

# The course of multidrug-resistant pulmonary tuberculosis in HIV-infected people with COVID-19

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

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**Aim.** To analyze the course of multidrug-resistant tuberculosis (MDR-TB) in HIV-infected people, depending on the time to COVID-19 diagnosis, using the example of clinical cases from our own observation.

**Materials and methods.** The article presents 3 clinical cases of our own observation of MDR-TB in HIV-infected persons depending on the time to COVID-19 diagnosis in patients, who were treated in the Pulmonary Tuberculosis Department No. 2, clinical base of the Department of Tuberculosis and Pulmonology ZSMU – Municipal non-profit enterprise “Zaporizhzhia Regional Phthisiopulmonology Clinical Medical and Diagnostic Center” of Zaporizhzhia Regional Council.

**Results.** In clinical case 1, in an HIV-infected patient, MDR TB was detected after COVID-19. This clinical case has shown that after mild and treated COVID-19, even on the background of severe immunosuppression, but with AMBT and ART timely prescribed, MDR-TB in the patient had a favorable course with positive dynamics. In clinical case 2, in an HIV-infected patient, MDR-TB was detected concomitantly with COVID-19. The clinical case indicated that the patient received all 3 therapies for MDR-TB, HIV and COVID-19 in full and on time. In contrast to clinical case 1, the patient was diagnosed with a more severe process that required a longer period of treatment, although it was effective. In clinical case 3, an HIV-infected patient with COVID-19 was diagnosed after 5 months of MDR-TB treatment. Against this background, there was culture positivity. But after prescription of appropriate COVID-19 treatment against the background of AMBT and ART, positive dynamics and culture negativity were determined. All 3 patients completed antimycobacterial therapy of MDR-TB with results – recovery.

**Conclusions.** Regardless of the HIV infection duration with underlying severe immunosuppression (<200 CD4 lymphocyte cells) and the time to COVID-19 diagnosis (before, during or after the diagnosis of MDR-TB) on the background of timely therapy of MDR-TB, HIV and COVID-19, positive results can be achieved while saving the lives of patients.

## Ключові слова:

мультирезистентний  
туберкульоз, ВІЛ-  
інфекція, COVID-19.

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## Перебіг мультирезистентного туберкульозу легень у ВІЛ-інфікованих осіб із COVID-19

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**Мета роботи** – на прикладі клінічних випадків проаналізувати перебіг мультирезистентного туберкульозу (MP ТБ) у ВІЛ-інфікованих осіб залежно від початку діагностики COVID-19.

**Матеріали та методи.** Наведено 3 клінічні випадки власного спостереження перебігу MP ТБ у ВІЛ-інфікованих осіб залежно від початку діагностики COVID-19. Усі пацієнти перебували на лікуванні у відділенні легеневого туберкульозу № 2 клінічної бази кафедри фтизіатрії і пульмонології ЗДМУ Комунального некомерційного підприємства «Запорізький регіональний фтизіопульмонологічний клінічний лікувально-діагностичний центр» Запорізької обласної ради.

**Результати.** У клінічному випадку 1 у ВІЛ-інфікованої пацієнтки MP ТБ виявили після перенесеного COVID-19. Після легкого та пролікованого COVID-19, навіть на тлі тяжкої імуносупресії, але при своєчасному призначенні антимікобактеріальної терапії (АМБТ) та антиретровірусної терапії (АРТ), у пацієнтки MP ТБ мав сприятливий перебіг із позитивною динамікою. У клінічному випадку 2 у ВІЛ-інфікованого пацієнта MP ТБ діагностували одночасно з COVID-19. На відміну від клінічного випадку 1, у пацієнта діагностували тяжкий процес, який потребував тривалішого лікування, яке, втім, було ефективним. У клінічному випадку 3 у ВІЛ-інфікованого пацієнта COVID-19 виявлено через 5 місяців лікування MP ТБ, на цьому тлі з'явилось бактерієвиділення. Після призначення відповідного лікування COVID-19 на тлі АМБТ та АРТ спостерігали позитивну динаміку з припиненням бактерієвиділення. Усі 3 пацієнти завершили курси антимікобактеріальної терапії MP ТБ, результат – одужання.

**Висновки.** Незалежно від тривалості ВІЛ-інфекції на тлі тяжкої імуносупресії (<200 клітин CD4-лімфоцитів) та від початку діагностики COVID-19 (до, під час або після діагностики MP ТБ) на тлі своєчасних терапій MP ТБ, ВІЛ-інфекції та COVID-19 можна досягти позитивних результатів зі збереженням життя пацієнтів.

In Ukraine, the severity of multidrug-resistant tuberculosis (MDR-TB) is very high, and the COVID-19 pandemic significantly worsens it, reducing the effectiveness of treatment and increasing the mortality rate of this patient group [1,2,3,8,12]. The reasons for this are the severity of both diseases and the similarity of the initial bronchopul-

monary symptoms [4, 11], which complicates the differential diagnosis and the timeliness of prescribing appropriate therapies. In addition, tuberculosis is sometimes diagnosed later than COVID-19, and as a result, the severity of the disease worsens, especially in patients with comorbidities [6]. Moreover, patients with COVID-19 and

tuberculosis co-infection are more likely to have severe disease and death compared to patients with COVID-19 alone [9].

However, Ş. Gül et al. [7] in their study did not observe an effect of the simultaneous course of tuberculosis and COVID-19 on morbidity or mortality. But the authors pointed out that patients with early tuberculosis (TB) disease in areas with a high Mycobacteria circulation might be at a greater risk of contracting COVID-19.

Data from a meta-analysis by Y. Gao et al. [5] showed that TB is associated with an increased risk of severe COVID-19, because when patients suffer from previous respiratory disease, resistance to viruses is low and they tend to develop acute respiratory distress syndrome.

Crisan-Dabija R. et al. [12] suggest, that the synergism of COVID-19 virus and TB, by interfering with the immune responses of the human body, contributes to more severe clinical evolution.

Therefore, TB may be a risk factor for the progression of COVID-19 with the development of severe complications, and COVID-19 contributes to the progression of TB [5].

