Antiretroviral drug resistance in HIV-infected patients in Colombia

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ABSTRACT

Background: Systematically obtained data on antiretroviral (ARV) resistance in Colombia are lacking. Local estimates of resistance are needed to guide testing, therapy, and policy.
Methods: A cross-sectional study was performed in ARV-naïve individuals and in patients with first ARV failure. Genotypic resistance testing was performed using Viro-seq. Predicted success to first- and second-line regimens recommended by the Colombian HIV treatment guidelines was estimated.
Results: One hundred and three naïve and 77 experienced patients were included. For naïve patients, resistance mutations were detected in 5.8%, with the most common mutations being 103N ($n = 5$; 4.9%) and 184 V ($n = 3$; 2.9%). CD4 count <200 cells/mm^3 ($p = 0.04$) and Centers for Disease Control and Prevention (CDC) category C ($p = 0.004$) were associated with primary resistance. For experienced individuals, regimens were non-nucleoside reverse transcriptase inhibitor (NNRTI)-based in 57.1%, protease inhibitor (PI)-based in 14.3%, boosted PI-based in 26.0%, and nucleoside reverse transcriptase inhibitor (NRTI)-based in 2.6% of the cases. Resistance mutations were found in 66 patients (85.7%) with failure. The most common mutations were 184 V ($n = 48$; 62.3%), 103N ($n = 37$; 48.1%), G190A/S ($n = 9$; 11.7%), and L90 M ($n = 9$; 11.7%). Twelve percent had thymidine analogue mutations (TAMs) but only 1% had more than 1 TAM. The predicted success of regimens recommended by the Colombian guidelines was 95% for naïve patients and 84% for experienced patients. Genotyping could increase the success rates to 100% and 94%, respectively.
Conclusions: The frequency of primary HIV resistance in Colombia is similar to estimates from other countries in Latin America. CD4 count and CDC category C may allow identification of most of the naïve patients who would benefit from resistance testing. Resistance testing could favorably impact therapy modification in about 5% and 10% of naïve and experienced patients, respectively.

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1. Introduction

There are about 2 million people living with HIV/AIDS in Latin America and the Caribbean, with 120 000 new cases and 70 000 estimated deaths in 2007 for the entire region.[1] Located in the northwestern corner of South America, Colombia has an estimated HIV prevalence rate of 0.6% and approximately 170 000 people living with HIV.[2] HIV/AIDS is the third most important cause of death in people between 15 and 49 years of age in Colombia, surpassed only by homicide, accidents, and other violent deaths.[3]

The availability of antiretroviral (ARV) therapy has changed the natural history of HIV infection dramatically,[4] and the rapid scale-up of ARV in resource-limited settings is an international priority.[5] However, as ARV therapy is expanded and rolled out, resistant viruses emerge. HIV resistance is considered a rising worldwide problem, and the World Health Organization (WHO) recommends HIV resistance surveillance as a component of ARV rollout programs.[6] The Colombian Obligatory Health Plan (Plan Obligatorio de Salud, POS), established by law in 1993, includes HIV/AIDS on its list of diseases that require high-cost treatments. This plan mandates the free provision of ARV therapy by Health Promoting Entities (Entidades Promotoras de Salud, EPS)[7] under the General Social Security Health System (Sistema General de Seguridad Social en Salud, SGSSS). As a result, 72% of the total ARV treatments in

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Colombia are provided by one of the EPSs. By 2007, it was estimated that 21 000 patients were receiving ARV therapy in Colombia, covering approximately 38% of those in need.[2] The restrictions in ARV therapy coverage result in part from the limitations in detection and diagnosis of HIV infection in the country. In fact, the Colombian government has estimated that 78.5% of the patients who are known to be HIV infected and who are affiliated to the SGSSS are receiving ARV treatment.[8] The efficacy of ARV therapy in Colombia has recently been evaluated[9] in a study that reported suboptimal virologic response rates. The authors postulated as one possible explanation a high frequency of circulating HIV-resistant viruses in the country.[9] Unfortunately, despite years of ARV utilization, no systematic studies evaluating HIV resistance have been performed in Colombia.

