BASELINE STUDY REPORT:

PRESCRIPTION PRACTICES FOR ANTIRETROVIRAL THERAPY IN COMPREHENSIVE CARE SERVICES OF THE DOMINICAN REPUBLIC

General Coordination:
National Pharmaceuticals Management Unit of the National Health Service (Unidad Nacional de Gestión de Medicamentos del Servicio Nacional de Salud)
General Directorate for the Control of Sexually Transmitted Infections and AIDS (Dirección General de Control de Infecciones de Transmisión Sexual y SIDA, or DIGECITSS)

Technical Consulting:
Dr. Claudia Valdez, Lead Consultant
Dr. Edgar Barillas, Senior Manager LAC
Systems for Improved Access to Pharmaceuticals and Services (SIAPS)
United States Agency for International Development (USAID)

May 2016
Santo Domingo, Dominican Republic.

CONTENTS

BACKGROUND

By April 2016, approximately 31,000 people living with HIV/AIDS (PLWHA)[1] were receiving antiretroviral therapy (ART) in the network of the National Health Service of the Dominican Republic (Servicio Nacional de Salud de República Dominicana), which is made up of public health facilities, private institutions, and non-governmental organizations (NGOs).

The General Directorate for the Control of Sexually Transmitted Infections and AIDS (Dirección General de Control de Infecciones de Transmisión Sexual y SIDA, or DIGECITSS), made the "National Guidelines for the Care of Sexually Transmitted Infections (Guía Nacional de Atención de las Infecciones de Transmisión Sexual)" official in 2014 and the "Guidelines for Early Diagnosis of Infants and Clinical Care for Pediatric HIV/AIDS (Guía de Diagnóstico Temprano en Infantes y Atención Clínica en VIH/SIDA Pediátrico)" in 2015. The standards for antiretroviral treatment for adults and children were established in these guidelines

The country's HIV care guidelines for adults established eleven treatment regimens, including three lines of therapeutics: four combinations were established in the first line, four in the second line, and three for the third line[2]-[3]. The regimens for adults are presented in Table 1.

The pediatric guidelines established two lines of treatment, the first line with four therapeutic regimens and one rescue line that includes three combinations. The regimens for pediatrics are presented in Table 2.

Table 1: List of Adult ARV Regimens to Assess, Contained in the Protocols

	Adult Regimens		
	Regimens	**Medications**	**Concentrations**
1st Line	AZT/3TC/NVP	Zidovudine/Lamivudine/Nevirapine	150/300/200mg
	TDF/3TC+EFV	Lamivudine/Tenofovir + Efavirenz	300/300mg+600mg
	AZT/3TC+EFV	Zidovudine/Lamivudine +Efavirenz	150/300mg+600mg
	ABC+3TC+EFV	Abacavir + Lamivudine + Efavirenz	300mg+ 150mg+600mg
2nd Line	TDF/3TC+LPV/r	Lamivudine/Tenofovir + Lopinavir/Ritonavir	300/300mg+200/50mg
	AZT/3TC+LPV/r	Zidovudine/Lamivudine + Lopinavir/Ritonavir	150/300mg+200/50mg
	AZT/3TC+LPV/r	Lamivudine/Abacavir + Lopinavir/Ritonavir	150/300mg+200/50mg
	AZT/3TC+LPV/r	Lamivudine/Tenofovir + Atazanavir/Ritonavir	300/300mg+200/50mg
3rd Line	TDF/3TC + DRV/r	Tenofovir + Lamivudine + Darunavir/Ritonavir	300mg+ 150mg+600/100mg
	ABC/3TC + DRV/r	Abacavir + Lamivudine + Darunavir/Ritonavir	300mg+ 150mg+600/100mg
	TDF/3TC + RAL/r	Tenofovir + Lamivudine + Raltegravir/Ritonavir	300mg+ 150mg+800/100mg

[1] April 2016 report, Social Policy Program Implementation Data Sheet (Formulario de Aplicación a Programas de Políticas Sociales, or FAPPS). National Health Service, Dominican Republic.
[2] National Guidelines for the Care of Sexually Transmitted Infections (Guía Nacional de Atención de las Infecciones de Transmisión Sexual). 2014. General Directorate of Sexually Transmitted Infections and Aids (Dirección General de Infecciones de Transmisión sexual y SIDA, or DIGECITSS), Ministry of Public Health, Dominican Republic.
[3]Guidelines for Early Diagnosis of Infants and Clinical Care for Pediatric HIV/AIDS (Guía de Diagnóstico Temprano en Infantes y Atención Clínica en VIH/SIDA Pediátrico). 2015. General Directorate of Sexually Transmitted Infections and AIDS (Dirección General de Infecciones de Transmisión sexual y SIDA, or DIGECITSS), Ministry of Public Health, Dominican Republic.

