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Transmitted Drug Resistance Among Antiretroviral-Naive Patients with Established HIV Type 1 Infection in Santo Domingo, Dominican Republic and Review of the Latin American and Caribbean Literature

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Abstract

Emergence of HIV resistance is a concerning consequence of global scale-up of antiretroviral therapy (ART). To date, there is no published information about HIV resistance from the Dominican Republic. The study's aim was to determine the prevalence of transmitted drug resistance (TDR) to reverse transcriptase and protease inhibitors in a sample of chronically HIV-1-infected patients in one clinic in Santo Domingo. The data are presented in the context of a review of the TDR literature from Latin America and the Caribbean. Genotype testing was successfully performed on 103 treatment-naive adults planning to initiate antiretroviral therapy; the World Health Organization (WHO) list of surveillance drug resistance mutations (SDRM) was used to determine the presence of TDR mutations. WHO SDRM were identified in eight patients (7.8%); none had received sdNVP. There were no significant differences in epidemiologic or clinical variables between those with or without WHO SDRM. The prevalence of WHO SDRM was 1.0% and 6.8% for nucleoside reverse transcriptase inhibitors and nonnucleoside reverse transcriptase inhibitors, respectively. No WHO SDRMs for protease inhibitors were identified. Among 12 studies of TDR in the region with a sample size of at least 100 subjects, the reported prevalence of SDRM ranged from 2.8% to 8.1%. The most commonly identified SDRM was K103N. This information adds to our understanding of the epidemiology of TDR in the region and the possible role such mutations could play in undermining first-line treatment. Ongoing surveillance is clearly needed to better understand the TDR phenomenon in the Caribbean.

Introduction

The Dominican Republic (DR), a resource-constrained country in the Caribbean, has an estimated 62,000 adults living with HIV.[1] Since 2003, the Dominican national HIV program has provided highly-active antiretroviral therapy (ART) free of charge to all those with HIV-1 infection who qualify. As of 2007, an estimated 30% (21–40%) of those who needed ART were receiving it.[2] However, HIV-1 plasma RNA level measurement, though offered through the national program, is not routinely available. Additionally, genotype analysis is not offered through the national program, and data on antiretroviral treatment outcomes in the country are scant.

In the DR and elsewhere, emergence of HIV resistance is a concerning consequence of global scale-up of ART.[3] When an individual is infected with an HIV-1 strain harboring drug resistance mutations, the phenomenon is referred to as transmitted drug resistance (TDR). The effects of TDR include

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restricted drug options and suboptimal treatment outcomes for patients with HIV,[4] which may weaken the effectiveness of the national HIV treatment program by diminishing the individual and public health benefits of ART. This is exacerbated by the general lack of access to HIV drug resistance testing and the limited antiretroviral drug formularies characteristic of programs in resource-limited settings. Additionally, a vicious cycle can develop once a pool of resistant virus becomes established, leading to still higher rates of transmitted resistance.[4]

In North America, Western Europe, and Australia where ART is already widely available, there is extensive documentation of regional variation in the prevalence of TDR.[4–6] Multisite cohort and cross-sectional studies in these regions reveal a TDR prevalence of approximately 7–16% (both recently and chronically infected individuals),[7–11] while prevalence in some populations appears much higher, reaching 24.1% in New York City[12] and 25.2% in San Diego.[13]

In comparison, TDR surveillance studies from the rest of the world provide a less complete picture.[4,6] Recent data from Africa and Asia show TDR prevalence to be less than 5% in multiple surveys,[4–6,14] but there is recent evidence of emerging resistance in some areas.[15–21] Most data published on TDR in Latin America and the Caribbean come from Brazil,[4–6] and there are no published studies that address resistance in treatment-naive patients from the Dominican Republic.

