

*O. V. Bachynska*¹ <https://orcid.org/0000-0001-5208-3133>

*I. T. Doan*² <https://orcid.org/0000-0002-2944-9384>

*V. V. Kozlov*³ <https://orcid.org/0000-0002-5454-4797>

*L. I. Hetman*⁴

*V. I. Romanchuk*⁴ <https://orcid.org/0009-0009-1099-7629>

*O. A. Gerasymenko*¹ <https://orcid.org/0000-0001-6064-8229>

*O. S. Sovirda*¹ <https://orcid.org/0000-0002-6728-0540>

PROBLEMATIC ISSUES OF PRESCRIBING ANTIRETROVIRAL THERAPY FOR HIV/TUBERCULOSIS CO-INFECTED PATIENTS IN UKRAINE

¹ Odesa National Medical University, Odesa, Ukraine

² International European University, Kyiv, Ukraine

³ Bogomolets National Medical University, Kyiv, Ukraine

⁴ State Institution "Public Health Center of the Ministry of Health of Ukraine", Kyiv, Ukraine

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O. V. Bachynska¹, I. T. Doan², V. V. Kozlov³, L. I. Hetman⁴, V. I. Romanchuk⁴, O. A. Gerasymenko¹, O. S. Sovirda¹
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Introduction. Thanks to antiretroviral therapy (ART), humanity has made progress in overcoming HIV infection. With adherence to treatment, ART suppresses HIV multiplication, promotes immune system maintenance and recovery, provides people living with HIV (PLHIV) with a familiar, quality-adjusted and long life, and prevents further HIV transmission. Although the recommendation to start ART in such patients as soon as possible, regardless of CD4 cell count, has been implemented since 2010, there is still a delay in prescribing ART in Ukraine.

Materials and methods. We conducted a desk study to identify problematic issues of delaying and/or not prescribing ART to patients with HIV/TB coinfection in Ukraine based on original observations, and analysis of scientific publications, regulations, and national and international standards of HIV/TB coinfection treatment.

Research findings and their discussion. It has been established that the regulatory documents governing the detection, registration, medical surveillance, and treatment of HIV infection and tuberculosis in Ukraine are in line with international recommendations. The prescription of ART for HIV/TB co-infected patients in Ukraine is related to anti-tuberculosis treatment. The timeframes for ART initiation after antituberculosis therapy (ATT) administration are up to 8 weeks (early initiation), after 8 weeks (delayed initiation) and up to 2 weeks (early initiation). According to new scientific evidence, ART should not be associated with ATT, and ART initiation after prescription of antimycobacterial therapy should be reduced to 2 weeks. ART initiation before 8 weeks should be delayed only in PLHIV receiving treatment for CNS localized TB.

Conclusion. The reasons for not prescribing and/or delaying the prescription of ART to patients with HIV/TB co-infection include the lengthy algorithm of TB diagnosis by a TB physician alone, and in some cases by a consilium of physicians; the refusal of medical institutions to conduct HIV testing using rapid tests, and the transfer of this HIV testing service to specialized laboratories using enzyme-linked immunosorbent assays (ELISA); the low level of HIV and TB screening among key populations at risk and education on HIV and TB prevention methods; and the low level of HIV and TB testing among key populations at risk.

Key words: HIV infection, tuberculosis, antiretroviral therapy, co-infection.

О. В. Бачинська¹, І. Т. Доан², В. В. Козлов³, Л. І. Гетьман⁴, В. І. Романчук⁴, О. А. Герасименко¹, О. С. Совірта¹
**ПРОБЛЕМНІ ПИТАННЯ ПРИЗНАЧЕННЯ АНТИРЕТРОВІРУСНОЇ ТЕРАПІЇ ХВОРИХ НА КО-ІНФЕКЦІЮ
ВІЛ/ТУБЕРКУЛЬОЗ В УКРАЇНІ**

¹ Одеський національний медичний університет, Одеса, Україна

² Міжнародний Європейський університет, Київ, Україна

³ Національний медичний університет імені О. О. Богомольця, Київ, Україна

⁴ ДУ «Центр громадського здоров'я МОЗ України», Київ, Україна

Починаючи від 2010 року в Україні антиретровірусна терапія (ART) має починатись у ВІЛ-позитивних людей незалежно від рівня CD4+ клітин, водночас доволі часто спостерігається затримка із призначенням ART.