Furthermore, COVID-19 occurs regardless of the occurrence of TB (before, during, or after the diagnosis of active TB), and TB is associated with an increased risk of mortality in patients with COVID-19 [11].

The risk factors for COVID-19 and TB are concomitant diseases, among them HIV infection [11]. The COVID-19 pandemic is a serious threat to people, living with HIV/AIDS. The risk of death from COVID-19 among people living with HIV/AIDS is 2 times higher than in the general population.

In countries with a high TB/HIV co-infection burden, where Ukraine is included, the COVID-19 pandemic is of justifiable concern, because these three diseases closely interact with each other.

In the literature, we have found only one article focused on the study of the simultaneous course of Multidrug-resistant TB (MDR-TB)/HIV/COVID-19. For example, J. L. Tamuzi et al. [10] in their study indicated TB as a risk factor for COVID-19 (severity and mortality) regardless of HIV status.

Thus, the features of the MDR-TB course in HIV-infected people with COVID-19 remain deficiently examined in the literature and is a topical issue today.

## Aim

To analyze the course of MDR-TB in HIV-infected people depending on the time to COVID-19 diagnosis using the example of clinical cases from our own observation.

## Materials and methods

The article presents 3 clinical cases of our own observation of MDR-TB in HIV-infected persons depending on the time to COVID-19 diagnosis in patients, who were treated at the Pulmonary Tuberculosis Department No. 2, clinical base of the Department of Tuberculosis and Pulmonology ZSMU – Municipal non-profit enterprise “Zaporizhzhia Regional Phthisiopulmonology Clinical Medical and Diagnostic Center” of Zaporizhzhia Regional Council (MNPE “ZRPCMDC” ZRC).

## Results

**Clinical case 1.** Patient K., 39 years old. From the anamnesis: HIV infection was detected on 07.2019. Antiretroviral therapy (ART) was started on 08.2019.

Associated with ART, the following dynamics of indicators were observed:

- 08.2019: CD<sub>4</sub> lymphocytes – 66 cells, viral load (VL) – 1086704 RNA-copies/ml,
- 01.2020: CD<sub>4</sub> lymphocytes – 225 cells, VL – 82 RNA-copies/ml,
- 07.2020: CD<sub>4</sub> lymphocytes – 173 cells, VL – 40 RNA-copies/ml,
- 12.2020: CD<sub>4</sub> lymphocytes – 164 cells, VL – 40 RNA-copies/ml.

In August 2020, a result of polymerase chain reaction (PCR) was positive, after contact with a man, who was diagnosed with COVID-19.

The course of COVID-19 on the background of HIV infection was mild (loss of smell, weakness, low-grade fever, mild cough), chest X-ray changes were not detected. COVID-19 treatment in combination with ART was effective and the control PCR result was negative. However, low – grade fever persisted in the patient. She had no past history of TB.

According to the comparison plain X-ray + lateral X-ray from 10.2020 (Fig. 1), the following changes were found: in the apical segment of the left lower lung lobe, there were numerous peribronchial foci, which merged into infiltrates up to 15 mm of homogeneous structure; other pulmonary fields without changes; structural roots; sinuses were free.

The patient was referred to MNPE “ZRPCMDC” ZRC for further examination.

Fibrobronchoscopy (FBS) revealed ulcerative tuberculosis B6, which was detected on the left with grade II stenosis. Mycobacterium tuberculosis (MBT) strain resistant to rifampicin (R) was isolated in bronchoalveolar lavage (BAL) by molecular genetic method (MG).

The results of the general blood analysis (GBA): hemoglobin (HGB) – 126 g/l, erythrocytes (RBC) –  $4.0 \times 10^{12}/l$ , leukocytes (WBC) –  $4.6 \times 10^9/l$ , platelets (PLT) –  $392 \times 10^9/l$ , eosinophils (EOS) – 0 %, banded neutrophils (b/n) – 1 %, segmented neutrophils (s/n) – 63 %, lymphocytes (LYM) – 29 %, monocytes (MONO) – 3 %, erythrocyte sedimentation rate (ESR) – 23 mm/hour.

Spirography revealed that there was no ventilatory insufficiency.

Electrocardiography (ECG) data: voltage was sufficient, sinus rhythm, heart rate (HR) 73 beats/min, electrical axis of the heart (EHA) was not deflected, moderate changes in the myocardium, QTcF = 391 msec.

Biochemical blood analysis: bilirubin total – 7.42  $\mu\text{mol}/l$ , thymol test – 6.41 U, ALT – 0.16, AST – 0.48, total protein (TP) – 79.5 g/l, glucose – 5.04 mmol/l.

Abdominal ultrasound: echo-signs of moderate diffuse changes of the liver, gallbladder deformation, chronic cholecystitis, diffuse pancreatic changes.

According to the obtained data, the diagnosis was established: rifampicin-resistant tuberculosis (Rif TB) (10.2020) infiltrating left lower lung lobe, Destruction +, MBT +, microscopy (M) –, MG +, Rif +. Extrapulmonary tuberculosis (EPTB), ulcerative B6 on the left. Category 4

