Antiretroviral purchasing and prescription practices in Mexico: constraints, challenges and opportunities

Claire Chaumont, MSc, MPH,[(1)] Sergio Bautista-Arredondo, MSc,[(1)] Juan José Calva, MD, MSc,[(2)]
Roberto Isaac Bahena-González, MSc,[(1)] Gerda Hitz Sánchez-Juárez, L en Der,[(3)]
Arturo González de Araujo-Muriel, L en Der,[(4)] Carlos Magis-Rodríguez, MD, MPH, PhD,[(5)] Mauricio Hernández-Ávila, MD, PhD.[(3)]

Abstract

Objective. This study examines the antiretroviral (ARV) market characteristics for drugs procured and prescribed to Mexico's Social Protection System in Health beneficiaries between 2008 and 2013, and compares them with international data. **Materials and methods**. Procurement information from the National Center for the Prevention and the Control of HIV/AIDS was analyzed to estimate volumes and prices of key ARV. Annual costs were compared with data from the World Health Organization's Global Price Reporting Mechanism for similar countries. Finally, regimens reported in the ARV Drug Management, Logistics and Surveillance System database were reviewed to identify prescription trends and model ARV expenditures until 2018. **Results**. Results show that the first-line ARV market is concentrated among a small number of patented treatments, in which prescription is clinically adequate, but which prices are higher than those paid by similar countries. The current set of legal and structural options available to policy makers to bring prices down is extremely limited. **Conclusions**. Different negotiation policies were not successful to decrease ARV high prices in the public health market. The closed list approach had a good impact on prescription quality but was ineffective in reduc-

Resumen

Objetivo. Este estudio analiza el mercado de los medicamentos antirretrovirales (ARV) adquiridos y prescritos a los beneficiarios del Seguro Popular entre 2008 y 2013, en México, comparándolo con información internacional. **Material y métodos**. Se analiza información sobre la compra de medicamentos por parte del Centro para la Prevención y el Control del VIH y el Sida (Censida) para estimar precios y volúmenes de compra de los principales ARV. Los costos anuales de tratamiento estimados fueron comparados con información del Global Price Reporting Mechanism (GPRM) de la Organización Mundial de la Salud, para países similares. Finalmente se revisaron los esquemas reportados en el Sistema de Administración, Logística y Vigilancia de ARV para identificar tendencias y proyectar el gasto en ARV hasta 2018. **Resultados**. El mercado mexicano de ARV está concentrado en pocos esquemas de primera línea y, aunque la prescripción es clínicamente adecuada, los precios son más altos que en otros países similares. El conjunto actual de opciones legales y estructurales disponibles para los formuladores de políticas para reducir los precios es muy limitado. **Conclusiones**. Las políticas de negociación han sido poco exitosas para disminuir los precios de los ARV en México. La Coordinating Commis-

(1) Centro de Investigación en Sistemas de Salud, Instituto Nacional de Salud Pública. Cuernavaca, México.
(2) Departamento de Enfermedades Infecciosas, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán. Distrito Federal, México.
(3) Instituto Nacional de Salud Pública. Cuernavaca, México.
(4) COFAPI México. México.
(5) Centro Nacional para la Prevención y Control del VIH y el Sida (Censida). Distrito Federal, México.

ing prices. The Coordinating Commission for Negotiating the Price of Medicines and other Health Supplies also failed to obtain adequate prices. To maximize purchase efficiency, policy makers should focus on finding long-term legal and political safeguards to counter the high prices imposed by pharmaceutical companies.

Key words: HIV; anti-retroviral agents; pharmaceutical policy; Mexico; Latin America

sion for Negotiating the Price of Medicines and other Health Supplies y la integración de las guías de tratamiento han tenido impacto significativo en la calidad de la prescripción, pero moderado en la reducción de precios. Por ello es necesario buscar garantías jurídicas y políticas a largo plazo para hacer frente a los altos precios de los ARV.

Palabras clave: VIH; antirretrovirales; políticafarmacéutica; México; América Latina

HIV/AIDS and antiretroviral drugs in Mexico

Since the first case of AIDS was diagnosed in Mexico in 1983, national authorities have developed and strengthened an organized response to address this threat. Antiretroviral drugs (ARV) universal coverage in Mexico was achieved in a staggered fashion: it was first introduced in 1997 for formal employees covered by public social security institutions and subsequently in 2003 for the rest of the population covered by the System for Social Protection in Health (SPSS, in Spanish), a comprehensive insurance covering a basic package of services, known as *Seguro Popular*. Between 2003 and 2012, coverage rose from 64 to 85% of the estimated total number of persons with HIV, including those still unaware of their serological status.[1]

The Mexican health system includes various state-controlled social security institutions that provide integral healthcare and social services to workers in the formal sector, including the Mexican Social Security Institute (IMSS), the Institute for Social Security and Services for State Workers (ISSSTE), specific funds for the army, the police and the national petroleum agency. In addition, the Ministry of Health and State Health Secretariats (SSa/SeSa) manage clinics and hospitals, accessed by the uninsured population as well as, since 2003, SPSS beneficiaries.[2,3]