The emergence of drug resistance is an inevitable consequence of widespread use of any antimicrobial therapy in a population. In the case of HIV therapy, this is a particular concern because of the inherent characteristics of the virus (i.e., its high mutation and replication rate), the need for lifelong treatment, the known pharmacodynamics of antiretrovirals, and the need to maintain high degrees of adherence to treatment to achieve durable virus suppression. Selected factors that may further contribute to TDR in resource-limited settings include inconsistent access to ART (such as stock-outs), insufficient numbers of trained HIV providers, adoption of prevention of mother-to-child transmission (PMTCT) protocols involving single-dose nevirapine (sdNVP),[22,23] inconsistent availability of viral load monitoring, and use of ART regimens that contain drugs with low genetic thresholds for resistance such as lamivudine, nevirapine, and efavirenz.[6]

The aim of this study was to determine the prevalence of TDR in a sample of treatment-naive, chronically HIV-1-infected patients in one clinical setting in Santo Domingo, Dominican Republic (Dominican Prevalence Study). We present these data in the context of a review of the literature of comparably sized studies regarding the prevalence of TDR in the Latin American and Caribbean regions (Regional Literature Review) to provide a perspective on this important region of the world.

Materials and Methods

Study population

Patients were selected for inclusion in the study as they enrolled in a prospective, observational cohort study of HIV treatment outcomes in the Dominican Republic from July 28, 2007 through February 9, 2010. Continuous recruitment and enrollment took place at the Instituto Dermatológico y Cirugía de la Piel "Dr. Huberto Bogaert Díaz" (IDCP), one of the sites of the cohort study. This clinical site, founded in 1965 for the treatment of leprosy and other skin disorders, provides ART for HIV-infected individuals in Santo Domingo as part of the national antiretroviral program in the Dominican Republic. The national antiretroviral program has adopted a public health approach with standardized first-line (NRTI + NNRTI) and second-line (NRTI + PI) regimens. Physicians and patient educators in the clinic offered enrollment to all individuals initiating ART. Of those offered enrollment, approximately 75% accepted; the primary reasons for refusal were living at a distance from the clinic or the inability to perform genotyping prior to ART initiation. At enrollment, patients were asked if they had ever taken antiretroviral therapy, excluding sdNVP administered in the context of PMTCT. Patients were included if they had diagnosed HIV infection, were age 18 years and older, planned to initiate antiretroviral therapy, and were willing to participate in the study. Patients were excluded if they had previously taken antiretroviral therapy, except as above.

Data collection

Basic demographic and clinical information, including age, sex, year of HIV diagnosis, HIV risk factor, receipt of sdNVP in the context of PMTCT, HIV status of past/current sexual partners, history of commercial sex work, number of lifetime partners, and prior travel outside the DR, was collected at the time of entry into the study by interview and by medical record review. Baseline $CD4^+$ cell counts and HIV-1 plasma RNA levels were collected within a window defined as those measured from 1 year prior to the genotype date and for up to 7 days afterward (provided ART had not yet been initiated).

Genotyping

Plasma was collected in Santo Domingo at the time of entry into the study and sent in batches several times yearly to the reference laboratory for genotype testing and subtype analysis using the GeneSeq HIV assay (Monogram Biosciences, Inc., South San Francisco, CA). This assay reports population-based amino acid coding sequences from amino acids 1 to 305 for the reverse transcriptase (RT) and 1 to 99 for the protease (PR). Results were received prospectively at an interval approximately 2 weeks to 4 months from the date of plasma sampling due to sample batching for genotyping. Mutations were classified as TDR according to the WHO list of surveillance drug resistance mutations (SDRM)[24] because of its focus on nonpolymorphic mutations.

Sample size

A power calculation for the detection of resistance in a population of antiretroviral-naive individuals shows a sample size of approximately 107 genotype tests would have a 95% confidence level to detect a 7.5% prevalence of transmitted drug resistance in the population (confidence interval of 5). Due to delays inherent in the batching of samples for genotype testing, the decision was made to report the current results upon achieving $n = 103$.

Statistical analysis

Statistical analysis was performed using SAS 9.2 (Cary, NC). Categorical variables were reported as frequencies, and

Table 1. Demographic and Immunologic Characteristics of $n=103$ Antiretroviral-Naive Patients Included in This Study

