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HIV-1 Transmitted Drug Resistance in Latin America and the Caribbean: What Do We Know?

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Abstract

Latin America and the Caribbean countries have increased the scaling-up of antiretroviral treatment in the last years. The increase of transmitted drug resistance has been feared due to the worrisome indicators associated with the emergence of drug resistance and monitored by the World Health Organization (WHO). Consequently, our aim was to review all relevant studies on transmitted drug resistance in Latin America and the Caribbean countries, to analyze its levels, to identify the frequency of transmitted drug resistance mutations, and to put these results in the context of the local Latin American and Caribbean countries settings.

A systematic search of Spanish, Portuguese, and English literature was performed in databases and international conferences for the period June 1999 to May 2011. In addition, sequences were downloaded from the Los Alamos and Stanford databases and the transmitted drug resistance was reanalyzed according to the WHO Surveillance Drug Resistance Mutation list 2009.

In total, 50 articles, 27 abstracts, and 1,922 patients were included. The resistance varied geographically, but most of the countries have reached the WHO threshold of 5% of resistance. According to the sequences available in public databases, the overall prevalence in Latin America and the Caribbean countries for the period 1996-2009 was 7.7% and by region it was 4.3% for the Caribbean, 3.9% for Mexico, 9.4% for Brazil, 10.5% for the Andean region and 4.9% for the Southern Cone. For the last four investigated years (2006-2009), the information was restricted to Brazilian and Venezuelan studies and revealed an overall transmitted drug resistance of 10%. Throughout the study period, limited information was available for the Caribbean and Central American countries. These findings support the need for developing comprehensive surveys of transmitted drug resistance in these regions. **(AIDS Rev. 2012;14:256-67)**

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Key words

HIV-1. Drug resistance. Latin America. Caribbean. Genotype. Naive.

Introduction

The horizontal transmission of an HIV-1 strain that already displayed the reverse transcriptase (RT) mutation T215F/Y was first described in a homosexual man in 1993[1]. As it was feared that transmitted drug resistance (TDR) could negatively impact the success of first-line antiretroviral therapy (ART), TDR was extensively studied in resource-rich countries. Retrospective studies provided evidence that infection with drug-resistant HIV-1 could also occur in other risk groups, and indicated increasing TDR levels and more extensive mutational patterns. As these studies were often small and based upon convenience sampling, prospective and representative population-based studies were set up in Europe, the USA and Canada to monitor the

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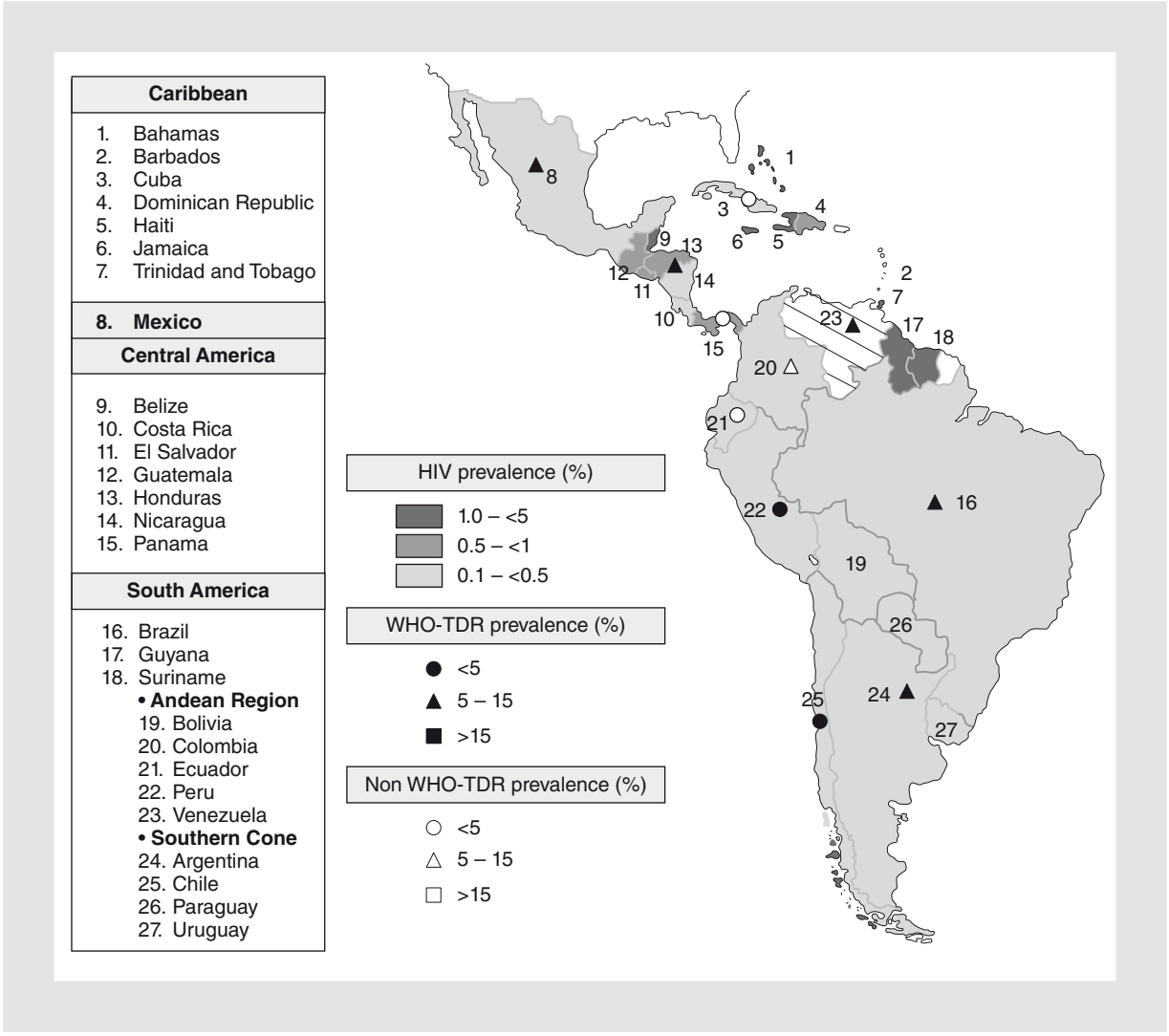