Country-specific HIV resistance knowledge is needed to guide ARV therapy and resistance testing policies.[10] HIV-resistant viruses can be transmitted and may affect the efficacy of ARV medications.[11] Guidelines from resource-rich countries recommend the performance of HIV resistance testing prior to the initiation of ARV therapy and whenever ARV therapy failure occurs.[12–14] However, resistance testing at the individual level may not be feasible in settings with significant resource limitations. As a result, the WHO recommends resistance testing at a population level in these settings.[5,6] Colombia is a country with intermediate resource limitations. National HIV/AIDS guidelines recommend resistance testing at a patient level only beyond the first ARV therapy failure, with decisions regarding ARV initiation and first ARV failure based solely on suggested regimens without the guidance of resistance testing.[15]

The objectives of the current study were: (1) to determine the prevalence and predictors of resistance in therapy-naïve individuals and in patients with first regimen failure in Colombia; (2) to describe the patterns of resistance in therapy-naïve individuals and in patients with first virologic failure; and (3) to calculate the rates of predicted success of first- and second-line regimens recommended by the Colombian HIV treatment guidelines.

2. Methods

We performed a prospective cross-sectional study that included adult patients with confirmed HIV infection who were unexposed to ARV therapy (naïve group) and patients with current ARV exposure diagnosed with first regimen virologic failure (first failure group). Virologic failure was defined according to the Colombian HIV guidelines[15] as two consecutive suboptimal viral load levels (detectable viral load in those with a therapy duration of ≥6 months, or viral load not decreased by at least 1 log per month in those with a therapy duration of <6 months) despite an attempt to optimize adherence, tolerance, and pharmacokinetic barriers. The Colombian HIV guidelines recommend repeating HIV viral load within 2 months once one viral load has been determined to be suboptimal, allowing for classification of patients as virologic failure or not within a follow-up period of 6 months or less. Patients failing a regimen for more than 6 months were excluded from the study. This was done to avoid including patients with prolonged virologic failure who were persistently taking a suboptimal regimen and therefore had higher risk for resistance mutation accumulation. Additionally, the viral load prior to enrollment was required to be ≥2000 copies. Viral load was performed using Versant bDNA 3.0 (Bayer), LCx HIV (Abbott), or Amplicor Monitor v1.5 (Roche) according to the preference of the participating institutions. A recent study showed good correlation and concordance of these three techniques in a sample of Colombian patients.[16]

We included HIV clinics from six regions of the country (Bogotá/ Cundinamarca, Valle del Cauca, Antioquia, Atlántico/Bolívar,

Santander, and Caldas/Risaralda) with the highest numbers of estimated HIV cases.[17] Eligible patients were sampled by convenience according to regional number of HIV cases, so that the proportion of cases included by region would reflect the proportion of cases contributed by that region to the total number of HIV cases in Colombia. Based on previous studies in the Latin American region,[10] we assumed a 6% prevalence of primary resistance for the purpose of sample size calculation. Using a margin of error of 5%, we calculated a target sample size of at least 87 naïve patients to be enrolled in the study.

Genotypic resistance testing was performed at a central laboratory (Centro Internacional de Entrenamiento e Investigaciones Médicas (CIDEIM), Cali, Colombia) using Viro-seq (Celera Diagnostics, Alameda, CA, USA) and following manufacturer instructions, as described elsewhere.[18]

For both groups, demographic, behavioral, and clinical variables were collected and resistance patterns and frequencies were described. Categoric variables included: gender, CD4 count category (below 200 cells/mm^3 or not), Centers for Disease Control and Prevention (CDC) classification category,[19] presumed mechanism of transmission, history of foreign travel, history of sexually transmitted infections (STI), and presence of reverse transcriptase (RT) or/and protease inhibitor (PI) mutations. Numeric variables included: age, number of sexual partners during previous 5 years, viral load, CD4 count, and presumed time at risk. Additional variables for patients failing therapy included: tolerance, adherence according to the simplified medication adherence questionnaire (SMAQ),[20] history of medication supply failure, and type of failing regimen (based on the third component of the regimen and according to the inclusion or not of generic medications; regimens using generic medications were classified as prequalified or not according to the WHO pre-qualification list (http://apps.who.int/prequal/); regimens that did not include generics were classified as 'innovator medications only').