Characteristic	*All patients* n *(or median)*	*%* *(or min.–max.)*	*Without TDR (WHO SDRM criteria)* n *(or median)*	*%* *(or min.–max.)*	*With TDR (WHO SDRM criteria)* n *(or median)*	*%* *(or min.–max.)*	*OR [95% CI]*	p-*value*
Total	103	100.0%	95	100.0%	8	100.0%	—	—
Men	47	46.1%	43	45.7%	4	50.0%	1.19 [0.28, 5.03]	0.82
Age at time of test (years)	38.6	17.8–62.5	38.9	17.8–62.5	35.4	24.0–55.7	—	0.25
Time since diagnosis (years)	3.0	0–19.0	3.5	0–19.0	1.0	0–7.0	—	0.08
HIV risk factor								
Heterosexual sex	82	82.8%	76	83.5%	6	75.0%	1.0	—
MSM	10	10.1%	9	9.9%	1	12.5%	1.41 [0.15, 13.05]	0.76
Other/multiple/unknown	7	7.1%	6	6.6%	1	12.5%	2.11 [0.22, 20.52]	0.52
Received sdNVP for PMTCT (females only)	7	13.7%	7	13.7%	0	0%	—	1.00
HIV status of past/current partners								
Negative	13	13.0%	12	13.0%	1	12.5%	1.0	—
Positive	53	53.0%	48	52.2%	5	62.5%	1.25 [0.13, 11.72]	0.85
Don't know	34	34.0%	32	34.8%	2	25.0%	0.75 [0.06, 9.05]	0.82
Prior/active commercial sex work	15	15.0%	13	14.1%	2	25.0%	2.03 [0.37, 11.14]	0.34
Number of lifetime partners	4	0–300	4	0–300	3.5	0–33	—	0.88
Prior travel outside the DR	10	9.9%	9	9.7%	1	12.5%	1.33 [0.15, 12.10]	0.80
Baseline[1] laboratory studies								
$CD4^+$ count (cells/μl)	216	5–724	218	5–724	185	101–236	—	0.28
HIV-1 plasma RNA (copies/ml)	59,604	320–2,836,323	61,919	320–2,836,323	23,226	4,618–102,185	—	0.25

[1]Baseline CD4 and HIV-1 plasma RNA level values were defined as those measured from 1 year prior to the genotype date and for up to 7 days afterward (provided ART had not yet been initiated).
sdNVP, single-dose nevirapine; PMTCT, prevention of mother-to-child transmission; MSM, men who have sex with men; DR, Dominican Republic.

numeric variables were summarized as medians and ranges. Additional analyses were performed to compare the characteristics of patients with and without TDR. Univariate testing was completed using the χ^2 or Fisher exact test (for categorical variables) and the Wilcoxon rank-sum test (for continuous variables). Variables were considered statistically significantly different if $p \leq 0.05$.

Ethical approval

All patients provided written informed consent prior to participating. This study was approved by the Dominican National Committee on Bioethics (CONABIOS), the IDCP Institutional Review Board, and the Columbia University Medical Center Institutional Review Board.

Results

A total of 104 antiretroviral-naive patients who met the study entry criteria and consented to participate in the study were enrolled and had specimens sent for resistance testing; all but one could be amplified and sequenced. Of the 103 samples sequenced, all were classified as subtype B. Epidemiologic and clinical information was available for 102 individuals. Table 1 shows the characteristics of the entire study population and also compares the groups with and without TDR as defined by the WHO list of SDRM.[17] The study population was 46.1% male with 82.8% reporting infection by heterosexual transmission. The median age was 38.6 years and the median time from diagnosis to genotype date was 3.0 years. Of 55 females in the study population, seven (12.7%) had previously received single-dose nevirapine (sdNVP) for PMTCT; none of these women exhibited TDR. Just over one-half of subjects (53.0%) had ever had an HIV-infected partner. Prior and/or active commercial sex work was reported by 15.0% of subjects; the median number of lifetime sexual partners was four. Prior international travel was reported by 9.9% of subjects. The median baseline $CD4^+$ count was 216 cells/μl. Among the 49 patients with available baseline HIV-1 plasma RNA levels, the median was 59,604 copies/ml. Baseline HIV-1 plasma RNA levels are not standard of care within the Dominican National HIV program, but these 49 patients were similar to the other 54 patients without baseline HIV-1 plasma RNA levels in all ways but one: their median baseline CD4 count was higher (226 vs. 177 cells/μl, $p = 0.03$). The median interval between HIV diagnosis and genotype was 1 year in those with mutations and 3.5 years in those without TDR; this difference was not significant ($p = 0.08$). There were no statistically significant differences between the groups for any other epidemiologic or clinical variables.

