Pretreatment HIV Drug-resistance Surveillance as a Tool for Monitoring and Control of the HIV/AIDS Epidemic in Cuba

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ABSTRACT

The HIV/AIDS epidemic is an ongoing threat to public health. Its elimination requires greater efforts to broaden antiretroviral treatment coverage, availability and personalization. HIV drug resistance is currently a global problem due to its continuing increase in recent years, undermining efficacy of antiretroviral therapy. Pretreatment HIV drug-resistance surveillance is part of WHO's strategy for addressing antiretroviral drug resistance.

This paper describes and analyzes pretreatment HIV drug-resistance surveillance in Cuba. It presents a chronology of HIV resistance studies in untreated patients, along with their results and programmatic actions related to first- and second-line treatment regimens. Cuba's incorporation into the Global HIV Drug Resistance Surveillance Laboratories Network and the advantages of having a WHO-designated laboratory in which to conduct periodic studies of HIV drug-resistance surveillance are described.

HIV drug-resistance surveillance in Cuba is a necessary tool in HIV/AIDS monitoring and control, as it obtains population-scale data used to inform programmatic decisions related to optimizing first- and second-line treatments for children and adults, as well as helping meet goals of eliminating HIV transmission.

KEYWORDS HIV; anti-HIV agents; drug resistance, viral; antiretroviral agents; Cuba

INTRODUCTION

Antiretroviral therapy (ART) is one of the most significant advances in battling the HIV/AIDS epidemic. Since ART does not eliminate the virus in individuals, treatment must be lifelong.[1]

Many factors can affect short- or long-term ART success, including poor adherence to treatment, drug intolerance, drug interactions, individual pharmacokinetic variations and preexisting drug resistance due to transmission of a resistant virus. Transmitted HIV drug resistance occurs when a person becomes infected with an antiretroviral (ARV) drug-resistant strain of HIV. This phenomenon may contribute to rising treatment failure rates, undermining long-term effectiveness of recommended first-line regimens.[2]

Faced with grave public health consequences associated with the emergence and transmission of HIV drug resistance, surveillance studies in untreated infected populations are crucial. An understanding of current patterns of pretreatment drug resistance can help clinicians select the most appropriate ART regimens, as well as anticipate trends that may affect optimization of resources allocated for effectively treating HIV-positive persons.[1,2]

IMPORTANCE

Pretreatment HIV drug-resistance surveillance is a vital tool in combatting the HIV/AIDS epidemic. This article describes and analyzes pretreatment HIV drug-resistance surveillance in Cuba, which has enabled identification of the most effective therapeutic combinations for achieving viral suppression and reducing transmission of resistant HIV variants; thus, Cuba expects to surpass 90% treatment adherence, proceeding towards WHO's goal of eliminating AIDS as a health problem by 2030.

Alerted to increasing HIV drug resistance in low- and middle-income countries in recent years, WHO has issued guidelines aimed at minimizing drug resistance and contributing to achieving targets for ending the HIV/AIDS epidemic by 2030.[3]

The Global Action Plan (GAP) on HIV drug resistance, created in 2017, established requirements for providing people living with HIV (PLHIV) with more effective treatments and for preventing drug resistance from undermining efforts to meet global health goals. GAP's strategic goals include increasing laboratory capacities for HIV drug-resistance genotyping, as well as adequate HIV drug-resistance monitoring and surveillance to obtain quality data through studies performed at regular intervals.[4]

Cuba has adopted WHO directives to confront HIV drug resistance. Monitoring and surveillance activities have been specified in several editions of the Cuban Ministry of Public Health's (MINSAP) National Strategic Plan for Sexually Transmitted Infections (STI), HIV/AIDS and Hepatitis.[5,6] Surveillance activities include periodic studies of HIV drug resistance in patients who have not received ART, useful to MINSAP as it evaluates current and potential treatment regimens, since pretreatment resistance to ARVs in use in Cuba can affect patient results and strategies for meeting national and global goals for HIV/AIDS elimination. This paper analyzes the role surveillance of pretreatment HIV drug resistance has had as a tool for monitoring and controlling the HIV/AIDS epidemic in Cuba.