Numeric variables were summarized as medians and ranges and categoric variables as frequencies. Predictors of resistance were explored by bivariate analysis using Fisher's exact test or the Chi-square test when appropriate for categoric variables and the Wilcoxon rank sum test for numeric variables. SAS software version 9.2 (Cary, NC, USA) was used for the analyses. p-Values of ≤0.05 were considered significant.

For the estimation of the predicted success rates to first- and second-line regimens recommended by the Colombian guidelines, we calculated the mutation score for each regimen component using the HIVdb genotypic resistance interpretation algorithm of Stanford University (http://hivdb.stanford.edu/index.html) according to the genotyping results for each patient. Each component contained in a regimen recommended by the Colombian guidelines was classified as 'active' if its mutation score was less than 30 (low level resistance if any) or 'inactive' if its mutation score was 30 or more. Regimens recommended were classified as having or not having predicted success depending on the number of 'active' components included in the regimen. If the regimen contained at least three 'active' components, then the regimen was classified as having predicted success. If the regimen contained fewer than three 'active' components, it was classified as not having predicted success. Because the guidelines recommend zidovudine (AZT)–lamivudine (3TC)–efavirenz as the preferred first-line regimen, all resistance profiles of therapy-naïve patients were evaluated to determine the predicted success of this combination. For second-line regimens, we estimated the predicted success of the regimens recommended by the Colombian guidelines (Table 1) according to the failing regimen.[15]

The study was approved by the ethics committees of participating institutions. A written informed consent was required for patient enrollment.

Table 1
Second-line regimens recommended by the Colombian HIV/AIDS guidelines

Failing regimen	Recommended second-line regimen
AZT (or D4T) + 3TC + efavirenz (or nevirapine)	ABC + DDI + (fosamprenavir ± ritonavir or saquinavir–ritonavir or lopinavir–ritonavir or atazanavir ± ritonavir)
AZT (or D4T) + 3TC + PI	ABC + DDI + efavirenz (or nevirapine)
DDI + 3TC + efavirenz (or nevirapine)	AZT (or D4T) + ABC + (fosamprenavir ± ritonavir or saquinavir–ritonavir or lopinavir–ritonavir or atazanavir ± ritonavir)
DDI + 3TC + PI	AZT (or D4T) + ABC + efavirenz (or nevirapine)
DDI + D4T + PI	3TC + ABC + efavirenz (or nevirapine)
DDI + D4T + efavirenz (or nevirapine)	3TC + ABC + (fosamprenavir ± ritonavir or saquinavir–ritonavir or lopinavir–ritonavir or atazanavir ± ritonavir)
AZT – 3TC – ABC	3TC + (D4T or DDI) + efavirenz (or nevirapine) + lopinavir–ritonavir

AZT, zidovudine; D4T, stavudine; 3TC, lamivudine; ABC, abacavir; DDI, didanosine; PI, protease inhibitor.

3. Results

A total of 180 patients were included, 103 in the naïve group and 77 in the first failure group. Characteristics of both groups are presented in Table 2. The frequency of resistance for the naïve group was 5.8% (95% confidence interval (CI) 1.3–10.3%) and the most common mutations encountered were K103N (five patients, 4.9%) and M184 V (three patients, 2.9%). Mutations T215Y, P225H, and M46L were found once each (1.0%). Three naïve patients (2.9%)

had mutations to more than one class: two had mutations K103N and M184 V and one had mutations K103N, M184 V, P225H, and T215Y. Three naïve patients had single class mutations: two had an isolated K103N mutation and one had an isolated M46L mutation. The median time at risk in this group was 6 years. We found a statistically significant association between CD4 count below 200 cells/mm^3 and CDC category C with the presence of primary resistance (Table 3).