Метою роботи було проведення аналізу причин затримки або непризначення ART для пацієнтів з ко-інфекцією ВІЛ/ТБ, базуючись на власних спостереженнях, аналізі наукових публікацій, національних і міжнародних стандартів лікування.

Встановлено, що причинами непризначення або затримки призначення ART для пацієнтів з ко-інфекцією ВІЛ/ТБ є продовження практики призначення протитуберкульозної терапії вузькими спеціалістами, проведення тестів на ВІЛ лише спеціалізованими лабораторіями з використанням фермент-пов'язаного імуносорбентного аналізу (ELISA), неналежне проведення скринінгових досліджень щодо виявлення ВІЛ і ТБ у групах ризику, недостатнє проведення освітньої роботи щодо попередження поширення ВІЛ і ТБ тощо.

Ключові слова: ВІЛ-інфекція, туберкульоз, антиретровірусна терапія, ко-інфекція.

Introduction. A recent UN report on HIV/AIDS says progress against the HIV epidemic has slowed significantly over the past two years due to the COVID-19 pandemic and other global crises. By early 2022, the number of people living with HIV (PLHIV) worldwide has reached 38.4 million, 75 per cent of whom are receiving ART; 5.9 million PLHIV do not know their HIV status. Attainment of the 95-95-95 Fast Track targets globally was 85-88-92 [1; 2].

The problem of HIV infection and tuberculosis has not only affected Ukraine but has become a great challenge to both healthcare institutions and the entire society. In addition, the problem's scale has proved to be very large, as Ukraine is among the top three countries in Eastern Europe and Central Asia in terms of HIV incidence, prevalence and mortality rates [1]. The morbidity rate in Ukraine was one of the highest in Europe in 2020: 39 per 100.000 inhabitants. In most cases, HIV infection was diagnosed in an advanced stage of the disease. From 37% to 75% of patients (depending on the region of Ukraine) had CD4 levels <350 cells/ μ L when admitted for medical observation, which, on the one hand, indicates a deep damage to the immune system of PLHIV, and on the other hand, a long period of transmission. The level of medical monitoring coverage of newly detected HIV-infected people was 82.7%, with significant regional variations from 47.3% to 100%.

One of the reasons for the late detection of HIV infection is that HIV infection does not have its own clinical picture and is manifested by various severe diseases, opportunistic infections, and tumors developing amidst immune system disorders.

Infection with *Mycobacterium tuberculosis* can occur at any age. In most cases, TB does not develop in people who are not infected with HIV. At the same time, TB is a severe problem for HIV-infected people: according to UNAIDS, it is one of the main causes of death. It is worth noting that TB can develop at any stage of HIV infection, with any number of CD4+ lymphocytes and is characterized by a variety of clinical manifestations (pulmonary and extrapulmonary) with a tendency to generalize the specific process. Treatment of TB in an HIV-positive person is longer and less effective. On the one hand, HIV infection increases the risk of developing active TB, and on the other hand, TB negatively affects the course of HIV infection. Following UNAIDS, PLHIV are 18 times more likely to have TB. Although 85 per cent of TB patients can be cured, the success rate for PLHIV is much lower – only about 77 per cent [3].

Although the detection rate of active TB cases among HIV-infected people under medical surveillance in Ukraine decreased to 12.9% in 2020, down from 20.3% in 2019,

HIV/TB coinfection is responsible for one in two AIDS-related deaths in Ukraine [1].

Humanity has made progress in overcoming HIV infection due to ART. While adhering to the treatment regimen, ART inhibits the multiplication of HIV, helps preserve and restore the immune system and provides PLHIV with the common, high-quality and long life.

Thus, early detection of HIV infection and early initiation of ART will, on the one hand, contribute to the prevention of opportunistic infections and, on the other hand, to public health by preventing or stopping further HIV transmission.