MONITORING PRE-TREATMENT HIV ANTIRETROVIRAL RESISTANCE IN CUBA

HIV drug resistance in untreated Cuban patients Since the first HIV-positive patient was diagnosed in Cuba in 1986, the national health system, through the National Program for the Prevention and Control of HIV/AIDS,[5,6] has designed strategies for the prevention, diagnosis, treatment and epidemiological surveillance of the disease.

Several studies have focused on determining which genetic variants of the virus are circulating in the seropositive Cuban popu-

lation, given their implications for diagnosis, transmissibility and clinical progression.[7–9]

Before ART was initiated in Cuba, a group of Cuban researchers, in collaboration with the Carlos III Health Institute (ISCIII) in Spain, conducted a pilot study to determine HIV drug-resistance prevalence in seropositive patients treated with monotherapeutic or two-drug ARV regimens, as well as in patients not receiving ARV. The results showed a low prevalence of mutations that generate resistance to reverse transcriptase inhibitors (RTI) and protease inhibitors (PI),[10] which aided in selecting ARVs that would later be produced by Cuba's domestic biopharmaceutical industry: zidovudine (AZT), nevirapine (NVP), lamivudine (3TC), stavudine (d4T), indinavir (IDV) and didadosine (DDI) (Table 1).[11]

The introduction of ART in Cuba in 2001 (with domestically-produced generic ARVs) helped reduce the incidence of opportunistic infections and mortality from HIV/AIDS, as well as improve quality of life in PLHIV.[11] By the end of 2018, more than 90% of all PLHIV who initiated treatment in 2007 remained alive.[5,6] However, prolonged ART use in the seropositive population is known to foster emergence of HIV drug-resistant genetic variants in these patients and therefore potential transmission of the resistant strains to the untreated HIV-positive population.[18]

Two years after the introduction of domestically-produced generic ARVs, another group of Cuban researchers in collaboration with the ISCIII in Spain evaluated HIV drug resistance in seropositive Cuban patients. That study included 249 untreated patients and detected a low prevalence (4%) of mutations associated with HIV drug resistance.[12] During 2007–2011 and 2009–2014, researchers at the Pedro Kourí Tropical Medicine Institute (IPK) in Havana studied changes in drug resistance in 152 treated and 342 untreated patients (samples obtained immediately prior to beginning treatment), and results showed moderate resistance prevalence (12.5% and 11.4%, respectively) (Table 1).[13,14]

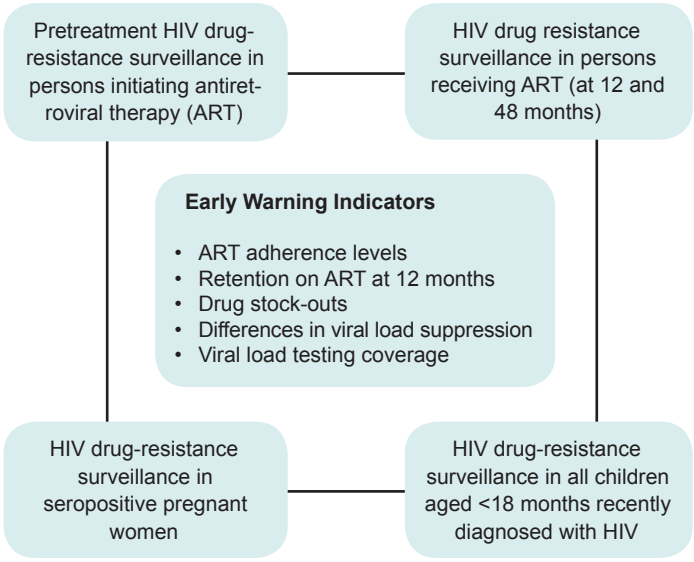
Although several factors interfere with the goal of achieving total ART coverage, Cuba has experienced a sustained increase, reaching approximately 83% of PLHIV.[6] In order to support this goal, and with financial assistance from the Global Fund to Fight AIDS, Tuberculosis and Malaria, HIV drug-resistance genotyping was introduced in 2009.