In the first failure group, the most common regimen was non-nucleoside reverse transcriptase inhibitor (NNRTI)-based, with AZT–3TC–efavirenz being the most common components (Table 4). Eighty-eight percent of the patients reported good tolerance and 70% were classified as adherent to therapy according to the SMAQ. Mutations to at least one class were found in 66 patients (85.7%, 95% CI 78–93%) overall. Of 44 patients failing an NNRTI-based regimen, 41 (93.2%) showed resistance mutations compared to 25 of 33 (76%) patients failing a non-NNRTI-based regimen ($p = 0.04$). Nucleoside reverse transcriptase inhibitor (NRTI) mutations were significantly more common in patients failing an NNRTI-based regimen ($p = 0.01$). Only one patient failing an NNRTI-based regimen was diagnosed with ≥2 thymidine analogue mutations (TAMs). The median age of patients with resistance mutations was higher than that of patients without resistance (40 years vs. 35 years, $p = 0.04$). Mutations were found in 10 of 11 patients (90.9%) reporting a history of medication supply failure. There was no association between generic components in a regimen and presence of resistance mutations. Table 5 describes in

Table 2
Demographic and clinical characteristics of enrolled patients

	Naïve group N = 103	First failure group N = 77
Categoric variables	n (%)	n (%)
Male gender	85 (82.5)	59 (75.3) [76.6]
History of STI	31 (30.1)	19 (25.3) [24.7]
Presumed mechanism of transmission[a]		
MSM	56 (54.9)	37 (48.7)
Heterosexual	46 (45.1)	39 (51.3)
Other	0 (0)	2 (2.3)[b] [2.6]
CDC category C	26 (25.2)	29 (37.7)
CD4 count <200 cells/mm^3	42 (40.8)	41 (54.6) [53.2]
Prevalence of resistance	6 (5.8)	66 (84) [85.7]
Numeric variables	Median (range)	Median (range)
Age	34 (18–59)	39 (23–68)
Number of sexual partners (last 5 years)	3 (0–250)	1 (0–20)
Number of STI last 5 years	0 (0–5)	0 (0–2)
CD4 count (cells/mm^3)	240 (7–837)	118 (4–573)
Viral load	57 858 (2384 to >750 000)	16 391 (1600 to >500 000)

STI, sexually transmitted infection; MSM, men who have sex with men; CDC, Centers for Disease Control and Prevention.
[a] Data missing for one patient in each group.
[b] Patients with more than one possible mechanism of transmission.

Table 3
Predictors of primary resistance

	Resistance N = 6	No resistance N = 97	p-Value[a]
Categoric variable	n (%)	n (%)	
CD4 count <200 cells/mm^3	5 (83)	37 (38)	0.04
CDC category C	5 (83)	21 (22)	0.004
Foreign travel	2 (33)	11 (11)	0.17
Numeric variable	Median (range)	Median (range)	
Number of sexual partners (5 years)[b]	5.5 (1–20)	2 (0–20)	0.13
Number of STI (5 years)[b]	0.5 (0–2)	0 (0–2)	0.17
CD4 count (cells/mm^3)	105 (48–282)	243 (7–837)	0.08

CDC, Centers for Disease Control and Prevention; STI, sexually transmitted infection.
[a] Fisher's exact test for categoric variables, Wilcoxon rank sum test for numeric variables.
[b] Excluding extreme values (>95th percentile).