The aim of the study was to identify problematic issues of delaying and/or not prescribing ART for patients with HIV/TB coinfection in Ukraine based on original observations and analysis of scientific publications, regulatory acts, and national and international standards of HIV/TB co-infection treatment.

Materials and methods. In our study, we used the reporting forms of the Central Health Service of the Ministry of Health of Ukraine on the incidence of HIV/TB co-infection in Ukraine during 2015-2021. We analyzed a list of international and national recommendations and standards, clinical protocols for the treatment of HIV/TB co-infection. Some provisions of current regulatory documents have been adapted, including standards and protocols for starting ART treatment in patients with HIV/TB co-infection, according to the multimodal strategy of the WHO, the experience of other authors on the reasons for delayed treatment and/or not prescribing ART to patients has been applied.

Epidemiological and statistical research methods were used.

Research findings and their discussion. The main criterion for prescribing ART to HIV-infected patients from the 1990s to 2015 was the number of CD4 cells/mm³ [4]. In those years, antiretroviral drugs (ARVs) were not widely used, especially in the early stages of infection, due to their toxicity and the low threshold for the development of resistance of viruses to their action. Medical supervision of HIV-infected patients was carried out, treatment of opportunistic infections and concomitant pathology was prescribed.

Later, more effective, less toxic ARV drugs and their combinations were introduced, and the optimal threshold of CD4 cells/mm³ for starting ART was raised. In 2002, the threshold of CD4 cells for starting ART was less than 250 cells/mm³, already in 2010 it was 350 cells/mm³ [5]. Since 2013, treatment has been started when the CD4 count is less than 500 cells/mm³ [6].

In 2016, WHO strongly recommended treatment for all, namely initiation of ART for all adults living with HIV, regardless of HIV clinical stage and at any CD4/mm³ count.

Implementation of this recommendation contributed to better access to treatment. In addition, in 2017, the WHO provided a recommendation to start ART as soon as a patient is diagnosed with HIV infection [7, 8, 9].

In our country, the implementation of this recommendation began in 2019 after the entry into force of the order of the Ministry of Health of Ukraine No. 1292 "On the approval of a new Clinical Protocol on the use of antiretroviral drugs for the treatment and prevention of HIV infection" [10]. Our study analyzed the results of the implementation of different levels of this clinical protocol in health care institutions of Ukraine. The document regulates the appointment of ART to all HIV-infected persons, regardless of the clinical stage of the disease and with any number of CD4 cells/mm³ (adults, pregnant and lactating women, adolescents (from 10 to 19 years old), children under 10 years old, and babies). Currently, the date of initiation of ART in Ukraine is not related to the number of CD4 cells/mm³.

We found that after the introduction of a new clinical protocol in 2019, according to the results of a retrospective epidemiological analysis of the incidence of tuberculosis in general and co-infection with HIV/TB in particular, the number of registered cases is steadily decreasing (Fig. 1).

Thus, during 2015–2019, the incidence rate of TB was 65.29±3.62 per 100 000 population; in 2020–2021 – 42.90±2.41, HIV/TB co-infection: 14.52±1.87 and 8.98±2.46, respectively (p<0.001; Pearson coefficient 0.95).

The proportion of HIV-infected people among TB patients ranged from 20.1 to 23.0%. The average HIV/TB incidence rate (new cases and relapses) in Ukraine in 2021 was 8.98 per 100 000 population, ranging from the highest level in Odessa region (33.1) to the lowest (1.2) in Ivano-Frankivsk region [1]. Adequate TB detection and treatment increases the life expectancy of PLHIV and reduces the severity of TB.