WHO recommends that countries with ART programs establish sentinel surveillance systems to detect HIV drug resistance and make evidence-based recommendations for preventing drug resistance. Such surveillance is aimed at minimizing the emergence of drug resistance, prolonging the efficacy of first- and second-line therapies, and selecting adequate therapeutic regimens for pre- and post-exposure prophylaxis (Figure 1).[3] In response to those recommendations, MINSAP decided that IPK and the AIDS Research Laboratory (LISIDA) would be in charge of HIV drug-resistance genotyping. Since then, surveillance of HIV drug resistance in a sample of patients with no prior treatment history was undertaken by LISIDA.[5,6]

Once infrastructure was created and staff trained, LISIDA initiated studies of HIV drug resistance in untreated individuals in June 2009. From that date until December 2016, with the permanent collaboration of primary healthcare teams at community polyclinics who were providing care to PLHIV in each province, 469 patients recently diagnosed with HIV infection who had not yet initiated ART were studied. Of those patients, 19% (89) presented a virus with some mutation associated with pretreatment HIV drug resistance: 10.4% (48) to nucleoside reverse-transcriptase inhibitors (NRTI), 12.8% (60) to non-nucleoside reverse-transcriptase inhibitors (NNRTI) and 2.8% (13) to protease inhibitors. The most frequent mutations were K103N/S and Y181C in the NNRTI family, which reduced susceptibility to drugs like NVP and efavirenz (EFV). In the NRTI family, the most frequent mutations were M184V/I (resistance to 3TC) and D67N (resistance to AZT).[15,16] The results showed a high prevalence of pretreatment HIV drug resistance and, consequently, the need to change first- and second-line therapeutic regimens used by the National Program for the Prevention and Control of HIV/AIDS. However, studies conducted in 2009–2016 did not take into account WHO recommendations for sampling and selection of individuals for surveillance of pretreatment drug resistance (Table 1).

In December 2016, LISIDA specialists, in collaboration with the MINSAP's STI, HIV/AIDS and Hepatitis Program and PAHO, designed a national survey of HIV drug resistance in pretreatment patients, following WHO recommendations,[3] aimed at estimating pretreatment HIV drug-resistance prevalence in the seropositive Cuban population.

Figure 1: Cuba's HIV drug-resistance surveillance and monitoring strategy*



*in accordance with WHO recommendations[3,4,6]

The survey was conducted from January to June 2017. Samples from 141 untreated patients from 15 municipalities were studied. Overall prevalence of pretreatment resistance was 29.8% (95% CI: 22.3–38.1). Prevalence for some NRTI was 10.6% (95% CI: 6.07–16.9); for some NNRTI, 23.4% (95% CI: 16.7–31.3); and for some PI, 1.4% (95% CI: 0.17–5.03) (Table 1).[17]

Determination of resistance levels to ARV combinations indicated that treatment would not be effective in 29.7% of patients initiating therapy with the AZT + 3TC + NVP regimen. The ATRIPLA combination of tenofovir (TDF), emtricitabine (FTC) and EFV would not be effective in 27.6% of patients initiating ART. The increase in NNRTI pretreatment drug resistance in Cuban HIV-positive

Table 1: Chronology of pretreatment HIV drug-resistance studies in Cuba

Year of Study	Institution	Patients (n)	First-line ART regimen	% Resistance				Recommendations to health authorities
				Some mutation	NRTI	NNRTI	PI	
1999[10]	LISIDA (collaboration with Carlos III Institute, Spain)	27	Monotherapy, two-drug ART, triple-drug ART	7.4	7.4	-	-	Introduce ART with ARV drugs produced in Cuba
2003[12]	IPK (collaboration with Carlos III Institute, Spain)	249	2 NRTI + 1 NNRTI*[5]	4	4	-	-	Increase HIV drug-resistance studies
2007–2011[13]	IPK	152	2 NRTI + 1 NNRTI*[5]	12.5	3.9	2.0	2.0	Genotyping needed prior to initiating ART
2009–2014[14]	IPK	342	2 NRTI + 1 NNRTI*[5]	11.4	7.9	5.3	2.9	National study needed with WHO representativeness criteria[3]
2009–2016 [15,16]	LISIDA	469	2 NRTI + 1 NNRTI*[5]	19	10.4	12.8	2.8	National study needed with WHO representativeness criteria[3]
2017[17]	LISIDA	141	2 NRTI + 1 NNRTI*[5]	29.8	10.6	23.4	1.4	No NNRTI prescription in first-line ART[6] Incorporate DTG in first-line ART[6]