In 2012, 71 599 individuals receive ARV through public channels, out of which almost 60% receive it through the SPSS and 30% through the IMSS.[1] Others patients receive it through the remaining public institutions. Although the country's HIV/AIDS response is coordinated at national level, in effect each public health institution finances and operates its own separate care program with its own ARV supply chain. As part of the SPSS, ARV are financed by the Fund for the Protection Against Catastrophic Expenditures (FPGC), which covers high complexity interventions for SPSS beneficiaries while their procurement, purchase and distribution are managed by the N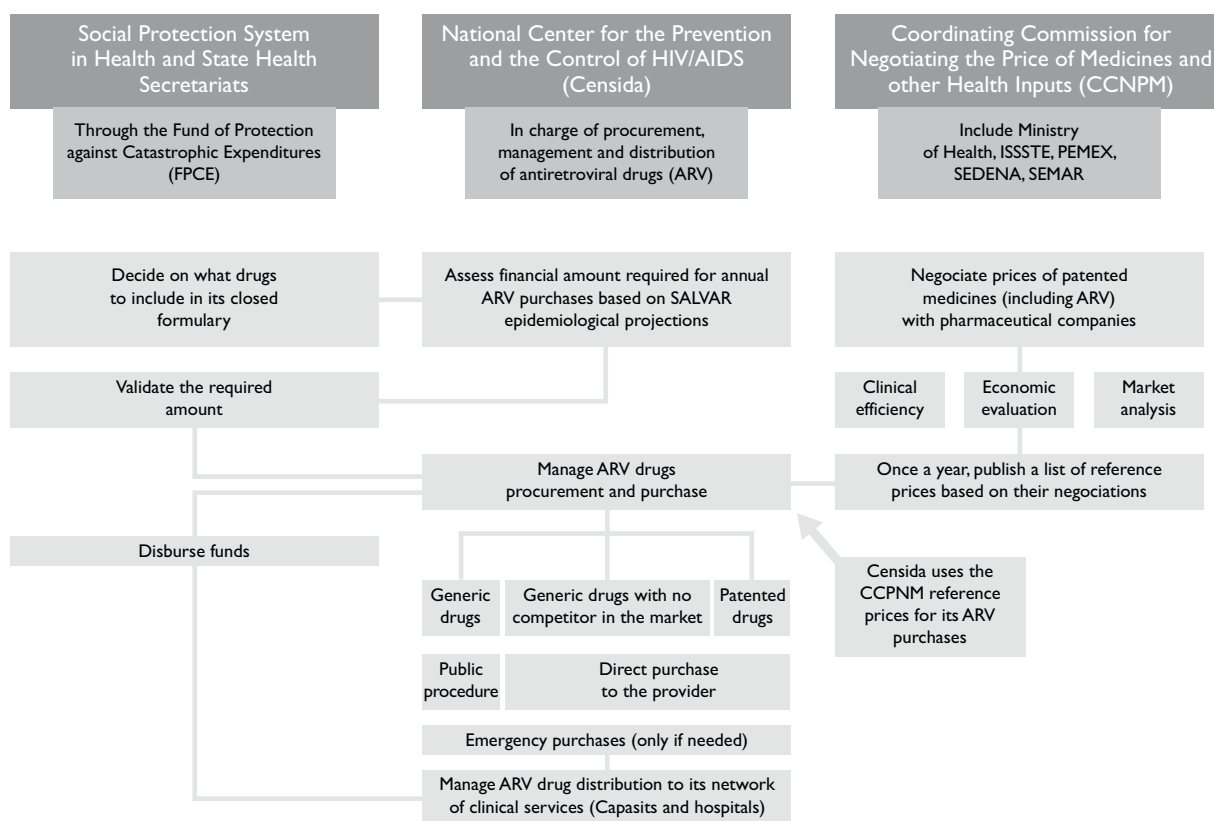ational Center for the Prevention and the Control of HIV/AIDS (Censida in Spanish), based on patients' prescription history (figure 1). SSa/SeSa hospitals and stand-alone HIV/STI clinics, known as Capasits, receive ARV from the national level, but can't purchase drugs themselves. Despite these independent financing, procurement and distribution processes, clinical guidelines regarding ARV dispensation for first, second and third line treatments are nationally defined and followed by clinicians across all public institutions.

ARV spending, the Coordinating Commision for Negotiating the Price of Medicines and other Health Supplies (CCNPM) and the closed formulary approach

Today, ARV drugs still account for a large part of treatment costs of HIV patients.[4,5] In the Latin American and Caribbean region, the Pan-American Health Organization indicates that in 2009-2010, spending on ARV drugs accounts on average for roughly 75% of the care and treatment budget and 46% of the total HIV budget of the average country of the region.[6]

A major cost driver is often the relatively high prices of ARV paid by public authorities. At global level, dramatic price reductions have been observed in recent years.[7,8] But middle-income countries have not benefited from this trend as much as their lower-income countries counterparts, and Mexico is no exception to this.[9-11] In 2012, Mexico's annual cost of regimen per patient was estimated at five times the median cost (352 US dollars or USD) of 17 LAC countries studied —a difference only partly explained by the different regimens chosen by countries for first, second and third line of treatment.[4] In addition, before 2008, prices paid by the Mexican government were on average eight times higher than prices paid by other upper middle income countries for similar drugs.[12]

In order to address this price gap, in 2008, the Mexican government created the CCNPM. The main duty of this Committee, which groups the most important

Social Protection System in Health and State Health Secretariats	National Center for the Prevention and the Control of HIV/AIDS (Censida)	Coordinating Commission for Negotiating the Price of Medicines and other Health Inputs (CCNPM)
Through the Fund of Protection against Catastrophic Expenditures (FPCE)	In charge of procurement, management and distribution of antiretroviral drugs (ARV)	Include Ministry of Health, ISSSTE, PEMEX, SEDENA, SEMAR

Decide on what drugs to include in its closed formulary

Assess financial amount required for annual ARV purchases based on SALVAR epidemiological projections

Negotiate prices of patented medicines (including ARV) with pharmaceutical companies

Validate the required amount

Clinical efficiency | Economic evaluation | Market analysis

Manage ARV drugs procurement and purchase

Once a year, publish a list of reference prices based on their negociations

Disburse funds

Generic drugs | Generic drugs with no competitor in the market | Patented drugs

Censida uses the CCPNM reference prices for its ARV purchases

Public procedure | Direct purchase to the provider

Emergency purchases (only if needed)

Manage ARV drug distribution to its network of clinical services (Capasits and hospitals)

SALVAR: Management, Logistics and Surveillance System
ISSSTE: Institute for Social Security and Services for State Workers
PEMEX: National Petroleum Agency
SEDENA: Army
SEMAR: Navy

FIGURE 1. ARV FUNDING, PROCUREMENT AND PURCHASING MECHANISMS AS PART OF THE SYSTEM FOR SOCIAL PROTECTION IN HEALTH IN MEXICO

public actors at national level, was to carry out price negotiations with pharmaceutical companies for various patented products, including antiretroviral drugs. Initially substantial reductions were obtained: annual direct savings obtained across all public expenditures on patented medicines since 2008 was estimated to be USD 355 million.[13] However, more recently, concerns have been raised that the CCNPM's work might not be effective to obtain further discounts in ARV prices.[10,11]

In addition, since 2009, Censida can only purchase drugs included in a nationally approved closed formulary, except in enforcement or appeal cases or with specific authorizations. Drugs included in this list are selected by a national committee, based on clinical guidelines.[14] This approach is expected to improve prescription practices, but also to contain costs.[15]

Current and future challenges linked to HIV/AIDS in Mexico

Furthermore, several trends linked to how ARV drugs are administered and purchased can have a profound impact on ARV expenditures.

