

# HEALTH MONITOR

## ENSURING WITH ARV DRUGS 2010-2016



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## ABBREVIATIONS

AMED	Medicines and Medical Devices Agency
ARV	Antiretroviral
MSM	Men who have sex with men
CD4	Immune system cells that are targeted by HIV
GF	Global Fund
IDA	International Dispensary Association
NNRTI	Non-nucleoside reverse transcriptase inhibitors
NRTI	Nucleoside reverse transcriptase inhibitors
PMSI HDCD	Public Medical-Sanitary Institution Hospital for Dermatology and Communicable Diseases
PI	Protease inhibitor
IP UCIMP DS	Public Institution - Coordination, Implementation and Monitoring Unit of the Health System Projects
STI	Sexually Transmitted Infections
HIV	Human Immunodeficiency Virus
CSW	Commercial Sex Workers
WHO	World Health Organization
NGO	Nongovernmental Organization
IDU	Injected Drug Users
PLHIV	People Living with HIV
PCR	Polymerase Chain Reaction
AIDS	Acquired Immunodeficiency Syndrome
ARVT	Antiretroviral Treatment
EU	European Union
UNAIDS	The Joint United Nations Programme on HIV and AIDS
UNDP	United Nations Development Programme
UNICEF	United Nations Children's Emergency Fund

## GENERAL BACKGROUND

The Republic of Moldova has a concentrated HIV epidemic among key populations (injecting drug users (IDU), commercial sex workers (CSW), men who have sex with men (MSM). It is estimated that there were 18,226 people infected with HIV in the Republic of Moldova in 2017<sup>1</sup>. Officially, 11043 HIV-infected people were registered on 1 January 2017, including 832 new cases detected during 2016<sup>1</sup>. Antiretroviral therapy is one of the most important factors contributing to maintaining good health condition for people living with HIV. According to UNAIDS data, the expansion of antiretroviral treatment primarily accounts for 48% decrease in AIDS-related mortality worldwide. At the same time, ARV treatment has proven to be effective on preventing HIV transmission. If an HIV-positive person receives ARV treatment, the risk of sexual transmission to the HIV negative partner is reduced by 96%.<sup>2</sup> According to studies in the field, every 1% increase in ARV treatment coverage reduces the incidence of HIV cases by 1.1-1.2%.<sup>3</sup>

Although today's therapeutic potential does not make possible the total cure of HIV infection, its transformation from a disease with unavoidable progression to a controlled chronic infection over a long period of time can be achieved through administration of specific treatment or antiretroviral therapy consisting in continuous adherence to a regimen containing at least 3 antiretroviral drugs. The life expectancy of a person receiving ARVT is approaching a normal one, and people living with HIV die for reasons other than HIV. One study showed that ARVT would lead to a median of 24.2 years of life.<sup>4</sup>

Following the emergence of new evidence based on a series of randomized multicenter studies, the World Health Organization reviewed the guidelines and recommendations on the timing of initiation of ARVT in 2015. Thus, the latest recommendations are to initiate ARVT as early as possible immediately after the diagnosis and regardless of the level of CD4 cell and / or viral load.<sup>5</sup>

Upon discontinuation of treatment, the disease starts to progress again. If the medications are not taken continuously and in optimal doses, the resistance of the virus to one or more drugs may occur and then line II regimens should be administered. In the case of

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<sup>1</sup> Monitoring the control of HIV infection in the Republic of Moldova, 2016

<sup>2</sup> UNAIDS Data 2017

<sup>3</sup> UNADS, 90-90-90 an ambitious treatment target to help end the AIDS epidemic.

<sup>4</sup> Hogg R., et al (2007). Life expectancy of persons at the time of initiating ART in high-income countries. 14th Conference on Retroviruses and Opportunistic Infections 2007; Abstract 972

<sup>5</sup> Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV, WHO, 2015

failure of different line II combinations, line III therapy with the latest antiretroviral drugs should be initiated. Therefore, any discontinuation of treatment, caused by the delay in drugs procurement and delivery or by the patient, may have negative consequences for treatment outcome.

Currently, more than 30 drugs are registered, which generally include 5 classes of active substances (Table 1). Likewise, there are different combinations of drugs and enhancers.

*Table 1. Main antiretroviral drugs and their classification*

	Drug substance (abbreviated)	Year of first approval
<b>Nucleoside reverse transcriptase inhibitors</b>	Abacavir (ABC)	1987
	Didanosine (ddl)	1991
	Lamivudine (3TC)	1996
	Stavudine (d4T)	1994
	Tenofovir disoproxil fumarate (TDF)	2001
	Zidovudine (AZT)	1986
	Emtricitabine (FTC)	2003
<b>Non-nucleoside reverse transcriptase inhibitors</b>	Efavirenz (EFV)	1997
	Nevirapine (NVP)	1996
	Etravirine (ETV)	2008
	Rilpivirine (RPV)	2011
	Delavirdine (DLV)	1997
<b>Protease inhibitors</b>	Lopinavir (LPV)	1995
	Ritonavir (RTV)	1996
	Atazanavir(ATV)	2003
	Darunavir (DRV)	2006
	Tipranavir (TPV)	2005
	Indinavir (IDV)	1996
	Saquinavir (SQV)	1995
	Fosamprenavir (FPV)	2003
<b>Fusion inhibitors</b>	Maraviroc (MVC)	2003
	Enfuvirtide (T-20)	2003
<b>Integrase inhibitors</b>	Raltegravir (RAL)	2007
	Dolutegravir (DTG)	2013
	Elvitegravir (EVG)	2012
<b>Combined drugs</b>	TDF+FTC+EFV (ATP)	
	TDF+3TC+EFV	
	TDF+FTC+RPV	
	DTG+ABC+3TC	
	AZT+ABC+3TC	
	AZT+3TC+NVP	
	AZT+3TC (CBV)	
	ABC+3TC	
	TDF+FTC	

Choosing the drug combination depends on a number of factors: approved treatment regimens at the country level, availability and price of drugs, adverse effects and laboratory clinical monitoring.<sup>6</sup> The selection of treatment schemes are based on World Health Organization's recommendations which are periodically updated based on new research in the field, emerging new drugs and the latest evidence and conclusions. Also, an important role for Europe is played by the recommendations issued by the European Clinical Society for AIDS that promotes excellence in standards of care, research and education in HIV infection and associated co-infections, whereas for the United States - by the Department of Health and Human Services, Panel on Antiretroviral Guidelines for Adults and Adolescents.

Universal access to treatment is one of the objectives of the ongoing National Program for Prevention and Control of HIV / AIDS and STIs in the Republic of Moldova, as it was in the case of previously implemented programs, starting from the premise that any person in need of treatment receives it.

The current study is a continuation of the study developed in 2013 under the "Health Monitor" project, which aimed at analyzing the situation regarding procurement of ARV drugs and identifying possible scenarios in the context of the transition from procurement of medications from the external resources to drug procurement from national public funds. In this study, the procurement aspects were analyzed during the transition period and some opportunities for future intervention were formulated.