Figure 1. *HIV and transmitted drug resistance (TDR) prevalence in Latin America and the Caribbean. This region is divided geographically in Caribbean (seven countries), Mexico, Central America (seven countries) and South America (12 countries). The latter region is subdivided based upon geographical, social and economic characteristics: the Andean region and Southern Cone. The HIV prevalence according to the UNAIDS report is shown in a grayscale[9]. Although the overall HIV prevalence in Venezuela (hatched) was 0.75% in 2004, the country was not visualized in a grayscale as the prevalence in 2007 varied between 1.62 % in metropolitan areas and 0.08% in more rural areas[90]. The TDR prevalence values from studies that followed the eligibility criteria of WHO surveys are represented in black figures, otherwise they are represented in white. Adapted from UNAIDS report, 2010.*

extent and dynamics of TDR[2-5]. The high rates of TDR (overall prevalence 8-9%) resulted in the recommendation of standard genotypic drug resistance testing to guide ART selection in therapy naive patients[6,7]. Recently, a large European multi-cohort study confirmed the importance of baseline drug resistance testing as patients with TDR and resistance to at least one prescribed drug were three times as likely to virologically fail within one year[8].

As access to ART has been implemented and scaled-up in Latin-America and the Caribbean (LAC) since more than a decade, concerns about the emergence and spread of TDR strains in LAC exist. In general, the prevalence of TDR depends mainly on the time since ART implementation, the scale of ART coverage, and the overall virologic success of the prescribed regimens. As the majority of HIV-1 patients in LAC started immediately on HAART, the rise in TDR was anticipated to be less extensive compared to resource-rich countries where sequential mono- and bitherapies were initially prescribed. Nevertheless, other factors unique to the particular setting of LAC could negatively influence TDR rates. For instance, the widespread use of standard first-line regimens based on