A study was conducted to identify the reasons for delaying and/or non-appointment of ART to tuberculosis patients at various stages of the organization of medical assistance to the population. Thus, according to the mentioned clinical protocol, the appointment of ART to people living with HIV

(PLHIV) without an established diagnosis of tuberculosis should begin within seven days from the date of diagnosis of HIV infection. However, in health care facilities providing medical care at all levels, the prescription of ART is usually associated with the prescription of anti-tuberculosis drugs (TBDs). According to the results of the study, doctors first confirmed the diagnosis of tuberculosis and prescribed anti-tuberculosis therapy, and then decided to prescribe ART. The dependence of the duration of ART prescription in patients with HIV/TB co-infection on the initiation of anti-tuberculosis treatment (ATP) was revealed.

Thus, an important aspect for the timely initiation of ART in patients with HIV infection is the accelerated diagnosis of the presence of tuberculosis in PLHIV through a thorough assessment of symptoms and signs, as well as diagnosis using a rapid molecular genetic method for the detection of the pathogen (Xpert MTB/RIF).

It was found that the delayed start of ART (within 8 weeks from the start of ATT) was prescribed to patients in 35.2% of newly registered cases of co-infection, and the early start of ART (within 2 weeks from the start of ATT) – in 10.5%. It is known that early initiation of ART is recommended for patients with co-infection who have significant immunosuppression (number of CD4 cells <50/mm³) [10, 13].

Currently, evidence is accumulating on the benefits of early initiation of ART in patients with HIV/TB co-infection [11, 12]. It is recommended to start ART as soon as possible in children living with HIV who are diagnosed with active tuberculosis, regardless of CD4 cell count/mm³ and clinical stage. It is recommended to start ART in these children within 8 weeks of starting ATT. According to the WHO Recommendations, which summarize the key principles of HIV prevention, testing, treatment, provision of services and monitoring, ART should be prescribed as soon as possible, no later than 7 days after the diagnosis of HIV infection for PLHIV without symptoms of tuberculosis, including children under 5 years of age, due to increased risk of death and disease progression.

At the same time, in Ukraine, the appointment of ART to patients with a newly diagnosed HIV infection in most cases, on average, takes place within 4 weeks.

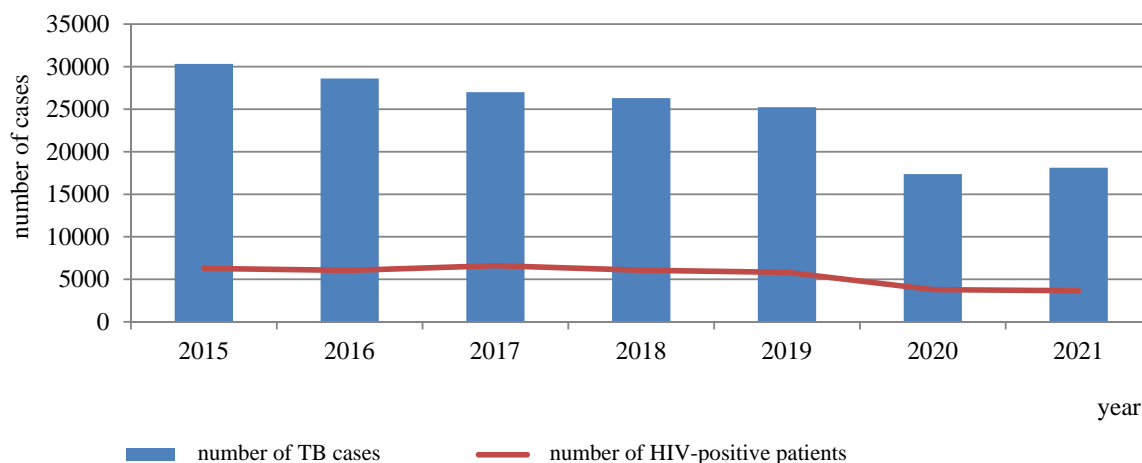


Fig. 1. Number of registered TB and HIV/TB cases (2015–2021)

According to the clinical protocol, HIV-infected persons with suspicion of tuberculosis, but without signs of meningitis, are prescribed ART, additional examination for tuberculosis and repeated medical consultation after 7 days. Currently, the analysis of the received data shows that only in 42.1% of cases, doctors complied with the requirements of timely prescription of ART due to the lack of test systems for the diagnosis of tuberculosis.