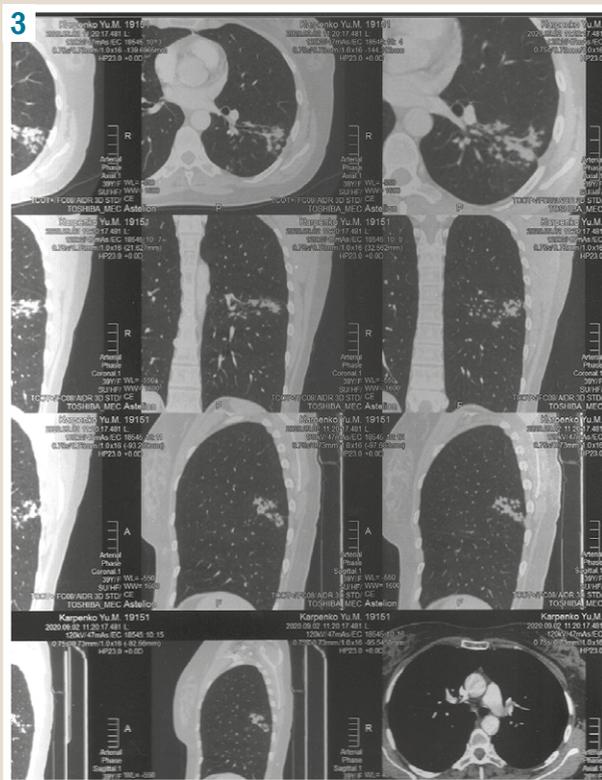
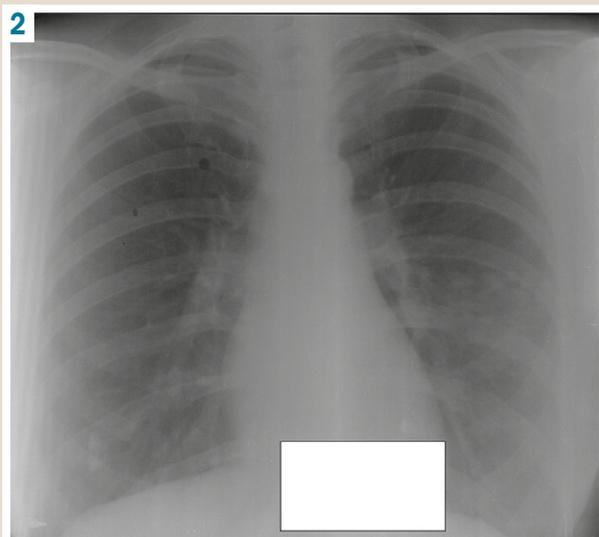
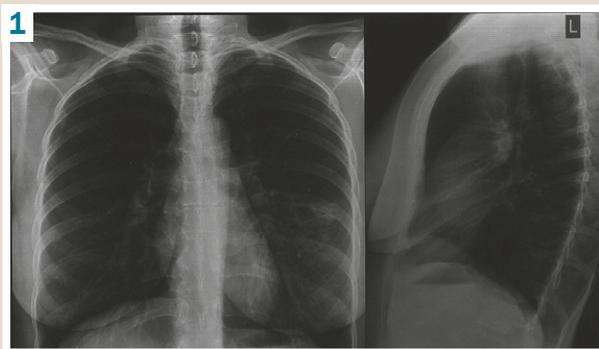


Fig. 1. Plain X-ray + lateral X-ray of the left lung from 10.2020.

Fig. 2. Chest X-ray from 01.2021 (after 3 months of AMBT).

Fig. 3. Chest CT from 02.2021 (after 4 months of AMBT).

(newly diagnosed tuberculosis (NDTB)). HIV infection, IV clinical stage.

The patient was hospitalized to the Pulmonary Tuberculosis Department No. 2 of MNPE “ZRPMDC” ZRC, where she was prescribed a course of antimycobacterial therapy (AMBT) according to the scheme for category 4. After 3 weeks, we obtained results of the BAL liquid culture showing resistance to isoniazid (H) and streptomycin (S). The diagnosis Rif TB was changed to multidrug-resistant TB (MDR-TB), culture (C) +, resistance 1 (HRS). The TB treatment regimen was not adjusted based on the drug susceptibility test (DST) data, because the HS resistance detected had no effect on the AMBT regimen previously prescribed.

After one month of AMBT, according to the data of the FBS from 11.2020, positive changes were diagnosed seen in resorption of B6 ulcerous TB on the left side; the previously detected stenosis was not diagnosed. At the same time, MBT was not isolated from the BAL and sputum.

After 3 weeks of AMBT (01.2021), a control chest X-ray examination (Fig. 2): polymorphic foci within the area of local fibrosis were diagnosed in the left lower lobe; the roots were structural; right side – without changes. Conclusion: positive radiological dynamics.

GBA: HGB – 118 g/l, RBC –  $3.77 \times 10^{12}/l$ , WBC –  $4.0 \times 10^9/l$ , PLT –  $214 \times 10^9/l$ , EOS – 1 %, banded neutrophils (b/n) – 6 %, segmented neutrophils (s/n) – 64 %, LYM – 26 %, MONO – 3 %, ESR – 5 mm/hour.

Biochemical blood analysis (01.2021): bilirubin total – 10.1  $\mu\text{mol/l}$ , thymol test – 2.07 U, ALT – 0.19, AST – 0.47, TP – 80.7 g/l, creatinine – 139.5  $\mu\text{mol/l}$ , glucose – 6.85 mmol/l. Sputum smear test: M –, MBT –.

After 4 months of AMBT (02.02.2021), chest computed tomography (CT) with bolus intravenous contrast enhancement was performed (Fig. 3): CT-signs of focal changes in the apical segment of the left lung, more probably of a specific infectious cause. On the left side of C6, multiple grouped, solid, rounded foci of the same type with homogeneous density and quite clear contours, ranging in size from 2 mm to 14 mm were detected. The draining bronchus had the largest focus.

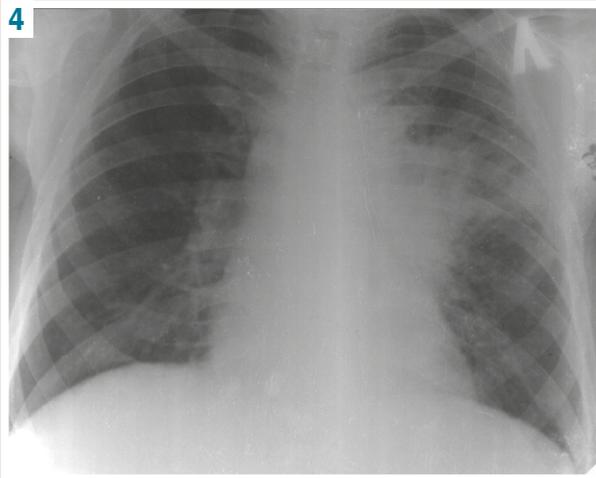
Taking into account the positive radiological dynamics, cultural negativity after 1 month since AMBT, the patient was discharged from the hospital for outpatient treatment.