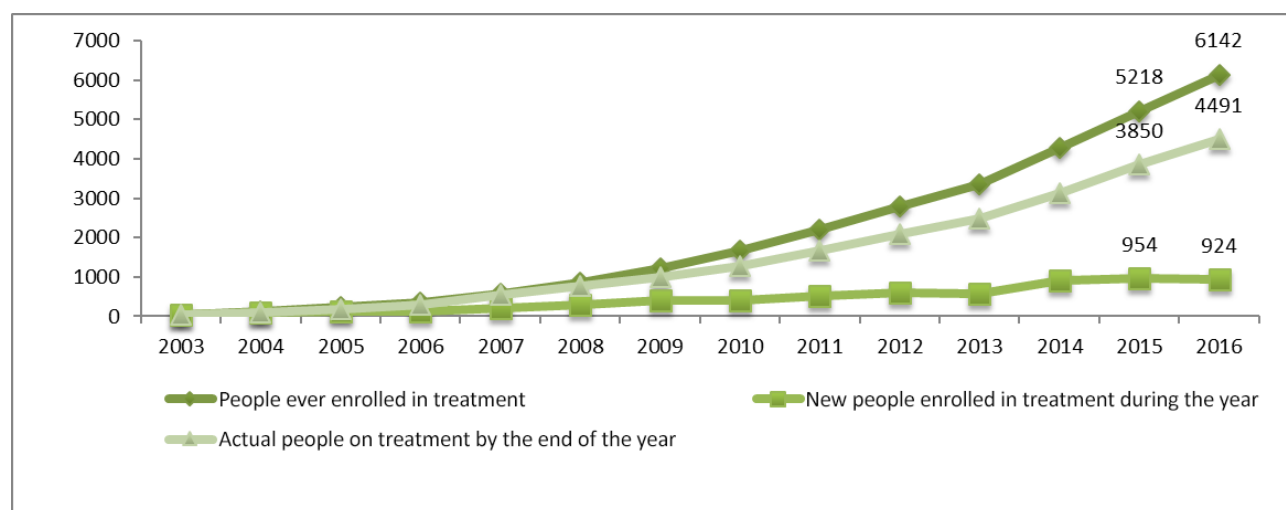
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<sup>6</sup> Introduction to HIV and AIDS treatment. <http://www.avert.org/treatment.htm>

## THE ESTIMATION OF THE NEEDS OF ARV TREATMENT IN THE REPUBLIC OF MOLDOVA

On 1 January 2017, 4491 people living with HIV were under antiretroviral treatment. During 2016, 924 people (907 adults and 17 children) initiated the treatment for the first time.<sup>7</sup>

*Figure 1. Total number of people enrolled in ARVT, reported de facto and enrolled annually for the years 2003-2016*



At the same time, according to the current National Clinical Protocol "HIV Infection in Adults and Adolescents", which also provides guidance for ARV treatment, on 1 January 2017, ARV treatment was needed by 5506 persons (80.6% of the people under active surveillance), ie an additional 1015 people with indications for treatment initiation who, for various reasons (migration, poor understanding of the benefits of treatment, lack of financial resources for traveling to the medical facility, etc.), do not administer ARVT.

Moreover, it should be noted that the estimated number of people who will need treatment was mathematically modeled using the information technology - Spectrum / EPP and is based on the number of people estimated to be infected with HIV in the Republic of Moldova, in line with the international methodology recommended by the Global WHO / UNAIDS working group on HIV / AIDS / STI surveillance. Thus, it is estimated that the ARVT will be needed by a cumulative number of 14690 persons in 2017, 15000 persons in 2018 and

<sup>7</sup> Monitoring the control of HIV infection in the Republic of Moldova, 2016

about 15307 persons in 2019<sup>7</sup>. It should also be noted that according to the 2015 revision of the WHO clinical recommendations, the initiation of ARV treatment should take place as early as possible, immediately after the diagnosis is established, and without taking into account the CD4 cell counts and the viral load.

These extended indications, once integrated into the national clinical protocol "HIV Infection in Adults and Adolescents" currently undergoing an update, will significantly change the prognosis of the number of patients requiring treatment and it will account for 90% of the number of patients estimated by Spectrum / EPP.

### **CURRENT ARV DRUGS PROCUREMENT MECHANISMS**

In the Republic of Moldova, antiretroviral treatment for HIV-infected people was first introduced in 2003. By 2014, the procurement of ARV drugs were exclusively covered from the Global Fund financial resources through IP UCIMP DS, the main governmental recipient of the Global Fund funds in the Republic of Moldova. In 2014, the process of gradual taking over of funding by the State Budget of several activities financially supported by the Global Fund began, which included the procurement of ARVs through AMED for 2014-2016 and through UNDP for 2017.

Estimates of the need for antiretroviral drugs are made by the PMSI HDCD based on the number of patients under treatment at the end of the year and the estimated number of new people initiating treatment in the following year, the planned treatment regimes and the factors that could cause the change of treatment or dose adjustment (for example resistance and adverse reactions, co-morbidities - TB, hepatitis, kidney damage, etc.), the period for which the needs are estimated, the daily dose taking into account the existing stock, including validity terms and spare storage. Based on these considerations, a table with the number of pills or milliliters for each ARV drug required for one full year is compiled. Subsequently, this list of needs is handed over to IP UCIMP DS and AMED (UNDP in 2017) according to procurement arrangements.

Based on this need for antiretroviral drugs, IP UCIMP DS calls for price quotations from "low cost" international procurement agencies such as IDA and UNICEF. After the submission of tenders, an evaluation committee examines the bids and decides the winner based on the lowest prices. The winning agent delivers the drugs in the country according to the established delivery schedule. Prices offered by international agencies are usually at Cost-IP (Incoterms

2012) delivery terms. Thus, responsibility for customs clearance, internal transportation (customs - warehouse), quality assurance is covered by IP UCIMP DS. The procurement is conducted at the end of the current calendar year to cover the needs of the following year and is usually done once a year, delivery is done in installments twice a year.

In accordance with the Ministry of Health's commitments to take over the coverage of antiretroviral treatment from the national resources, the first procurement was carried out in 2014, assuring the patients on the right river bank who were to initiate ARVT along that year with required drugs, with gradual takeover of the complete coverage of line I drugs and partly of line II drugs by 2016.

*Table 2. Ensuring the procurement of ARV drugs at the cost of the State Budgets 2014-2016*

Type of drugs	Number of covered patients		
	2014	2015	2016
<b>Procurement year</b>			
<b>Line I dugs</b>	422	2416	2861
<b>Line II dugs</b>	0	0	156
<b>Line III dugs</b>	0	0	0
<b>Children</b>	10	70	84
<b>Prevention of maternal-fetal transmission (number of mother/newborn pairs)</b>	135	125	150
<b>Emergency prophylaxis kits</b>	50	50	50

AMED carries out a local procurement process: with the announcement of the procedure, the list of drugs, the quality requirements, etc. Once the bids have been received, a preestablished commission examines the bids and designates the winner based on the lowest prices. The winning agent delivers the drugs in the country according to the predefined delivery schedule and is responsible for customs clearance, internal transportation (customs, warehousing), and quality assurance.

The procurement is carried out at the beginning of the current calendar year to cover the needs of the current year (due to state budget constraints) and is usually executed once a year, delivery is done in installments twice a year. During these 3 years of procurement experience through AMED, there were cases when for some items, there were no offers and they asked UCIMP to procure them.



In order to assure the provision of antiretroviral drugs along with other medications in 2017, the Ministry of Health, Labor, and Social Protection requested assistance in the procurement and management of the supply chain of essential drugs from UNDP. The objectives of this request were to increase the transparency of the procurement process and to ensure continuity in the supply of medicines, as well as to reduce the supply period and costs and to improve the quality of the procured drugs.

For 2017, it was planned to procure ARV drugs for patients who are on line I treatment - 100%, line II treatment - 60% of adults, 100% - children, 150 kits for prevention of vertical HIV transmission, and 50 kits for emergency prophylaxis.

UNDP procurement procedures follow both UN and international standards and their underlying principles can be found at the following link: [http://www.md.undp.org/content/dam/moldova/docs/Publications/GHID\\_INTREBARI\\_RASP\\_UNSURE\\_RO\\_final.pdf](http://www.md.undp.org/content/dam/moldova/docs/Publications/GHID_INTREBARI_RASP_UNSURE_RO_final.pdf).