Table 4
Antiretroviral regimen types and regimen components in patients with first regimen failure

Type of ARV regimen	n (%)
NNRTI	44 (57.1)
Boosted PI	20 (26.0)
Non-boosted PI	11 (14.3)
NRTI	2 (2.6)
Innovator medications only	29 (38.2)
Non-prequalified generic medication	25 (32.9)
Prequalified generic medication	22 (28.9)
Regimen components	n (%)
AZT–3TC–efavirenz	23 (30.0)
AZT–3TC–nevirapine	11 (14.3)
AZT–3TC–nelfinavir	8 (10.4)
AZT–3TC–LPV–RTV	7 (9.1)
D4T–3TC–efavirenz	4 (5.2)
D4T–3TC–LPV–RTV	4 (5.2)
AZT–3TC–IDV–RTV	3 (3.9)
ABC–3TC–efavirenz	2 (2.6)
AZT–3TC–ATZ–RTV	2 (2.6)
AZT–3TC–ABC	2 (2.6)
Other	11 (14.3)

ARV, antiretroviral; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor, NRTI, nucleoside reverse transcriptase inhibitor; AZT, zidovudine; 3TC, lamivudine; LPV, lopinavir; RTV, ritonavir; D4T, stavudine; IDV, indinavir; ABC, abacavir; ATZ, atazanavir.

Table 5
Resistance mutations in patients with first antiretroviral failure

Mutation	Overall (N = 77)	NNRTI failure (N = 44)	PI failure (N = 31)
NRTI	52 (67.5)	35 (79.5)	15 (48.4)[a]
NNRTI	48 (62.3)	37 (84.1)	10 (32.3)
PI	22 (28.6)	6 (13.6)	16 (51.6)
≥1 class	66 (85.7)	41 (93.2)	23 (74.2)
≥2 classes	49 (63.6)	33 (75)	15 (48.4)
≥3 classes	7 (9.1)	3 (6.8)	3 (9.7)
NRTI			
M184V	48 (62.3)	33 (75)	13 (41.9)
D67N	1 (1.3)	1 (2.3)	0 (0)
T69D	2 (2.6)	1 (2.3)	1 (3.2)
T69N	2 (2.6)	2 (4.6)	0 (0)
69ins	1 (1.3)	0 (0)	1 (3.2)
K70R	3 (3.9)	3 (6.8)	0 (0)
T215I	1 (1.3)	1 (2.3)	0 (0)
T215Y/F	6 (7.8)	4 (9.1)	2 (6.4)
K219E/Q	1 (1.3)	1 (2.3)	0 (0)
L74V	6 (7.8)	4 (9.1)	2 (6.4)
L74I	1 (1.3)	1 (2.3)	0 (0)
V75A	1 (1.3)	1 (2.3)	0 (0)
TAM	9 (11.7)	7 (15.9)	2 (6.4)
≥2 TAM	1 (1.3)	1 (2.3)	0 (0)
NNRTI			
K103N	37 (48.1)	29 (65.9)	7 (22.6)
G190A/S	9 (11.7)	6 (13.6)	3 (9.7)
Y181C	5 (6.5)	4 (9.1)	1 (3.2)
P225H	4 (5.2)	4 (9.1)	0 (0)
Y188H/L	4 (5.2)	4 (9.1)	0 (0)
K101E	3 (3.9)	1 (2.3)	2 (6.4)
V106A	1 (1.3)	1 (2.3)	0 (0)
V106M	1 (1.3)	1 (2.3)	0 (0)
V179D	1 (1.3)	1 (2.3)	0 (0)
V108I	1 (1.3)	0 (0)	1 (3.2)
A98G	1 (1.3)	0 (0)	1 (3.2)
PI			
D30N	6 (7.8)	0 (0)	6 (19.4)
G48V	1 (1.3)	0 (0)	1 (3.2)
I50L	1 (1.3)	0 (0)	1 (3.2)
M46I	3 (3.9)	0 (0)	3 (9.7)
V82A	4 (5.2)	1 (2.3)	3 (9.7)
I84V	2 (2.6)	1 (2.3)	1 (3.2)
I54V	2 (2.6)	0 (0)	2 (6.4)
L90M	9 (11.7)	2 (4.6)	7 (22.6)

Results are n (%).
NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TAM, thymidine analogue mutations.
[a] p = 0.01 when compared to patients failing NNRTI.

detail the resistance patterns encountered in patients with first regimen failure.