Table 2: List of Pediatric ARV Regimens to Assess, Contained in the Protocols

	Pediatric Regimens		
	Regimens	**Medications**	**Concentrations**
1st Line	AZT/3TC+NVP	Zidovudine/Lamivudine/Nevirapine	300mg+150mg+200mg or suspension
	AZT/3TC+LOP/RIT	Zidovudine/Lamivudine/Lopinavir/Ritonavir	300mg+150mg+200/50mg or suspension
	AZT/3TC+EFV	Zidovudine/Lamivudine + Efavirenz	300mg+150mg+600mg or suspension
	TDF+3TC+EFV	Tenofovir/Lamivudine + Efavirenz	300mg+150mg+600mg or suspension
2nd Line	DDI+ABC+Lop/r	Didanosine+Abacavir+Lopinavir/Ritonavir	250mg+300+200/50mg tablets or suspension
	TDF+3TC+Lop/r	Tenofovir+Lamivudine+Lopinavir/Ritonavir	300mg+150mg+200/50mg tablets or suspension
	ABC+3TC+Lop/r	Abacavir+Lamivudine+Lopinavir/Ritonavir	300mg+150mg+200/50mg tablets or suspension

The programming for ARV purchases considers these treatment standards for new cases. Even so, the consumption report from the Integrated Medicine and Supply Management System (Sistema Único de Gestión de Medicamentos e Insumos, SUGEMI) for the October-December quarter of 2015 showed a 200% increase with respect to historic consumption of medicines for third-line therapeutics and 120% for second-line. The increase in the use of these medicines suggests a lack of adherence to the guidelines and implicated an increase in purchases of approximately DOP$ 23 million above what was programmed for 2015.

The purpose of this study is to determine if the current prescription practices adhere to the national therapeutic guidelines. Finding notable discrepancies between the prescription practices and the guidelines would explain unjustified expenses in ARV therapy and the stockout problems and overstocks that occasionally occur.

SCOPE

Geographic: Comprehensive Care Services (Servicios de Atención Integral, or SAI) for HIV and AIDS in the nine Regional Health Services (Servicios Regionales de Salud, or SRS) were included.
Procedural: The study covered the current ARV prescription practices and the sources of information used by prescribers.

OBJECTIVES

General

Get to know the ARV prescription practices in the SAIs.

Specific

1. Contrast the current prescription practices with those established in the national therapeutic guidelines.
2. Establish the implications of a lack of adherence to national therapeutic guidelines in terms of consumption of medicines that doesn't correspond to the programmed quantities and unjustified costs of procurement for PLWHA care.
3. Provide elements for the construction and development of educational tools to promote correct prescriptions with adherence to the national therapeutic guidelines.

METHODOLOGY AND DESIGN OF THE STUDY

The type of study: Exploratory, descriptive, and retrospective cross-sectional. The sampling was proactive in its criteria, intentional and selective, that covered twenty-eight HIV Comprehensive Care Services (Servicios de Atención Integral, or SAI). The unit of observation was the prescription practices of at least two doctors per selected SAI. To have a better sample representation, the following criteria were used for SAI selection:

- **Institutional Affiliation**: twenty-one SAIs located in the Specialized Healthcare Centers (Centros Especializados de Atencion en Salud, or CEAS) of the public sector (SNS and Armed Forces), one in the private sector, and six in NGOs.
- **Demand for Care**: of the twenty-eight selected SAIs, twelve showed a high demand (more than 800-2,800 PLWHA undergoing ART) and sixteen showed a medium/low demand (less than 300-800 PLWHA undergoing ART).
- **Regional Representation**: all of the regions were represented in the sampling, with at least two SAIs from each. The distribution considered the demographic density and the demand for care; as such, the SAIs in the metropolitan region represented 39% of the sampling.
- **Rurality**: twenty urban (71%) and eight (29%) rural health facilities were included.