First, the differential pricing structure introduced in recent years by pharmaceutical companies to provide ARV medicines to low-income countries at prices systematically lower than those in high-income countries, led to the disappearance of standardized discount programs for middle-income countries such as Mexico. It creates an arbitrary division between countries and/or markets, as no international norm exists regarding what criteria should be used to determine which country should obtain lower prices.[16] For example, until 2013,

Bristol-Myers (BMS) included all sub-Saharan countries except Southern African countries in its category 1, leading these latter countries to pay more for BMS second-line drug Atazanavir than other countries with lower HIV prevalence and sometimes, higher income.[5,16,17]

Second, the implementation of the 2014 Mexican clinical guidelines, which build upon and exceed the 2013 World Health Organization's (WHO) clinical guidelines by expanding eligibility for ARV to all persons diagnosed with HIV regardless of CD4 threshold or clinical symptoms will mean that more people living with HIV (PLHIV) will be in need of antiretroviral therapy (ART) in coming years.[14,18] WHO's new guidelines also strongly recommend the use of Fixed Drugs Combinations (FDG) for their numerous advantages in terms of prescription practices, patient adherence and drug resistance. These newer products are usually more expensive and widely patented, leading to more pressures on national budgets for HIV/AIDS.[19]

These changes place a threat on a system already stretched to the limit. Projections show that the sustainability of ARV provision for both IMSS and the SPSS could be problematic in coming years.[20] In 2011, spending related to HIV/AIDS accounted for 32.4% of the FPGC's total spending.[21]

The objective of this paper is to estimate the budget allocated to ARV drugs in Mexico from 2008 to 2013 and to contextualize it within the market characteristics of ARV drugs in Mexico. Six years after the creation of the CCNPM, it is essential to understand the market characteristics of ARV purchases in Mexico in order to design effective policies to contain further budget increase, respond to the needs of the Mexican population, and maintain universal access to ARV treatment for persons with HIV.

Material and methods

We developed a multi-layered methodology to approach this research question. First, procurement and price information provided by Censida was used to analyze trends in volumes and prices of main patented and generic drugs purchased for the SPSS. We reviewed the list of prices for each type of drugs negotiated by the CCNPM between 2007 and 2012 as well as the description of all ARV transactions undertaken by Censida between April 2010 and March 2012 (which corresponds to the government's fiscal years). In order to compare prices between different presentations and dosages, we calculated the average annual cost per year of treatment for each type of drug, using most recent WHO guidelines.[13] All figures were converted to US dollars using the average exchange rate USD/MXN for

the year of analysis and deflated to 2010 US dollars. It is worth noting that the reference prices negotiated by the CCNPM apply to all public purchases of patented ARV.

Second, we performed an analysis of the antiretroviral regimens reported in the ARV Drug Management, Logistics and Surveillance System (SALVAR) database,[22] a national database used to monitor ARV prescriptions among SPSS patients, to investigate whether ARV expenditures could be explained by poor clinical prescription practices. We reviewed the last prescription registered per patient, per year, between 2008 and 2013 to identify prescription trends. In addition, we analyzed prescription patterns at one specific point in time (September 30, 2013) to determine the proportion of prescriptions that were consistent with current clinical guidelines.

Third, we compared annual costs of ARV for Mexico with comparable data from countries with similar income levels between 2007 and 2013. For this purpose, we used information from the WHO's Global Price Reporting Mechanism (GPRM), which contains information on procurement transactions of drugs and diagnostic tests for HIV, TB and Malaria, provided on a voluntary basis by international agencies, WHO regional offices and member countries. This analysis was performed for the eight most important patented drugs. To prevent overrepresentation of specific countries, we calculated an average procurement cost per year per country, weighted by transaction volumes. We calculated then an average procurement cost per World Bank income group.[23] Mexico was compared with upper-middle income countries (GNI per capita between USD 4 125 and 12 746).[23] Prices paid by high-income and low-middle income countries are also reported for information purposes. All results were converted to 2010 US dollars. Finally, it is important to note that transactions are reported in the GPRM database under different international commerce terms (Incoterms) meaning agreements in terms of transport, delivery, freight and insurance may vary, while in Mexico, prices negotiated by the CCNPM usually include the complete handling and distribution of the product. Estimations show these additional services usually represent between 3 to 15% of the *Ex Works* price —the initial price without any additional service.[24]

Finally, we modeled the evolution of ARV expenditure from 2008 to 2013, based on data from June 2008 to June 2013, from both the SALVAR database, and its quarterly bulletins.[25] First, we projected the number of patients until June 2018, under two different scenarios: scenario 1 assumes that between 2013 and 2018, the number of patients will increase at a similar rate than between 2008 and 2013 (4%); scenario 2 assumes the rate

would slowly decrease to reach 0% by 2018 —simulating that enrollment will slow down in future years as coverage reaches its maximum. Then, based on historical average annual ARV costs per patient registered in SAL-VAR between 2008 and 2013 (converted to US Dollars using average exchange rates for each given year), we projected future average annual ARV costs per patient until 2018. Results were presented in nominal terms. Combining our projections in terms of total number of patients and average costs per patient, we finally projected the total annual costs to be borne by the SPSS until 2018 to purchase ARV drugs.

Authorization to access data was granted by relevant authorities. No ethical approval was asked for, as the project only required secondary sources' analysis, and did not involve any human beings.

Results

Current and future ARV expenditures

Between 2010 and 2012, the FPGC, through Censida, spent a total of USD 400.39 million for the purchase of close to 3 million packages of antiretroviral medicines. ARV drugs purchased included 17 patented and 18 generic drugs, out of which seven were purchased through a competitive process and 11 were directly because of lack of multiple offerings in the market (table I). Patented drugs represented 83% of total expenditures for the period, and only eight patented drugs represented 78%. Price reductions obtained by the CCNPM between 2008 and 2013 were minimum, often similar or lower than the price reduction obtained in the sole year 2008 (table I).