Of 103 patients, antiretroviral-associated TDR, as classified by the WHO list of SDRM in the infecting virus, was identified in eight (7.8%). Nonpolymorphic nucleoside reverse transcriptase inhibitor (NRTI)-associated DRMs and nonpolymorphic nonnucleoside reverse transcriptase inhibitor (NNRTIs)-associated DRMs were found in one (1.0%) and seven (6.8%) samples, respectively. No patients appeared to have evidence of nonpolymorphic PI-associated DRMs and no patients harbored mutations to more than one antiretroviral therapy drug class.

The specific SDRMs are shown in Table 2. The only NRTI mutation identified was M184M/V. The most common NNRTI SDRM identified was K103N (3); the next most common mutations were K101E (2) and Y181C (2). Table 2 also contains basic demographic and clinical information about the eight patients with TDR as classified by WHO SDRM.

Regional literature review

To review all published studies of TDR in RT and PR in HIV-1-infected adults in Latin America and the Caribbean, a search in Pubmed was undertaken. All studies found by this search were examined; 12 studies of TDR in Latin America and the Caribbean with a sample size of at least 100 adult subjects were identified (Table 3). More than half of the studies were from Brazil[25–30]; the other five countries represented included Colombia,[31] Honduras,[32,33] Cuba,[34] Argentina,[35] and Peru.[36] In most of the studies reviewed, subtype B was the predominant subtype identified, although several other subtypes were present at a prevalence of greater than 10%, including subtype C in Brazil,[25,27,29,30] and recombinant forms in Brazil,[30] as well as in Argentina and Cuba.[34,35] Additionally, one study from Brazil reported non-B, non-C subtypes at a prevalence of 17.0%[29]; further subtype analysis was not reported.

Classifications of drug resistance mutations varied across the studies, and the overall reported prevalence of TDR ranged from 2.8% in Porto Alegre, Brazil[25] to 8.1% in Brazil.[27] When the analysis was repeated using only those mutations

Table 2. Characteristics of the Eight Patients with Drug Resistance Mutations

ID	*Age at time of testing (years)*	*Sex*	*Year of diagnosis*	*Approximate number of years from diagnosis to genotype*	*Baseline CD4 cell count (cells/μl)*	*Baseline HIV-1 plasma RNA level (copies/μl)*	*Mutations to NRTI*	*Mutations to NNRTI*	*Mutations to PI*
1	42	M	2004	4	236	39,056	—	**K103N, Y181C**	—
2	26	F	2009	1	142	—	—	**K103N**	—
3	35	F	2008	1	178	7,396	—	**K103N**	—
4	35	M	2001	7	116	102,585	—	**K101E**	—
5	31	F	2009	0	—	4,618	—	**K101E**	—
6	35	M	2007	2	209	—	—	**Y181C**	—
7	24	F	2007	1	224	—	—	**V106A**	—
8	55	M	2008	0	101	—	M184V	—	—

NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.
Mutations in bold indicate mutations that confer resistance to all NNRTIs available as first-line therapy in the country.

Table 3. Summary of 12 Studies of Transmitted Drug Resistance in Antiretroviral-Naive Patients from the Latin American and Caribbean Region