In each one of the selected SAIs, the main informer was the clinical prescriber. Given that there is usually more than one per SAI, the criteria for selection were the following:

- **Demonstrated time of service**: Given that the study is retrospective, priority was given to the doctor in charge of clinical care in the SAI with more than one year of service.
- **Adult and/or child care**: If more than one clinician met the previous criteria, the clinician whose practice included adult and pediatric patients was selected.

Methods of Collection, Processing, and Analysis

The collected information was provided by multiple sources and categorized as such:

Interviews with prescribers: The collection of information was carried out by means of interviews with the selected prescribers. To these ends, a semi-structured instrument was developed with closed and open questions. This instrument was previously validated by experts from the HIV program and the SNS before its application. The instrument included questions related to the prescription of the ARVs, including:

- Criteria for inclusion in antiretroviral therapy (ART) for new patients with positive diagnosis.
- Criteria for selection of first, second, and third lines of treatment.
- Criteria used to consider therapeutic failures.
- Training or continuous education on the therapies that the prescribers had gone through.
- Sources of information for updates on the use of therapies.
- Opinion and perception on the utilization of visual materials as a strategy to improve prescription.

Review of treatment files: ten treatment files were reviewed per SAI for two types of sample populations: 1) New patients receiving ART for less than six months; 2) Patients receiving ART for more than two years. In total, 202 files were analyzed. The selection of the files was carried out via a random, systematic method.

RESULTS

The country has seventy-two SAIs; the total evaluated was twenty-eight, representing 40% of the total of SAIs in the country and 80% of HIV care at the national level. The unit of observation was the prescription practices of at least two doctors from each SAI for a total of fifty interviewed doctors (Table 1).

Table 1: Evaluated Health Facilities and Personnel

Health Facilities	***#***	***Total %***
Public SAIs	21	75%
NGO SAIs	6	21%
Private SAIs	1	4%
Total	28	100%

Health Personnel Interviewed	***#***	***Total %***
Public SAIs	34	68%
NGO SAIs	14	28%
Private SAIs	2	4%
Total	50	100%

Source: Data collection file from the study on HIV Care Services.

In accordance to the objectives of the study, the findings are grouped in two sections: *prescription practices* and *associated problems*.

1. Prescription Practices

The DIGECITSS made official the "**National Guidelines for the Care of Sexually Transmitted Diseases** (***Guía Nacional de Atención de las Infecciones de Transmisión Sexual***)" in 2014 and the "**Guidelines for Early Diagnosis of Infants and Clinical Care for Pediatric HIV/AIDS (*Guía de Diagnóstico Temprano en Infantes y Atención Clínica en VIH/SIDA Pediátrico*)"** in 2015. These establish the standards for antiretroviral treatment of adults and children, regulate the combinations of ARVs that must be used in each of the regimens, and establish the criteria for the change to rescue or third line (with a special genotyping test and authorization from the DIGECITSS).

Out of the total of interviewed prescribers, 84% (42/50) demonstrated that they knew and met the clinical, immunological, and virological criteria[4] for inclusion in ART according to the national care guidelines, while 16% stated that they do not apply these criteria. However, upon investigating specifically about the regimens, only 72% (36/50) of the prescribers selected first-line regimens recommended in the national care guidelines. Of the prescribers, 28% (14/50) expressed that they do not currently use the guidelines

[4] Established criteria in the Care Guidelines: Clinical Criteria: Presence of an opportunistic infection (OI); Immunological Criteria: If the CD4 < 500; Virological Criteria: VL > 50 thousand copies; Pregnancy, Coinfection with TB or Hepatitis, Nephropathy or heart disease. For children, these do not apply, since all children diagnosed with HIV receive ART.

for selection of treatment regimens, stating that they base the selection on their clinical experience or international references.

In regards to meeting the criteria for therapeutic failure[5] for changing to second-line regimens, 100% (50/50) stated that they use the national guidelines as a reference in the decision to move to another regimen; even so, only 62% (31/50) conformed to the criteria in the guidelines. Of the prescribers, 22% (11/50) expressed that they carried out changes based on suspicion of deterioration of the patient's condition, and 16% (8/50) of the prescribers change regimens when the patient expresses that they do not tolerate the first-line therapy. Among pediatric prescribers, no differences from what is determined in the treatment guidelines were observed, as they establish individualized treatments and doses adjusted by age.