Table I

ARV DRUGS PROCURED BY CENSIDA IN MEXICO: TOTAL EXPENDITURES, VOLUMES AND ESTIMATED ANNUAL COSTS OF TREATMENT. 2010-2012*

Drug name	Expenditures (in millions - 2010 USD) ‡					Volume (number of packages - in thousands)		
	2010 $	2011 $	2012 $	Total $	%	2012	Total	%
Emtricitabine+Tenofovir	41.37	21.54	64.51	127.42	32	431.4	789.0	27
Lopinavir+Ritonavir	21.75	5.34	32.66	59.74	15	175.8	288.3	10
Atazanavir	12.63	4.74	22.93	40.30	10	112.6	189.3	6
Efavirenz+Emtricitabine+Tenofovir			36.20	36.20	9	194.0	194.0	7
Efavirenz	6.91	9.14	1.56	17.61	4	49.3	482.5	16
Ritonavir	4.70	5.14	3.82	13.66	3	26.9	87.0	3
Raltegravir	2.72	3.23	3.45	9.39	2	7.8	19.1	1
Tenofovir	2.92	1.08	5.57	9.58	2	39.5	65.0	2
Others - Patented drugs	4.59	3.68	8.34	16.60	4	46.2	107.1	4
Others - Generic drugs	26.90	14.97	28.00	69.88	17	309.6	722.8	25
Total	124.50	68.85	207.05	400.39		$1 393.08	$2 944.14	

Drug name	Estimated cost of treatment per year (2010 USD)§							Variation (2007-2008) %	Variation (since 2008 or most recent year) %	Variation (Total period) %
	2007 $	2008 $	2009 $	2010 $	2011 $	2012 $	2013 $			
Atazanavir	4 282	3 257	2 586	2 731	2 822	2 481	2 629	-24	-19	-39
Efavirenz	924	519	412	435	464	386	402	-44	-23	-57
Efavirenz+Emtricitabine+Tenofovir						2 272	2 345		-3	-3
Emtricitabine+Tenofovir	3 565	2 613	2 075	2 081	2 271	1 820	2 014	-27	-23	-44
Lopinavir+Ritonavir	5 571	4 773	3 368	3 173	2 927	2 447	2 520	-14	-47	-55
Raltegravir		7 445	5 911	6 305	6 451	5 412	5 368		-28	-28
Ritonavir	1 015	957	714	719	704	618	648	-6	-32	-36
Tenofovir	2 376	2 263	1 796	1 898	1 939	1 719	1 785	-5	-21	-25

* Adjusted in USD 2010

‡ Expenditures are presented for 2010 to 2012

§ Annual costs of treatment are calculated using annual negotiated prices from the CCNPM between 2007 and 2013 and recommendations from the most recent WHO clinical guidelines

ARV prescriptions

Prescription trends between 2008 and 2013 showed a clear tendency towards simplification. By September 30, 2013, the SALVAR database registers several different antiretroviral combinations prescribed to 53 357 registered patients, including first-second and third line treatments, salvage and switched/simplified regimens. Ninety percent of the total number of registered patients (48 282) received one of 22 main regimens (table II).

Of 48 282 patients, 35.5% were prescribed a regimen comprising a protease inhibitor. In 68% of all patients, a regimen comprising a single tablet of a 2-drug co-formulated NRTI: Tenofovir/Emtricitabine (Truvada plus a third component) or a single tablet of a 3-drug combination (2-NRTI plus one NNRTI): Tenofovir/Emtricitabine/Efavirenz (Atripla) and in 18.4%, a regimen

comprising a single tablet of coformulated Lopinavir/Ritonavir (Kaletra), were prescribed.

Among the 22 antiretroviral-combinations mostly prescribed in 2013, the following issues are worth highlighting:

First, all regimens could be labeled as highly active antiretroviral therapy. All, except one, were a 3-drug combination composed of a backbone of two nucleos(t)ide analogues reverse transcriptase inhibitors (NRTI) plus a third component (a non-nucleoside reverse transcriptase inhibitor or a Ritonavir-boosted protease inhibitor). The exceptional regimen was composed by three extended-activity antiretrovirals (Ritonavir-boosted Darunavir plus Etravirine plus Raltegravir) commonly prescribed as a deep salvage regimen for heavily treated patients. Among patients infected with drug-susceptible virus and with optimal compliance,

Table II
DRUGS PRESCRIBED IN THE SPSS SCHEME, REPORTED IN THE SALVAR DATABASE IN MEXICO (2008-2013)

Main drug combinations prescribed to ART patients in the public SPSS scheme in Mexico	December 2008	December 2009	December 2010	December 2011	December 2012	September 2013
[Efavirenz 600 mg / Emtricitabine 200 mg / Tenofovir 300 mg]	10	15	16	59	5 827	22 595
[Emtricitabine / Tenofovir 300/200 mg] + [Lopinavir 200 mg / Ritonavir 50 mg]	1 555	2 344	2 982	3 557	3 957	4 670
Atazanavir 300 mg + Ritonavir 100 mg (bottle) + [Emtricitabine / Tenofovir 300/200 mg]	1 005	1 685	2 463	3 114	3 651	4 561
Efavirenz 600 mg + [Abacavir / Lamivudine 600 mg/300 mg]	343	705	1 021	1 543	2 177	3 334
Nevirapine 200 mg + [Emtricitabine / Tenofovir 300/200 mg]	783	1 065	1 486	2 049	2 245	2 362
Efavirenz 600 mg + [Lamivudine / Zidovudine 150 mg/300 mg]	4 240	3 879	3 394	3 141	3 034	1 405
Ritonavir 100 mg (bottle) + Saquinavir 500 mg + [Emtricitabine / Tenofovir 300/200 mg]	591	961	1 299	1 396	1 383	1 389
[Lamivudine / Zidovudine 150 mg/300mg] + [Lopinavir 200 mg / Ritonavir 50mg]	945	1 025	1 100	1 407	1 783	1 294
[Abacavir / Lamivudine 600 mg/300 mg] + [Lopinavir 200 mg / Ritonavir 50 mg]	136	262	397	542	737	1 192
Atazanavir 300 mg + Ritonavir 100 mg (bottle) + [Abacavir / Lamivudine 600 mg/300 mg]	95	210	389	580	797	1 177
Nevirapine 200 mg + [Abacavir / Lamivudine 600 mg/300 mg]	62	121	183	334	461	604
Nevirapine 200 mg + [Lamivudine / Zidovudine 150 mg/300 mg]	1 363	1 323	1 149	1 147	1 097	583
Tenofovir 300 mg + Zidovudine 250 mg+ [Lopinavir 200 mg / Ritonavir 50 mg]	11	17	43	80	156	484
Ritonavir 100 mg (bottle) + Saquinavir 500 mg + [Abacavir / Lamivudine 600 mg/300 mg]	69	153	257	339	396	427
Abacavir 300 mg + Didanosine 250 mg + [Lopinavir 200 mg / Ritonavir 50 mg]	19	23	27	29	27	356
Ritonavir 100 mg (bottle) + Saquinavir 500 mg + [Lamivudine / Zidovudine 150 mg/300 mg]	473	506	546	523	490	356
Abacavir 300 mg + Tenofovir 300 mg + [Lopinavir 200 mg / Ritonavir 50 mg]	111	136	169	171	217	352
Efavirenz 600 mg + [Emtricitabine / Tenofovir 300/200 mg]	5 061	7 758	10 571	13 633	12 354	248
Atazanavir 300 mg + Ritonavir 100 mg (bottle) + [Lamivudine / Zidovudine 150 mg/300 mg]	340	337	334	338	340	238
[Lamivudine / Zidovudine 150 mg/300 mg]+ [Lopinavir Ritonavir Sol. 8.0 g/2.0g]	3	5	12	19	24	236
Tenofovir 300 mg +Zidovudine 250 mg + Atazanavir 300 mg + Ritonavir 100 mg	3	12	31	51	91	220
Darunavir+Ritonavir+Raltegrarivr+Etravirine	0	2	13	75	92	199
Other drug combinations	10 256	9 924	8 949	8 265	7 989	5 075
Total patients - All drug combinations	27 474	32 468	37 043	42 544	49 434	53 357