First author (year of publication)	*Country city/region*	n	*Time period*	*Prevalent HIV-1 subtypes*	*Risk*	*Prevalence of TDR mutations associated with resistance (as cited by author)*	*Prevalence of TDR mutations associated with resistance (based on WHO SDRM list)*			
						Any	*Any*	*NRTI*	*NNRTI*	*PI*
Murillo (2010)[32]	Honduras—multiple regions	200	April 2004–April 2007	B (99%); 2 samples could not be classified	Heterosexual (86%); MSM (14%)	14 (7.0%)	14 (7.0%)	6 (3.0%)	10 (5.0%)	1 (0.05%)
DiazGranados (2010)[31]	Colombia—multiple regions	103	Not provided	Not provided	MSM (54.9%), heterosexual (45.1%)	6 (5.8%)	6 (5.8%)	3 (2.9%)	5 (4.9%)	1 (1.0%)
Inocencio (2010)[29]	Brazil—multiple regions	210	2007–2008	Subtype B most prevalent in all cities (72%), except Porto Alegre, where C is highly prevalent (69%)	Heterosexual (56.1%), homosexual (23.6%), bisexual (11%)	17 (8.1%)	14 (6.7%)	4 (1.9%)	6 (2.9%)	5 (2.4%)
Sprinz (2009)[29]	Brazil—Brazilian cities ($n=13$)	387	March 2007–Sept. 2007	B (66.0%); C (12.8%); non-B, non-C (17.0%); not available (4.3%)	Heterosexual (54.3%); MSM (43.2%); IDU (2.5%)	22 (5.7%)	17 (4.4%)	3 (0.8%)	14 (3.6%)	4 (1.0%)
Lloyd (2008)[33]	Honduras—San Pedro Sula and Tegucigalpa	239	July 2002–June 2003	B (99.1%); F1 (0.3%); AD recombinant (0.3%); C (0.3%)	Not provided	18 (7.5%)	18 (7.5%)[a]	15 (6.3%)[a]	12 (5.0%)[a]	4 (1.7%)
Gonzales (2007)[26]	Brazil—São Paulo	123	March 2002–December 2006	B (82%); F (6.5%); C (5.7%)	Heterosexual (exact % not provided)	8 (6.5%)	7 (5.6%)	4 (3.2%)	3 (2.4%)	3 (2.4%)
Dilernia (2007)[35]	Argentina—Buenos Aires	284	March 2003–October 2005	Intersubtype BF recombinants (51.8%); B (45.1%); non-B-non-BF variants (3.2%)	Heterosexual (49.3%); MSM (46.5%); IDU (2.1%); missing data (2.1%)	12 (4.2%)	9 (3.2%)	4 (1.4%)	3 (1.0%)	4 (1.4%)
Pérez (2007)[34]	Cuba—Havana	250	May–Sept. 2003	B (43.6%); unique recombinant forms (21.6%); C (4.0%); G (2.8%); 7 (2.8%)	Mostly MSM, but some women (exact % not provided)	Not reported	9 (3.6%)	9 (3.6%)	None	None
Lama (2006)[36]	Peru—Lima and 5 other cities	359	Oct. 2002–March 2003	B (100%)	MSM	12 (3.3%)	12 (3.3%)[b]	8 (2.2%)[b]	3 (0.8%)	7 (1.9%)
Barreto (2006)[29]	Brazil—São Paulo	341	July 1998–March 2002	B (81.2%); recombinant strains (7.5%); F1 (7.3%); C (3.8%)	Not provided (all were blood donors)	21 (6.1%)	18 (5.3%)	12 (3.5%)	3 (0.9%)	5 (1.5%)
Rodrigues (2006)[25]	Brazil—Porto Alegre	108	?2004	C (58%); B (32%); F1 (3%)	Heterosexual (exact % not provided)	3 (2.8%)	4 (3.7%)	1 (0.9%)	3 (2.8%)	None
Brindeiro (2003)[30]	Brazil—metropolitan regions in 8 different Brazilian states	409	2001	B (62.5%; 64.9%); C (29.5%, 22.8%); F (8.0%, 11.8%) based on RT and PR genomic regions, respectively	Heterosexual (61.7%); homosexual (19.7%); bisexual (7.2%); other/multiple (6.5%); IDU (5.0%)	22 (6.4%)	17 (4.2%)	8 (2.3%)	1 (0.2%)	8 (2.3%)

[a]Published prevalence is slightly lower than reported here because the authors counted V1181 as an NRTI mutation and V1081 and K238N/T as NNRTI mutations.
[b]Published prevalence is slightly lower than reported here because the authors counted T69D as an NRTI mutation.
$n>100$ subjects (listed in reverse chronologic order).

appearing on the WHO list of SDRMs[24] to establish consistent criteria across studies, the prevalence ranged from 3.2% in Buenos Aires, Argentina[35] to 7.0% in two cities of Honduras.[32] Multiclass drug resistance was rare; Diazgranados *et al*.[31] described the highest prevalence (3 of 103, 2.9%) in Colombia.

The frequency of each SDRM in these studies was also assessed. The most commonly identified SDRM was K103N, a mutation conferring resistance to nevirapine and efavirenz, the NNRTIs available in resource-limited settings. All but one study reported the presence of this SDRM. The second most common mutations were M184V and M41L, both of which confer resistance to NRTIs. PI mutations were much less widely identified; the most commonly identified PI mutation was L90M.