According to the national care guidelines, the second-line regimen for adults is lopinavir 200mg/ ritonavir 50mg. The study showed that only 60% (30/50) of the prescribers selected this regimen. The remaining 40% (20/50) selected regimens that were not in accordance with the national treatment guidelines, including the use of atazanavir (which is a second option of the second line) and raltegravir (third line). In the reviewed documents, the rationale for the use of ARVs that do not correspond to the established regimens was not recorded (Table 2).

[5] Evaluation under the criteria for regimen failure according to the Care Guidelines: OI recurring, Stage 4 (WHO); CD4 < 50% initial value, VL >5,000 copies/mL and/or genotyping test.

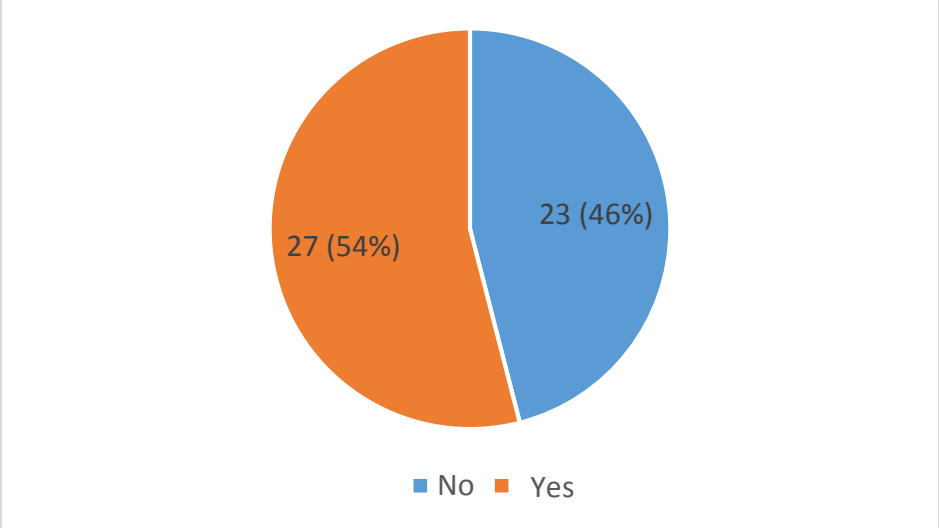
Table 2: Selection of Second-Line ART According to Prescribers

Regimen	# of Prescribers	%
In Accordance with Treatment Guidelines Tenofovir + Lamivudine + Lopinavir/rtv	30	60 %
Not In Accordance with Treatment Guidelines Zidovudine or Tenofovir + Lamivudine + Atazanavir/ritonavir	15	30 %
Tenofovir + Lamivudine + Raltegravir/ritonavir	5	10 %
Total	**50**	**100%**

Source: Data collection file from the study on HIV Care Services.

In regards to meeting the criteria for therapeutic failures[6] for changing to third-line regimens, 54% (27/50) of the prescribers said that they use the national guidelines for the decision to change regimens; while 46% (23/50) expressed that they do not conform to the criteria established in the national guidelines. The prescribers that said they do not adhere to the guidelines said that they carried out changes based on suspicion of deterioration of the patient's condition and/or if the patient expresses that they do not tolerate the therapy (Figure 1).

Figure 1: Percentage of Prescribers Stating Adherence or Non-Adherence to the National Treatment Guidelines for the Change to Third-Line Regimens



Source: Data collection file from the study on HIV Care Services.

According to the national guidelines, the third-line regimen for adults includes raltegravir 800mg/ritonavir 100mg or Darunavir/ritonavir 600/100 mg. The study showed that 28% (14/50) selected the treatment regimen in agreement with the national guidelines. The 72% (36/50) that did not adhere to the guidelines used second-line medicines like atazanavir and lopinavir/ritonavir (Table 3).

[6] Evaluation under the criteria for treatment failure following the Care Guidelines: recurrent IO, Stage 4 (WHO); CD4 < 50% initial value, VL >5,000 copies/mL and/or genotyping test.