**Clinical case 2.** Patient C., 37 years old. From the anamnesis: HIV infection was detected on 10.2005. However, ART started only on 07.2010. She had no previous TB history.

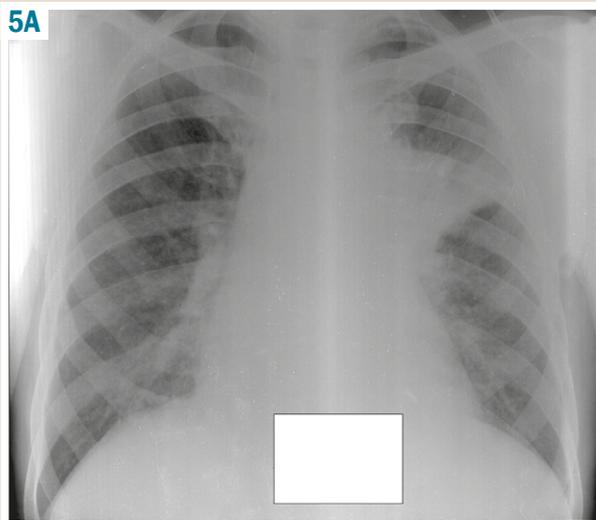
Dynamics of indicators:

- 03.2017: CD<sub>4</sub> lymphocytes – 289 cells, VL – RNA-copies/ml,
- 02.2018: CD<sub>4</sub> lymphocytes – 95 cells, VL – < RNA-copies/ml,
- 09.2020: CD<sub>4</sub> lymphocytes – 100 cells, VL – 46 RNA-copies/ml.

In April 2020, the patient complained of taste and smell loss, weakness, fever up to 38 °C, cough and scarce



**Fig. 4.** Plain X-ray from 04.2020.

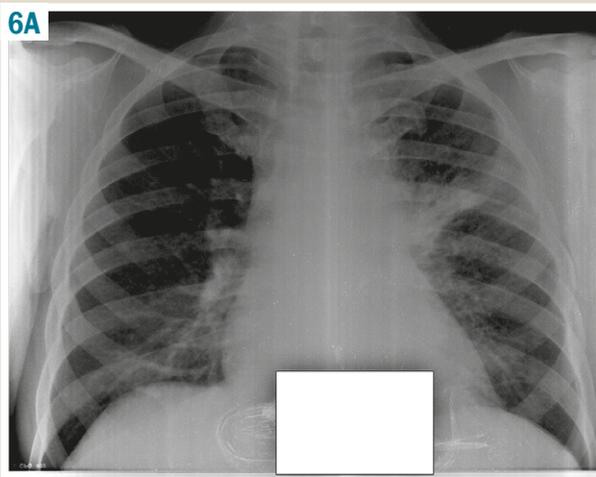


**Fig. 5A.** Plain chest X-ray from 06.2020.

**Fig. 5B.** Tomography of the left upper lung lobe 9.0 from 06.2020.

**Fig. 6A.** Plain chest X-ray from 08.2020.

**Fig. 6B.** Tomography of the left upper lung lobe 9.0 from 08.2020.



sputum, chest pain and shortness of breath during exercise. Firstly, a PCR was performed, as the patient had contact with COVID-19 patient whose result was positive. A family physician prescribed an appropriate treatment for 10 days, at the end of which, PCR test result was negative for COVID-19. The general condition did not improve. Chest X-ray from 04.2020 (Fig. 4) revealed the follow-

ing changes: a massive area of infiltration in S1 + 2 on the left connected with the infiltrated root of the lung; destruction up to 2.0 cm in diameter seen in the infiltration zone.

The patient was referred to MNPE "ZRPCMDC" ZRC for further examination, after being detected with the X-ray changes.

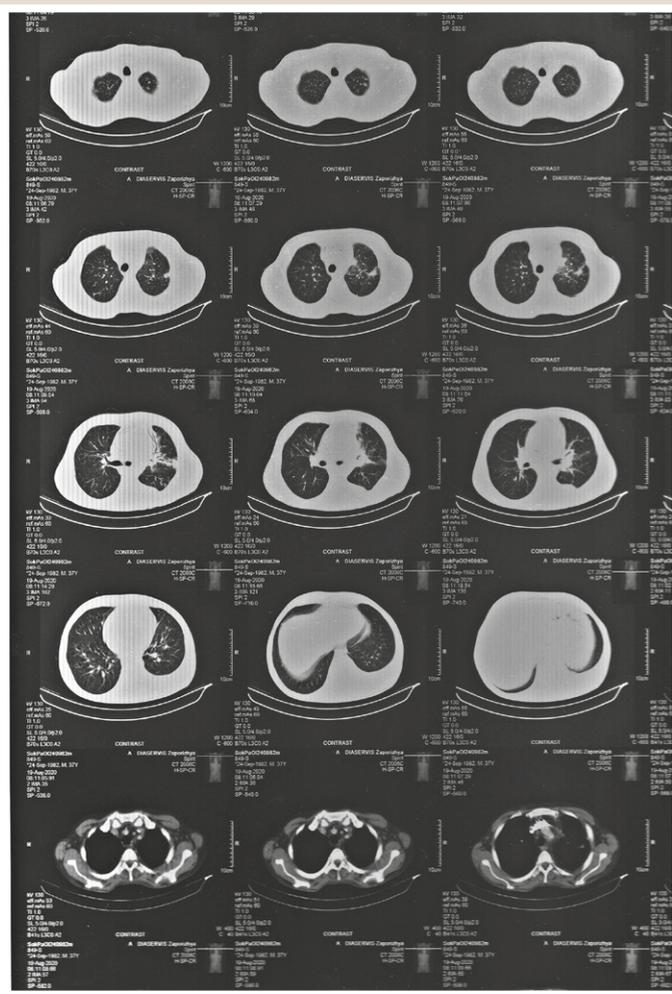


Fig. 7. Chest CT from 08.2020.

Rifampicin-resistant MBT were isolated from the sputum: M +, MG +, Rif +.