Discussion

The overall prevalence of WHO-defined TDR described in this study of adults in Santo Domingo, Dominican Republic is 7.8%; 8 of 103 patients had mutations that confer at least intermediate resistance to one of the two classes that form first-line ART in the country (NRTIs, NNRTIs). Had genotype testing not been available, such mutations would compromise the response to all the first line antiretroviral regimens available in the DR, impacting subsequent ART outcomes and placing others at risk for continued transmission of resistant virus.

This 7.8% prevalence is somewhat higher than that described in other populations of antiretroviral-naive adults in Latin American and the Caribbean such as those examined in this literature review, with the exception of a Honduran study[32] and a large Brazilian study[27]; these two studies are among the most recent (in terms of year of sampling for TDR and publication date). The comparability of the three studies might reflect a regional trend toward greater prevalence of resistance as ART has been available for increasing periods of time in each country studied, which would be consistent with data from a 13 site cross-sectional study in sub-Saharan Africa where the risk of TDR was associated with the year of the initiation of ART scale-up in each country.[17]

The higher prevalence of TDR in the DR may also relate to the extensive travel between the United States and the DR undertaken by Dominicans.[37] Although individuals who traveled outside the DR prior to entry into the prevalence study were no more likely to have TDR than those who did not travel in this patient population, the "air bridge" (a term used to describe the pattern of circular migration between the United States, particularly New York City, and the DR) may still be linked to the transmission of drug resistant HIV-1, as previously implicated in transmission of bacteria.[38]

No single demographic or clinical characteristic was associated with TDR in a statistically significant manner in our study. Although this may be a function of sample size rather than lack of association, the finding largely mirrors other studies from the region in which there were no such findings, although one study in São Paulo, Brazil found a higher proportion of TDR among the recently diagnosed.[28] In another Brazilian study, having a partner taking ART was associated with a greater probability of resistance.[29] Of note, this absence of demographic or clinical characteristics associated with TDR complicates the possible implementation of a strategy of targeted baseline genotype testing based on patient profile.

The most common mutation present in this Dominican study was K103N, probably indicating the aggregated effects of the extensive use of NNRTIs as part of first-line ART in the Dominican national program (including the use of single-dose nevirapine as part of PMTCT), the low genetic barrier to resistance of most NNRTIs, and the limited reversion to wild-type over time combined with the relative fitness of mutants with this mutation.[4] The absence of PI mutations in this population likely reflects both the limited use of PIs, the relatively high genetic barrier to resistance of this class, and the infrequency of their transmission[39] despite their relative persistence in chronically infected individuals.[40] The finding that K103N was the most common mutation was similar to the findings of a number of Latin American and Caribbean studies reviewed here; it was the most commonly identified mutation in 6 of the 13 studies.

Women who received sdNVP in the context of PMTCT were included in our study, despite the potential for confounding if NNRTI-associated SDRMs had been detected, because the sdNVP regimen should contribute only to single-class resistance (i.e., NNRTI resistance, and not NRTI or PI resistance). As no SDRMs from any drug class were detected in this subgroup, inclusion of this subgroup makes our prevalence determination of 7.8% a conservative one.

This study was limited by its small size and single-site enrollment. As these patients represent a convenience sample of those enrolled in an observational cohort, selection bias may have been introduced. Additionally, a median of 3 years had elapsed between diagnosis and genotype in these patients. Although there is evidence to suggest that most TDR mutations persist, it is possible that there was either reversion to either wild-type virus or to other codons, leading to a possible underestimation of TDR.[5]

This study presents an estimation of the prevalence of TDR in a sample of treatment-naive, chronically HIV-1-infected patients in the DR and places it in a regional context. It is hoped that such information will ultimately help providers and public health officials working in this part of the world to better understand the epidemiology of TDR and the role such mutations could play in undermining the efficacy of first-line treatment regimens. Each new patient represents an opportunity for clinicians and health systems alike: If drug access, prescribing, and adherence can be optimized and prevention messages reinforced, development of resistance can be minimized and, should it develop, dissemination can be contained. Moreover, improvements in existing treatment programs can lead to declines in the prevalence of TDR,[41] underscoring the importance of employing early warning indicators[42] and maintaining accurate monitoring. Further ongoing surveillance of acutely or recently infected individuals is clearly needed to better understand the TDR phenomenon in the country and the extent to which the rates may rise with continued ART scale-up.

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Author Disclosure Statement

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