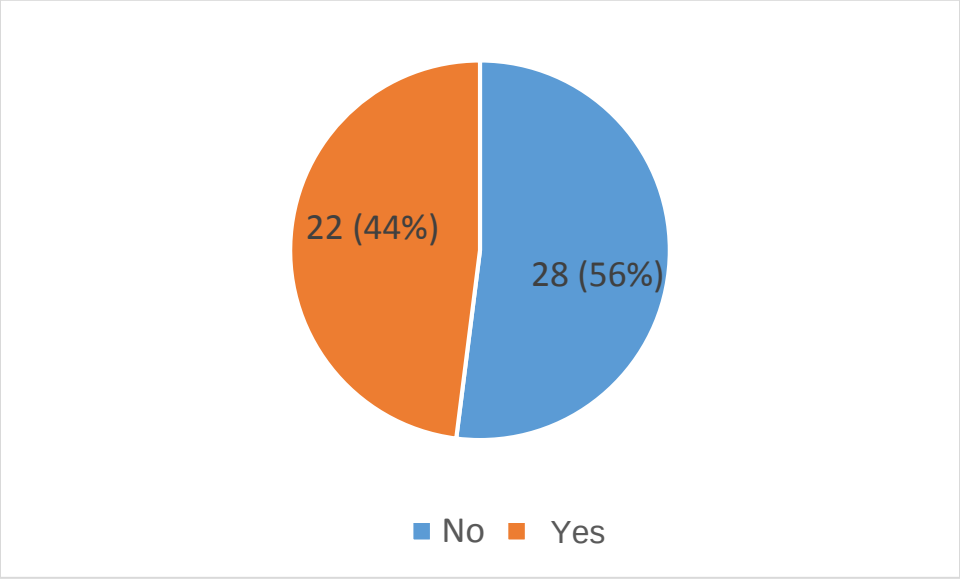
Table 3: Selection of Third-Line ARV

Regimen	Prescribers	%
In Accordance with Guidelines		
Tenofovir + Lamivudine + Raltegravir or Darunavir	14	28 %
Not In Accordance with Guidelines		
Tenofovir + Lamivudine + Lopinavir/ritonir	16	32 %
Zidovudine or Tenofovir + Lamivudine + Atazanavir/ritonavir	20	40 %
Total	**50**	**100 %**

Source: Data collection file from the study on HIV Care Services.

The national guidelines for adults establish that changes to third-line regimens have to be authorized by the DIGECITSS[7]. The study showed that 56% (28/50) of the prescribers did not solicit this authorization, claiming that the DIGECITSS does not respond with the needed promptness (Figure 2).

Figure 2: Solicitation of Authorization from the DIGECITSS for Regimen Changes, Number and Percentage of Prescribers



Source: Data collection file from the study on HIV Care Services.

To corroborate the correlation between the interviews and the prescriptions, 202 files from adult and pediatric patients under treatment during 2015 were reviewed. These were selected via a random, systematic method and divided into two groups of patients: 1) Newly admitted patients with less than six months since beginning therapy; 2) Patients receiving more than two years of ART.

[7] National Guidelines for the Care of Sexually Transmitted Infections. 2014. General Directorate of Sexually Transmitted Infections and AIDS (Dirección General de Infecciones de Transmisión sexual y SIDA, or DIGECITSS), Ministry of Public Health, Dominican Republic.

Review of the files showed that 69% (138/202) of the patients were prescribed the therapeutic regimen that conforms to the protocols and lines of treatment; while 31% (61/202) of the patients were not prescribed in accordance with the established lines of treatment. The study showed that 5% (5/99) of newly admitted adult patients were prescribed third-line regimen medicines (raltegravir/ritonavir) without the backing of clinical tests and authorizations, as established in the national guidelines.

A review of clinical documentation also showed that for 27% (27/99) of newly admitted patients, the average time of change to second and third-line regimens was two months; while for patients with more than two years in therapy the average time was fifteen months (twelve month median) ranging between six to eighty-four months. At the international level, the recommendation for retention or continuation of a patient in first line is an average of five years, if there are no complications that merit changes of regimens[8].

2. Problems and Associated Factors

The study evaluated aspects related to the training and supervision of prescribing personnel in the SAIs as possible reasons for compliance or noncompliance to the HIV treatment guidelines.

Of the prescribers, 94% (47/50) stated that they select medicines and make changes to treatment regimens based on reference documentation; of these, 54% use the national treatment guidelines, 18% publications from independent clinical societies, 12% documentation from pharmaceutical laboratories, and 10% review publications from international agencies, like the World Health Organization. The remaining 6% stated they do not use reference documents (Table 4).