ART: Antiretroviral therapy; ARV: antiretroviral drugs; DTG: dolutegravir (integrase inhibitor); IPK: Pedro Kourí Tropical Medicine Institute; LISIDA: AIDS Research Laboratory; NNRTI: non-nucleoside reverse transcriptase inhibitors (efavirenz, nevirapine); NRTI: nucleoside reverse transcriptase inhibitors (zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir; PI: protease inhibitors (indinavir, saquinavir, nelfinavir, ritonavir, amprenavir, lopinavir/ritonavir)

*includes combination therapies: AZT + 3TC + NVP; AZT + 3TC + efavirenz (EFV); tenofovir (TDF) + 3TC + NVP; TDF + 3TC + EFV; ATRIPLA: TDF + emtricitabine (FTC) + EFV

patients who participated in the national survey demonstrated the need to evaluate switching to more appropriate and effective ART regimens and strengthening prevention and surveillance of HIV drug resistance.[17]

WHO recommends against NNRTIs in first-line therapy if prevalence of resistance to this family of drugs is >10% and if not possible to eliminate NNRTI, suggests considering HIV drug-resistance genotyping before prescribing treatment.[19] One recommendation suggests incorporating the integrase inhibitor dolutegravir (DTG), which has a high genetic barrier and can rapidly attain undetectable values of plasma viral load.[20] This drug was added to first-line ART combinations in Cuba starting in the last quarter of 2018, one of MINSAP's rapid responses for confronting the high levels of HIV drug resistance detected,[6] thereby obtaining a higher percentage of PLHIV with viral suppression.

Confronting HIV drug resistance should involve educational and preventive interventions with PLHIV on the importance of adhering to treatment along with systematic monitoring of early warning indicators of HIV drug resistance (such as treatment retention, viral load coverage, systematic provision of drugs to pharmacy networks, etc.).

According to WHO criteria, lowering the prevalence of pretreatment HIV drug resistance to <10% will enable Cuba to maintain its achievement as the first country in the world to eliminate mother-to-child HIV transmission[21] and contribute towards its goal of meeting the third 90 in the 90-90-90 treatment targets proposed by the Joint UN Program on HIV/AIDS (UNAIDS) for 2020, which aim to have ≥90% PLHIV on treatment regimens living with undetectable viral loads.[22]

Cuba's incorporation into WHO Global HIV Drug Resistance Network (HIVResNet) laboratories The WHO HIVResNet global laboratory network includes national and regional laboratories, along with specialized international laboratories accredited by WHO, responsible for conducting HIV drug-resistance tests.[23] Depending on their capacity, experience and technical resources, each laboratory carries out specific functions supporting the network's national, regional and global needs.

All national surveys of HIV drug resistance require testing in a WHO-accredited laboratory. The accreditation process is undertaken only by laboratories designated by national authorities to test samples gathered as part of HIV drug-resistance surveys recommended by WHO. Generally, WHO accredits only one laboratory per country, whose primary task is providing high-quality genotyping results, pertinent to national ART programs and supporting public health approaches to ART.[23]

Cuba initiated a national survey to assess variation in pretreatment HIV drug resistance in 2017. MINSAP nominated LISIDA for evaluation and designation by WHO as a National Drug Resistance Laboratory and member of HIVResNet. That same year, WHO experts visited LISIDA, having previously reviewed an accreditation checklist assessing the laboratory's experience and capacity for HIV sequencing, as well as several quality indicators, such as staff competencies, facilities, equipment, management practices, financial security and sustainability, and participation in a WHO External Evaluation Program. The results of the evaluation process were satisfactory and even exceeded criteria for WHO acceptance and designation as a National Reference Laboratory and member of HIVResNet (https:// who.int/temas/global-hiv-hepatitis-and stis-programmes/hiv/treatment/hiv-drug-resistance).

As part of the designation process and as a useful resource for evaluating laboratories' competence in editing and analyzing HIV genetic sequences obtained in HIV drug-resistance genotyping, WHO incorporated dry-panel testing, a novel alternative for quality control, consisting of a group of sequences from HIV protease and reverse transcriptase enzyme regions. This test involved editing and analyzing the sequences, demonstrating competency in quality assurance, data management and reporting.

