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Assessment of bronchiectasis in adult HIV/AIDS patients

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Abstract

Background: Immunodeficiencies should be suspected in cases of primary identified bronchiectasis in adults. Moldova is among the countries with a continuous increase in the number of HIV-infected adults. Impaired immune system and chronic inflammation contribute to the progression of bronchiectasis in HIV patients. The aim of the study was to present the clinical, imaging, bacteriological peculiarities and outcomes in adult patients with bronchiectasis and HIV/AIDS infection.

Material and methods: This case series involved 11 patients with HIV/AIDS and bronchiectasis, selected from a prospective study conducted on 490 patients diagnosed with non-cystic fibrosis bronchiectasis in a tertiary care hospital, between 2015–2019. Clinical, microbiological and radiological data, associated comorbidities and severity scores were analysed. Statistical analysis was performed using the SPSS 23 program.

Results: The mean age was 39 years (range 25-65 years), with a male predominance (54%). A CD4 count <200 *cells/mm*^{3} was identified in 6 cases. The mReiff score (6.8±4.6) showed a significant correlation with Bhalla score (9.72±4.5), r=0.66 (p<0.05). BSI score (11.7±3) reflects better the severity of the disease, showing a significant correlation with the Bhalla imaging score (r=0.62, p<0.05). Assessing the impact of comorbidities (BACI index 5.4±4.3 and Charlson index 6.9±1.3), the BACI index better reflected the severity of the disease in this group of patients, demonstrating a strong correlation with BSI (r =0.62, p<0.05). Only 3 patients (27%) were over 1-year follow-up.

Conclusions: Bronchiectasis is one of the common pulmonary manifestations of HIV/AIDS infection, being responsible for a number of chronic respiratory symptoms and the risk of premature death.

Key words: bronchiectasis, HIV/AIDS, mReiff score, Bhalla score, Charlson index, BACI index.

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Introduction

Recently, the Republic of Moldova is placed among the countries, which show a continuous increase in the number of adults infected with human immunodeficiency virus (HIV). Rates of newly-diagnosed HIV infections vary widely across countries of Europe, Moldova being ranked the 4th after Russia, Ukraine and Belarus (in 2018 – 22.3 per 100 000 population; 905 new cases) according to WHO data [1, 2]. There are alarming data regarding the delayed diagnosis (at the stage of acquired immunodeficiency syndrome), involving a large number of patients with CD4 T lymphocyte levels below 200/*mm*^{3}. In 2018 out of 696 primary identified cases, 85% (592 patients) were tested for CD4 level, of whom 223 were at the last HIV infection stage with CD4 below 200/*mm*^{3} [2]. Lung infections are among the main manifestations for which patients seek medical advice, it is also a common cause of mortality in AIDS (acquired immunodeficiency syndrome) cases.

Both primary and secondary immunodeficiencies should be suspected in all cases of identified primary bronchiectasis, especially in adult patients under 40 years of age [3, 4]. Untreated HIV infection is characterized by a progressive decrease level of helper T lymphocytes (CD4). Immune system damage accompanied by chronic inflammation contributes to the progression of bronchiectasis in HIV patients [5, 6], although in adult patients evidence is provided in favour of multifactorial involvement in both etiology and progression of bronchial wall lesions [5, 7]. More publications come up with arguments that show damage not only to the immune response (from helper T lymphocyte deficiency, impaired local response of macrophages and monocytes), but also the direct effect on bronchial walls due to intercurrent infections (pneumonia or tuberculosis) and the association of chronic obstructive pulmonary disease in adult patients with bronchiectasis and HIV infection [5, 7, 8].

The study aims to present the clinical, imaging, bacteriological peculiarities and outcomes in adult patients with bronchiectasis and HIV/AIDS infection.

Material and methods

A series of cases diagnosed with HIV/AIDS infection and bronchiectasis selected from the prospective study that included a group of 490 adult patients with non-cystic fibrosis (NCF) bronchiectasis evaluated at *Chiril Draganiuc* Hospital during 2015-2019. Each patient signed the informed consent. Demographics, clinical characteristics,