## **EVOLUTION OF ARV DRUGS PRICES DURING 2010-2017**

### **Method of analysis**

For analyzing the evolution of antiretroviral drug costs, the data on the ARV drugs prices provided by IP UCIMP DS, AMED, PMSI HDCD were used. The quoted prices are final ones and include all related costs up to storage in the warehouse. For the comparative analysis of the costs for ARV products procured by different countries from the Global Fund resources, the information from the Global Fund's website, published under the so-called "Price and Quality Reporting" (PQR) was used<sup>8</sup>, which is a publicly accessible online database that collects data on procurement transactions made by the Global Fund within its program support from Principal Recipients and publishes it. These prices are also final, encompassing all related costs.

The Global Fund reference price<sup>9</sup> is established by the Pooled Procurement Mechanism Reference Pricing: ARVs (PPM), based on agreements with antiretroviral drug manufacturers to provide the lowest prices and to ensure sustainability and delivery in a timely manner of the entire spectrum of required ARV drugs. The Global Fund recommends using these reference prices in the budgeting of resources for the procurement of ARV drugs and for all price quotations.

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<sup>8</sup> <https://bip2-ext.theglobalfund.org/analytics/saw.dll?Dashboard>

<sup>9</sup> Global Fund reference price – pooled procurement mechanism reference pricing: ARVs

The international reference price<sup>10</sup> determines the likely cost of the pharmaceutical product. It can be used as a reference for comparing the current price with the prices available on the international market.

Prices are quoted in US dollars (prices submitted by IP UCIMP RSS were provided in US dollars, those submitted by AMED were converted into US dollars using the annual MDL / USD rate and prices submitted by SDMC PPM for 2017 were at a rate of 1USD = 20.01 MDL, the exchange rate on the date of payment (UN rate)).

*Table 3. Evolution of ARV treatment cost 2015-2017, prices in USD*

N d/o	ARV drug names	2015		2016		2017	
		UCIMP	AMED	UCIMP	AMED	UCIMP	UNDP
1	(AZT+3TC) 300mg+150mg	19300.68	22499.31	9334.36	4952.14	18792.72	17061
2	EFV 600mg	11510.52	13837.07	4320	0	5200.39	0
3	(TDF+3TC+EFV) 300mg+300mg+600mg	72826.62	100209.48	57302.4	101040.77	73292.27	81158.14
4	(TDF+FTC+EFV) 300mg+200mg+600mg	79108.54	161900.23	61792.65	236402	72380.88	221410
5	(AZT+3TC+NVP) 300mg+150mg+200mg	21702.9	23682	2972.46	0	9015.58	3478
6	(TDF+3TC) 300mg+300mg	13045.46	6372.57	8426	0	14451.03	0
7	NVP 200mg	1383.51	1354.57	1262.52	1564.15	1689,12	1560
8	TDF 300mg	660	6876.9	793.8		1919.41	105
9	(ABC+3TC) 600mg+300mg	22583.84	83351.43	5712.15	143763.12	45367.8	0
10	(TDF+FTC) 300mg+200mg	21317.32	0	14793.6	0	20186.32	0
11	DRV 600mg	118131.51	0	31452.48	0	36459.46	0
12	ATV 300mg	2200	0	3498.65	0	5409.6	0
13	(AZT+3TC) 30mg+60mg	0	0	780.9	7166.2	0	3002.07
14	(ABC+3TC) 60mg+30mg	0	0	5335.2	10212.57	1852.2	1047
15	AZT 100mg	237	7795.5	0	0	0	0
16	3TC 150mg	196.9	451.66	0	0	0	0
17	EFV 50mg	865.26	0	0	0	0	0
18	EVF 200mg	449.44	726.35	1963.84	0	1252.96	569
19	AZT 10mg/ml	103.2	2993.7	908.65	2675.15	690.3	630
20	3TC 10mg/ml	1804.04	9024.85	62.85	640.84	174	273
21	ABC 20mg/ml	3679.92	5684.12	0	0	0	321
22	NVP 10mg/ml	0		157.8	673.43	183.5	274.56
23	LPV/r 200mg+50mg	490838.4	114860	172368	0	548476.8	91927.23
24	LPV/r 100mg+25mg	0	0	9902.56	22973.16	1384.68	5140.8
25	r100mg	4844.97	0	23198.5	0	14064.27	0
26	LPV/r 80mg+20mg/ml	4499.2	5872.5	2736	0	4924.8	6069.51
<b>SUBTOTAL, USD</b>		891254.2	567492.2	419075.4	532063.5	875479	434026.24
<b>TOTAL, USD</b>		<b>1,458,746</b>		<b>951,138.9</b>		<b>1,309,505.24</b>	

<sup>10</sup> International Reference Price – Center for Pharmaceutical Management of Management Sciences for Health

It is worth mentioning that although the number of patients enrolled in the treatment increases, the overall cost of ARV drugs is relatively constant considering the drop in prices and the development of generic products. A noticeable occurrence in 2016 was the procurement by IP UCIMP RSS of the generic version of Line III drugs - Darunavir from the Global Fund resources with USD 109.21 per bottle compared to USD 752.43 for the original product in 2015.

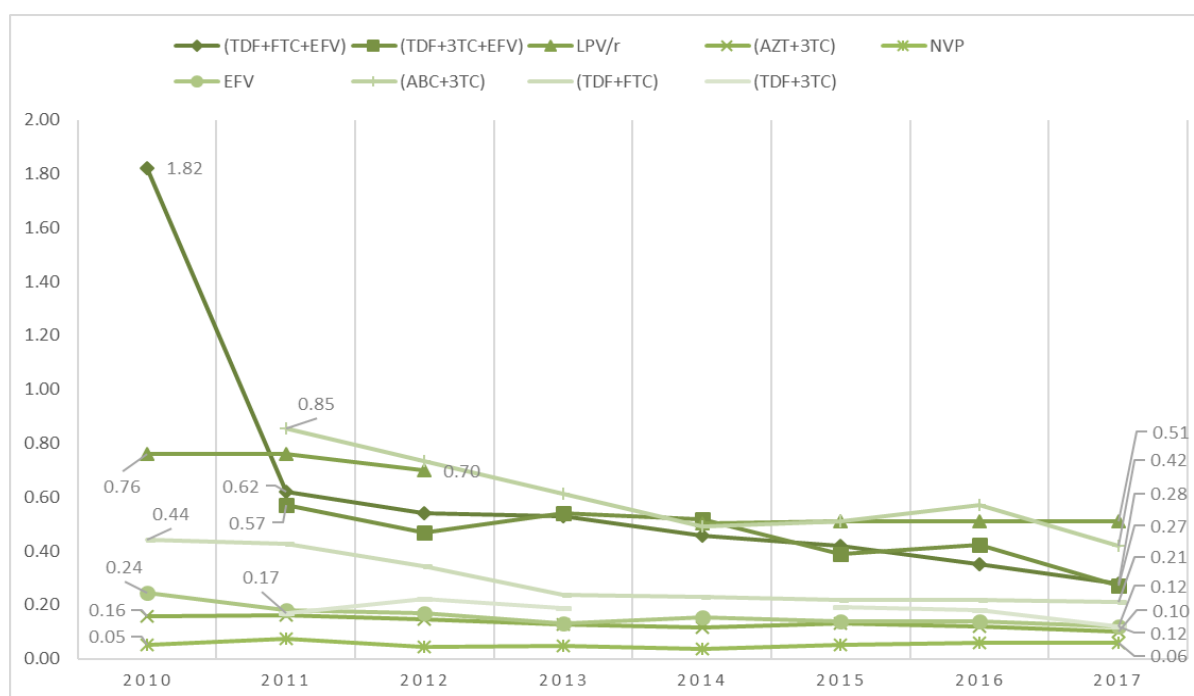
The table below shows the dynamics of patient distribution on treatment lines:

*Table 3. Dynamics of patient distribution on treatment lines and schemes 2014-2016*