According to the order, HIV-infected individuals who are also diagnosed with TB and are already receiving treatment for TB must start ART within two weeks, regardless of their CD4/mm³ count. HIV-infected persons who have a confirmed diagnosis of tuberculosis and do not receive ART and treatment for tuberculosis are initially prescribed ATT and only two weeks later – ART. For PLHIV receiving treatment for clinically or laboratory-confirmed central nervous system TB, ART should be delayed and initiated no earlier than 8 weeks after initiation of TB treatment [7].

According to global estimates, the annual risk of developing active tuberculosis in HIV-infected patients with latent tuberculosis infection (LTI) is 3–12 times higher than in the general population. Treatment of PLHIV infected with LTI reduces the risk of tuberculosis by 62% and the risk of death by 26%. Therefore, prevention of tuberculosis through screening for timely detection and treatment of LTI is one of the main components of clinical management of PLHIV in Ukraine [1].

In Ukraine, the treatment of tuberculosis in HIV-infected patients is carried out according to the same scheme and duration as in HIV-negative patients. If the patient is already taking ART, it is continued and, if necessary, the treatment is adjusted taking into account the clinical situation (compatibility of ART and antimycobacterial drugs, replacement therapy). According to the Unified Clinical Protocol for providing medical care to patients with co-infection (TB/HIV/AIDS), the reason for delaying ART is the toxic effect of the simultaneous combination of ART and ATT [13]. Delay in early initiation of ART in HIV-infected individuals with central nervous system tuberculosis is associated with life-threatening complications and serious adverse reactions in these patients.

According to the results of our study, one of the most serious reasons for the delay in the appointment of ART for patients with HIV/TB co-infection in medical institutions in Ukraine is the progression of the disease to tuberculosis after the appointment of ART. This phenomenon is described in the literature as immune reconstitution syndrome (IRS) against the background of antiviral therapy, the occurrence of which can reduce the effectiveness of tuberculosis treatment and contribute to the progression of the disease [14, 15].

We analyzed the literature sources regarding the frequency and severity of toxicity and adverse reactions due to the simultaneous use of ART and second-line antituberculosis drugs. At the same time, there is scientific evidence that the risk of adverse reactions to both antituberculosis drugs and other drugs increases with increasing levels of immunosuppression [7]. Taking into account the above, we have proposed to prescribe ART as soon as possible to HIV-infected persons with suspicion of tuberculosis or with

diagnosed tuberculosis, which indicates the need to make appropriate changes to the legal documents regulating the treatment of HIV/TB co-infection in Ukraine.

According to our research, in Ukraine, the system of providing medical care to HIV-infected people is organized in such a way that ART can be prescribed by a doctor of a health care institution who studied at an internship in one of the medical specialties, studied at thematic advanced training courses on diagnostics, prevention, HIV/AIDS treatment in higher education institutions and post-graduate education institutions [10, 16], which contributes to the early coverage of these patients on ART. At the same time, it should be noted that it is the phthisiatrician who is responsible for diagnostics and prescription of ATT.

Success in overcoming the HIV epidemic in Ukraine primarily depends on the coverage of PLHIV on ART in the early stages of the infectious process. It has been proven that such conditions significantly reduce the rate of infection. Of particular importance in the fight against HIV infection is the early detection of HIV-infected persons among key population groups, where the incidence rate is the highest [17]. According to the results of our study, the incidence rate among key groups is 10 times higher than among the general population (1.68%).

Considering the danger of HIV/TB co-infection both for the patient and for the spread of the combined HIV/TB epidemic, the regulatory and legal documents of Ukraine provide for the organization of HIV counseling and testing for all persons with symptoms of tuberculosis and, conversely, tuberculosis testing of all HIV-infected since 2006 [19, 20]. It should be noted that the strengths of this approach are that the HIV and tuberculosis screening service is integrated at all levels of health care provision. As for HIV, there are different algorithms for screening, verification and identification of HIV using different methods (rapid tests, ELISA, PCR) [18]. Screening for HIV and tuberculosis is included in the service packages of the medical guarantee program, namely the phthisiatric package of the National Health Service, which is a motivating factor for screening for HIV and tuberculosis.