biological, imaging, and microbiological data (bacteriological examinations of sputum and bronchoalveolar lavage) were obtained and summarized in tables 1-4. The disease outcomes were analysed up to 1 year after being included in the study. HIV infection was confirmed by the positive WESTERN BLOT test, performed after obtaining two HIV-positive ELISA tests. All patients underwent the thoracic high-resolution computed tomography (HRCT) scan that assessed the morphology of bronchial dilatations (cylindrical, varicose and cystic), their distribution and the associated imaging lesions (cavities, calcification of lymph nodes, parenchymal calcifications, interstitial or consolidation syndromes). The Reiff (modified Reiff) [9, 10] and Bhalla [11] imaging scores were calculated. Bronchiectasis severity was evaluated using BSI (Bronchiectasis Severity Index) and FACED scores [12, 13]. Imaging signs of pulmonary hypertension on thoracic HRCT were also evaluated. Validated measuring instruments were used to assess comorbidities and their impact on the evolution of the disease, namely the Charlson Comorbidity Index [14] and the BACI index (Bronchiectasis Aetiology and CO-Morbidity Index) [15].

Table 1

Demographic characteristics and comorbidities of HIV/AIDS patients with bronchiectasis

	Age /Gender / Environment U/R	BMI, kg/m^2	Smoker/SI	Migrant worker	Comorbidities
Pt. 1	26/M/R	17.3	Yes/10 p/y	Yes, Russia	Oropharyngeal candidiasis Wasting syndrome
Pt. 2	42/F/R	17.3	No	husband was a migrant worker in Russia	Mastoidectomy Kidney stones Anaemia Keratitis Pulmonary cryptococcosis Wasting syndrome
Pt. 3	35/F/R	19.8	No	No	Pneumocystis pneumonia Multiple lung abscesses Anaemia
Pt. 4	32/F/U	11.4	Yes/15p/y	Yes, Russia	Anaemia Stomatitis Cutaneous mycosis Wasting syndrome
Pt. 5	22/M/R	20.1	No	No	Anaemia Pneumocystis pneumonia
Pt. 6	27/M/R	16	No	No	Anaemia Pneumocystis pneumonia Wasting syndrome Esophageal candidiasis
Pt. 7	65/F/R	22.6	Yes/20p/y	No	Pulmonary cryptococcosis Anaemia
Pt. 8	28/M/R	14.5	Yes/8p/y	Yes, Russia	Pulmonary cryptococcosis Anaemia Pneumocystis pneumonia Wasting syndrome Kaposi's sarcoma
Pt. 9	33/M/R	20	Yes/8p/y	Yes, Greece	Oropharyngeal candidiasis Pneumocystis pneumonia Anaemia
Pt.10	46/M/U	16.3	Yes/15 p/y	Yes, Russia	Anaemia Oropharyngeal candidiasis Pulmonary aspergillosis Pulmonary tuberculosis Wasting syndrome
Pt.11	35/F/R	16.3	No	Yes, Russia	Anaemia Oropharyngeal candidiasis Wasting syndrome Pneumocystis pneumonia

Note: U – urban, R – rural; SI – smoking index; p/y – pack/years.

Results

The prevalence of patients with bronchiectasis and HIV/AIDS infection in the group of patients with non-cystic fibrosis bronchiectasis (490 patients) was 2% (11 patients). The mean age was 39.2±13.5 (26-65) years, 63% – under 35 years old, 6 male patients (54%). No patient was a drug user, whereas 82% came from rural areas and 73% (8 patients) were married. Migrant worker status was identified in 64% of cases (tab. 1), migration to Russia being the most frequently reported (6 patients). All patients were hospitalized at least once during the last year in the departments of district medical facilities due to respiratory infections of unspecified etiology and diarrheic syndrome of unspecified etiology. Only two patients knew their HIV-infected status (though didn't use antiretroviral treatment) at the time of being included in our study, 82% have been primarily diagnosed with HIV/AIDS. All patients were at the last stage of HIV infection (clinical category C) with multiple comorbidities (tab. 2) and severe weight deficit, the mean BMI (body mass index) being of 17.4±3.4 kg/m^2. Only 3 patients (27%) had a BMI above 18.5 kg/m^2 (tab. 1). Out of 7 patients in whom the level of CD4 lymphocytes was evaluated (mean 82±125/ mm^3, range 4-350), 6 patients had a level below 200/mm^3 (3 cases had a critical level ≤ 5/mm^3 and also had more severe lung lesions). Cough with purulent sputum was identified in all cases (7 patients reported amounts of more than 50 *ml* of sputum/24 *hours*) and 4 patients had several episodes of hemoptysis. Most cases showed significant co-morbid conditions. Anaemia was found in 10 patients (91%), the most severe cases (haemoglobin level below 70 *g/l*) were associated with more extensive lung changes and chronic diarrhea.