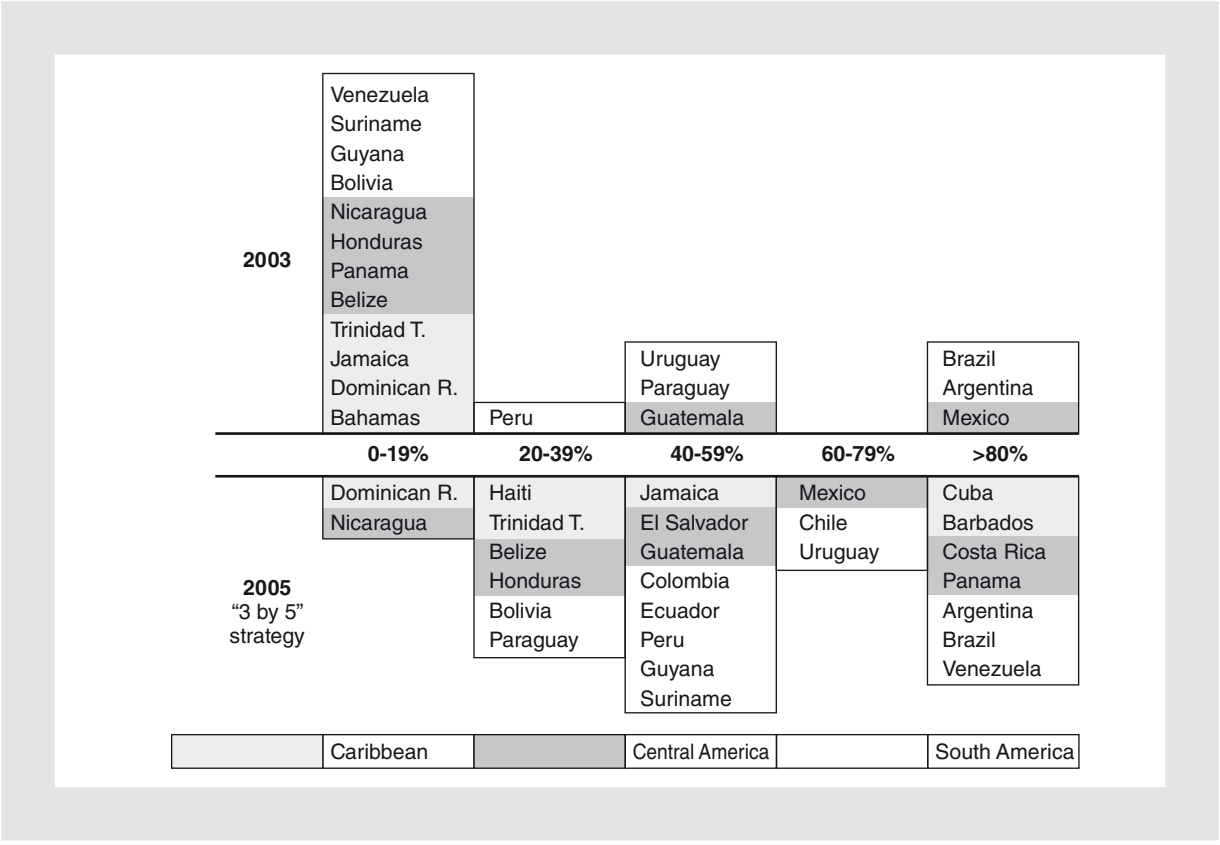

Figure 2. *Scaling-up of antiretroviral therapy (ART). The scaling-up of ART in 2003 and after the "3 by 5" strategy launched by WHO and UNAIDS. The "3 by 5" stands for treatment for three million HIV/AIDS patients in low-middle income countries by 2005 (see details in the UNAIDS report "3 by 5" and beyond)[51]. The regions are shown in a grayscale. Progress in access to treatment is shown as a shift to the right for a country, comparing 2003 (upper panel) with 2005 (lower panel). Countries are scaled as percentage (%) of those diagnosed and eligible for treatment that actually received treatment. The scale is shown in the middle panel. Data were not available for Barbados, Chile, Colombia, Costa Rica, Cuba, Ecuador, El Salvador and Haiti in 2003. Adapted from UNAIDS[51]. Trinidad T: Trinidad and Tobago; Dominican R: Dominican Republic.*

low genetic barrier non-nucleoside RT inhibitors (NNRTI) in the absence of drug resistance testing, together with limited access to second-line therapies, could promote emergence of drug resistance and its subsequent spread to new HIV-1 infections. The LAC is a heterogeneous region that differs extensively in geographical, social and economic characteristics that influence the HIV epidemiology and clinical care facilities. The HIV-1 burden varies considerably between and within the 27 countries belonging to LAC (Fig. 1). In 2009, 1.7 million people were living with HIV-1 in LAC, of which one-third lived in Brazil, and HIV-1 prevalence values ranged between 0.1% in Cuba and 3.1% in Bahamas[9]. Brazil and Argentina took a leading role in the area by providing ART since 1991-1992 and by setting up national programs to provide free access to HAART, clinical care and laboratory monitoring (Fig. 2)[10,11]. Currently, Cuba, Chile and Nicaragua achieve global access, and Argentina, Brazil, Dominican Republic, Mexico and Uruguay are near to universal-coverage levels. However, in other LAC countries ART scale-up has been rather slow and only reached ART coverage between 20% in Bolivia and 66% in Paraguay with still limited access to laboratory testing and second-line regimens[12].

The scope of this review was to collect all relevant studies on TDR in LAC, to analyze TDR levels, to identify the frequency of TDR mutations, and to put these results in the context of the local LAC settings.

Transmitted drug resistance surveillance and early warning indicators

Recently, the fear of TDR in developing countries reappeared due to the worrying reports of early warning indicators in Africa, the Caribbean and Central America[13-16]. Early warning indicators were developed by the WHO as indicators for the prevention of drug

resistance. They include ART prescribing practices, lost-to-follow-up, retention of first-line therapies, viral suppression and percentage of discontinued drug supplies[13,16]. These indicators alert earlier than prospective surveys about the potential of increasing TDR rates.

Few studies have evaluated early warning indicators in LAC. Most of the studies were restricted to Brazil or to the seven AIDS programs from the CCASAnet Cohort[17,18]. Lost-to-follow-up was 6% overall, but large differences were observed between the different AIDS healthcare institutions (between 0.6% in Honduras to 17% in Argentina)[17]. In El Salvador, Guatemala, Honduras and Nicaragua, only seven of 13 sites accomplished the goal of ≤ 20% lost-to-follow-up, and 38 of 55 sites in the Caribbean[13,14]. Low numbers of retention in first-line therapy were also observed in LAC, ranging from 16% in Honduras to 36% in Peru. Adverse events were the main cause in 14% of cases, predominantly linked to zidovudine (hematological toxicity in 7%) and nevirapine (skin rash in 3%)[17,18].

To standardize TDR surveillance studies, the WHO has developed minimum recommendations for developing countries to enable comparison. Briefly, the criteria are: a minimum of 47 samples from small geographic areas within countries where ART has been available for more than three years to at least 20% of the eligible HIV-1 population; HIV-1 infection should have been confirmed by laboratory criteria; participants should not have received any antiviral drug; and if female they should have been younger than 25 years at their first pregnancy. The inclusion of individuals with less than three years of HIV-1 infection or/and laboratory evidence of seroconversion or recent infection are required. If the information is accessible, demographic data like transmission risk group, clinical data like non-AIDS stage, or laboratory data like CD4 > 500 cells/ml, and no previous positive HIV-1 test are desirable[19,20]. In addition, the analysis of resistance should be done with the WHO Surveillance Drug Resistance Mutation (SDRM) list, which is updated periodically and excludes highly polymorphic positions[21]. Nevertheless, some SDRM do occur naturally in therapy naive individuals, which might inflate the estimates of TDR. The working group decided to retain these mutations within the list as stricter inclusion criteria would result in the omission of important drug resistance mutations and these particular mutations might have been the result of unreported therapy exposure or truly TDR within the therapy naive dataset[21].