Our research identified a number of problematic aspects related to the late detection of HIV-infected persons in Ukraine, including the insufficient level of provision of test systems for rapid testing, especially for persons from key groups. Thus, the specification of the primary health care package of the National Health Service of Ukraine provides for HIV testing by a family doctor using rapid tests. At the same time, health care facilities providing primary health care, which include primary health care centers, and health care facilities providing secondary health care, which include multidisciplinary intensive care hospitals, hospitals general and rehabilitation treatment, medical advisory and diagnostic centers, specialized medical centers, may transfer HIV testing functions to specialized laboratories for ELISA screening or other laboratories that conduct such tests. In view of this, diagnosis takes significantly longer and increases the risk that the patient will not return to the health care institution that referred him for examination, resulting in the loss of the opportunity to prescribe ART. This situation also occurs in health care institutions that do not purchase rapid tests for timely diagnosis of HIV.

Another problem is the unavailability of testing for key population groups. According to our data, in Ukraine during 2015–2021, the highest incidence rates of HIV and tuberculosis were recorded among injecting drug users (IDUs), commercial sex workers (CWWs) and other persons who do not take care of their own health and often apply to healthcare institutions in the late stages of HIV infection. Thus, these individuals have been a source of HIV transmission for a long time. Therefore, as the results of our study show, the search for ways to inform and convince individuals from key groups about the expediency of HIV testing and the effectiveness of prescribed ART and ATT remains relevant in our country to this day.

We have proposed ways to encourage people from key population groups to get tested for HIV. Yes, this is involvement in the dissemination of information about the possibility of testing, in the very process of testing persons who are trusted in this social group, even if they do not have a medical education. Another factor that will contribute to the popularization of testing and treatment of HIV infection and tuberculosis is the social support of HIV-infected people. For this, it is necessary to make appropriate changes to some regulatory documents approved in Ukraine, taking into account the updated (2021) WHO recommendations, which allow independent testing for HIV diagnosis by any persons without special medical education who have received training on the use of rapid tests [7].

In our opinion, simultaneous screening for HIV and tuberculosis among persons of key groups is also an important measure that can affect the deadline for prescribing ART in Ukraine. However, if screening and verification of the diagnosis of HIV is possible in any health care institution, then confirmation of the diagnosis of tuberculosis requires the involvement of specialized laboratories, since not all health care institutions have the ability to detect the causative agent of tuberculosis by molecular genetic methods.

An urgent issue is the uninterrupted supply of health care facilities with medical products for the determination of HIV serological markers with high sensitivity and high specificity for effective screening, verification and identification of HIV. After establishing a diagnosis of HIV infection, PLHIV, with their voluntary consent, must be registered and medically monitored for the rest of their lives. However, according to the results of present study, only 62.6% of such persons are monitored and supported in health care institutions in Ukraine. Dispensary monitoring of patients is systematic and continues throughout the patient's life and includes periodic medical examinations, laboratory, instrumental examinations and consultations of other specialists. A significant proportion of HIV-infected people are not registered and do not receive ART. Thus, according to the results of research conducted in African countries, only 10 to 14% of HIV-positive persons went to health care facilities for medical help, less than a quarter of them agreed to start treatment [7].

The goal of medical supervision of PLHIV is timely detection of the threat of disease progression, provision of effective medical care and necessary advisory, psychological and other support. An important part of this medical monitoring is screening for tuberculosis. All PLHIV should

be screened for tuberculosis at every scheduled visit to the doctor or when there are relevant complaints, regardless of where they receive medical care [7, 21]. In Ukraine, according to the Standard of Medical Care for Tuberculosis Patients, approved by the order of the Ministry of Health of Ukraine, systematic screening for tuberculosis of PLHIV is carried out by an infectious disease doctor who prescribes ART to an HIV-infected person [22].