Table 4: Sources Consulted by the Interviewed Prescribers

Source	Prevalence	%
National Guidelines and Protocols	27	54 %
International Guidelines and Protocols from Medical or Independent Societies	9	18 %
Documents from Laboratories/Medical Sales Representatives	6	12 %
Guidelines and Protocols from International Agencies such as the World Health Organization	5	10 %
None	3	6 %
Total	**50**	**100.0%**

Source: Data collection file from the study on HIV Care Services.

Of the prescribers, 80% (40/50) responded that they had participated in a workshop, training course, or refresher course on the use of ARVs in the last twelve months and 20% (10/50) responded that they had received no form of training or education. The institutions that held the training sessions, according to those interviewed, were the Ministry of Public Health, laboratories, and specialized medical societies.

[8] ARV Treatment Guidelines, 2015. PAHO. Unified directives on the use of antiretrovirals in the treatment and prevention of HIV infection.

The study looked into the sources most consulted by prescribers regarding possible interactions or effects of the combinations of medicines. Only 58% stated the use of the national guidelines, 34% consult with colleagues, and 8% international publications.

Table 5: Sources Consulted on Adverse Effects and Interactions

Source	Prevalence	%
National Guidelines or Protocols	29	58 %
Consulting with Colleagues	17	34 %
International Journal Publications	4	8 %
Total	**50**	**100 %**

Source: Data collection file from the study on HIV Care Services.

Of the prescribers, 54% (27/50) stated they had never been supervised in the past twenty-four months. Of the 46% that were supervised, 30% stated that they received supervision by personnel from the Ministry of Public Health and 16% could not identify the origin of the supervisor.

Table 6: Supervision of Prescription and Use of ARVs in the Twenty-Four Months Prior to the Study

Origin of the Supervisor	Prevalence	%
Was Not Supervised	27	54 %
Supervision Was Carried Out by a Domestic Program or the Ministry of Public Health or the National Health Service	15	30 %
Supervision Was Carried Out by Personnel from an Unknown Origin	8	16 %
Overall Total	**50**	**100 %**

Source: Data collection file from the study on HIV Care Services.

The study included a prescriber opinion survey on the usefulness of offering literature or visual instructional materials for improving prescriptions. All 100% responded positively. Of these, 46% recommended the use of desktop brochures and 26% stated a preference for the use of posters to be hung on the walls of doctor's offices.

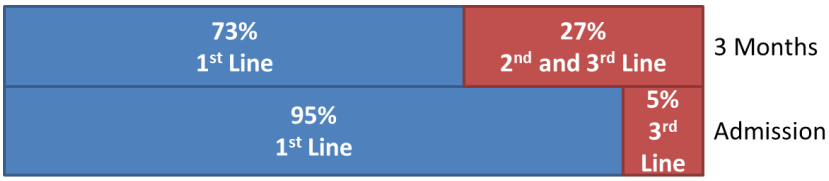
DISCUSSION AND ANALYSIS

In countries with high adherence to international recommendations, it is reported that approximately 75% of patients are found in first-line regimens, 20% in second-line regimens, and less than 5% in rescue or third-line treatment[9]. The patients in first line should stay in those regimens for up to five years[10]. The changes in regimens between second line and third line happen twelve months and twenty-four months after the initiation of treatment. The change should be determined by immunological, virological and clinical criteria defined at the international level.

In the Dominican Republic, 77% of the patients are in first-line regimens, 23% in second-line regimens, and less than 1% in third-line regimens. Nevertheless, this study demonstrated that in the studied SAIs the average time for moving to second and third-line regimens is three months for new patients and fifteen months for patients with more than two years of treatment. In both cases, no evidence was found that supports the early change in treatment.

Of the new patients, 27% were moved to the second and third line three months after the initiation of ART, and 5% of the new patients are immediately started on third-line treatment (Figure 3).

