



# Pharmacoepidemiological Analysis Of The Costs Of Changing Antiretroviral Therapy Regimen In Hiv-Infected Patients In The Syrian Arab Republic

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## Abstract

The aim of the study was to optimize the approach to the treatment of HIV-infected patients in the Syrian Arab Republic based on data from the pharmaco-economic analysis. The frequency of changing the original HIV treatment regimen was high and was due to adverse drug reactions in 48.5% of cases. The change in the cost of treatment when replacing antiretroviral therapy regimens depending on the reason for the replacement was analyzed. In addition, the cost of various 1st, 2nd and 3rd line antiretroviral therapy regimens was studied. The results of pharmaco-economic analysis performed can be used to select the initial antiretroviral therapy regimen and replace it if necessary.

**Keywords:** HIV, antiretroviral therapy, costs, pharmaco-economic analysis, Syrian Arab Republic.

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## Introduction

Today, the spread of HIV infection is one of the global problems of modern society around the world [8, 10, 11, 16, 25 and 27]. In recent years, HIV epidemiological studies in the Middle East and North Africa (MENA) have begun to address the lack of data on HIV in the region [6, 7, 17, 18, 12, 20, 21, 23, 24 and 27].

The MENA region is characterized by an increase in the number of new AIDS cases despite predominantly low HIV prevalence compared to the rest of the world. New HIV infections in MENA increased by 12% compared to 2010, and AIDS-related deaths increased by 11%, according to UNAIDS 2018 [9]. It should be noted that the achievement of the UNAIDS 90-

90-90 targets still faces a number of difficulties in European countries and North America, and in the MENA region the situation is even more difficult in many respects [13, 15, 26]. Only 50% of people living with HIV knew their HIV status at the end of 2017 and the gap in reaching 90% of the program was 87,100. Antiretroviral therapy (ARVT) was provided to only 29% of patients with HIV, and viral suppression was achieved only 22% of treated patients.

To date, no complex marketing, pharmaco-epidemiological, pharmaco-economic and sociological studies of ARVT regimens have been conducted in the Syrian Arab Republic (SAR), which determines the relevance and practical significance of the study.

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The purpose of the study is to optimize the approach to the treatment of HIV-infected patients in SAR based on data from the pharmacoeconomic analysis.

To achieve this goal, the following tasks were formulated:

- 1) to study the structure of applied ARVT regimens in HIV-infected patients in SAR;
- 2) to identify the frequency of replacement of ARVT regimens and analyze their reasons;
- 3) to conduct the pharmacoeconomic analysis ("cost-effectiveness") of the ARVT regimens used in SAR and evaluate the costs of changing the ARVT regimens.

### Materials and methods

The retrospective pharmacoepidemiological analysis of medical records of 201 HIV-diagnosed patients receiving ARVT, registered with the National AIDS Center in Damascus (SAR) at the end of 2018, was carried out. The average age of patients was  $41.1 \pm 11.6$  years. Among patients there were 132 (65.7%) men and 39 (34.3%) women.

The study was carried out at the Department of General and Clinical Pharmacology of the Medical Institute of the Peoples' Friendship University of Russia (RUDN).

Search operations were carried out by constructing SQL server queries in the MOA environment with subsequent data processing in Microsoft Office Excel.

To estimate the cost of antiretroviral drugs (ARVs) used as part of ARVT regimens, we used data on the total number of purchased drugs and their cost at the end of the auction, provided by the Ministry of Health of Damascus (SAR). To calculate prices in rubles, currency conversion was carried out as of January 01, 2021.

To obtain the price per unit of the drug, the cost of a lot of each drug was divided by the number of tablets in the lot. To obtain the price for one package, the unit price of the drug was multiplied by the number of units of the drug in the package.

The cost of each component of the ARVT regimen was calculated using the formula:, where  $X_i$  – the cost of drug provision during the study period; P – price per package of a medicinal product; Q – number of tablets in a package; N – frequency of reception; L – treatment period.

For clinical and economic evaluation of the costs of pharmacotherapy of patients, the integrated ABC/VEN analysis was used [11]. ABC analysis was performed with the trade names of drugs.

The unit of ARVT effectiveness was the percentage of treatment effectiveness. The efficiency of each regimen was calculated by the formula;

where X – effectiveness of the pharmacotherapy regimen, %; F – the number of effective patients in the context of the regimen; G – total number of patients in the context of the regimen.