We established that during 2015–2021, all HIV-infected patients underwent an X-ray examination of the chest organs during registration in the health care system. In addition, in 2022, an order of the Ministry of Health of Ukraine was issued, which regulates the procedure for organizing the detection of tuberculosis and latent tuberculosis infection among persons of key groups both at the primary level and at the level of specialized and highly specialized care [23]. The implementation of this order improved the detection of tuberculosis patients. General practitioners (family medicine) re-examined the composition of the population they serve, especially key groups, and created a comprehensive list of persons for systematic screening for HIV and TB. This will help to significantly affect the completeness of detection of infected people in the future. It should be noted that, according to the Standard [22], systematic screening for tuberculosis among adults and adolescents living with HIV requires X-ray examination of chest organs and laboratory examination of sputum using molecular rapid diagnostic tests when any of the following symptoms are detected: cough during examination, fever, weight loss, or night sweats; level of C-reactive protein >5 mg/l. At the outpatient stage, a sequential screening algorithm for PLHIV is used among adults and children over 10 years of age. Xpert MTB/RIF®(Ultra) screening is used only at the stationary stage. According to the results of our research, tuberculin skin test (TST) or gamma interferon release analysis are used only regional centers of socially significant diseases to detect latent tuberculosis infection.

At the screening stage, when signs of tuberculosis are detected, the referral period for further examination is 3 working days. In the case of a positive result of any of the prescribed microbiological studies, it is necessary to immediately contact a phthisiologist to confirm the diagnosis and prescribe treatment [21]. According to the results of our research, one of the additional reasons for the delay in the appointment of ART in Ukraine is the untimely examination of HIV-positive persons for tuberculosis and the delay in the medical examination by a phthisiatrician. Diagnosis of tuberculosis consists in determining the localization of the pathological process, microbiological confirmation of tuberculosis and identification of the causative agent, as well as mandatory determination of the sensitivity of mycobacterium tuberculosis to drugs used for treatment [22]. The diagnosis of tuberculosis or the presence of LTI on the basis of epidemiological, clinical, laboratory and other data is made by a phthisiatrician. Difficult-to-diagnose cases of pulmonary/extrapulmonary tuberculosis without bacterial isolation and coordination of antimycobacterial therapy (PTB) regimens for patients with drug-resistant tuberculosis (DR-TB) are carried out by the medical council of the regional anti-tuberculosis institution. institution/phthisiopulmonology center [22].

In Ukraine, all HIV-infected people receiving ART are regularly screened for tuberculosis symptoms using a screening questionnaire. If necessary, the Xpert MTB/RIF molecular genetic method is used instead of the traditional microscopic culture study [11].

Therefore, taking into account the existing time-consuming algorithm of screening for tuberculosis, the authority to establish the diagnosis of the disease only by a phthisiatrician or a medical board is also, in some cases, the reason for delaying the appointment of ART to HIV/TB co-infected patients. Especially considering that the appointment of ART occurs after the diagnosis of TB in PLWH and the appointment of ATT.

Before receiving free ART treatment in Ukraine, according to the order of the Ministry of Health of Ukraine [24], patients with HIV/TB co-infection must first register and be identified in the electronic health care system. You can enter information into the Patient Register and confirm its authenticity in two ways today: via SMS (the most common and convenient); and by documents (alternatively) if the patient does not have a mobile phone. In some cases, PLWH, especially from key groups, do not have a mobile phone or a passport, which leads to difficulties in entering them into the Patient Register and prescribing ART.

Separate regulatory documents provide for separate paper registers of HIV-infected and tuberculosis patients, which, in our opinion, only leads to an increase in the burden on the medical worker when performing this work, reduces the effectiveness of medical supervision of PLHIV, and lengthens the duration of the procedure appointment of ART to patients with HIV/TB co-infection. The results obtained by us from the analysis of the epidemic process of HIV/TB co-infection in Ukraine indicate the need to create an electronic register of such patients, which will generally improve the quality of data collection and analysis, ensure effective planning of the purchase and distribution of medical drugs both for the treatment of HIV infection, and anti-tuberculosis drugs.