The assessment of the impact of comorbidities on the severity of bronchiectasis revealed the BACI index 5.4±4.3 and the Charlson index 6.9±1.3. The BACI index better reflects the severity of the disease in patients with bronchiectasis and HIV/AIDS infection demonstrating a strong correlation with BSI (r=0.62, p <0.05).

The analysis of the thoracic HRCT scans showed an extremely polymorphic nature of the imaging lesions (tab. 3) at the time of inclusion in the study. The predominance of tubular (cylindrical) bronchiectasis was recorded (fig. 1-3). Six patients presenting exclusively cylindrical type of bronchiectasis, localized in all lobes revealed a 6-pont mReiff score and only 4 patients (36%) presented a score below 6 points. The severity of bronchiectasis extension was highlighted by the mReiff imaging score (6.8±4.6 points), which, although simplified, showed a strong correlation with the Bhalla score (9.72±4.5; r=0.66; p <0.05).

Bronchiolitis imaging features were present in 5 patients (fig. 1, 3). Only one patient presented lung parenchyma calcifications, and another one showed calcifications in the bronchial walls (fig. 3). Imaging signs of pulmonary hypertension (HTP) with pulmonary artery trunk diameter over 27 *mm* and pulmonary artery diameter ratio to ascending aortic diameter above 0.9 were present in 3 patients (fig. 4). Analysing the BSI (11.7±3) and FACED (2.9±0.9) severity scores, BSI better reflects the severity of the disease in this etiological group of NCF bronchiectasis, and a good correlation with the Bhalla imaging score was demonstrated (r=0.62, p <0.05).

Imaging signs suggestive of pneumonia caused by *Pneumocystis jiroveci* were identified in 7 patients (fig. 1), whereas the bacteriological confirmation was obtained only

Table 2

Individual characteristics and outcomes of HIV-infected patients with bronchiectasis

	HIV infection detected in the current hospitalization	CD4 cells/mm³	Duration of hospitalization/ antiretroviral treatment initiated during hospitalization	*Deceased (D)/Survived (S)
Pt. 1	Yes	N/D	7 days/No	S
Pt. 2	Yes	N/D	14 days /No	S
Pt. 3	No	5	36 days /No	D
Pt. 4	Yes	5	12 days /No	D
Pt. 5	Yes	122	18 days /No	D
Pt. 6	Yes	N/D	7 days /No	D
Pt. 7	Yes	N/D	29 days /No	D
Pt. 8	No	4	38 days /Yes	D
Pt. 9	Yes	39	21 days /Yes	S
Pt.10	No, he has known about HIV status for 3 years	350	32 days /No	D
Pt.11	Yes	50	8 days /No	D

Note: N/D – No data

* – Deceased (D)/Survived (S) one year after being included in the study.

in one case (tab. 3, 4). It is still challenging to identify the pathogens responsible for pulmonary infections in severely immunocompromised patients, requiring the exclusion of opportunistic infections, fungal infections, mycobacteria, and viruses in addition to Gram-positive and Gram-negative pathogenic bacteria.

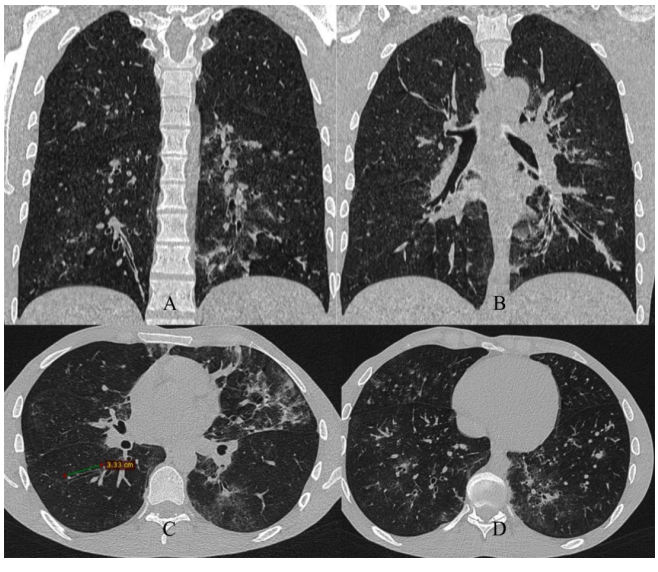

Fig. 1. Chest HRCT images of patient 1

Thoracic high-resolution CT in coronal (A, B) and axial (C, D) reconstructions of a 26-year-old man primarily diagnosed with HIV/AIDS shows bilateral cylindrical bronchiectasis and bronchial wall thickening that is more prominent in the lower lobes. A number of areas demonstrating the "signet ring" and the "tram tracks" signs, or lack of tapering when viewed in longitudinal cross-section (some of them are amputated due to endobronchial secretions). The presence of "ground glass" opacities was recorded that might be the imaging expression of an opportunistic infection (*P. jiroveci*) that was not actually confirmed in this case.