GBA: HGB – 70 g/l, RBC –  $2.7 \times 10^{12}/l$ , WBC –  $3.5 \times 10^9/l$ , PLT –  $590 \times 10^9/l$ , EOS – 0 %, banded neutrophils (b/n) – 8 %, segmented neutrophils (s/n) – 62 %, LYM – 24 %, MONO – 6 %, ESR – 67 mm/hour.

Biochemical blood analysis: bilirubin total – 7.21  $\mu\text{mol}/l$ , thymol test – 5.7 U, ALT – 0.24, AST – 0.29, TP – 65.2 g/l, creatinine – 90.2  $\mu\text{mol}/l$ , glucose – 5.1 mmol/l.

Spirography revealed: degree I respiratory insufficiency.

ECG data: voltage was sufficient, sinus rhythm, HR 116 beats/min., normal EHA position, incomplete right bundle branch block (incomplete RBBB), diffuse myocardial changes, QTcF = 391 msec.

According to the data obtained, the diagnosis was established: Rif TB (30.04.2020) infiltrative of the left upper lung lobe, Destruction +, MBT +, M +, MG +, Rif +. Category 4 (NDTB). HIV infection, IV clinical stage.

The patient was hospitalized to the Pulmonary Tuberculosis Department No. 2 MNPE “ZRPCMDC” ZRC, where she was prescribed a course of AMBT according to the scheme for category 4. We obtained results of the liquid sputum culture showing resistance to isoniazid (H), rifampicin (R),

pyrazinamide (Z), ethambutol (E). The diagnosis Rif TB was changed to MDR-TB, C +, resistance 1 (HRZE). The TB treatment regimen was not adjusted based on the DST data, because the HRZE resistance detected had no effect on the AMBT regimen previously prescribed.

After 2 months of AMBT (06.2020), the patient was sputum culture positive despite the negative radiological dynamics.

Plain chest X-ray + CT of the left upper lung lobe 9.0 (Fig. 5A, 5B): in S1 + 2 of the left lung, the massive area of infiltration was connected with the infiltrated root of the lung; a destruction up to 2.5 cm was seen in the zone of infiltration; in the left lower lung lobe and in the right lung – numerous foci of dissemination; sinuses were free.

GBA: HGB – 67 g/l, RBC –  $2.51 \times 10^{12}/l$ , WBC –  $3.5 \times 10^9/l$ , PLT –  $584 \times 10^9/l$ , EOS – 0 %, banded neutrophils (b/n) – 7 %, segmented neutrophils (s/n) – 63 %, LYM – 24 %, MONO – 6 %, ESR – 65 mm/hour.

Biochemical blood analysis: bilirubin total – 8.38  $\mu\text{mol}/l$ , thymol test – 15.34 U, ALT – 0.26, AST – 0.38, TP – 67.6 g/l, creatinine – 102.3  $\mu\text{mol}/l$ , glucose – 5.3 mmol/l.

Ultrasound of the hepatobiliary and urogenital system: enlargement and diffuse changes with focal liver fibrosis, diffuse changes in the renal parenchyma.

After 4 months of AMBT (08.2020), there was sputum culture-negative conversion, and the radiological dynamics was positive.

Plain chest X-ray + CT of the left upper lung lobe 9.0 (Fig. 6A, 6B): in the left upper lung lobe, the focal infiltration was partially resorbed, destruction was not defined; in the right lung, the foci of dissemination were partially resorbed.

The patient, on his own initiative, underwent chest CT in 08.2020 (Fig. 7): left-sided plural effusion of 106 × 28 mm and pleural miliary foci of 3–2 mm were defined. Multiple compacted foci from 2–3 mm to 10–13 mm in diameter were defined in C1/2, C3, C6 of the left lung. An infiltrate of 75 × 30 mm in size with lumens of deformed bronchi was seen in C3 of the left lung and paramediastinal lobe. Areas of “frosted glass” were not detected.

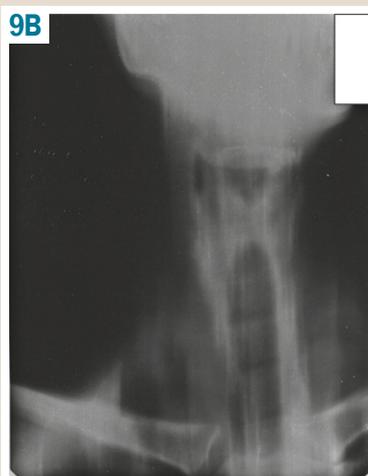
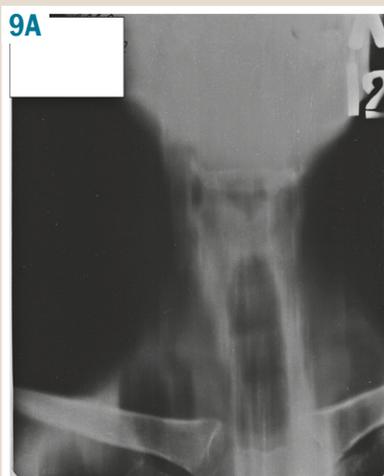
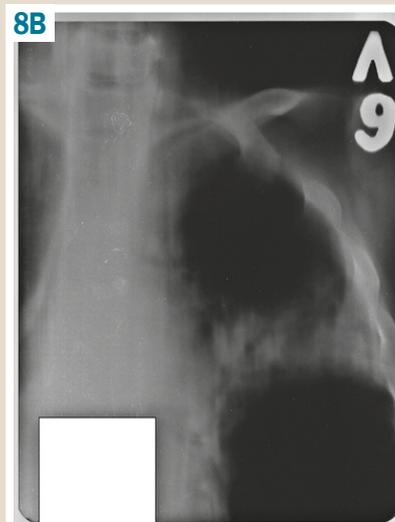
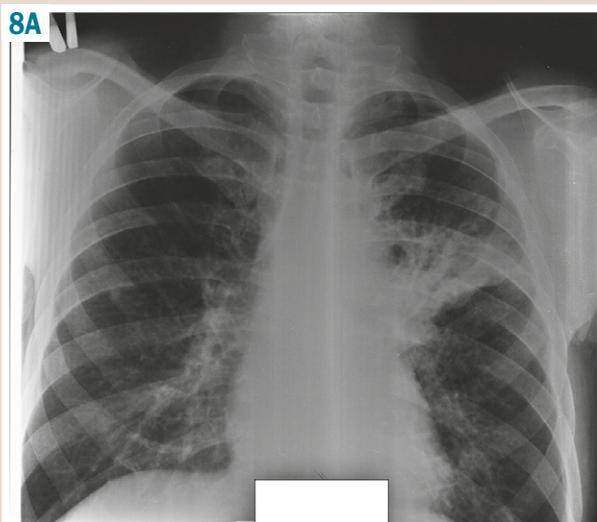
After 6 months of AMBT (10.2020), the patient was sputum culture negative, but the radiological dynamics became worse.