Taking into account the active processes of digitalization in Ukraine, including its use in health care institutions, in order to reduce the time of initiation of ART for patients with HIV/TB co-infection, it is advisable to consider the issue of implementing an electronic tool (software) for tracking all PLHIV who are under surveillance. The introduction of such a tool will make it possible to conduct constant counseling of patients, monitor the reception of ART, adjust treatment, etc.

Taking into account that when TB is suspected in PLHIV, the patient is referred to the phthisiatric service to establish a final diagnosis of tuberculosis and prescribe ATT, we believe that training phthisiatric doctors in the management of HIV infection cases will speed up the appointment of ART in HIV infection/TB co-infection, based on international guidelines documents, which indicate that "... in countries with a high prevalence of HIV infection and tuberculosis, it is recommended to start ART in anti-tuberculosis dispensaries with further referral for continued HIV and ART treatment to specialized institutions" [7]. Another reason for the delay in the appointment of ART both in Ukraine and in other countries [7] is untimely procurement of medicines for ART by health care institutions and errors

in planning the amount of needs. In the same time, the earlier beginning of ART can be achieved with additional immunoglobulin G (IgG) administration [25,26].

Adherence to ART is one of the main factors affecting the initiation of ART [27]. Treatment should not be started without established adherence. Adherence is achieved during pre-test information and post-test counseling of HIV-positive patients, which is not always carried out efficiently in conditions of limited time, and in some cases is not carried out at all in health care institutions of Ukraine and even under martial law. All of the above points to the important conclusion that people with HIV infection who have no contraindications to start ART quickly should be given full information about the benefits of ART, as well as an offer to start treatment immediately, including the possibility to start treatment in the same day. A very important solution to the problem of timely prescribing of treatment to patients with HIV/TB co-infection is training for medical professionals, which will help shorten the time to start ART. The training of health workers should include approaches focused on the ability to establish trusting relationships with patients, explaining the importance of rapid initiation of ART in patients with HIV/TB co-infection.

Conclusions.

1. The regulatory and legal documents created and implemented in Ukraine, which regulate the detection, registration, medical monitoring and treatment of HIV infection and tuberculosis, correspond to international recommendations.

2. It was established that the timing of prescribing ART for patients with HIV/TB co-infection in Ukraine is related to the prescribing of anti-tuberculosis treatment. The term of starting ART after prescribing antituberculosis treatment is up to 8 weeks (early start), after 8 weeks (delayed start) and up to 2 weeks (early start; without antituberculosis treatment). It is necessary to make changes to the existing state of the case, because the appointment of ART should not be associated with ATT, and the initiation of ART after the appointment of antimycobacterial therapy should be reduced to 2 weeks. The start of ART is delayed for up to 8 weeks only in PLWH receiving treatment for CNS TB.

3. The reasons for non-appointment and/or delay in the appointment of ART for patients with HIV/TB co-infection are the long algorithm of establishing the diagnosis of TB only by a phthisiologist, and in some cases by a council of doctors; the impossibility of conducting HIV testing with express tests in a number of health care facilities, and the transfer of this HIV testing service to specialized laboratories using the enzyme immunoassay (ELISA) method; low-quality screening examinations for HIV infection and tuberculosis among key risk groups and insufficient or absent educational work on ways to prevent HIV infection and tuberculosis, risks of infection, availability and effectiveness of ART and anti-tuberculosis therapy; untimely procurement of antiretroviral drugs (ARVs) and provision of them to all health care facilities where ART is prescribed.

4. Involvement in HIV testing of people who do not have a medical education, but they are trusted in this social group, can improve the detection rate and ART appointment time. Other ways of shortening the terms of prescribing

ART for patients with HIV/TB co-infection in Ukraine: integration of prescribing ART into the phthisiatric service; improvement of mechanisms for planning the amount of needs for ARV drugs, express tests, creating their stock, distribution among health care institutions that provide ART prescribing services; training of medical workers (ART service providers) in a patient-oriented approach, combating stigmatization and discrimination, establishing trusting relationships with patients, dispelling myths about HIV and ART.

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Електронна адреса для листування elena202320bachinska@gmail.com