Epidemiology of transmitted drug resistance in Latin America and the Caribbean

Due to the low achievement of early warning indicators in several LAC countries, available publications on TDR were reviewed using a systematic search strategy (Fig. 3; see Supplementary methods). Fifty articles and 27 abstracts were retained (Tables 1, 2, 3). Approximately half of the studies originated from Brazil (53.2%, 41/77). Ten studies were from Mexico (13%, 10/77), three from the Caribbean (3.9%, 3/77), four from Central America (5.2%, 4/77), 12 from the Southern Cone (15.6%, 12/77) and seven (9.1%, 7/77) from the Andean region.

Heterosexual contacts and men who have sex with men (MSM) were the most frequent transmission risk factors. Six studies were performed in specific patient populations such as blood donors[22-24], female sex workers[25], intravenous drug users[26] and a combination of the latter two[27].

Eleven studies used the Serological Testing Algorithm for Recent HIV Seroconversion (STARHS)[28] strategy to differentiate between recent or chronic infection[24,29-36]. In five other studies, the distinction between recent and chronic infection was based upon previous negative serology test results 9-18 months before diagnosis date[37-41].

Although plasma was widely used as source material, peripheral blood mononuclear cells (PBMC) and dried blood samples (DBS) were also used in nine and two studies, respectively. In most of the studies, in-house methodologies were used to generate sequences, followed by Trugene® (seven) and ViroSeq® (six) (Table 1). The genotypic resistance interpretation algorithm HIVdb was widely used for TDR analysis. Twenty-one studies used the International AIDS Society list and 19 studies the SDRM list. The version of the respective algorithms and lists were often not mentioned in the original publication.

The TDR levels as reported within the original publications are shown in tables 2 and 3. In summary, the prevalence of TDR ranged from 0 to 7.4% in the Caribbean for 1996-2003, from 2.8 to 18% in Mexico for 2001-2010, from 0 to 11.6% in Central America for 2002-2007, from 0 to 41% in Brazil for 1994-2010, from 3 to 11% in the Andean Region for 1998-2007 and from 2.5 to 18.8% in the Southern Cone for 1997-2009.

Due to the heterogeneity of mutation lists used within the original studies, TDR was reanalyzed using the SDRM list 2009 and resulted in TDR prevalence values between 0 and 8.3% in the Caribbean, 2.8 and 6.8% in Mexico, 0 and 7.5% in Central America, 1.3 and