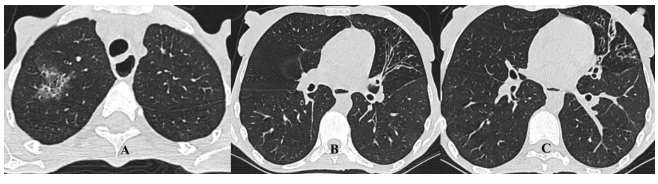

Fig. 2. Chest HRCT images of patient 4

Axial lung window HRCT sections (A, B, C) of a 32-year-old woman showing more severe bronchial dilatations (varicose and cystic) in the lingual segments (C). Tubular bronchiectasis was identified in the right upper lobe (A) as well as in the immediately subpleural areas of the left lung. The hypotrophy of the muscle and of the subcutaneous adipose tissue at the level of the thorax could be seen, the patient being with the lowest BMI 11 kg/m^2 (33 *kg* at a height of 175 *cm*) among all the patients included in the study. There was an evidence of dilation of the oesophagus (A).

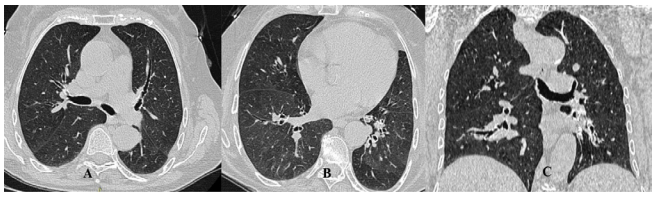

Fig. 3. Chest HRCT images of patient 7

HRCT images of the chest in the oldest patient aged 65 from this series, diagnosed primarily with HIV/AIDS infection, showing bilateral tubular bronchiectasis. There are focal areas of decreased attenuation with a mosaic aspect of the lung fields (B, C), findings consistent with constrictive obliterative bronchiolitis. Bronchial walls and aortic arch calcifications were recorded (A, C).

Table 3

Distribution of bronchiectasis and associated imaging lesions

	Bronchiectasis distribution /morphological type	m Reiff score	Bhalla score	Imaging signs of bronchiolitis	Consolidation syndrome	Interstitial syndrome	PA:Ao ratio > 0.9
Pt. 1	RUL, RML, RLL, LUL, lingula, LLL/ tubular	6	7	Yes	No	Yes	No
Pt. 2	RUL, RML, RLL, LUL, lingula, LLL/ tubular	6	7	No	No	No	No
Pt. 3	RUL, RML, RLL, LUL, lingula, LLL/ tubular, cystic	18	14	No	No	No	Yes
Pt. 4	RUL, RML, RLL, LUL, lingula, LLL/ tubular, cystic	8	16	No	Yes	Yes	No
Pt. 5	RUL, RML, RLL, LUL, lingula, LLL/ tubular	6	6	Yes	No	Yes	No
Pt. 6	RLL, LUL, lingula, LLL/ tubular, cystic	6	10	No	Yes	Yes	No
Pt. 7	RLL, lingula, LLL/ tubular	3	10	Yes	No	Yes	No
Pt. 8	RUL, RLL, LLL/ tubular, cystic	5	13	Yes	No	No	No
Pt. 9	RUL, LUL/ tubular	2	4	No	Yes	Yes	No
Pt.10	RUL, RML, RLL, lingula, LLL/ tubular, cystic	12	16	Yes	No	No	Yes
Pt.11	RUL, RML, LUL/ tubular	3	4	No	No	Yes	Yes

Note: RUL – right upper lobe, RML – right middle lobe, RLL – right lower lobe, LUL – left upper lobe, LLL – left lower lobe, PHT – pulmonary hypertension, CT – computer tomography, PA:Ao ratio – ratio of pulmonary artery diameter to ascending aortic diameter.