The predicted success rate of regimens recommended by the Colombian guidelines was 95% for naïve patients and 84% for experienced patients. Based on currently available ARVs in Colombia, genotyping could increase the predicted success rates to 100% in naïve individuals and 94% in those with first regimen failure.

4. Discussion

The frequency of HIV resistance in ARV-naïve individuals in Colombia is similar to figures from other areas in Latin America, which have reported primary resistance rates of 1.8–6.6%.[21–26] A worldwide surveillance program (Worldwide analysis of resistance transmission over time of chronically and acute infected HIV patients; WATCH) found that the rate of resistance (to any drug) among treatment-naïve individuals was 6.4% in Latin America.[10] These estimates are lower than those reported for many areas in North America.[23,27] We believe that our sample is representative of the general Colombian population of naïve patients because of our

method of sampling and because the clinical and demographic characteristics of our patients are very similar to those reported in HIV reports for the country of Colombia.[2,17] Our finding is against the hypothesis suggesting that high levels of resistance may explain the suboptimal virologic response estimated recently in a cohort of ARV therapy in Colombia.[9] Therefore, the low response rate observed in that study may be secondary to other factors, including the use of suboptimal regimens, limited expertise from HIV providers in Colombia, limited patient adherence, and erratic supply of medications. The Colombian government has since lead a multi-sector response to optimize HIV management. The recently approved Colombian guidelines for the management of HIV/AIDS[15] have addressed issues of provider expertise and regimen optimization and adherence, recommending a minimum level of expertise by HIV providers, the use of regimens with very high expected success rates, and the establishment of adherence programs in every HIV clinic in the country. Additionally, the government of Colombia has since instituted a nationwide programmatic management model that addresses, among many other things, the issue of consistent medication supply to patients.[28] Given these nationwide initiatives, a new study evaluating current rates of optimal virologic response in Colombia is desirable.

Acknowledging the need for larger confirmatory studies, we believe that our estimates may be used by policy makers to define research priorities and to cautiously guide the use of resistance testing in this middle-income country. Given the relatively low frequency of resistance in naïve individuals, systematic testing of HIV resistance before therapy initiation may not be justified yet, but further studies and surveillance should be continued because resistance rates are expected to rise as ARV use is expanded. Our analysis suggests that the majority of patients with primary resistance have advanced disease (category C of CDC classification or CD4 count below 200 cells/mm^3). Other studies done in Latin America have not found this association.[26] Our finding also appears to be inconsistent with previous reports that have shown that the frequency of resistance is higher in recently infected individuals.[29] However, it is likely that our study included predominantly chronically infected patients and therefore it cannot be compared to studies that have included patients with recent HIV infection. We believe that a possible explanation for our observation is that patients with advanced disease may have had more opportunities for re-infection with a resistant virus strain if they continued to engage in high-risk behaviors. In other words, duration of HIV infection may be a surrogate marker of time at risk for re-infection with potentially resistant strains. This is also suggested by the trend we found for the association between number of sexual partners and number of STIs and resistance in naïve patients. While clearly not definitive, our data support the use of genotype resistance testing for naïve patients with CD4 cell counts below 200 cells/mm^3 or for those who are classified as CDC category C who are going to initiate ARV therapy (Table 6). Alternatively, patients with these criteria may be considered candidates for boosted-PI rather than NNRTI-based therapy.

Table 6
Suggested expanded indications for genotype resistance testing for the country of Colombia

Antiretroviral-naïve individuals
Patients with CD4 count below 200 cells/mm^{3a}
Patients classified as CDC category C[a]
Patients with first regimen failure
PI-based failing regimen
Patients with advanced failures (beyond first regimen failure)[b]

CDC, Centers for Disease Control and Prevention; PI, protease inhibitor.
[a] Alternatively these patients may be considered candidates to initiate PI-based therapy.
[b] This indication is recommended in the current Colombian HIV guidelines.