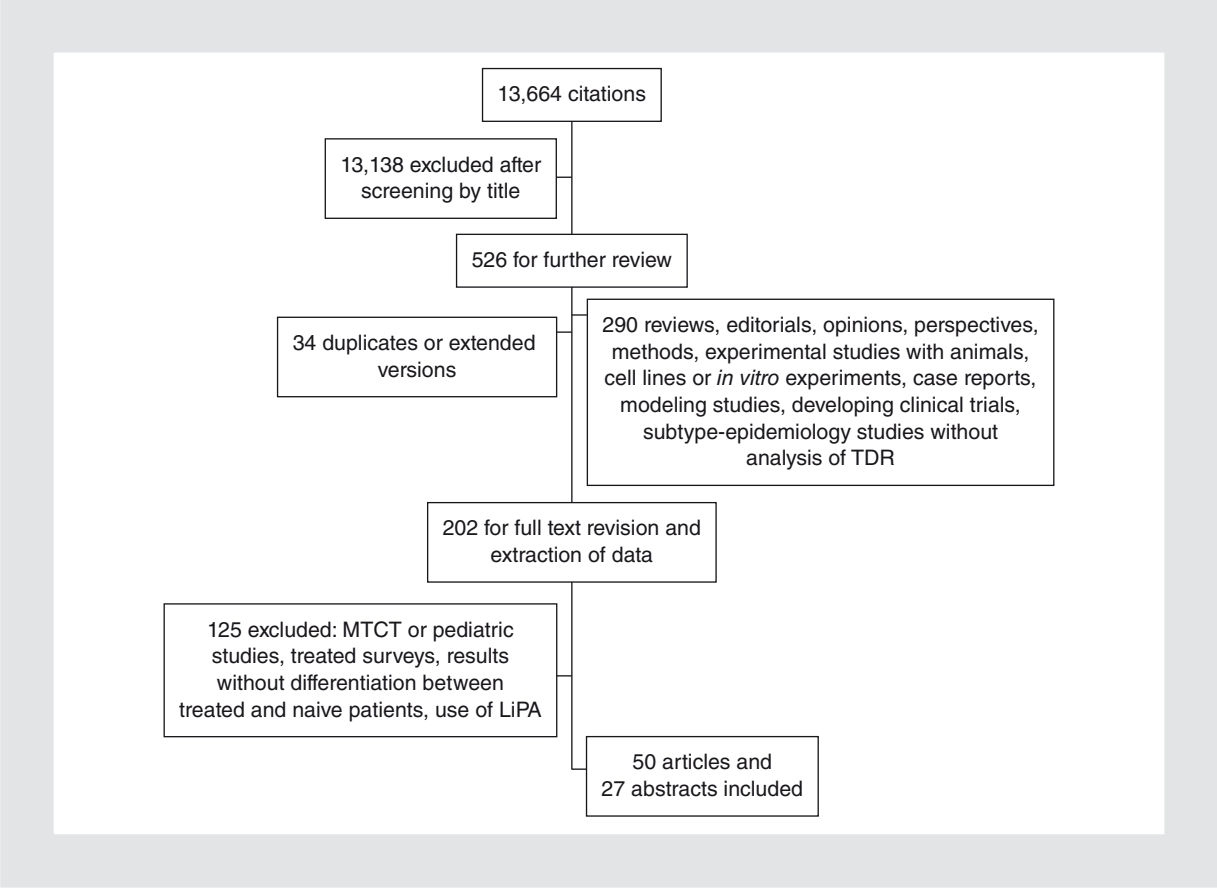

Figure 3. *Selection of studies on transmitted drug resistance (TDR). MTCT: Mother-to-child transmission; LiPA: Line Probe Assay.*

20.3% in Brazil, 0 and 13% in the Andean region and from 1.6 to 12% in the Southern Cone. For comparison, values reported in 14 studies that followed the WHO surveillance criteria for TDR monitoring are also displayed in tables 1 and 2[22,24,29,31-33,35,36,38,39,41-46].

For 10 studies, the presence of TDR in each sample could be directly linked to the respective transmission risk factor[25,31-33,37,41,44,47-49] and combining this data did not reveal any difference in TDR rate between heterosexuals (37/522, 7.1%) and MSM (39/757, 5.2%). One study that solely sampled blood donors from São Paulo (Brazil) showed a TDR of 5.6% in 1998-2002 (19/341)[22], whereas another study sampling in a broader geographical area revealed only a TDR of 1.3% in 2000-2004 (1/74)[24]. The majority of patients included in studies where differentiation between recent and chronic infection was made were chronically infected and therefore differences in TDR between both groups could not be investigated. However, two studies did report a difference[22,44]. For three studies that included at least 50 recent infections, TDR values were 4% (3/74) in Chile[38], 7.7% (4/52) in Argentina[41], and 8.1% (17/210) in Brazil[39].

To obtain a better understanding of the reported TDR rates, public databases were searched and 1,922 relevant HIV-1 sequences were retained for analysis (Fig. 4 A). Based upon automated subtyping[50], HIV-1 subtype B was the most frequent subtype (65.7%, 1,262/1,922), followed by subtype C (14.4%, 276/1,922), BF recombinants (8.7%, 168/1,922) and subtype F1 (4%, 77/1,922); the latter two mainly originated from Brazil and Argentina (BF: 99.4%, 167/168; F1: 98.7%, 76/77). The remaining genetic variants were circulating recombinant forms (CRF) such as CRF31_BC and CRF29_BF in Brazil, CRF_18cpx and CRF19_cpx in Cuba, and BD, BC and CF1 recombinants in Brazil and the Southern Cone.

In LAC, overall TDR prevalence was 7.7% (148/1,922; 95% CI: 6.54-8.98) for the period from 1996 to 2009. The TDR by region was 4.3% in Caribbean for 1996-2005 (8/186; 95% CI: 1.87-8.29), 3.9% in Mexico for 2002-2005 (2/51; 95% CI: 1.87-8.29), 9.4% in Brazil for 1998-2009 (99/1,056; 95% CI: 7.68-11.3), 10.5% in the Andean Region for 1999-2007 (15/142; 95% CI: 6.03-16.82), and 4.9% in the Southern Cone for 1997-2005 (24/487; 95% CI: 3.2-7.24). The NRTI resistance was

A

Country	Year							Total
	96-97	98-99	00-01	02-03	04-05	06-07	08-09	
BR	–	10/66	23/244	6/68	14/213	33/337	13/128	99/1,056
AR	1/28	–	1/47	13/274	4/59	–	–	19/408
VE	–	2/31	–	0/12	–	8/62	–	10/105
CH	–	–	5/79	–	–	–	–	5/79
TT	–	–	1/61	0/2	–	–	–	1/63
MX	–	–	–	2/40	0/11	–	–	2/51
CO	–	–	5/37	–	–	–	–	5/37
CU	–	3/25	–	–	–	–	–	3/25
BB	2/24	–	–	–	–	–	–	2/24
DO	–	–	–	1/12	0/5	–	–	1/17
HT	–	–	–	–	0/16	–	–	0/16
Other	–	–	1/40	–	0/1	–	–	1/41
Total	3/52	15/122	36/508	22/408	18/305	41/399	13/128	148/1,922

B

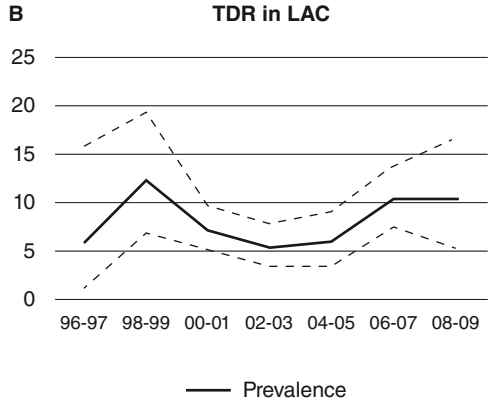

Figure 4. *Prevalence of transmitted drug resistance (TDR) and mutations in Latin America and the Caribbean (LAC). See Supplementary methods.* ***A:*** *TDR prevalence in LAC. The number of sequences with evidence of TDR (numerator) and the total number of sequences included (denominator) divided according to country and sampling period.* ***B:*** *The prevalence of TDR (%) according to sampling period (black line) and the 95% confidence intervals (gray dashes). BR: Brazil; AR: Argentina; VE: Venezuela; CH: Chile; TT: Trinidad and Tobago; MX: Mexico; CO: Colombia; CU: Cuba; BB: Barbados; DO: Dominican Republic; HT: Haiti; Other: include other Caribbean islands.*