Figure 3: Movement between ART Regimens in Evaluated SAIs

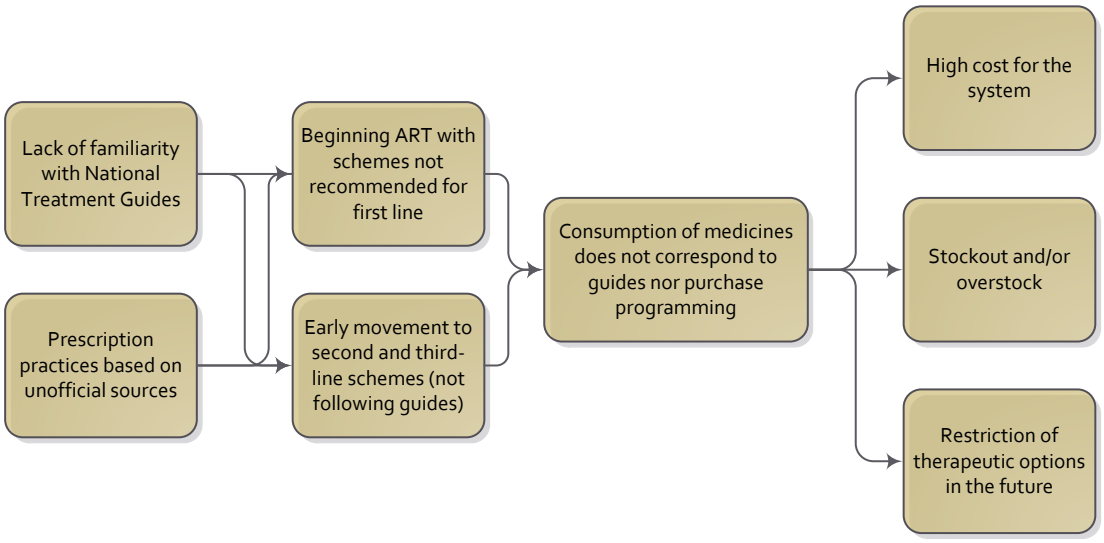


If the prescription practices in the SAIs follow the international standards, or the best practices in other countries (five year retention in first line), the savings in the studied SAIs would be DOP$ 126,000 per patient per year, for a total of DOP$ 4 million per year.

The problems derived from the lack of adherence to the national guidelines go further than the cost to the system: the early use of second and third-line medicines exhausts the possibility for further changes, when the patient really needs them. Furthermore, the use of therapeutics not established in the guidelines, generates unanticipated consumption of some drugs, causing overstocks in some cases and stockouts in others (Figure 4).

[9] Pan American Health Organization (PAHO); World Health Organization (WHO). 2014. Antiretroviral Treatment in the Spotlight: A Public Health Analysis in Latin America and the Caribbean.
[10] Martínez JM, Sánchez-Rubio J, Ontañón A, Ibáñez N, Montojo C. Study of the durability of the triple antiretroviral regimens. Med Clin(Barc) 2004; 122: 693-95.

Figure 4: Causes and Effects Derived from Misuse of ARV



The solution to the majority of these problems is the strict adherence to the treatment guidelines. Its publication and dissemination must be reinforced, as the study suggests, with concise materials that are available in the prescriber's office. The educational interventions must be reinforced with regulatory actions (regulated use of third-line medicines, for example), and administrative actions (sanctions on the prescribers), if the educational actions don't have the desired impact.

CONCLUSIONS

1. **Limited adherence to the national therapeutic guidelines**: The prescription of ARVs is not carried out with adherence to the national therapeutic guidelines. Some prescribers showed that they are not familiar with the lines of treatment and the medicines that make up the combinations and stated that they do not ask for authorization from authorities for making changes to regimens.
2. **Lack of Continuous Education for Prescribers**: Among the factors related to incorrect prescription of ARVs is a lack of trustworthy informational literature and the absence of training programs and continuous education from national health institutions.
3. **Lack of Supervision and Monitoring of ARV Use:** The study showed there is little supervision and a system for systematic monitoring of ARV use is absent.

RECOMMENDATIONS

1. Development of educational tools that promote correct prescription with adherence to the national therapeutic guidelines.
2. Establishment of a system for monitoring the use of ARVs with an early alert for irrational prescription practices, accompanied by periodic supervisions and corrective administrative measures.

This document can be quoted using the following reference:

Valdez, C; Barillas, E; Díaz, M; Ledesma, J; Marte, Y. (2016). *Baseline study report: Prescription practices for antiretroviral therapy in comprehensive care services of the Dominican Republic. Santo Domingo, República Dominicana.* Presentado a la Agencia de los Estados Unidos para el Desarrollo Internacional por el Programa Systems for Improved Access to Pharmaceuticals and Services (SIAPS). Arlington, VA: Management Sciences for Health; 2016