate TDR levels in the Guatemalan setting. Most TDR cases were associated with NNRTIs, which is consistent with the broad use of this ARV drug family in treatment regimens in the country and with the low genetic barrier of these ARV drugs for the development of resistance. Although enrolment bias could exist, the present cohort is highly representative of the population seeking medical care at the most important HIV referral center in the country. Further and continuous TDR surveillance, as well as larger cohorts, will be necessary to gain more in-depth knowledge of TDR spread and trends in Guatemala and to support HIV management and treatment outcomes in the country.

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RESUMEN

Prevalencia y patrones de farmacorresistencia transmitida del VIH en Guatemala

Objetivo. Evaluar la diversidad del virus de la inmunodeficiencia humana (VIH) y la prevalencia de la farmacorresistencia transmitida en Guatemala.

Métodos. Entre octubre del 2010 y marzo del 2011 se incluyeron en el estudio 145 pacientes no tratados anteriormente con antirretrovirales, derivados al Hospital Roosevelt en la Ciudad de Guatemala. Se obtuvieron las secuencias *pol* a partir del VIH plasmático y se evaluó la farmacorresistencia transmitida con el algoritmo de Stanford y la lista de mutaciones para la vigilancia de la farmacorresistencia transmitida de la Organización Mundial de la Salud (OMS).

Resultados. El subtipo B del VIH fue sumamente prevalente en Guatemala (96,6%, 140/145), y se encontró una prevalencia de formas recombinantes BF1 de 2,8% (4/145) y una prevalencia del subtipo C del virus de 0,7% (1/145). La prevalencia de la farmacorresistencia transmitida durante el período de estudio fue de 8,3% (12/145) según el algoritmo de la base de datos de Stanford (puntuación > 15) y la lista de mutaciones para la vigilancia de la farmacorresistencia transmitida de la OMS. En la mayoría de los casos, la farmacorresistencia transmitida se asoció con los inhibidores de la transcriptasa inversa no análogos de nucleósidos (ITINN) (83,3%, 10/12); en la cohorte se observó una baja prevalencia asociada con los inhibidores de la transcriptasa inversa análogos de nucleósidos y con los inhibidores de la proteasa (< 1% para ambas familias de fármacos). Se encontró una baja selección de mutaciones causantes de farmacorresistencia debidas a los antirretrovirales, excepto en las mutaciones asociadas a los ITINN. Las mutaciones importantes relacionadas con los ITINN, como K101E, K103N y E138K, mostraron frecuencias más elevadas que las esperadas en las poblaciones vírgenes de tratamiento antirretroviral. En las personas con un nivel de escolaridad más elevado se encontró un mayor riesgo de farmacorresistencia transmitida (razón de posibilidades 4,14; $P = 0,0264$).

Conclusiones. Este estudio representa uno de los primeros intentos de describir la diversidad del VIH, y la prevalencia de la farmacorresistencia transmitida y sus tendencias en Guatemala. La prevalencia de la farmacorresistencia transmitida en Guatemala presentó un nivel intermedio y en la mayoría de los casos se asoció con los ITINN. Se necesita una vigilancia más intensa y sostenida de la farmacorresistencia transmitida para conocer más exhaustivamente su grado de diseminación y sus tendencias en Guatemala, al igual que para optimizar los resultados del tratamiento antirretroviral en el país.

Palabras clave VIH; farmacorresistencia viral; epidemiología molecular; vigilancia epidemiológica; Guatemala.