Treatment line	Drug schemes	% of people on ARVT		
		2014	2015	2016
Line I	(TDF+FTC+EFV)	39.18	46.08	45.91
	(TDF+3TC+EFV)	25.29	26.81	27.77
	(AZT+3TC+NVP)	7.54	5.14	4.99
	(AZT+3TC)+EFV	6.77	3.25	3.14
	(AZT+3TC)+LPV/r	5.42	0.55	1.65
	(ABC+3TC)+EFV	2.12	2.36	1.60
	(TDF+3TC)+NVP	1.73	1.51	1.02
	Other	0.90	2.03	2.85
	<b>SUBTOTAL</b>	<b>88.96</b>	<b>87.71</b>	<b>88.67</b>
Line II	(TDF+FTC)+LPV/r	4.46	3.30	2.92
	(TDF+3TC)+LPV/r	3.47	3.01	2.03
	(ABC+3TC)+LPV/r	1.41	2.03	1.76
	(AZT+3TC)+LPV/r		2.70	3.47
	Other	1.22	0.83	0.76
		<b>SUBTOTAL</b>	<b>10.56</b>	<b>11.87</b>
Line III	(TDF+FTC)+ATV/r	0.19	0.00	0.00
	(ABC+3TC)+DRV/r	0.00	0.10	0.04
	(TDF+FTC)+DRV/r	0.19	0.23	0.29
	(AZT+3TC)+DRV/r			0.04
	(AZT+3TC)+TDF+DRV/r	0.10	0.08	0.02
		<b>SUBTOTAL</b>	<b>0.48</b>	<b>0.42</b>
	<b>TOTAL</b>	<b>100.00</b>	<b>100.00</b>	<b>100.00</b>

As reported in the above table, despite de fact that the Republic of Moldova has over 10 years of experience in ARV treatment management, about 90% of patients are on I line regimens. The majority of manufacturers of the most used antiretroviral drugs are manufacturers of generics drugs, which are pre-qualified by the WHO and which in order to maintain its competitiveness on the market, reduce prices every year. Figure 2 and Table 4 show the prices per pill/ml of the 7 most commonly used ARV drugs.

*Figure 2. Evolution of cost per pill of the most commonly used ARV drugs procured from the Global Fund resources, 2010-2017*

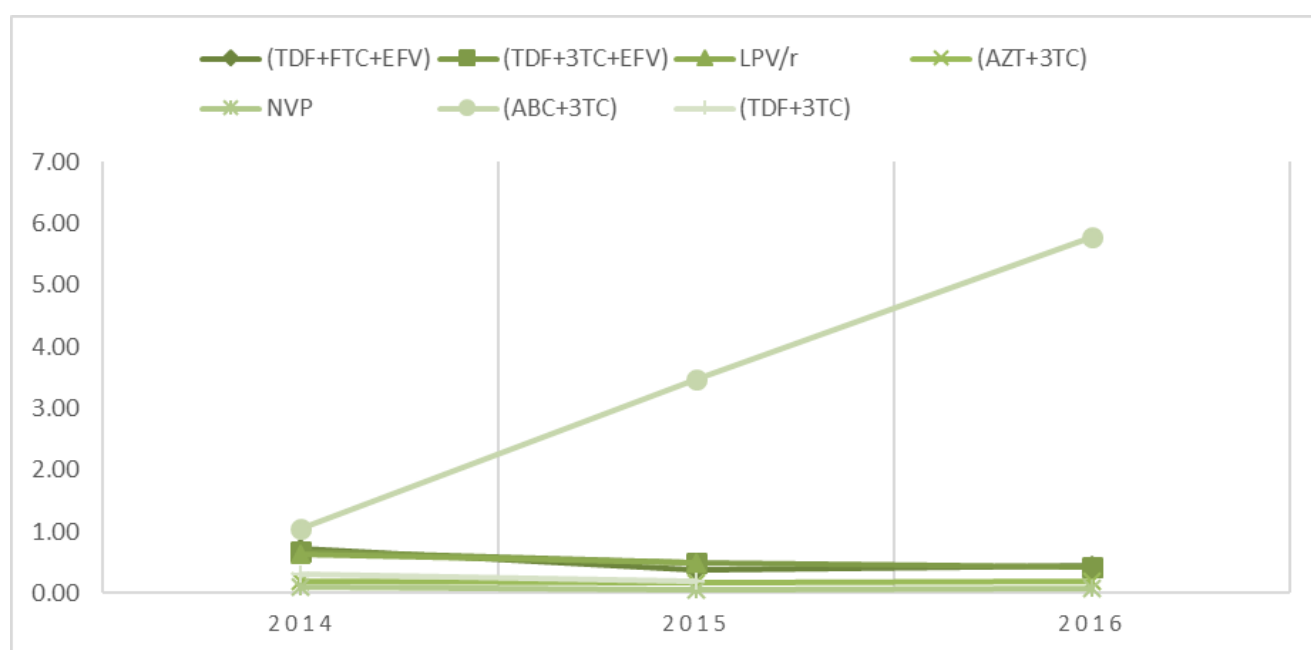


*Table 4. Evolution of cost per pill of the most commonly used ARV drugs procured from the Global Fund resources, 2010-2017*

	2010	2011	2012	2013	2014	2015	2016	2017	Price difference 2016-2017	Price difference 2010-2017
(TDF+FTC+EFV)	1.82	0.62	0.54	0.53	0.46	0.42	0.35	0.27	-20%	-85%
(TDF+3TC+EFV)	...	0.57	0.47	0.54	0.52	0.39	0.42	0.27	-36%	-53%
LPV/r (120+50mg)	0.76	0.76	0.70	...	0.50	0.51	0.51	0.51	0%	-33%
(AZT300mg+3TC 150mg)	0.16	0.16	0.15	0.13	0.12	0.13	0.12	0.10	-17%	-38%
NVP	0.05	0.07	0.04	0.05	0.04	0.05	0.06	0.06	0%	20%
EFV 600mg	0.24	0.18	0.17	0.13	0.15	0.14	0.14	0.12	-14%	-50%
(ABC 600mg+3TC 300mg)	..	0.85	0.73	0.61	0.49	0.51	0.57	0.42	-26%	-51%

The most impressive price drop occurred in the case of the combined drug (Tenofovir + Emtricitabine + Efavirenz), where the price per pill decreased more than 6 times from US \$ 1.82 in 2010 to US \$ 0.27 in 2017. (Figure 2, Table 4). This substantial reduction has taken place due to the procurement of generic equivalent starting with 2011, compared to the procurement of the original medication in 2010. In the case of procurements made by the Medicines and Medical Devices Agency from the State Budget resources, the trends are shown in Figure 3 and Table 5.

*Figure 3. Evolution of cost per pill of the most commonly used ARV drugs procured from the State Budget funds, 2014-2016*



*Table 5. Price per pill of the most commonly used ARV drugs procured from the State Budget funds, 2014-2016*

ARV drugs	2014	2015	2016	Difference 2015-2016	Difference 2014-2016
(TDF+FTC+EFV)	0.72	0.38	0.45	18%	-38%
(TDF+3TC+EFV)	0.67	0.50	0.42	-16%	-37%
LPV/r	0.63	0.48	-	-	-
(AZT+3TC)	0.20	0.17	0.20	18%	0%
NVP	0.10	0.05	0.08	60%	-20%
(ABC+3TC)	1.04	3.48	5.78	66%	456%
(TDF+3TC)	0.29	0.19	-	-	-

The information above shows that there is a decrease in prices, but to a smaller degree compared to the ones within UCIMP procurements. At the same time, in the case of the (ABC + 3TC) drug, there is evidence of price increases, which for the 2 years period has multiplied five-fold within the national procurement and with a difference of up to 900% compared to the prices paid by UCIMP. It is worth mentioning that the drugs procured by AMED are original and the ones procured by UCIMP are generic.