4.4% (84/1,922; 95% CI: 3.54-5.38), NNRTI resistance was 2.3% (44/1,922; 95% CI: 1.71-3.06), and protease inhibitor (PI) resistance was 2.08% (40/1,922; 95% CI: 1.53-2.82). Of the TDR cases, 5.4% (8/148) and 6.8% (10/148) had dual class resistance towards NRTI + NNRTI and NRTI + PI, respectively. Triple-class resistance was only detected in 0.7% (1/148) of the TDR cases. The overall TDR time trend was not significant, although two TDR peaks above 9% were observed for the periods 1998-1999 and 2006-2007 (Fig. 4 B). The separate time trend analysis for the countries that contributed the majority of samples (Argentina and Brazil) were also not significant, neither were the trends for the individual drug classes (NRTI, NNRTI and PI).

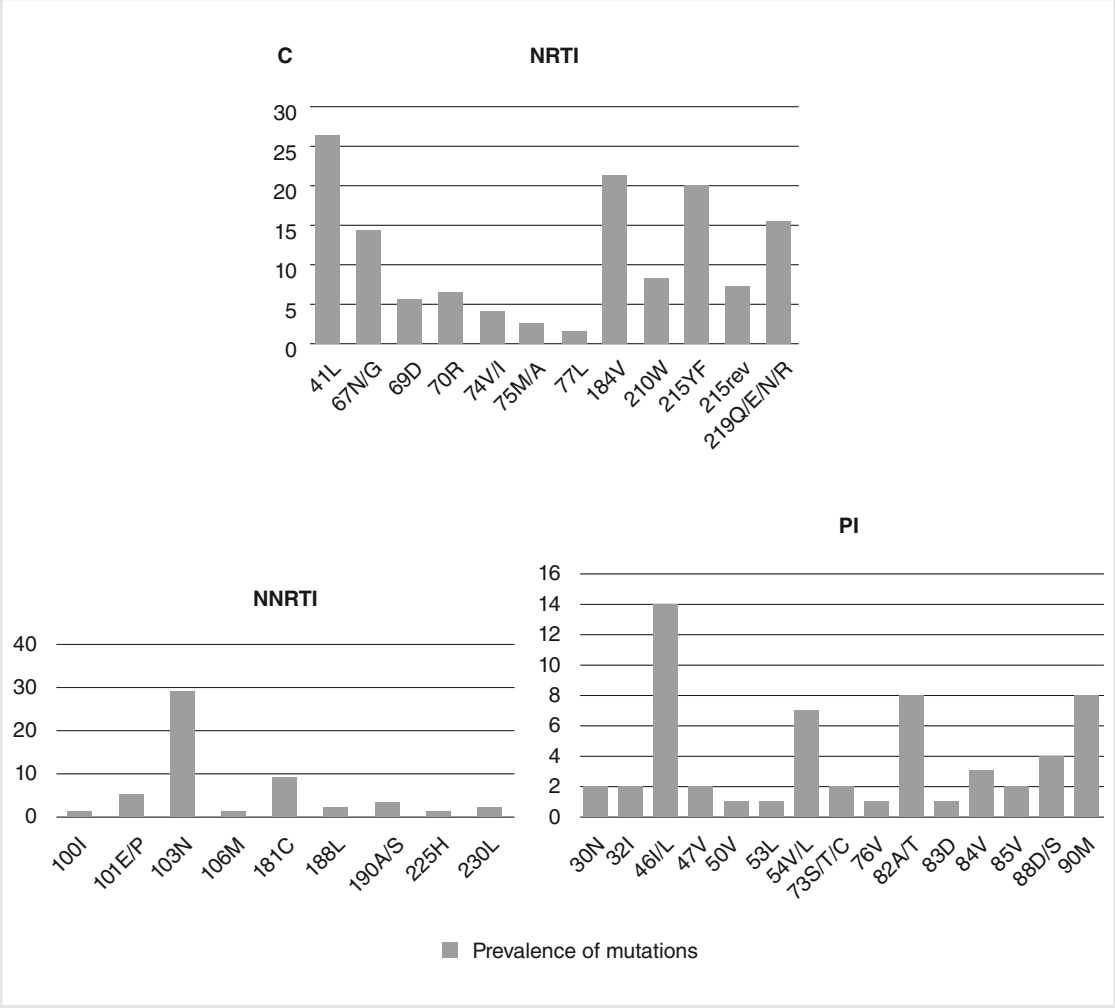

Figure 4. *Prevalence of transmitted drug resistance (TDR) and mutations in Latin America and the Caribbean (LAC). See Supplementary methods.* ***C:*** *The number of sequences with SDRM mutations against nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors (PI).*

The 103N mutation was the most frequently observed mutation (29/148, 19.6%), followed by 215Y/F/rev (27/148, 18.2%) and 41L (26/148, 17.6%) (Fig. 4 C). Time trends analysis for the individual mutations 41L and 103N did not reveal any significant changes. The frequency of the most prevalent TDR mutations, such as 41L, 184V, 103N, 46I/L, 82A/T and 90M, was compared with frequencies in the following studies in the USA, Canada and Europe[2,3,5], but no significant differences were observed.