To calculate the cost-effectiveness ratio (CER) for each pharmacotherapy regimen, that is, the cost per unit of efficiency, we used the following formula;

where CER – cost-effectiveness ratio; DC – direct costs of drug treatment; Ef – treatment success rate.

The incremental rate (ICER) was calculated as follows [5];

where ICER – cost of an additional unit of efficiency;  $DC_1$ ,  $DC_2$  – direct costs of different treatment regimens;  $Ef_1$ ,  $Ef_2$  – efficacy of compared pharmacotherapy regimens.

To study the sustainability of the cost-effectiveness data obtained in the study, one and two-way sensitivity analyses were performed for pharmacoeconomically sound treatment regimens in the context of therapy, taking into account the minimum cost of generics. To conduct the one-way analysis, it was assumed that prices in the pharmaceutical market would increase. Based on this, the change in the CER coefficient was determined.

To calculate the cost of the prescribed ARVT regimen, the summation of the costs of its components was carried out. Based on the data obtained, the average cost of combinations of certain classes of ARVs was calculated.

### Results and discussion

According to medical records, it was established that HIV-infected patients in SAR were prescribed the following treatment regimens as 1st line therapy:

- TDF+FTC+EFV (Viraday) (n=155, 50.3%);
- AZT+3TC+NVP (Duovir-n) (n=95, 30.8%);
- D4T+ABC+3TC (n=23, 7.4%);
- TDF+FTC\_LPV/r (n=16, 5.1%);
- AZT+3TC+LPV/r (n=10, 3.2%);
- 3TC child+ABC+LPV/r (n=6, 1.9%);
- LPV/ r+ABC+3TC (n=1, 0.9%).



Table 1 shows changes in the treatment regimen in 2018 compared to 2017.

**Table 1** Changes in ARVT regimens in SAR in 2018 compared to 2017.

Treatment regimen	2017	2018	Dynamics, %
Viraday, TDF+FTC+EFV	89	118	+ 32,58
Duovir-n, AZT+3TC+NVP	49	38	- 22,45
Kaltra+Truvada, TDF+FTC_LPV/r	21	9	-57,14
Kaltra+Duovir, AZT+3TC+LPV/r	12	6	-50,00
3TC child+ABC+LPV/r child	0	6	+100
D4T+ABC+3TC	0	23	+100
LPV/ r+ABC+3TC	0	1	+100
In total	171	201	-

3 new ARVT regimens were added in 2018 – 3TC child+ABC+LPV/r child (n=6,1.9%); D4T +ABC +3TC Dolyutegravir+Abacavir Sulfate +Lamivudine (n=23, 7. 4%) and LPV /r+ ABC+3TC kaletra+Abacavir Sulfate+ Lamivudine (n=1, 0.9%).

At the beginning of 2019, the 1st ARVT regimen was changed in 241 patients (78.2%). Adverse drug reactions were the most common reason for changing treatment regimens (n=117, 48. 5%). When prescribing ARVT, it is recommended to use the least toxic regimens with fixed doses of drugs [2]. However, the complexity of choosing a therapeutic regimen for HIV infection lies in the need for a combination of 2 to 5 ARVs with different pharmacokinetics and pharmacodynamics, each of which has toxicity and adverse reactions that can be potentiated [8].

Other reasons for changing the ARVT regimen were the absence of the drug (n=40, 16.6%), the

prescription of antiviral pharmacotherapy for chronic hepatitis C (n=29, 12.0%), pregnancy planning or its onset (n=21, 8.7%), development of HIV drug resistance (n=14, 5.8%), change in drug regimen to improve treatment adherence (n=13, 5.3%) and immunological treatment failure (n=7, 2.9%).

Considering that the quality of life of patients depends on the degree of control over HIV [4], a nucleoside analogue in combination with a protease inhibitor (PI), integrase or entry inhibitors is considered to be rational combinations of ARVT [1]. A total of 159 drug changes were performed in our study, with 81 drugs (50.9%) belonged to the nucleoside reverse transcriptase inhibitor (NRTI) group, 47 drugs (29.5%) belonged to the protease inhibitor group, and 31 drugs (19. 5%) belonged to the group of non-nucleoside reverse transcriptase inhibitors (NNRTIs).