high rates of maximal viral suppression and immune reconstitution could be expected with such drug combinations.

Second, 13 regimens —representing 90.5% of patients receiving one of these 22 combinations— were drug combinations commonly recommended as first-line therapy (for treatment naïve patients) according to 2012 national guidelines.[26] Four regimens were drug combinations commonly recommended as salvage therapy after the loss of virologic control (3% of patients). One regimen was a drug combination commonly prescribed as deep salvage therapy in heavily antiretroviral-experienced patients (0.5 % of patients). Four regimens were drug combinations less satisfactory than the preferred or alternative first-line antiretroviral regimens (6% of patients).

Third, no antiretroviral components (or drug combination) inadequate as initial therapy (because of its potential significant toxicity, significant inferior virologic efficacy, antagonism or limited clinical trial experience) were included.

In summary, in 2013, the vast majority of regimens prescribed to SPSS patients were made in accordance with national guidelines.

Comparison between Mexican and international procurement prices

The international comparison showed that between 2007 and 2013, annual costs of treatment resulting from the CCNPM negotiated prices were on average higher than those paid by similar upper-middle income countries. Prices were also higher than those paid by lower-middle income countries. Finally, in some cases, CCNPM prices were also higher than those negotiated by high-income countries (table III).

The generic version of all the drugs studied was bought at significant lower prices by countries with similar income, leading to lower annual costs of treatment. For countries acquiring original versions of the patented drugs, the price paid by Mexico was usually higher than prices negotiated by upper-middle income countries, except Efavirenz and Atazanavir, which were purchased at a lower value. Although differences in Incoterms may explain part of this difference, it is unlikely it explains all of it, as prices paid by Mexico were sometimes up to five times higher than prices paid by similar countries.

Financial projections

Projections show that by June 2018 the number of SPSS patients under treatment could reach between 72 149

and 87 972 patients (scenarios 1 and 2) while, based on historical rate, the cost of ART per patient should reach USD 2 725 by 2018 (figure 2). Therefore, total annual ARV expenditures would increase or stabilize between USD 197 and 240 million by 2018 (scenarios 1 and 2). In other words, the decrease in ARV prices will not be sufficient to compensate the increase of new patients (figure 3).

Discussion

Summary and significance of findings

The creation of the CCNPM in 2008 triggered hopes that it would permit better price negotiations and a more efficient control of ARV purchases. Five years on, this study found evidence that its achievements, although significant at the beginning, were not sufficient to curb ARV spending in the country. Price reductions obtained after 2008 have been minimal and therefore, only had a marginal effect on spending control, as they couldn't compensate for the number of patients in need of treatment, which more than doubled during the same period. Simple projections suggest that annual ARV spending will continue to rise, or merely stabilize by 2018 if no additional measure is taken.

In addition, the introduction of a drugs' formulary, which aligned Censida's procurement practices with national ART guidelines, has remained ineffective to negotiate price reductions with pharmaceutical companies after its initial introduction in 2009. As shown by Bautista-Arredondo and colleagues, between 1997 and 2001, ARV prescription practices across the public sector were largely inconsistent with clinical guidelines.[27] To the contrary, our study shows that by 2013, clinical prescriptions are mostly aligned with national guidelines. However, this simplification in prescription practices has not led to a reduction in ARV prices.

As a consequence, Mexico's ARV market is moving towards a simpler, more concentrated mix of products, which public institutions continue to pay at prices significantly higher than countries with similar incomes. These market characteristics mean Mexico has only a narrow set of options available to policy makers when it comes to controlling ARV purchases: initiatives to further improve prescription practices or to increase competition for the purchase of generic drugs are both likely to have a marginal impact on spending control.

However, the set of legal and structural options available to policy makers to bring patented drugs prices down is extremely limited. First, Mexico is a signatory of The Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), which regulates intellectual property protection and requires all

Table III

COMPARISON OF AVERAGE ANNUAL TREATMENT COST PER DRUG BETWEEN MEXICO AND HIGH, UPPER-MIDDLE AND LOWER-MIDDLE INCOME COUNTRIES (GPRM DATABASE 2007 TO 2013 – ADJUSTED IN USD 2010)*