For 447 sequences, information was available on whether it concerned a recent or a chronic infection. However, the TDR rate did not differ significantly between recent (4/52, 7.7%) and chronic (41/395, 10.4%) infections. The prevalence of TDR did differ between sequences obtained from PBMC or plasma (1,712 sequences included). The TDR was significantly higher in PBMC than plasma (33/285, 11.6%, vs. 98/1,427, 6.8%). However, the exclusion of PBMC samples did not significantly impact the overall TDR (7%; 95% CI: 5.83-8.37). Other factors were not evaluated because of lack of information.

Caribbean and Central America

According to the UNAIDS-WHO report, only a minimum ART coverage was implemented in the Caribbean region in 2001[51]. However, coverage increased with extra funding to, for example, 20% in Haiti and

Dominican Republic in 2005 (Fig. 2)[51]. As a result, TDR ranged from 0% in several islands in 2000 to 3.6% in Cuba in 2003[52-55]. In Cuba there was already limited access to mono- and bitherapy before 2000, which could explain the level of TDR observed in 2003 and its frequency of the NRTI drug class[53]. The overall TDR was estimated to be 4.3% and this was based upon reanalysis using the WHO TDR surveillance list of the collected sequences that were available in public databases and that were sampled in the time period 2000-2005[21].

From Central America, only fragmented data was available for two countries of this region. Indeed, only four publications and no sequences were retained after our search in public databases. A Panamanian study showed no TDR mutations in 2005, but NRTI and NNRTI TDR increased in a later report[56,57]. However, in the later study the exact sampling years were unspecified. Reports that studied the TDR rate in Honduras showed a prevalence of 9.2% in 2002-2003 and a prevalence of 7% in 2004-2007[44,58]. In Honduras and Panama, TDR was mainly restricted to NRTI and NNRTI drug classes, explained by the first-line therapy options in these countries[44,57].

Mexico

Reanalysis of Mexican sequences revealed TDR prevalence of 3.9% in the period 2002-2005. This result is substantially lower than the 16% reported by Escoto, et al.[59], which might be partly explained by the algorithm used to interpret drug resistance as it also included polymorphisms. However, the TDR prevalence of 16% also differed from values obtained in other studies[27,60], suggesting that the heterogeneity in ART availability between the different regions in Mexico might also impact TDR rates, although further research is warranted[60]. A recent comprehensive WHO-survey determined that Mexico has reached 6.8% of TDR for the period 2005-2010[45]. This overall rate of TDR remained stable at the national level. However, decreasing trends for NNRTI and increasing trends for PI TDR were observed. The frequency of mutations was 4.2% for NRTI (mainly type TAM I pathway), 1.9% for NNRTI (mostly 103N), and 1.8% for PI (90M)[45].

Andean Region

In the Andean Region, the TDR prevalence was 10.5% according to sequences sampled in the years 1999, 2001, 2003, and 2007. However, these sequences were mainly collected in Venezuela[46,61,62]. A WHO survey performed in Venezuela reported at least 7% TDR according to the French ANRS algorithm, and this value rose to 12.9% when the SDRM list was used for interpretation[46]. In this study, drug resistance to all three drug classes was observed. The high TDR rates may be a consequence of the early introduction of ART as part of an AIDS National Program that was initiated in 2000 and mainly focused in the capital where the surveys were performed. Additionally, one report mentioned that patients receiving ART and displaying poor adherence or engagement with the healthcare system were an important source of HIV-1 transmission and TDR in Venezuela[63].

In that era, free access to ART was also guaranteed in other countries belonging to that region (Fig. 2). However, scaling-up moved slowly and, for example, in Colombia and Peru scale-up reached only 34 and 57%, respectively, in 2010 according to UNAIDS[12]. One Colombian survey showed a TDR of 5.8% according to the HIVdb algorithm. The sequences from this study were not available for reanalysis with SDRM 2009, but other Colombian sequences that could be accessed did not reveal significant differences in TDR[64]. Two studies in Peru and Ecuador revealed low TDR rates of 3.3 and 4.3%, respectively, in 2002-2003[32,65]. However, it is worrying that all drug classes were affected in these countries. It is unknown whether polymorphisms might have affected these values as data was unavailable for reassessment with SDRM 2009.

Brazil

The overall TDR rate in Brazil was investigated by reanalyzing 1,056 sequences that covered the period 1998-2009 and this resulted in a value of 9.4%.

Before 1998, only a few small-sized studies were performed[26,66]. Barreto, et al.[22] reported a TDR prevalence of 5.6% in 1998-2002 in a group of 341 blood donors, using a WHO survey approach. Noteworthy, this study was able to include 16% recent infections and they displayed a TDR rate of 12%, indicating high transmission rates of drug-resistant strains in São Paulo City at that particular time point[22].

Several studies performed between 2000 and 2004, one WHO survey[24], and one large nationwide study that sampled in 2001[67], showed that the TDR was below 5%[35,49,68-71]. This apparent decrease of TDR could be related to the predominant inclusion of chronically infected individuals. However, other reports showed that TDR was still above 5%[72-74]. These discordances

are presumably due to the heterogeneity of the included studies and the geographical variation of TDR.