Plain chest X-ray + CT of the left upper lung lobe 9.0 (Fig. 8A, 8B): the increased in size infiltration area in the left upper lung lobe extending to the root of the lung was seen; bronchial lumens were traced against the background of infiltration, destruction was not defined; in the left lower lung lobe and in the right lung, numerous focal shadows of medium intensity were revealed against the background of a deformed lung pattern; the structure of the left root was reduced, the right root – without changes.

The patient was diagnosed with worsened asphyxia, so a control spirometry was performed: degree II respiratory insufficiency.

ECG data: voltage was sufficient, sinus rhythm, HR 87 beats/min., normal EHA position, incomplete RBBB, diffuse myocardial changes, QTcF = 412 msec.

GBA: HGB – 116 g/l, RBC –  $3.6 \times 10^{12}/l$ , WBC –  $4.6 \times 10^9/l$ , PLT –  $260 \times 10^9/l$ , EOS – 0 %, banded neutrophils (b/n) – 6 %, segmented neutrophils (s/n) – 62 %, LYM – 24 %, MONO – 8 %, ESR – 15 mm/hour.



**Fig. 8A.** Plain chest X-ray from 10.2020.

**Fig. 8B.** Tomography of the left upper lung lobe 9.0 from 10.2020.

**Fig. 9A.** Laryngeal tomography 12.

**Fig. 9B.** Laryngeal tomography 12.5.

Biochemical blood analysis: bilirubin total – 7.8  $\mu\text{mol/l}$ , thymol test – 8.34 U, ALT – 0.16, AST – 0.24, TP – 60.6 g/l, creatinine – 89.9  $\mu\text{mol/l}$ , glucose – 5.1 mmol/l. The patient was discharged from the hospital for outpatient treatment.

**Clinical case 3.** Patient K., 52 years old. From the anamnesis: HIV infection was first detected in 2015 during the treatment of NDTB. He refused ART. Anti-TB treatment was effective and the patient recovered.

In August 2020, the patient complained of throat irritation, hoarseness of voice, discomfort when swallowing, and foreign body sensation in his throat. The patient went to an otorhinolaryngologist, who prescribed him an examination.

Thus, the laryngeal tomography of 12.0–12.5 (Fig. 9A, 9B) showed asymmetry of the aryepiglottic fold on the right side due to an additional mass in it. Pyriform sinuses were not changed. Supraglottic and subglottic spaces – without changes. Conclusion: neoplasm of the right cranial – epiglottis fold.

Otorhinolaryngological conclusion: laryngeal neoplasms. Recommendations: laryngeal biopsy, CT/magnetic resonance tomography (MRI) of the neck, FBS, a consultation with an oncologist.

The patient categorically refused to be consulted by the oncologist.

On the tomography of the upper lung lobes 7.0–9.0 (Fig. 10), the following changes were found: merging infiltrations with destructions up to 1.0 cm in diameter in the upper lung lobes (more on the left) and in the left C6.

The patient was referred to MNPE “ZRPMDC” ZRC for further examination.

MBT were isolated from the sputum: M +, MG +, Rif +, C +, resistance 1 (HR).

GBA: HGB – 124 g/l, RBC –  $3.89 \times 10^{12}/\text{l}$ , WBC –  $6.75 \times 10^9/\text{l}$ , PLT –  $590 \times 10^9/\text{l}$ , EOS – 3 %, banded neutrophils (b/n) – 6 %, segmented neutrophils (s/n) – 64 %, LYM – 19 %, MONO – 8 %, ESR – 46 mm/hour.

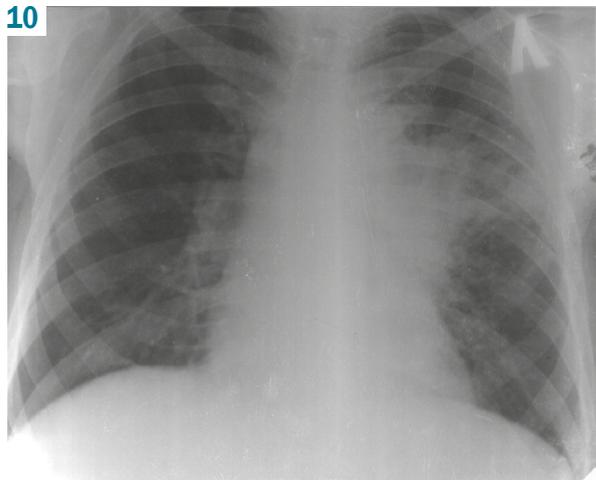
Biochemical blood analysis: bilirubin total – 9.42  $\mu\text{mol/l}$ , thymol test – 11.6 U, ALT – 0.85, AST – 0.64, TP – 67.5 g/l, creatinine – 171  $\mu\text{mol/l}$ , glucose – 5.38 mmol/l.

Spirography revealed no respiratory insufficiency.

ECG data: voltage was reduced, sinus rhythm, HR 75 beats/min, left EHA deviation, diffuse myocardial changes, QTcF = 383 msec. Blood test for CD4 lymphocytes – 146 cells.

An infectiologist consultation: HIV infection, IV clinical stage. Oropharyngeal candidiasis.