Table 6 shows a comparative cost analysis of ARV drugs for cases when the same product was procured both from public resources and from GF resource over the last 4 years.

*Table 6. Cost difference by procurement agency for 2014-2017*

ARV drug/ Years / Procurement agency	2014			2015			2016			2017		
	UCIM P	AME D	Differenc e	UCIM P	AME D	Differenc e	UCIM P	AME D	Differenc e %	UCIM P	UND P	Differenc e
(TDF+FTC+EFV)	0.46	0.72	58%	0.42	0.38	-10%	0.35	0.45	30%	0.28	0.23	-18%
(TDF+3TC+EFV)	0.52	0.67	29%	0.39	0.50	28%	0.42	0.42	0%	0.27	0.24	-11%
LPV/r	0.50	0.63	24%	0.51	0.48	-6%	0.51			0.51	0.46	-10%
(AZT+3TC)	0.12	0.20	69%	0.13	0.17	31%	0.12	0.20	64%	0.1	0.1	0%
NVP	0.04	0.10	163%	0.05	0.05	0	0.06	0.08	36%	0.06	0.03	-50%
(ABC+3TC)	0.49	1.04	111%	0.51	3.48	583%	0.57	5.78	914%			

Thus, in the first year of national procurement, in 2014, there were essential differences between the procurement costs paid by AMED compared to those paid by UCIMP, the difference being over 20%, even up to 160% with higher prices within national procurements.

In 2015, the results are completely different, the cost being lower within national procurements compared to those covered by GF for three products (TDF + FTC + EFV), LPV/r and NVP, the difference in price being maintained for (TDF + FTC + EFV), and the difference being decreased from 69% to 31% for (AZT + 3TC).

In 2016, the price situation changed significantly again, which rendered impossible to establish a consistent trend of change: the acquisition prices within the national procurement increased in 2016 compared to 2015 for 4 out of 6 products, and for those procured by GF for 3 out of 6 products and remained unchanged for one product. In this context, the price comparison between the two sources for 2016 reveals again a difference of 30% and higher for 4 out of 5 drugs in the detriment of those procured from public resources and lack of difference for the 5th product. In particular, astounding is the cost increase of the ABC + 3TC

drug, which surpasses by 900% the price paid by UCIMP. It should be mentioned that the original drug was procured from national resources, but it is not clear why it was not possible to obtain the offer for the generic product.

In 2017, the procurement mechanism of UNDP was used for the procurement from the State Budget funds. Comparative data show that:

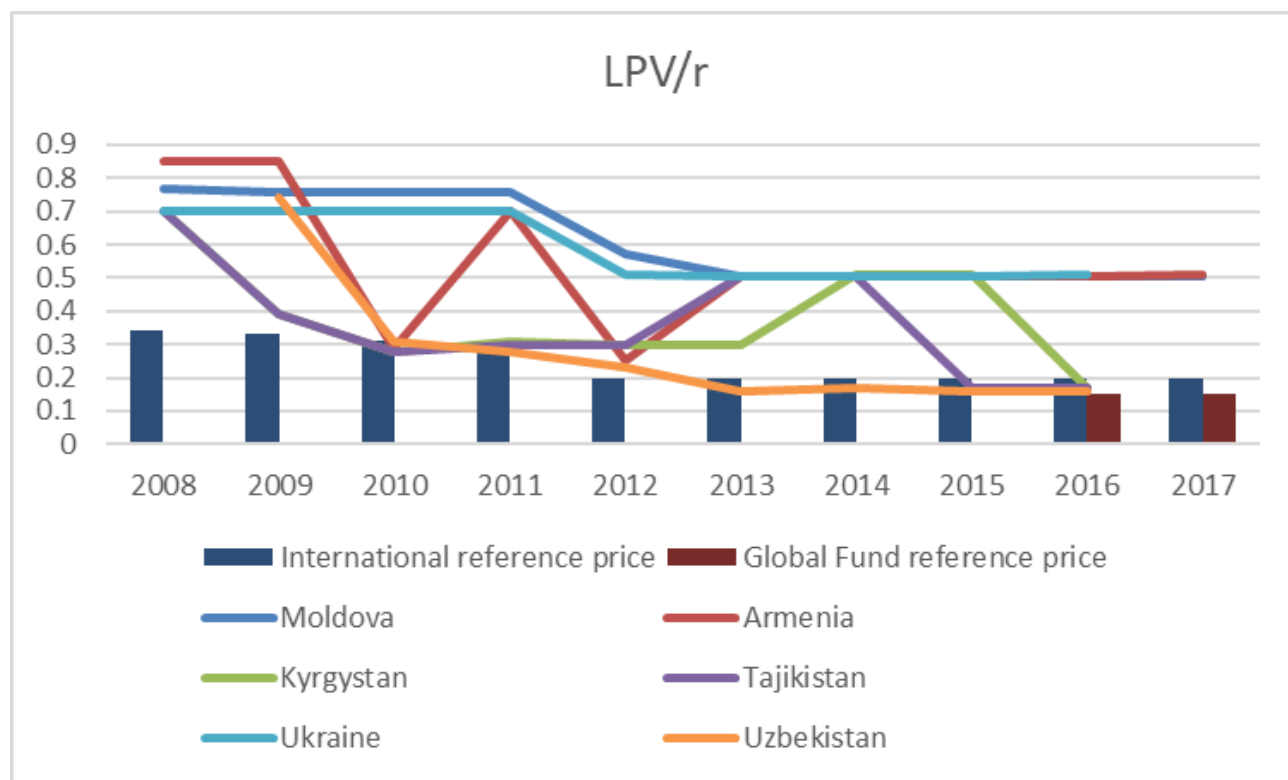
- The procurement price for 4 out of 5 products is 10% -50% lower in case of procurement through UNDP mechanism compared to UCIMP, some of them are up to 80% cheaper (Lamivudine)
- The drug prices in case of procurement through UNDP mechanism are significantly lower than the AMED procurement prices from the previous year, but given the fact that the procurement year was not the same, they can not be directly compared.

### **Comparative analysis of procurement prices for some ARV products against the reference prices.**

According to the current National Clinical Protocol «HIV Infection in Adults and Adolescents », the Lopinavir / ritonavir drug is the elective product for the line II regimens, the number of patients receiving this medication constitutes 96% of the patients who receive the second line ARV treatment and 14.3% of all ARVT patients at the beginning of 2017. At the same time, in 2017, 50% of the funds for ARV drugs were used to purchase LPV/r. For this reason, in the study we analyzed the evolution of prices and the aspects that influence it.

Considering that this product is procured directly from the original drug manufacturer, which is patented in Eurasia with activity in the Republic of Moldova, the evolution of prices does not seem encouraging at all. On the contrary, the price remains constant for both children and adults formula. Considering the monopolistic position, the original drug manufacturer offers roughly the same price for all its products over the past 5 years, regardless of the quantity, which is growing. (Figure 4 and 5). Moreover, the price of Lopinavir / Ritonavir drugs offered to Moldova, Armenia, Ukraine and Tajikistan far exceeds the price offered to other countries in the region, such as Uzbekistan or Kyrgyzstan, as well as the international reference price and the Global Fund price (Figure 4 ). These differences deserve a more thorough analysis to understand their causes in the region.