The cost of 1st line ARVT regimens and the frequency of their prescription are shown in Table 2.

When choosing an ARVT regimen, according to international recommendations, along with the safety of therapy, its pharmaco-economic efficiency is taken into account [3]. To assess the pharmaco-economic effectiveness of therapy, the most optimal method is the cost-effectiveness method, which allows you to combine the indicators of the clinical effectiveness of the drug and the cost of achieving such effectiveness into a single whole [5].

**Table 2** Cost of 1st line ARVT regimens and frequency of their administration

№	ARVT regimen			Frequency of administration, %	The cost of therapy, rub.		USD
					month	year	year
1	AZT/3TC	EFV		34.5	4421,3	53056,1	1689,8
2	AZT/3TC	LPV/r		13.8	10484,5	125814,4	4007,1
3	Φ-A3T	ddI	EFV	6.9	8223,2	98678,4	3142,8
4	AZT	ddI	LPV/r	5.2	10351,9	124222,8	3956,4
5	Φ-A3T	3TC	NVP	5.2	7521,9	90262,7	2874,8
6	ABC	3TC	EFV	5.2	7390,8	88689,7	2824,7
7	AZT/3TC	NVP		5.2	4835,7	58028,2	1848,1
8	ABC/3TC	DRV/r		3.4	22962,4	275548,2	8775,9
9	ABC/3TC	LPV/r		1.7	13493,0	161916,6	5156,9
10	D4T	3TC	ATV	1.7	13104,4	157253,2	5008,4
11	AZT/3TC	ATV		1.7	12518,1	150217,2	4784,3
12	ddI	3TC	LPV/r	1.7	11263,0	135156,1	4304,6
13	d4T	3TC	LPV/r	1.7	11070,9	132850,4	4231,2
14	TDF	3TC	EFV	1.7	10602,9	127235,0	4052,3
15	ABC/3TC	EFV		1.7	7428,0	89135,9	2838,9
16	Φ-A3T	3TC	EFV	1.7	7107,6	85290,7	2716,4
17	D4T	3TC	EFV	1.7	5007,7	60092,1	1913,9
18	ddI	AZT	EFV	1.7	4288,7	51464,5	1639,1
19	AZT	3TC	NVP	1.7	3979,1	47749,4	1520,8
	Mean				9266,1	111192,7	3548,8



Of particular interest from the point of view of drug supply costs is the choice of the 1st ART regimen for patients who have not previously received treatment. The average cost of the 1st prescribed treatment regimen was 9266.1 rubles/month, while the first ten most expensive 1st-line regimens include a PI-class drug as the third component. The average cost

of 2NRTI+PI regimens was 13,556.6 rubles/month, which is 2 times higher than the average cost of a 2NRTI+NNRTI regimen. Table 3 shows the cost of 2nd and 3rd line ARVT regimens that were used when replacing 1st line therapy.

**Table 3** Cost of 2nd and 3rd line ARVT regimens

№	ARVT regimen			The cost of therapy, rub.		USD
				month	year	year
1	ABC/3TC	DRV/r	T-20	89453,9	1073446,5	34188,2
2	ABC/3TC	LPV/r	T-20	79982,7	959792,5	30568,4
3	ABC/3TC	RAL		38241,7	458899,9	14615,5
4	AZT/3TC	RAL		35235,0	422820,1	13466,4
5	ABC/3TC	ETV		25519,0	306228,3	9753,1
6	ABC/3TC	DRV/r		22962,4	275548,2	8775,9
7	ABC/3TC	ATV/r		16346,3	196155,5	6247,4
8	ABC/3TC	LPV/r		13493,0	161916,6	5156,9
Mean				40154,2	481850,9	15346,5

The average cost of 2nd line therapy turned out to be 4 times higher than the average cost of 1st line therapy (40154.2 rubles/month versus 9266.1 rubles/month, respectively), which is associated with the use of expensive new generation drugs.

Table 4 shows the change in the cost of therapy in case of changing the original treatment regimen for various reasons.

The share of costs in case of replacement of the 1st ARVT regimen in case of therapy failure was

43.0%, in case of development of adverse drug reactions it was 36.0%, in case of drug supply problems it was 11.0%.