Since LISIDA's designation as a member of HIVResNet, the laboratory has participated in three dry-panel tests with satisfactory results (94.7–100 points; minimum 85 points required), demonstrating good performance (compliance with Good Laboratory Practices) and competence in data management and reporting.

Results of the 2017 national pretreatment HIV drug-resistance survey were entered into the WHO database and included in its annual HIV Drug Resistance Report in 2019.[24]

LISIDA has played an active role in HIVResNet since joining the network, which has led to the introduction of new methodologies for analyzing HIV drug resistance in Cuba. Its specialists have participated in virtual meetings and seminars, as well as the annual HIVResNet meeting during the 28th International Workshop on HIV Drug Resistance and Treatment Strategies in 2019 (www.hivresistance2019.co.za).

Projections for surveillance of HIV drug resistance in Cuba

Results of the 2017 national HIV drug-resistance survey were presented in different settings (virtual meetings, workshops) to a representative group of doctors caring for PLHIV in Cuba. These exchanges led to National Technical Team approval of new therapeutic regimens accepted in the National Strategic Plan 2018–2023.[6] HIV drug resistance has been a recurring topic in national meetings of the Cuban PLHIV Network, leading to creation of prevention-based strategies to help minimize the emergence of HIV drug resistance through promoting ART adherence and systematic monitoring of early warning indicators. Offering seminars, workshops and conferences for clinicians caring for PLHIV on HIV drug resistance and the use of genotyping in clinical practice is one of the objectives of both MINSAP's STI, HIV/AIDS and Hepatitis Program and laboratory personnel in charge of genotyping in Cuba (LISIDA and IPK).

Incorporating DTG in first-line ART regimens in Cuba involved introducing genotyping to detect HIV resistance to integrase inhibitors, since this is a mandatory requirement for national laboratories accredited by WHO. Having a validated test capable of detecting primary and secondary mutations associated with the emergence of resistance to integrase inhibitors makes it possible to evaluate resistance to these ARV in ART regimens used in Cuba.

LISIDA is working toward validation of HIV drug-resistance genotyping using dry blood on filter paper, given the advantages of this type of sample in terms of transportation and conservation. Incorporation of new technologies for determining HIV drug resistance will strengthen the laboratory by acquiring the Sentosa SQ HIV platform (Vela Diagnostic, Germany), which detects mutations associated with resistance in protease, reverse transcriptase and integrase genes, using next-generation sequencing. In this way, LISIDA will meet one of the HIVResNet goals related to the transition from HIV drug-resistance genotyping based on the Sanger sequencing method,[2] to next-generation sequencing.

As the national reference laboratory for surveillance of HIV resistance and a member of HIVResNet and the national reference laboratory for surveillance of HIV resistance, LISIDA will begin surveying adults receiving ART in 2021 for the purpose of estimating prevalence on a national scale of 1) viral load suppression, and 2) HIV drug resistance in populations that have received ART for 12 months (±3 months) and for ≥48 months. Results of this national survey will contribute fundamental information about the efficacy of the program for achieving maximum viral suppression and document appropriate selection and optimal management of second-line treatments. The National Program can also use the results to detect deficiencies in service provision and implement policies to improve results at individual and population levels.

CONCLUSIONS

In Cuba, pretreatment surveillance has been an efficient tool for detecting high levels of HIV drug resistance to NNRTI, thus prompting adoption of more effective therapeutic combinations to increase viral suppression, lower transmission of HIV drug-resistant variants and thus facilitate ART success. The comprehensive approach, focused research and enhanced laboratory capacity will make substantial contributions to HIV drug-resistance surveillance in PLHIV populations and to achieving WHO goals for eliminating HIV/AIDS as a public health problem by 2030.

ACKNOWLEDGEMENTS

The authors of this study wish to pay posthumous tribute to Dr María Isela Lantero-Abreu, one of the co-authors of this manuscript who died on February 14, 2021. The results presented in this work constitute one of the many contributions made by Dr Lantero-Abreu to improving the lives of people living with HIV and ameliorating the effects of the disease in the Cuban population, as director of Cuba's STI/HIV/AIDS and Hepatitis Program for 30 years.

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Submitted: October 4, 2020
Approved for publication: April 8, 2021
Disclosures: None

https://doi.org/10.37757/MR2021.V23.N2.11