Figure 4. Evolution of the cost per pill of LPV/r procured from Global Fund resources against the countries and reference prices, 2008-2017



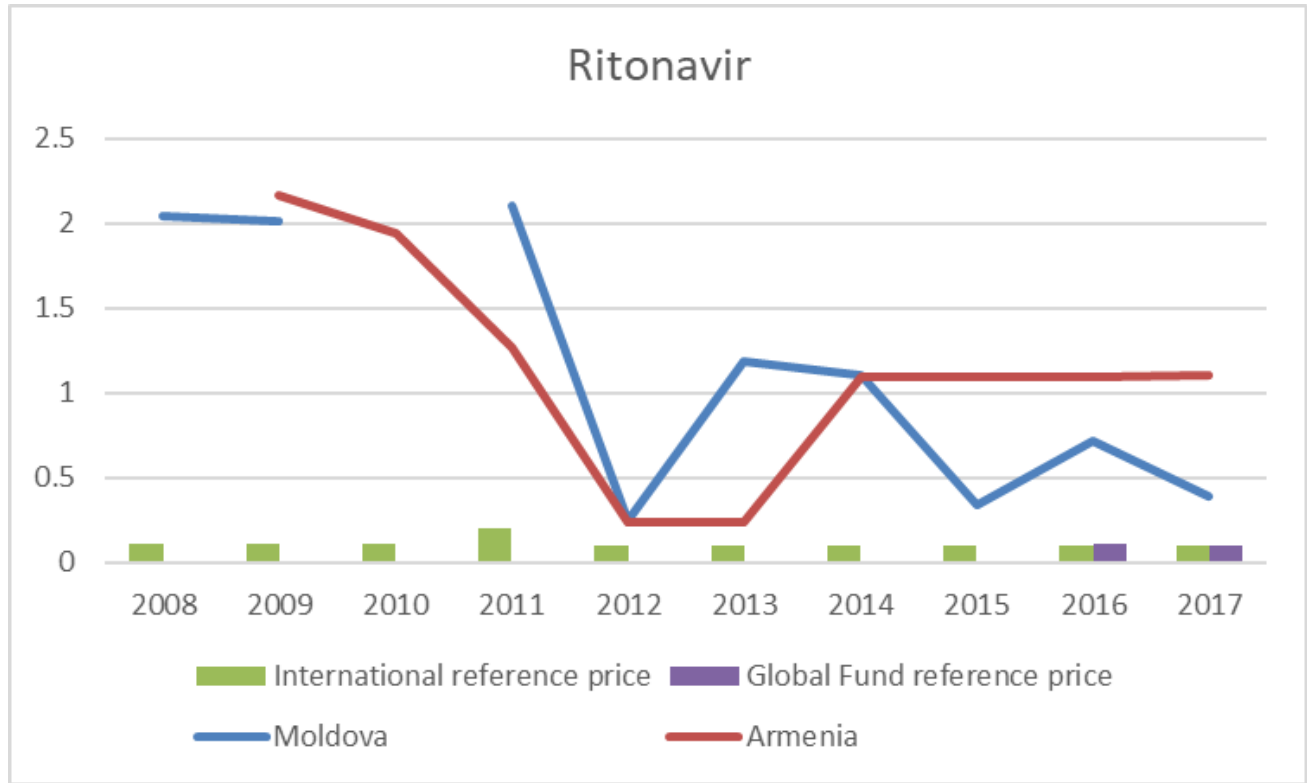
In 2012, IP UCIMP negotiated a price drop of about 28% for Lopinavir-Ritonavir pills and oral solutions, but the cost of these products remains high.

On the other hand, the generic alternatives of the drugs would have the potential to significantly reduce the cost of ARVT. For example, the figure below shows that in case of Ritonavir, 2011 was the only year when the generic version of the drug was procured and the price was *8 times lower*: \$ 2.1 /pill for 2010 compared to \$ 0.25 /pill for 2011. As shown in Figure 5 below, the price of Ritonavire for Armenia and Moldova<sup>11</sup> exceeds both the international reference price and the Global Fund reference price.

<sup>11</sup> The comparison was only made with Armenia because only this country has consistently procured this product from Global Fund funds.

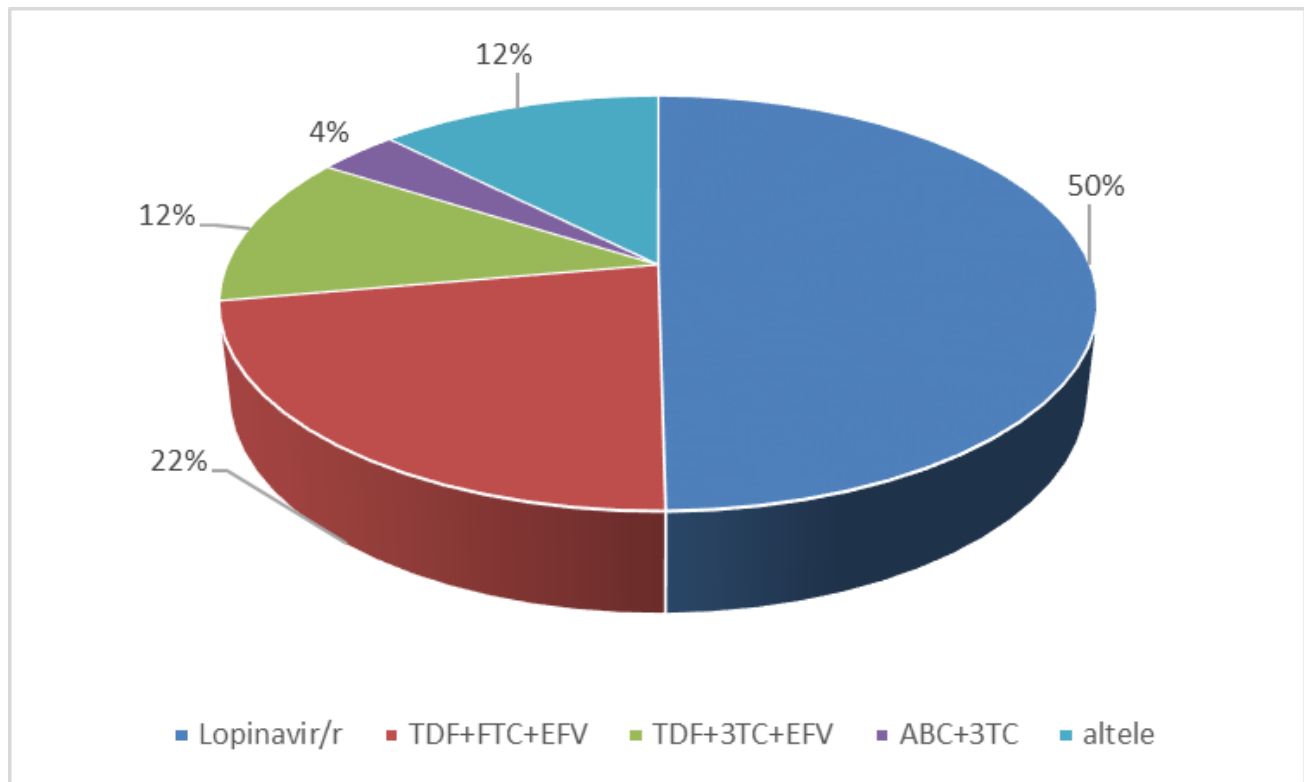


Figure 5. Evolution of the cost per pill of the RTV procured from Global Fund funds: Moldova and Armenia 2008-2017



The analysis of 2011 ARVT procurement data showed that expenditures for LPV/r accounted for almost half (47%) of the total cost of ARVT, although only 18% of patients needed this medication. As shown in figure 6 below, in 2017 the cost of LPV/r was of 49.7% from the total cost of ARV products, and the medication was prescribed for 14.3% of people following the LPV/r schemes and for an additional number of people that initiated the therapy with this medication during 2017.

Figure 6. Distribution of financial resources in 2017 for procurement of ARV drugs



By analyzing the procurement prices of the most used antiretroviral products compared to the international and Global Fund reference prices, we can follow a dynamic decrease in costs but, which remain higher compared to other countries and reference prices. (Figures 7-10).