When replacing the initially prescribed ARVT regimen, the cost of providing patients with drugs increased by 460798.5 rubles/month or 10017.4 rubles/month on average per 1 patient who changed the regimen, since a more expensive treatment regimen was prescribed.

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**Table 4** Changing the cost of treatment when replacing ARVT regimens depending on the reason for the replacement

№	Reason for changing the ARVT regimen	Case frequency	Average cost, month / rub.		Change in cost, month / rub.	
			initial regimen	prescribed treatment regimen	in total	per patient
1	Side effects of ARVT	48,5%	8291.7	11147.7	+166898,9 - 26484.6	+5057,5 -802,6
2	Absence of the drug	16,5%	8654.7	9877.6	+ 50342,8 -21107,7	+4576,6 -2464,3
3	Treatment failure	8,7%	11271.4	30208.7	+189373,5	+23671,7
4	Pregnancy planning	8,7%	6970.5	11283.36	+44397,0	+4439,7
5	Optimization of treatment regimen	5,2%	8963.4	10594.45	+9786,3	+1631,0
In total					+460798,5 -54860,1	+10017,4 -1192,6

**Conclusion**

The pharmacoepidemiological analysis revealed a high rate of replacement of ARVT regimens, mainly due to clinically significant adverse

reactions to ARVs. The average cost of 2nd line ARVT per month exceeds the average cost of 1st line therapy by 4 times, which is associated with the use of expensive new generation drugs.





The average cost of 1st-line regimens based on 2NRTI+PI is 2 times higher than the average cost of regimens based on 2NRTI+NNRTI, which, along with clinical aspects, raises the question of the advisability of prescribing them as 1st-line regimens and emphasizes the need for further pharmaco-economic studies in order to substantiate the optimal choice of ARVT regimens.

When replacing the initially prescribed ARVT regimen, the cost of providing patients with drugs increased by 10,017.4 rubles per month on average per 1 patient who changed the regimen. The data obtained confirm the need for prescribing drugs with a higher safety profile as first-line regimens, strengthening measures to increase patient adherence to treatment, as well as improving the organization of drug supply in medical institutions. The combination of these measures will reduce the high costs of frequent replacement of the ARVT regimen.