Name of drug	Originator version								Generic version							
	2007	2008	2009	2010	2011	2012	2013	Total Period	2007	2008	2009	2010	2011	2012	2013	Total Period
Atazanavir																
Mexico	4 282	3 257	2 586	2 731	2 822	2 481	2 629	2 970								
HIC			2 320 (1)					2 320 (1)					248 (3)			248 (3)
UMIC	3 526 (4)	5 061 (13)	5 649 (13)	2 711 (47)	518 (104)			3 987 (181)		5 299 (1)				269 (8)	228 (1)	767 (16)
LMIC	342 (1)	2 774 (6)				352 (1)		1 803 (8)				307 (4)	255 (23)	272 (6)	238 (2)	265 (35)
Efavirenz																
Mexico	924	519	412	435	464	386	402	506								
HIC	242 (6)	234 (5)	237 (3)	370 (2)				271 (16)	209 (15)	173 (19)	122 (20)	69 (17)	59 (10)	43 (2)		132 (83)
UMIC	986 (161)	496 (293)	360 (63)	280 (44)	441 (32)			580 (593)	249 (62)	187 (227)	100 (120)	76 (242)	66 (287)	88 (82)	141 (14)	127 (1 034)
LMIC	542 (51)	551 (17)	397 (8)	313 (4)	484 (1)			505 (81)	240 (197)	179 (245)	115 (258)	71 (326)	65 (246)	59 (186)	54 (13)	117 (1 471)
Efavirenz+Emtricitabine+Tenofovir																
Mexico						2 272	2 345	2 308								
HIC			611 (1)		868 (15)			740 (16)					191 (1)	156 (1)		174 (2)
UMIC	733 (1)	636 (9)	619 (16)	636 (3)	595 (1)			631 (30)				242 (3)	226 (6)	186 (14)	143 (5)	199 (28)
LMIC										725 (3)	243 (6)	245 (34)	220 (44)	175 (58)	155 (7)	231 (152)
Emtricitabine+Tenofovir																
Mexico	3 565	2 613	2 075	2 081	2 271	1 820	2 014	2 348								152
HIC													112 (1)	72 (1)		92 (2)
UMIC									510 (12)	456 (80)	262 (16)	152 (85)	191 (134)	90 (21)	225 (3)	202 (351)
LMIC									336 (21)	337 (63)	233 (51)	165 (86)	122 (55)	94 (63)	75 (10)	168 (349)
Lopinavir+Ritonavir																
Mexico	5 571	4 773	3 368	3 116	2 870	2 389	2 515	3 514								
HIC	1 222 (7)	1 404 (8)	1 442 (12)		427 (2)			1 260 (29)	950 (3)	1 388 (1)	573 (3)	426 (6)	405 (4)	266 (1)		599 (18)
UMIC	1 394 (85)	1 286 (203)	1 316 (87)	956 (85)	454 (31)	383 (104)	277 (1)	1 103 (596)	1 860 (3)	1 169 (11)	663 (27)	473 (48)	420 (38)	353 (23)		577 (150)
LMIC	980 (113)	831 (107)	786 (92)	627 (77)	547 (68)	448 (18)	254 (2)	736 (477)	903 (14)	652 (37)	521 (48)	442 (104)	409 (79)	333 (63)	272 (13)	461 (358)
Ritonavir																
Mexico	1 015	957	714	719	704	618	648	768								
HIC									258 (3)	190 (2)	371 (3)		180 (5)	206 (8)		216 (21)
UMIC									67 (2)	195 (4)	105 (1)	181 (3)	199 (11)	169 (6)		169 (27)
LMIC																
Tenofovir																
Mexico	2 376	2 263	1 796	1 898	1 939	1 719	1 785	1 907								
HIC	254 (1)	247 (5)						226 (6)	214 (3)	201 (2)	150 (4)	96 (4)	82 (1)	69 (1)		147 (15)
UMIC	292 (9)	375 (14)	362 (32)	237 (13)	317 (2)			335 (70)	237 (32)	225 (122)	169 (38)	115 (147)	87 (142)	63 (21)	118 (5)	134 (507)
LMIC	268 (40)	307 (10)	300 (18)	177 (5)				275 (73)	210 (29)	181 (69)	135 (58)	93 (97)	82 (77)	60 (33)	53 (6)	113 (369)

* Numbers in () correspond to the number of observations for each year. Raltegavir is not presented here due to the lack of information in the database

HIC: High-income countries, according to World Bank classification
UMIC: Upper middle-income countries, according to World Bank classification
LMIC: Low middle-income countries, according to World Bank classification
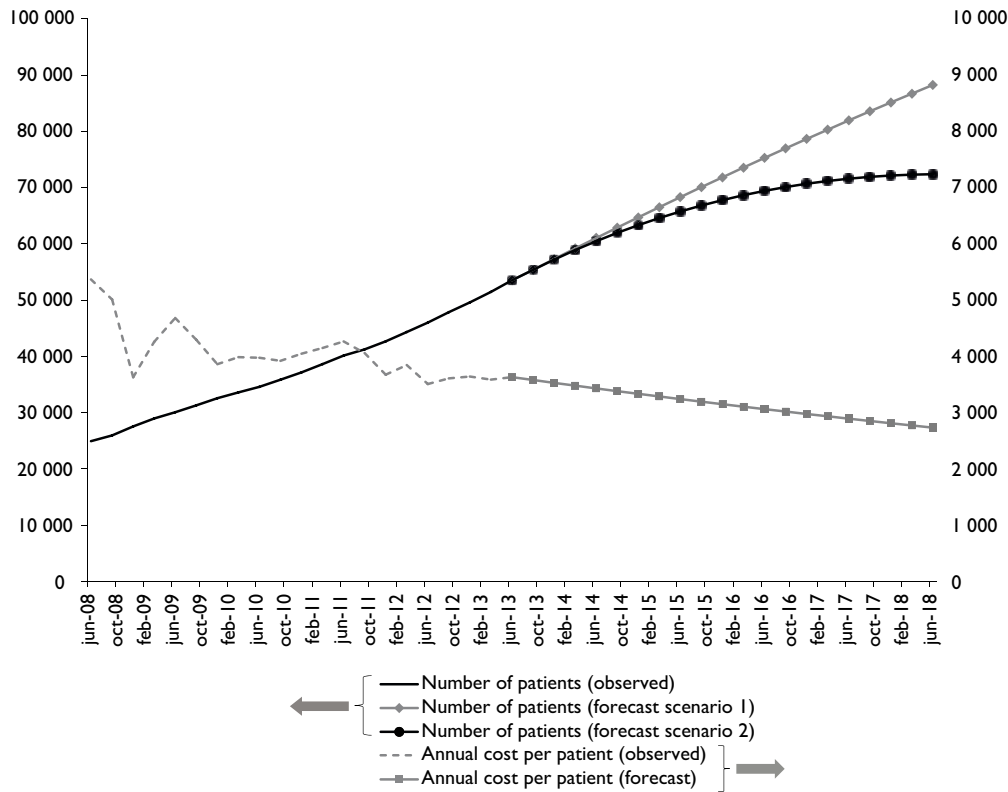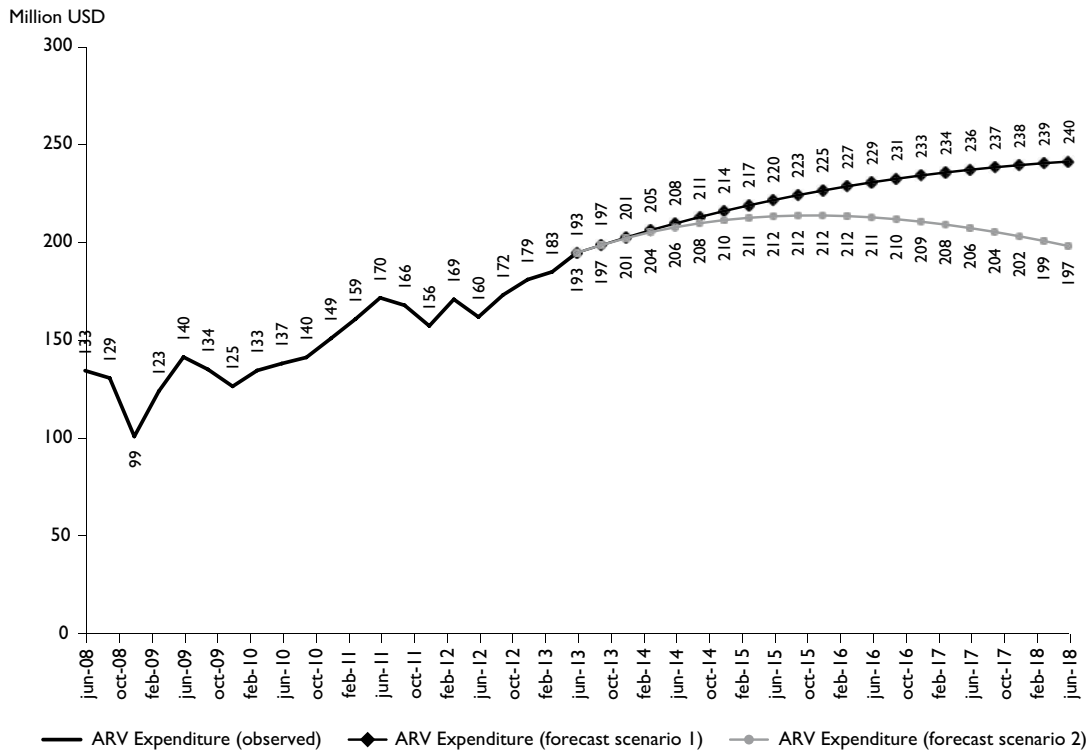
Source: reference 25