Figure 7. Cost dynamics for the TDF + FTC + EFV combined drug procured from the Global Fund resources against other countries and reference prices

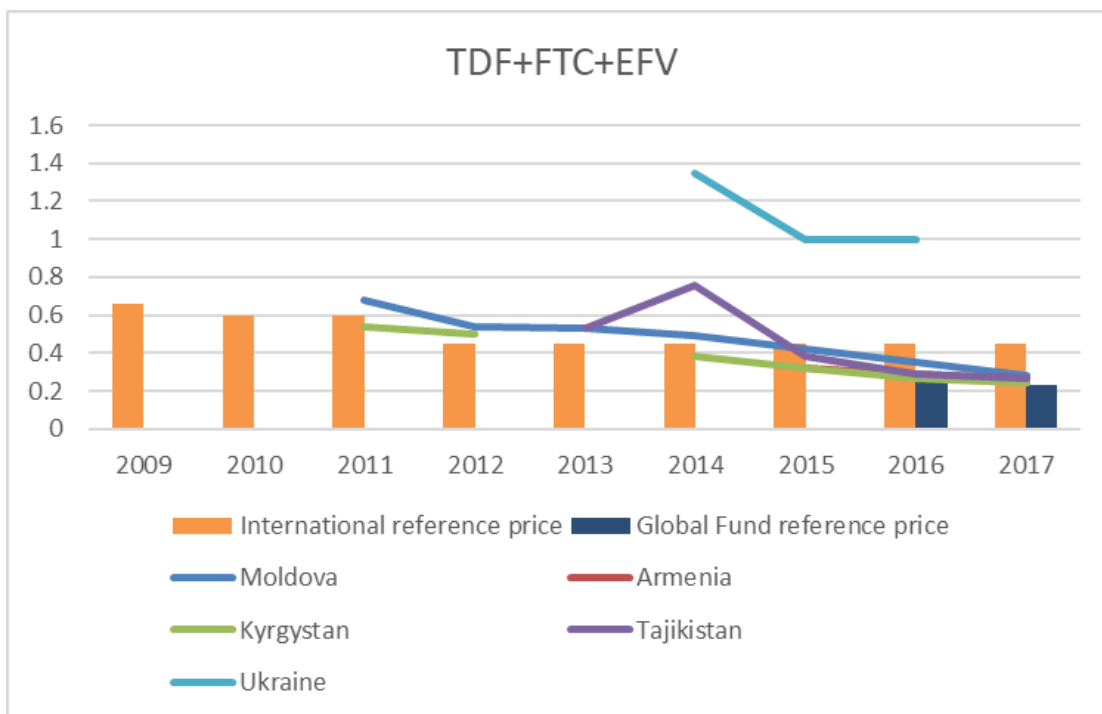


Figure 8. Cost dynamics for TDF + 3TC + EFV combined drug procured from the Global Fund resources against other countries and reference prices

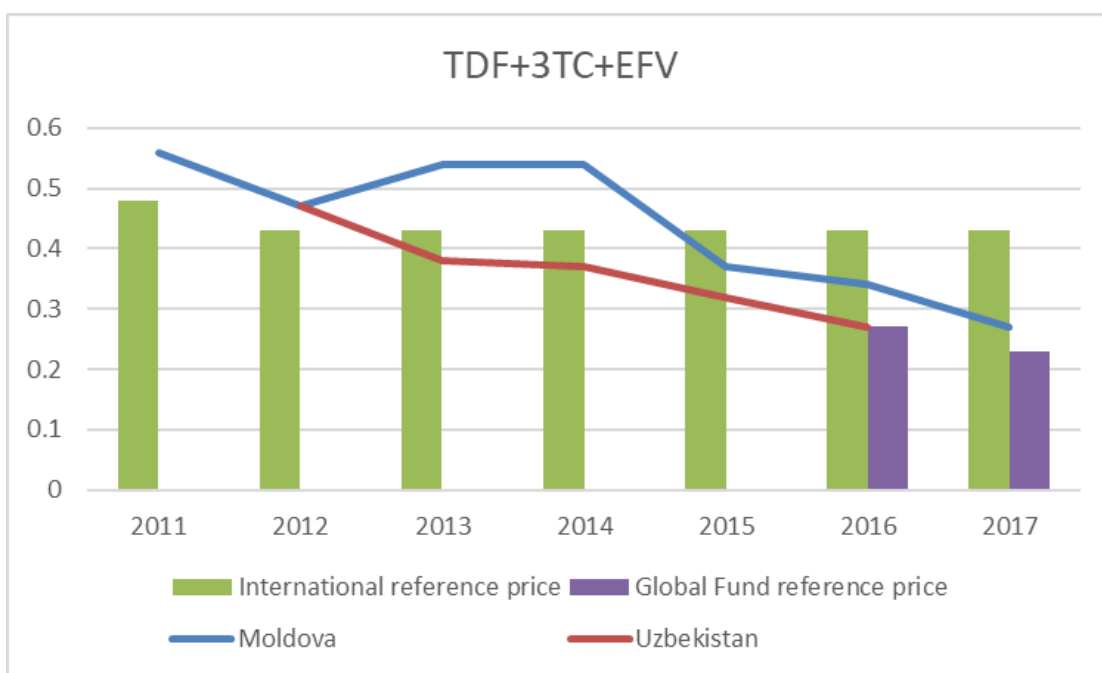


Figure 9. Cost dynamics for Nevirapine 200mg drug procured from the Global Fund resources against other countries and reference prices