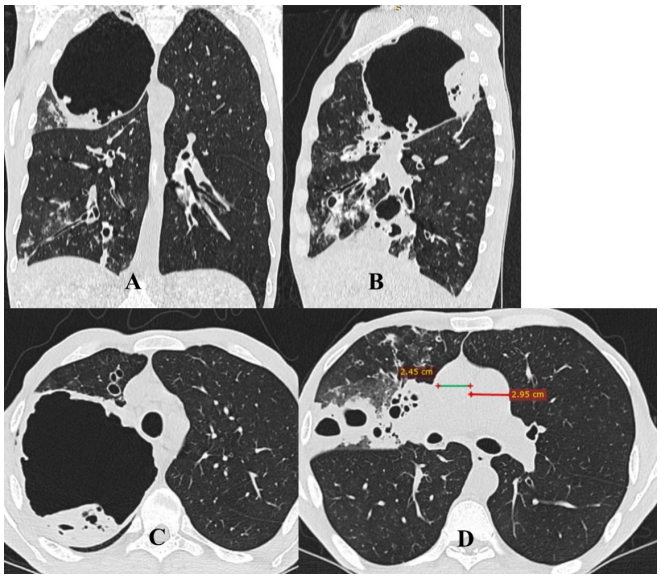

Fig. 4. Chest HRCT images of patient 10

Chest HRCT images of a 46-year-old patient, being HIV- infected for 3 years (without antiretroviral therapy) showed an extensive lung damage, the upper right lobe being replaced by a cavity (A-C), with an intracavitary content, (suggestive of *fungus ball*). Multiple tubular and cystic bronchiectasis, some with hydroaeric level, more prominent on the right. Dilatation of the pulmonary artery (2.95 *cm*) was noted in relation to the ascending aorta (D). Ratio of pulmonary artery diameter to ascending aortic diameter was 1.2 (> 0.9 suggestive of pulmonary hypertension).

Bacteriological confirmation of *M. tuberculosis* infection was confirmed in none of the suspected patients; however, in 4 cases presenting cavitary lesions and/or consolidations, the diagnosis of pulmonary tuberculosis was established based on clinical and radiological criteria. Two patients could not tolerate the anti-tuberculosis medication due to its side effects. Fungal infections viz. *Cryptococcus neoformans* was identified in 3 cases and *Candida spp*- in 7 cases (tab. 4).

Only 3 patients (27%) survived one year after being included in the study and continue the antiretroviral treatment (ART) and 2 patients died during hospitalization (patient 7 and patient 10).

Discussion

The prevalence of patients with immunodeficiencies in the aetiological structure of NCF bronchiectasis cases varies from 6% to 14% in adults, being higher among children 20–34% [16]. Recurrent respiratory tract infections, both viral and bacterial, along with HIV infection cause a decrease in innate immunity (due to a progressive loss of CD4 cells), which yields a persistent inflammatory state in the lower respiratory tract. Furthermore, in these patients, HIV infection may cause an inflammatory obliterative bronchiolitis, which would facilitate and contribute to the remodelling of the airways and the development of bronchiectasis [17].

Bronchiectasis is a progressive airway disease, anatomically defined by abnormal and progressive dilation of the bronchi, clinically manifested by persistent cough, sputum production, and recurrent respiratory tract infections, that are considered one of the most important aetiological factors in the development of bronchiectasis in HIV infected patients [17]. Microbial toxins and persistent inflammation compromise mucociliary clearance, which leads to increased susceptibility for microbial colonization, and

Table 4

Microbiology data and diagnosticated opportunistic infections

	Sputum cultures results	Bacteriological confirmation of *M. tuberculosis*	Clinically and radiologically diagnosed TB case	Clinically and radiologically diagnosed Pneumocystis pneumonia
Pt. 1	*Candida albicans*	No	No	No
Pt. 2	*Cryptococcus neoformans* *Candida albicans*	No	No	No
Pt. 3	*S. aureus* *E. coli* *Candida albicans*	No	Yes, anti-TB treatment not tolerated	Yes
Pt. 4	*Streptococcus gr D*	No	Yes, anti-TB treatment refused	No
Pt. 5	*Streptococcus gr D*	No	No	Yes
Pt. 6	*Kl. pneumoniae* *Candida krusei*	No	No	Yes
Pt. 7	*Cryptococcus neoformans*	No	No	Yes
Pt. 8	*Cryptococcus neoformans* *Citrobacter freundii*	No	Yes	Yes
Pt. 9	*Pseudomonas aeruginosa* *E. coli* *Candida albicans*	No	No	Yes
Pt.10	*Moraxella*	No	Yes	No
Pt.11	*Candida albicans* *Pneumocystis jiroveci*	No	No	Yes

create a self-perpetuating cycle [18]. Malnutrition, aspiration pneumonitis due to gastroesophageal reflux disease, esophageal candidiasis are among the multiple factors that have been incriminated to complement the appearance of bronchiectasis in this group of patients [18-20].