The diagnosis was established: MDR-TB (31.08.2020) infiltrative upper lobe of the left lung, Destruction +, MBT +, M +, MG +, Rif +, C +, Resistance 1 (HR).



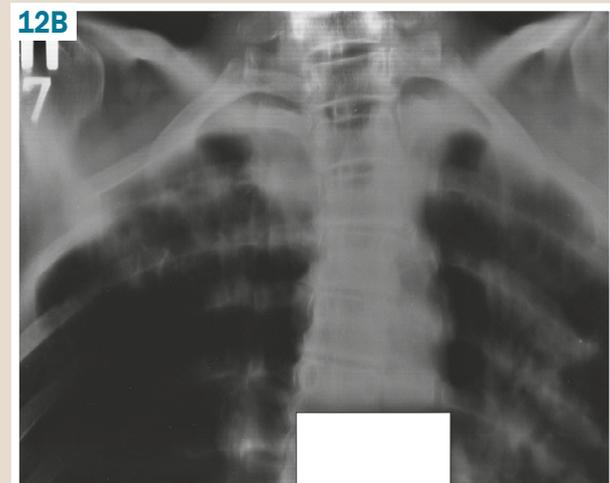
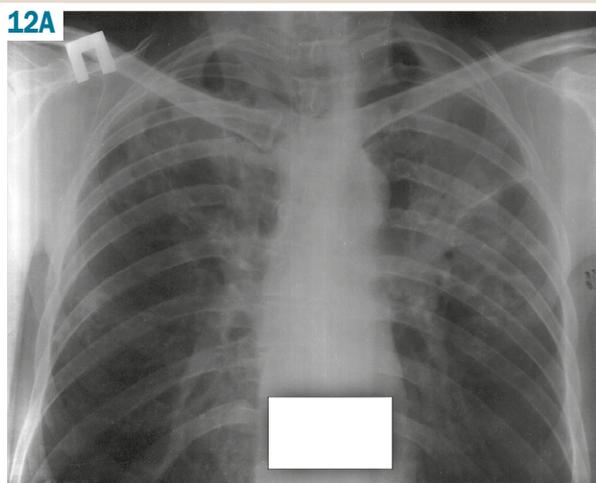
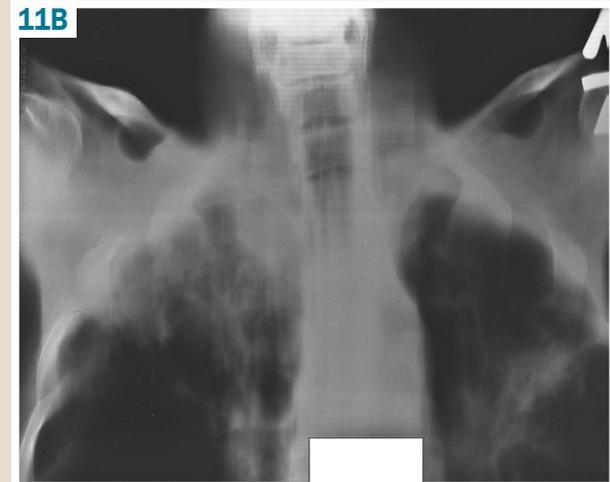
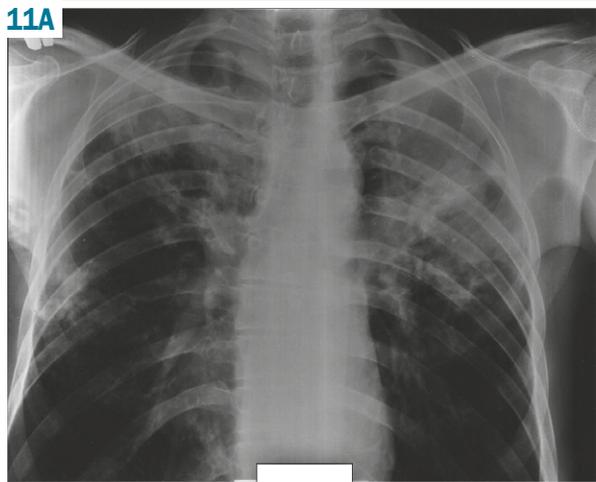
**Fig. 10.** Tomography of the upper lung lobes 7.0–9.0.

**Fig. 11A.** Plain chest X-ray from 10.2020.

**Fig. 11B.** Tomography of the upper lung lobes from 10.2020.

**Fig. 12A.** Plain chest X-ray from 01.2021.

**Fig. 12B.** Tomography of the upper lung lobes from 01.2021.



Category 4 (recurrent tuberculosis). HIV infection, IV clinical stage. Oropharyngeal candidiasis. Laryngeal neoplasms.

The patient was hospitalized to the Pulmonary Tuberculosis Department No. 2 MNPE “ZRPCMDC” ZRC, where he was prescribed a course of AMBT, according to the scheme for category 4, ART and treatment of opportunistic infections (biseptol, fluconazole).

After 2 months of AMBT (11.2020), positive dynamics were determined, manifesting by sputum culture negativity (M –, C –) and partial resorption of infiltrative changes in the lungs. Plain chest X-ray + Tomography of the upper lung lobes 7.0 (Fig. 11A, 11B).

GBA: HGB – 148 g/l, RBC –  $4.62 \times 10^{12}/l$ , WBC –  $8.6 \times 10^9/l$ , EOS – 1 %, banded neutrophils (b/n) – 6 %,

segmented neutrophils (s/n) – 55 %, LYM – 30 %, MONO – 8 %, ESR – 48 mm/hour.

Biochemical blood analysis: bilirubin total – 10.2  $\mu\text{mol/l}$ , thymol test – 11.2 U, ALT – 0.1, AST – 0.45, TP – 68.6 g/l, creatinine – 171  $\mu\text{mol/l}$ , glucose – 5.2 mmol/l.

After 4 months of AMBT (01.2021), sputum culture was negative (M–, C–), and radiological dynamics was positive.