Since 2005, the TDR rates remained above 5%, with 7% in Curitiba and 8% in Porto Alegre and Santa Catarina[30,36,67,72]. Nationwide studies reported 5.2% TDR in 2007[75], 8.1% in 2008[39] and 12.3% in 2008-2010[43]. The apparent nationwide increase of TDR in Brazil could not be confirmed in our analysis. This might be explained by the large variations in TDR between and within Brazilian regions that were included in our dataset.

Since 2007, TDR per drug class remained stable, with overall values ranging between 5-15%, NNRTI 3-6%, NRTI 2-6%, and PI 1-3%[29,39,47,48,75]. The last WHO survey showed resistance against NRTI in 7.6%, followed by 4% against NNRTI and PI[43].

Southern Cone

As 84% of the Southern Cone sequences originated from Argentina, general conclusions cannot be made for this region. Nevertheless, their reanalysis using SDRM 2009 resulted in a TDR prevalence of 4.9% for the years 1996-2005. In Argentina, the number of studies and their respective sample size remained limited before 2000-2003[25,76]. However, since 2003 several nationwide surveillance studies have been developed that reported TDR rates that ranged from 3.9% in 2003-2005 to 8.4% in 2006-2008[31,33,41,77]. The last reported WHO survey showed a substantial level of resistance towards NNRTI (5.6%), NRTI (4.2%), and PI (3%)[33]. Another study that was performed in recently infected individuals between 2004 and 2009 also supported the 8% of TDR with predominance of NNRTI resistance[78]. Almost all Argentinean studies documented TDR against the three common drug classes. In Chile, TDR was less extensive, with an overall TDR of 6.2% in 2000-2005 that slightly decreased to 4% in 2006-2008[38,79]. In this country, TDR mutations were mainly restricted to NRTI and NNRTI.

Transmitted drug resistance in Latin America and the Caribbean: What do we know?

This review showed a TDR of 7.7% in 1,922 therapy naive HIV-1 patients. However, the majority of sequences were obtained from Brazil, Argentina, Mexico, and Chile, countries that correspond to half of the people living with HIV-1 in LAC. This percentage is higher than for other developing countries[80-82], but similar to the 6.4% reported by the WATCH study that included seven studies since 2000-2006[22,41,61,66,68,76,80,83], and similar to TDR rates in Europe, Canada, and the USA[2-5]. Although no significant trend in TDR was observed in this analysis, two peaks were observed in 1998-1999 and 2006-2007. These peaks overlapped, with a high inclusion of sequences from Brazil and Venezuela, countries characterized with the highest TDR rates in LAC.

Although the analysis has been standardized, implementing the SDRM 2009 list for interpretation of drug resistance, we acknowledge the limitations of this study. The included studies differed, for example, in the intrinsic characteristics of the analyzed population (age, risk factor of transmission, geographical and socioeconomic factors), design of the study (method of sampling, type of study, criteria or exclusion criteria), clinical characteristics (recent or chronic infection, immunological status, viral load), drug resistance testing (sample type, sequencing method, sequence quality, algorithm used for the analysis of mutations), ART-related factors in the treated population (mono- or bitherapy history, HAART scale-up, delay of start therapy, availability of new compounds, pharmacogenetics, toxicity, adherence problems, drug failure) and viral factors (subtype, fitness)[84-86]. For example, in one Brazilian study 20% TDR was reported in PBMC samples[34]. However, PBMC testing is more apt to detect drug resistance mutations than plasma, and the intrinsic regional characteristics of the population might impede the generalization of these results[34,87].

Although the MSM group is one of the main drivers of the LAC epidemic and they are 33.3 times more likely to be HIV-1 positive[88], we did not find differences in the TDR rates between heterosexuals and MSM. More studies are necessary to understand the trends of TDR, especially in MSM because the risk of imprisonment in some countries of the Caribbean and the stigma in LAC could hinder the accurate evaluation of this population, especially when TDR prevalence has been reported to range between 3.3% in Peru for 2002 to 17% in Brazil for 2010[32,88,89].

In regard to distribution of mutations, since NNRTI have been used widely in LAC as first-line therapy consequently, the amino acid change in position 103 was the most frequent in the sequences analyzed and in the studies included (Fig. 4 C). The amino acid change 215 and 41 were frequently found in this review. However, 184V was more frequently detected in this study than in European or North American reports, even though the difference was not statistically significant[2-5]. In general, similar patterns have been found in other developing countries but, in the resource-rich settings, NNRTI resistance seems to be stabilizing, probably

due to the changes in therapy prescriptions[4,81]. Overall, this review did not observe trends in particular drug resistance patterns in the analyzed sequences obtained from LAC.

Conclusions

The overall TDR prevalence in LAC was 7.7% for the period 1996-2009 and reached 10% in the last four investigated years when data was solely restricted to Brazil and Venezuela. Additionally, large geographical differences have been found. Although lack of information for the Caribbean and Central America prevents us from drawing general conclusions, the reported TDR in Cuba and other Caribbean islands is still under the 5% WHO threshold. However, Honduras, Mexico and South American countries have passed the 5% threshold, with the exception of Chile. The limited information available for most of the countries should encourage the development of surveys for drug resistance in newly infected people.

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