FIGURE 2. EVOLUTION OF TOTAL ANNUAL ART COSTS AND NUMBER OF PATIENTS ON TREATMENT BETWEEN 2008 AND 2018 IN MEXICO (NOMINAL USD)

signatories to introduce 20-year patents in all fields of technology.[28] The TRIPS provides limited flexibilities to bend intellectual property rules in specific public health cases, but Mexico's compliance with the North American Free Trade Agreement (NAFTA) limits its ability to use them. In particular, this means that Mexico can't use the sole argument of excessive prices to make use of obligatory licenses to override patent monopoly and allow generic manufacturers to produce and market affordable versions of patented drugs.

In addition, internal Mexican laws related to intellectual property as well as the registration and procurement of medicines limit widely its possibilities to bring ARV prices down. For example, Mexican law does not allow drug importation from providers outside Mexico except from the patent owner or authorized licensee; meaning public institutions can't import patented drugs from countries acquiring them at cheaper prices. For the same reason, Mexico can't import patented drugs through the Pan-American Health Organization

(PAHO)'s Strategic Fund, which helps negotiate low ARV prices for its members States. Current regulations regarding clinical data protection also prevent generic companies to access clinical trial results for five years, meaning any company willing to enter the market would have to perform new trials to prove drug efficacy during this period. This mechanism favors producers of patented drugs, as it usually limits market competition even when patents have already expired. In other words, the current set of international and national laws and treaties applicable to Mexico impedes its policy makers to use existing legal mechanisms to bring ARV prices down.

Fortunately, indirect changes to the legal and structural regulations can also influence future ARV price negotiations. For example, mechanisms guiding intellectual property implementation and violations could be strengthened to prevent abuses from pharmaceutical companies. This could lead to a better control of existing practices such as "evergreening", by which

Source: reference 25

Figure 3. Projected and observed ARV expenditures borne by Censida in Mexico between 2008 and 2013 (nominal USD)

pharmaceutical companies operate minor variations to their products to extend patent monopolies and prevent the entry of competitors into the market. Other reforms include tightening the criteria for medicines to be included in the SPSS essential medicines list, reducing the data exclusivity period's length, or imposing tighter economic criteria for the commercial registration of new drugs or inclusion in the SPSS list of essential medicines. Both Censida and the CCNPM have a role to play in driving forward these structural and legal reforms.

In particular, the following policy reforms could impact ARV price negotiations in Mexico:

• Modify existing guidelines to include a new drug's ceiling price and/or a new criteria measuring its financial impact on government's expenditures to evaluate its inclusion in the SPSS list of essential medicines.
• Align procurement calendars between Censida and other public institutions to increase the government's negotiation power with pharmaceutical companies, both for patented and generic drugs.

• Strengthen Censida's leadership, both in terms of procurement mechanisms within the MoH and as part of the CCNPM.
• Better understand how transport, customs and distribution affect final ARV prices, to prevent pharmaceutical's double exclusivity on patent and distribution.

Limitations

This study presents data from the SPSS, which only covers 60% of all patients on ARV treatment in the country, as data from other major public institutions could not be secured. As such, our results are not representative of all public ARV purchases at national level. Analysis of data from these alternative public institutions is essential to get a more precise picture of ARV prescriptions and purchase practices at the national level.

In addition, our financial projections do not present a precise modeling of future spending, as it assumes the mix of ARV prescribed will remain equal in the future. Therefore, it does not take into account changes

in prescription guidelines after 2012, drug innovations or changes in policies potentially affecting the number of patients in first, second and third line treatment.

Finally, despite being the most complete database available on international procurement transactions, GPRM provides little information regarding transactions made by upper-middle income countries. Therefore, comparisons with a wide range of countries could not be performed. Differences in Incoterms also slightly distort the comparison —although they don't change its general conclusion.

Conclusion

Like many upper middle-income countries with concentrated HIV epidemics, Mexico faces a complex situation: its level of income does not allow it to access preferred pricing schemes or benefit from global initiatives for ARV procurement, which would allegedly lighten the burden ARV purchases represent for its public finances. At the same time, it lacks the legal flexibility to implement cheaper alternatives, such as compulsory licenses.