Patients with HIV infection became a common reality in daily clinical practice of a general physician and of a pneumologist as well. As the life expectancy of HIV-infected patients increased due to prevention and treatment of opportunistic infections, an early recognition of bronchiectasis and its associated features may have an important role for disease outcome. The key element for the diagnosis of bronchiectasis is the imaging technique. Thoracic HRCT scan, replacing the more invasive bronchography, is considered more sensitive to identify and assess the severity of bronchiectasis.

Plenty of scientific papers have been published, describing pulmonary complications in HIV-infected patients, most of them including advanced immunosuppression cases, have focused on the evaluation and treatment of infections with opportunistic germs. First studies presenting bronchiectasis in HIV-infected patients included a small series of cases, Holmes and co-authors published the first 5 cases in 1992 [5, 21, 22]. Several authors have concluded that acute bronchitis is the most common pulmonary manifestation in HIV-infected patients and retrospective studies have shown that in AIDS patients bronchiectasis has a higher incidence [19, 23]. Similar to the results from the case series analysed by McGuinness (12 patients) [22] in our study, the airway lesions, as well as those identified in the lung parenchyma, were found to be much more extensive than would have been expected according the history of lung infections reported by patients. Verghese and co-authors concluded that recurrent bacterial infections (especially *S. aureus, H. influenza, B. cepacia*, and *S. pneumoniae*) contribute to the development of bronchiectasis in HIV-infected individuals much more frequently than previously considered [21].

In 1997 King and co-authors, analysing chest CT images of a group of 50 HIV-infected patients (without history of AIDS or lung infections until inclusion in the study) and another group of 11 HIV-negative control subjects, demonstrated the presence of bronchiectasis in 36% of HIV infected patients and none in HIV-negative subjects. The authors hypothesised that lung and airway lesions in HIV-infected patients were present before the onset and development of lung infectious complications. Bronchial dilatation was found to be caused by bronchiolitis obliterans, elevated level of neutrophils in the airways and lymphocytic interstitial pneumonia [23].

Despite significant progress in understanding HIV infection, including prevention strategies, chemoprophylaxis, and antiretroviral therapy, the incidence of HIV-related diseases remains high in Moldova [1, 2]. Although the patients included in our study had a history of lung infections, the diagnosis, evaluation of the etiology and severity of bronchiectasis were neglected, most patients being identified with severe lung damage at the stage of establishing HIV status. Among the pulmonary complications, HIV/AIDS patients showed a higher occurrence for infections (especially pulmonary tuberculosis, pneumocystis pneumonia and various other opportunistic infections) thus, the development of bronchiectasis might be accelerated in this patient population.

Patients often underestimate their symptoms and refer to a doctor at the stage of advanced disease with limited management opportunities. Unfortunately, even after establishing the diagnosis of HIV/AIDS infection in the patients of our study, in some cases it was not possible to initiate ART, due to various difficulties (wasting syndrome, dyspeptic syndrome, religious and cultural considerations, poverty, inadequate referral system and poor adherence to treatment) which may have contributed to a high mortality rate, thus leading to 73% of deaths in this case series. Countries with limited resources face more difficulties in managing chronic diseases and bronchiectasis and HIV/AIDS are no exception. It would be advisable to test for HIV infection as part of the diagnostic process not only the patients with HIV risk factors, but also the group of primary identified patients with bronchiectasis, especially in countries with high incidence of HIV infection, such as the Republic of Moldova.

Conclusions

Bronchiectasis is one of the common pulmonary manifestations of HIV/AIDS infection, being responsible for a number of chronic respiratory symptoms and a risk factor for premature death.

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OM drafted the first manuscript and interpreted the data, DR acquired the data, DT acquired the data, VB revised the manuscript critically. All the authors revised and approved the final version of the manuscript.

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Conflict of Interests
The authors have no conflict of interests to declare.