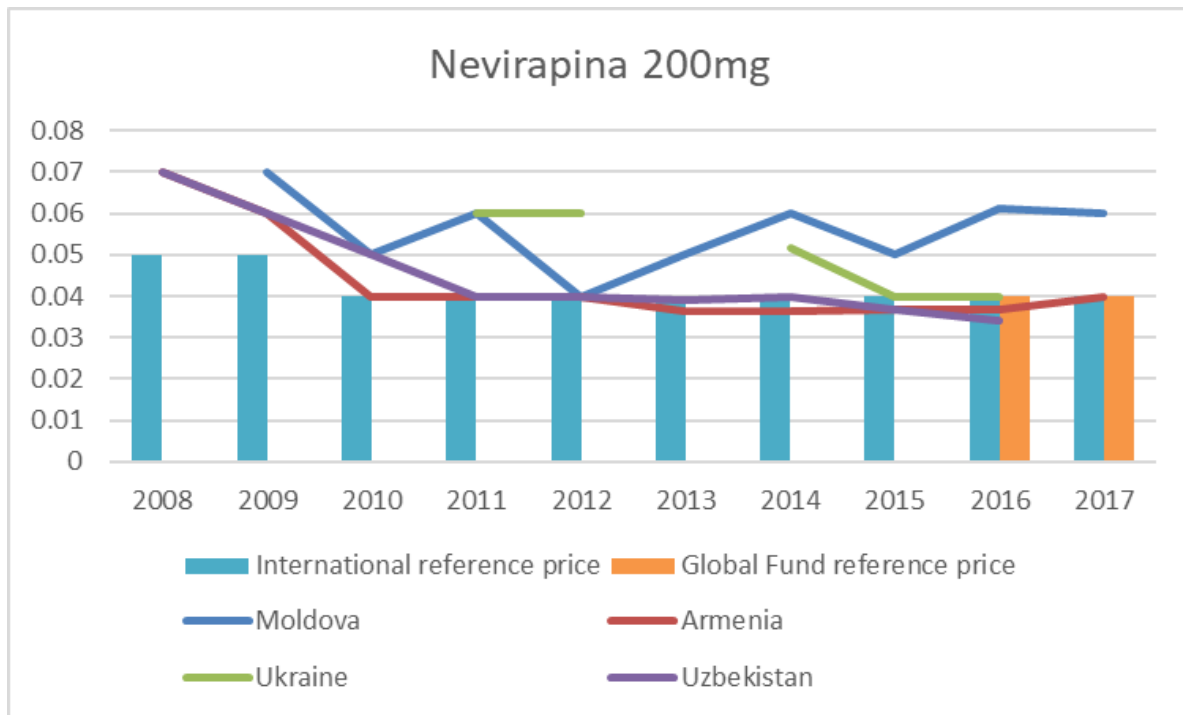
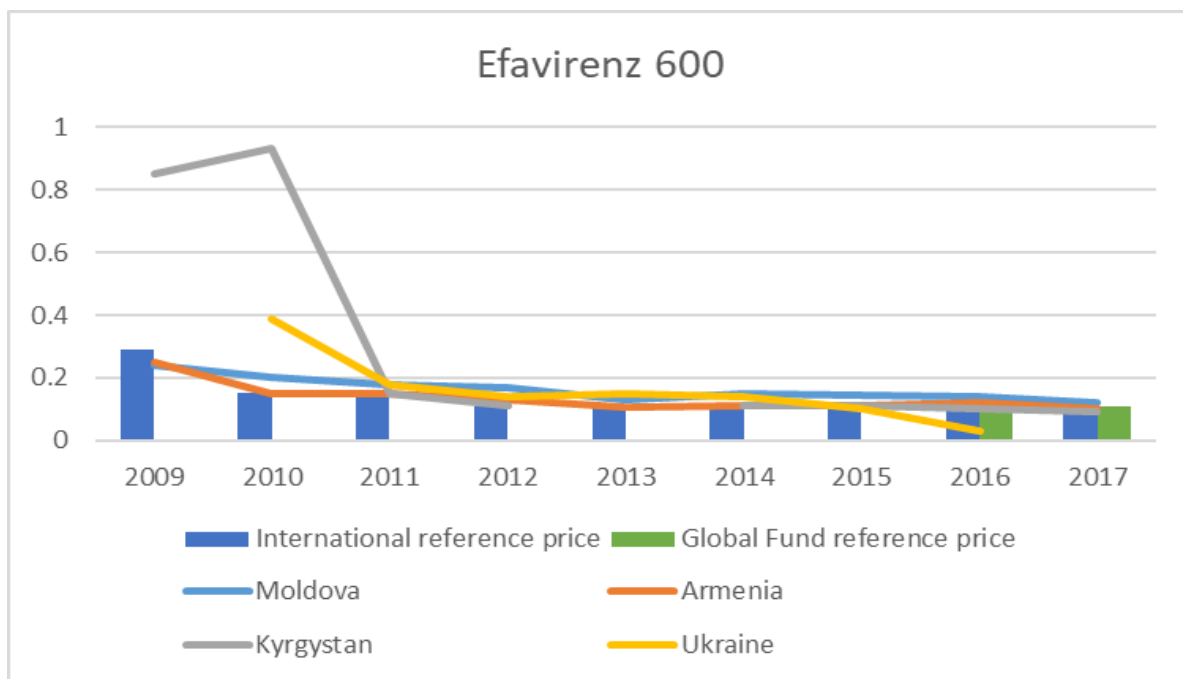


Figure 10. Cost dynamics for Efavirenz 600mg drug procured from Global Fund sources against other countries and reference prices



Analyzing the cost dynamics per scheme, depending on the procurement agency (Table 7), we have noticed a decrease in time of costs within UCIMP procurements, lack of tendencies within AMED procurements, the lowest price being recorded within UNDP procurements and maintenance of high costs of schemes that include LPV/r.

*Table 7. Cost Dynamics per scheme depending on procurement agency, 2010-2017*

ARV Scheme	2010	2011	2012	2013	2014	2015	2016	2017				
	UCIMP	UCIMP	UCIMP	UCIMP	UCIMP	AMED	UCIMP	AMED	UCIMP	AMED	UCIMP	UNDP
(TDF+FTC+EFV)	656.16	222.84	194.4	190.68	163.90	258.54	151.20	135.44	126.00	163.70	100.80	84.00
(TDF+3TC+EFV)		204.96	169.2	194.52	185.96	240.59	140.40	180.21	122.40	152.14	97.20	85.20
(AZT+3TC)+LPV/r	1205.28	1207.92	1112.88		810.51	1045.97	828.00	813.79	820.80		806.40	734.76
(TDF+FTC)+LPV/r	1251.48	1245.6	1129.92		809.23		813.60		813.60		810.00	
(TDF+3TC)+LPV/r		1152.24	1086.72				802.80		799.20		777.60	
(ABC+3TC)+LPV/r		1399.2	1270.44		903.36	1276.81	918.00	1944.38	939.60		885.60	

## CONCLUSIONS

Up to the present, the Republic of Moldova has used 3 antiretroviral procurement mechanisms, which have shown some advantages and disadvantages. Considering that ARV drugs procurement through UCIMP is only valid for the period of receiving Global Fund support, which is decreasing, and the fact that procurement through UNDP is also a short-term solution, it is necessary to strengthen the capacities of the state institutions to ensure full volume of quality and cost-effective ARV products for the future in a sustainable manner.

The most important aspects of ARV procurement during 2010-2017 are the following:

1. In the case of procurement from the Global Fund sources by UCIMP, we found:
  - Maintaining the tendency of lowering prices for most ARV products;
  - Procurement of generic drugs instead of original drugs, in case of lack of patent coverage (Darunavir);
  - Despite the price negotiation for the LPV/r drug with patent coverage, and obtaining of a 28% price reduction in 2012, this practice has not been repeated,

i.e. we found price stagnation for this product at a fairly high-level compared to the prices for other countries and the reference prices;

- Though the prices for most of the products are declining, they are found to be higher than the Global Fund reference prices.

2. In the case of procurement made from the State Budget funds by AMED, we found:

- In 2014, the first year when AMED made the procurements, as anticipated, the prices were higher by 24-163% than those obtained by UCIMP.
- In 2015, there was an unexpected situation, the cost difference decreased, being by 28-31% cheaper for two products procured by UCIMP, and by 10% cheaper for one of the products procured by AMED (it should be mentioned that it was the combined drug for first-line treatment) and by 31% for another of the two products. At the same time, there was a 583% difference for one of the AMED procured drugs, which is explained by the fact that the original product was procured.
- In 2016, it is of notice that the downward trend in prices is not maintained, and the product procured in 2015 with a price higher by 583% is procured in the original version again but at a price which is 914% higher.

3. In the case of the procurement made from the State Budget resources by UNDP we found out that:

- i. the procurement prices were lower compared to the prices obtained by UCIMP, the difference ranging between 10 and 80%.

The above-mentioned facts show that the possibilities of obtaining the best prices are not fully exploited, which impede us to cover a higher number of PTH with ARV treatment under the same budget, which would be in line with the National Program objective on increasing the ARV treatment coverage, including ARV drugs and with the context of current austerity budget.

## INTERVENTION OPPORTUNITIES

Considering the gradual takeover of ARV drugs procurement from the State Budget funds and the economic situation of the country, the following opportunities should be explored to assure a more efficient use of the Global Fund resources:

1. The short-term use of the UNDP procurement mechanism for procurement of ARV drugs from both public money and Global Fund resources.
2. Switching to the use of the Wambo "pooled" procurement mechanism developed by the Global Fund, available for main recipients and for countries starting with 2016.
3. Modify the national legal framework for public procurement to create procurement conditions for important public health medications through global procurement agencies.
4. Optimize treatment regimens in place. For example, to consider the use of the TDF + 3TC + DTG combination for Scheme I treatment, which according to the agreement between the drug manufacturers on the one hand, and the country governments, international agencies and donors, on the other hand, will cost USD 75 per patient per year for the Republic of Moldova. Explore other alternatives for cost-effective ARVs.
5. Develop and implement policies and actions to lower prices of ARV drugs.
6. Ensure transparency of procurement irrespective of sources of funding and procurement agency.
7. Involvement of civil society in monitoring the procurement of ARV drugs.