This study has brought further lights to the issue of ARV purchases and prescription in Mexico by showing that the market for ARV drugs in Mexico tends to become simpler and more in line with prescription guidelines, meaning that most of the ARV expenditures is now concentrated on a small number of patented drugs, for which procurement and purchasing processes are tightly regulated. To maximize purchase efficiency, policy makers should focus on finding long-term legal and political safeguards to counter the high prices imposed by pharmaceutical companies. Only then can Mexico expect to curb its future ARV expenditures.

Acknowledgments

References

1. Centro Nacional para la Prevención y el Control del VIH/sida. El VIH/sida en México en 2012. Mexico: Censida, 2012.
2. Frenk J, González-Pier E, Gómez-Dantés O, Lezana MA, Knaul MF. Comprehensive reform to improve health system performance in Mexico. Lancet 2006;368:1524-1534 doi: 10.1016/S0140-6736(06)69564-0 pmid:17071286.
3. Bonilla-Chacín ME, Aguilera N. UNICO Studies Series. The Mexican Social Protection System in Health. Washington, DC: The World Bank, 2013.
4. Wirtz VJ, Santa-Ana-Téllez Y, Trout C, Kaplan A. Allocating scarce financial resources for HIV treatment: benchmarking prices of antiretroviral medicines in Latin America. Health Policy Plan 2012;27:638-648.
5. Médecins Sans Frontières. Untangling the web of antiretroviral price reductions. 16th ed. Paris: MSF, 2013.
6. Pan American Health Organization. Antiretroviral treatment in the spotlight: a public health analysis in Latin America and the Caribbean. Washington, DC: PAHO, 2013.
7. Bendavid E, Leroux E, Bhattacharya J, Smith N, Miller G. The relation of price of antiretroviral drugs and foreign assistance with coverage of HIV treatment in Africa: retrospective study. BMJ 2010;341:c6218.
8. Lucchini, S, Ciss B, Duran S, de Cenival M, Comiti C, Gaudry M, *et al*. Decrease in prices of antiretroviral drugs for developing countries: from political "philanthropy" to regulated markets. Paris: ANRS, 2003:169-211.
9. Vasan A, Hoos D, Mukherjee J, Farmer P, Rosenfield A, Perriëns J. The pricing and procurement of antiretroviral drugs: an observational study of data from the Global Fund. Bull World Health Organ 2006;84(5):393-398.
10. Wirtz V, Forsythe S, Valencia-Mendoza A, Bautista-Arredondo S. Factors influencing global antiretroviral procurement prices. BMC Public Health 2009;9(suppl 1):S6.
11. Waning B, Kaplan W, King A, Lawrence D, Leufkens H, Fox M. Global strategies to reduce the price of antiretroviral medicines: evidence from transactional databases. Bull World Health Organ 2009;87:520-528.
12. Adesina A, Wirtz VJ, Dratler S. Reforming antiretroviral price negotiations and public procurement: the Mexican experience. Health Policy Plan 2012;28(1):1-10.
13. Gómez-Dantés O, Wirtz VJ, Reich M, Terrazasc P, Ortiz M. A new entity for the negotiation of public procurement prices for patented medicines in Mexico. Bull World Health Organ 2012;90:788-792.
14. Centro Nacional para la prevención y el control del VIH/SIDA (Censida). Guía de manejo antiretroviral de las personas con VIH. 6th ed. Mexico: Censida, 2014.
15. Neumann PJ. Evidence-based and value-based formulary guidelines. Health Affairs 2004;23(1):124-134.
16. Moon S, Jambert E, Childs M, von Schoen-Angerer T. A win-win solution?: a critical analysis of tiered pricing to improve access to medicines in developing countries. Global Health 2011;7:39.
17. Médecins Sans Frontières. Untangling the web of antiretroviral price reductions. 15th ed. Paris: MSF, 2012.
18. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: WHO, 2013.
19. Waning B, Kyle M, Diedrichsen E, Soucy L, Hochstadt J, Bärnighausen T, *et al*. Intervening in global markets to improve access to HIV/AIDS treatment: an analysis of international policies and the dynamics of global antiretroviral medicines markets. Global Health 2010;6:9.
20. Ministry of Health, Economic Analysis Unit. Costos de la terapia antirretroviral y su impacto en el financiamiento público. Mexico: 2011 [accessed on January 28, 2015]. Available at: http://www.censida.salud.gob.mx/congreso2011/Presentacion_CongresoVIH_Tabasco_v270711.pdf
21. Comisión Nacional de Protección Social en Salud. Fideicomiso del Sistema de Protección Social en Salud. Auditoría Financiera y de Cumplimiento N° 11-0-12U00-02-0428 DS-056 [accessed on January 28, 2015]. Available at: http://www.asf.gob.mx/trans/informes/ir2011i/Grupos/Desarrollo_Social/2011_0428_a.pdf.
22. Secretaría de Salud, Subsecretaría de Prevención y Promoción de la Salud, Centro Nacional para la Prevención y el Control del VIH y el Sida. Sistema de Administración y Logística de ARV (SALVAR) [base de datos en Internet]. México: Censida, 2006 [accessed on March 1, 2014]. Available at: http://www.censida.salud.gob.mx/interior/atencion/bol_salvar.html

23. Country and Londing groups by income. Data from the World Bank [accessed on January 28, 2015]. Available at: http://data.worldbank.org/about/country-and-lending-groups

24. Management Sciences for Health and World Health Organization. International drug price indicator guide. Medford, MA: MSH, 2012.

25. Comisión Nacional de Protección Social en Salud, SALVAR. Quarterly Bulletins 1 to 21. from June 2008 to June 2013 [online documents] [accessed at november 14, 2015]. Available at: http://www.censida.salud.gob.mx/interior/atencion/bol_salvar.html

26. Centro Nacional para la prevención y el control del VIH/SIDA (Censida). Guía de manejo antiretroviral de las personas con VIH. 5th Ed. Mexico: Censida, 2012.

27. Bautista-Arredondo S, Mane A, Bertozzi SM. Economic impact of antiretroviral therapy prescription decisions in the context of rapid scaling-up of access to treatment: lessons from Mexico. AIDS 2006;20(1):101-109. PubMed PMID:16327325.

28. Hoen E, Berger J, Calmy A, Moon S. Driving a decade of change: HIV/AIDS, patents and Access to medicines for all. J Int AIDS Soc 2011;14:15.