Plain chest X-ray + Tomography of the upper lung lobes 7.0 (Fig. 12A, 12B): fibro-bullous changes, polymorphic foci and infiltrates with destructions up to 1.0 cm in diameter were identified on the right upper lobe and C6 on the background of mixed fibrosis.

In the left upper lobe, pneumatosis was reduced, interlobar pleura was compacted at the level of the posterior third rib. In the middle pulmonary field, polyfibrosis, localized polymorphic foci and infiltrates with destructions from 0.5 cm to 2.0 cm in diameter were seen with a wide extension to the root. The root was deformed, fibrously modified, pulled up to the upper. Pulmonary heart.

GBA: HGB – 130 g/l, RBC –  $4.0 \times 10^{12}/\text{l}$ , WBC –  $5.2 \times 10^9/\text{l}$ , EOS – 4 %, banded neutrophils (b/n) – 5 %, segmented neutrophils – 59 %, LYM – 28 %, MONO – 4 %, ESR – 12 mm/hour.

Biochemical blood analysis: bilirubin total – 9.1  $\mu\text{mol/l}$ , thymol test – 6.3 U, ALT – 0.26, AST – 0.31, TP – 68.6 g/l, creatinine – 119  $\mu\text{mol/l}$ , glucose – 5.6 mmol/l.

In February 2021, the patient complained of fever up to 38, smell loss, shortness of breath and cough. The PCR result on COVID-19 was positive. Spirography revealed degree II respiratory insufficiency.

GBA: HGB – 148 g/l, RBC –  $4.9 \times 10^{12}/\text{l}$ , WBC –  $5.2 \times 10^9/\text{l}$ , PLT –  $530 \times 10^9/\text{l}$ , EOS – 1 %, banded neutrophils – 3 %, segmented neutrophils – 57 %, LYM – 31 %, MONO – 8 %, ESR – 34 mm/hour.

Along with such findings, sputum culture was positive: M (1+).

The additional COVID-19 treatment was prescribed for the patient.

In March 2021 (one month after the diagnosis of COVID-19), the patient was sputum culture negative (M–), and blood inflammatory changes were resolved being characteristic of COVID-19.

GBA: HGB – 145 g/l, RBC –  $3.9 \times 10^{12}/\text{l}$ , WBC –  $5.3 \times 10^9/\text{l}$ , PLT –  $246 \times 10^9/\text{l}$ , EOS – 3 %, banded neutrophils – 6 %, segmented neutrophils – 58 %, LYM – 29 %, MONO – 4 %, ESR – 15 mm/hour.

The patient was discharged from the hospital for outpatient treatment.

## Discussion

In clinical case 1, in the HIV-infected patient, MDR-TB was detected after COVID-19 diagnosis. The patient was HIV-positive for a year and received ART since HIV infection was diagnosed. All the time, the patient was determined with severe immunosuppression (<200 CD4-lymphocyte cells). She had no previous history of TB. TB was detected after 2 months following COVID-19, which was effectively treated. The course of COVID-19 was not difficult and without X-ray changes. But after the COVID-19, subfebrile temperature persisted, which became the reason for the X-ray examination, where characteristics of TB changes

were found. This clinical case has shown that after mild and treated COVID-19, even on the background of severe immunosuppression, but with timely prescribed AMBT and ART, the MDR-TB course in patient was favorable with positive dynamics.

In clinical case 2, in the HIV-infected patient, MDR-TB was detected concomitantly with COVID-19. The patient was HIV-infected for 15 years and received ART for 10 years since diagnosis of HIV infection. He had no past history of TB. During 4 months of AMBT, the patient had severe hematological changes characteristic of COVID-19, which indicated a significant effect of active COVID-19 process on the background of severe immunosuppression caused by HIV infection (100 CD4 lymphocyte cells). These changes might have inhibited the rapid achievement of positive results in the treatment of MDR-TB. At the same time, after 6 months, respiratory insufficiency worsened in the patient. The clinical case has indicated that the patient received all 3 therapies for MDR-TB, HIV and COVID-19 in full and on time. In contrast to clinical case 1, the patient was diagnosed with a more severe process that required a longer period of treatment, although it was effective.

In clinical case 3, the HIV-infected patient with COVID-19 was diagnosed after 5 months of MDR-TB treatment. The patient suffered from HIV infection for 5 years, did not receive ART (refusal). The patient also had severe immunosuppression caused by HIV infection (146 CD4 lymphocyte cells). He started ART only during the treatment of MDR-TB, so 5 years after the diagnosis of HIV infection. The patient had the past history of TB (5 years ago). MDR-TB was detected during examination as a result of laryngeal neoplasm diagnosis. After 2 months of AMBT, the positive dynamics was determined manifesting by sputum culture negativity (M–, C–) and partial resorption of infiltrative changes in the lungs. But after 5 months of AMBT, the patient was diagnosed with COVID-19 with severe clinical symptoms, increasing intoxication and bronchopulmonary syndromes. Alongside this, sputum culture was positive. But after prescription of appropriate COVID-19 treatment against the background of AMBT and ART, positive dynamics and culture negativity were determined.

All 3 patients completed AMBT of MDR-TB with result – recovery.

As we can see, COVID-19 occurred independently of the MDR-TB occurrence (before, during or after the diagnosis of active TB) in HIV-infected patients, confirming the data of D. Visca et al. [11] and disproving the data of Y. Gao et al. [5]. In the HIV-infected patient with recurrent TB (clinical case 3), COVID-19 synergism with MDR-TB contributed to the more severe course and more severe clinical evolution, which complemented the data of J. L. Tamuzi et al. [10] and R. Crisan-Dabija et al. [12].

## Conclusions

Regardless of the HIV infection duration with underlying severe immunosuppression (<200 CD4 lymphocyte cells) and the time to COVID-19 diagnosis (before, during or after the diagnosis of MDR-TB) on the background of timely therapy of MDR-TB, HIV and COVID-19, positive results can be achieved while saving the lives of patients.

**Prospects for further research.** Further study of interesting and relevant clinical cases of MDR-TB course in combination with other diseases in order to determine the prognosis for patients' life and management tactics.

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