The frequency of resistance in patients with first therapy failure was, as expected, high, and similar to that reported in other studies.[24,27] In general, the presence of multiple TAMs is of concern in patients failing first-line therapy in settings where second-line ARV options are limited.[27,30] This is particularly problematic in settings where viral load monitoring is done infrequently, potentially allowing the accumulation of resistance mutations when patients continue a non-suppressive regimen.[5] The frequency of TAM mutations in our study was 11.7%, but multiple TAMs were found in only 1.3% of individuals with first regimen failure. This suggests that virologic failures can be diagnosed relatively early with the recommended monitoring strategy of the current Colombian HIV guidelines (viral load testing at 6-month intervals for those patients with optimal viral load and within 2 months after detection of first suboptimal viral load). Because of the low frequency of multiple TAMs, second-line regimens recommended by the Colombian HIV guidelines have an acceptable predicted success rate, higher than that estimated in other resource-limited countries.[30] This difference may be partially explained by the fact that we excluded patients with virologic failure of more than 6 months duration. Interestingly, the majority of the guideline regimens classified as not having predicted success (57%) in our study resulted from the selection of an NNRTI with double NRTI as second-line regimen in patients failing PI-based regimens who had NNRTI resistance detected by genotype. Therefore, it seems prudent to consider genotype resistance testing in Colombian patients failing first ARV therapy when the failing regimen is PI-based (Table 6), awaiting larger studies and surveys. An important limitation of second-line regimens in Colombia is the unavailability of tenofovir in the Colombian markets. If tenofovir was available for use, the estimated predicted success rate of a second-line regimen selected with genotype could increase from 94% to 99%. Once tenofovir becomes available in Colombian markets, the HIV guidelines would need to be updated to introduce this medication as an alternative in patients with failing ARVs and possibly as a component of first-line regimens as well, depending on acquisition cost and other considerations.

Our study has several limitations. The relatively small overall sample and the few patients with resistance in the naïve group impact the precision of our estimates and introduce the possibility of random errors. Therefore, larger studies should be carried out to confirm our findings. We also believe that there may be a selection bias for the treatment experienced group given the high frequency of NNRTI resistance encountered in patients failing a PI-based regimen (32%), clearly beyond that expected based on our findings in the naïve group. This suggests that some patients considered eligible for the study because of presumptive first ARV failure were instead having more advanced failures and likely had been exposed in the past to regimens containing NNRTIs. This would overestimate the presence of resistance mutations and underestimate the predicted efficacy of the regimens proposed by the Colombian guidelines. In an attempt to clarify this, we contacted the primary providers who included patients as 'first therapy failure' for whom genotyping revealed resistance to NNRTI but were exposed to PI (therefore having no history of NNRTI exposure). All these providers stated that to the best of their knowledge the patients had not been previously exposed to antiretroviral medications. If a possible bias did not result from provider knowingly enrolling ineligible patients, it may have still resulted from patients providing inaccurate and misleading information to their treating physicians. We cannot determine whether the chain of trust for information accuracy was compromised at any level, and only further studies will allow clarification of this finding. Our estimates of predicted success rates are not based on longitudinal data but on a somewhat arbitrary definition that uses a single time-point genotypic resistance interpretation.[31] Some patients meeting our definition of predicted success might have not responded if followed longitudinally, and some patients not meeting our definition might have actually responded when followed over time. Our study did not discriminate between recent infections and chronic infections in the ARV-naïve sample. Given that the average time at risk reported by participants was prolonged (6 years), we believe that the majority of the patients included in our naïve group were in fact chronically infected. Finally, our study did not include phylogenetic HIV analysis. However, prior studies have indicated that the predominant HIV viruses circulating in Colombia belong to serotype B.[32,33]

In conclusion, the frequency of resistance before therapy initiation in Colombia is similar to estimates from other countries in Latin America. In naïve individuals, CD4 count and CDC category C may allow identification of most of the naïve patients who would benefit from resistance testing. Genotype resistance testing could favorably impact therapy modification in about 5% and 10% of naïve and experienced patients, respectively. These estimates may be used by local policy makers to define the role of resistance testing in Colombian patients infected with HIV.

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