## References

- Afonina L. Yu. HIV infection and AIDS: national guidance / edited by Academician of the Russian Academy of Medical Sciences V.V. Pokrovsky. Moscow: GEOTAR-Media, 2013. 608 p.
- Blokh A. I., Pasechnik O. A. The burden of disease and the lost life potential of the population due to HIV infection // HIV infection and immunosuppression. 2017. V. 9. № 3. P. 91-97.
- Screening and antiretroviral therapy in adults and adolescents. Clinical protocol for the WHO European Region. Geneva, WHO, 2012. 91 p.
- Ulyukin I. M. Influence of antiretroviral therapy on the main spheres of life of patients with HIV infection // Bulletin of St. Petersburg State University. Series 11. 2013. Release 2. P. 153-160.
- Yagudina R. I., Serpik V. G. On the possibilities of combining the analysis of "impact on the budget" and the analysis of "cost-effectiveness" - the creation of a "3D" pharmaco-economic model // Pharmaco-economics: theory and practice. 2014. V.2. №3. P. 5-8.
- Abu-Raddad L. J., Akala F. A., Semini I., et al. HIV/AIDS Epidemic in the Middle East and North Africa. Time for strategizing action. Washington : The World Bank, 2010. 310 p.
- Abu-Raddad L. J., Hilmi N., Mutmaz G., et al. Epidemiology of HIV infection in the Middle East and North Africa // AIDS. 2010. Vol. 24. P. 5-23. doi: 10.1097/01.aids.0000386729.56683.33.
- Chakroun M., Razik F., Karkouri M., et al. HIV epidemic in the Maghreb. Magnitude, trend and management // Tunis Med. 2018. Vol. 96. Vol. 10-11. P. 599-605.
- Chemaitelly H., Weiss H.A., Calvert C., et al. HIV epidemiology among female sex workers and their clients in the Middle East and North Africa: systematic review, meta-analyses, and meta-regressions // BMC Med. 2019. Vol. 17 (1). P. 119.
- Gangcuangro L. M. HIV crisis in the Philippines: urgent actions needed // The Lancet. 2019. Vol. 4 (2). e84. DOI:https://doi.org/10.1016/S2468-2667(18)30265-2.
- Global HIV/AIDS Overview: сайт. 2021. URL: https://www.hiv.gov/federal-response/pepfar-global-aids/global-hiv-aids-overview.
- Gökengin D., Dorroudi F., Tohme, et al. HIV/AIDS: trends in the Middle East and North Africa region // International Journal of Infectious Diseases. 2016. Vol. 44. P. 66-73. DOI:https://doi.org/10.1016/j.ijid.2015.11.008.
- González-Alcaide G., Menchi-Elanzi M., Nacarapa E., et al. HIV/AIDS research in Africa and the Middle East: participation and equity in North-South collaborations and relationships // Global Health. 2020. Vol. 16 (83). https://doi.org/10.1186/s12992-020-00609-9.
- Hogg R., Lima V., Sterne J. A. Antiretroviral Therapy Cohort Collaboration. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies // Lancet. 2008. Vol. 26. P. 293-299.
- Joulaei H., Shooshtarian S., Dianatinasab M. Is UNAIDS 90-90-90 target a Dream or a Reality for Middle East and North Africa Region on Ending the AIDS Epidemic? A Review Study // AIDS Rev. 2018. Vol. 20 (2). P. 83-93.
- Luz P. M., Veloso V.G., Grinsztejn B. The HIV epidemic in Latin America: accomplishments and challenges on treatment and prevention // Curr Opin HIV AIDS. 2019. Vol.14 (5). P. 366-373.
- Middle East and North Africa / UNAIDS. Joint United Nations Programme on HIV/AIDS. 2006. URL: https://www.who.int/hiv/mediacentre/200605-FS\_MENA\_en.pdf.
- Miles to go. The response to HIV in the Middle East and North Africa / Global AIDS update, 2018. 50 p. URL: https://www.unaids.org/sites/default/files/media\_asset/miles-to-go\_middle-east-and-north-africa\_en.pdf.
- Mondi A., Cozzi-Lepri Tavelli A., De Luca A., et al. Icona Foundation Study Group. Effectiveness of dolutegravir-based regimens as either first-line or switch antiretroviral therapy: data from the Icona cohort // J. Int. AIDS Soc. 2019. Vol. 22 (1). e25227.
- Mumtaz G. R., Weiss H. A., Thomas S. L., et al. HIV among People Who Inject Drugs in the Middle East and North Africa: Systematic Review and Data Synthesis // PLOS Medicine. 2014. Vol. 11 (6). e10016663. DOI: https://doi.org/10.1371/journal.pmed.1001663.
- Mutmaz G. R., Riedner G., Abu-Raddad L. J. The emerging face of the HIV epidemic in the Middle East and North Africa // Wolters Kluwer Health. Epidemiology: concentrated epidemics. Vol. 9 (2). P. 183-191. URL: https://researchonline.lshtm.ac.uk/id/eprint/2025547/1/cohiv-9-183.pdf.
- Mutmaz G., Hilmi N., Akala F. A., et al. P1-S1.17 HIV-1 molecular epidemiology in the Middle East and North Africa // Sexually Transmitted Infections. 2011. Vol. 87. A106-A106. DOI:10.1136/sextrans-2011-050108.17.
- Obermeyer C. M. HIV in the Middle East // BMJ. 2006. Vol. 333. P. 851-854. https://doi.org/10.1136/bmj.38994.400370.7C.
- Oraby D. Women living with HIV in the Middle East and North Africa // The Lancet. Public Health. 2018. Vol. 3



(2). e63. DOI:[https://doi.org/10.1016/S2468-2667\(18\)30007-0](https://doi.org/10.1016/S2468-2667(18)30007-0).

Saag M. S., Gandhi R.T., Hoy J. F., et al. Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults: 2020 Recommendations of the International Antiviral Society-USA Panel // JAMA. 2020. Vol. 324 (16). P. 1651-1669.

Setayesh H., Roudi-Fahimi F., El Feki S., et al. HIV and AIDS in the Middle East and North Africa / Population Reference Bureau. 2014. 32 p.

URL:<https://www.prb.org/wp-content/uploads/2014/06/mena-hiv-aids-report.pdf>.

Yasaveev I. Not an epidemic, but a global problem: the authorities' construction of HIV/AIDS in Russia // Medicine (Baltimore). 2020. Vol. 99 (21). e18945.

