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Frequency and risk factors of venous thromboembolic complications in patients with active pulmonary tuberculosis and HIV/TB co-infection (tuberculosis and thrombosis)

Учесталост и фактори ризика за венске тромбоемболијске компликације код пацијената са активном плућном туберкулозом и коинфекцијом ХИВ/ТБ (туберкулоза и тромбоза)

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SUMMARY

Introduction/Aim Venous thromboembolism complications (VTEC) include: deep vein thrombosis (DVT), superficial vein thrombosis (SVT) and pulmonary embolism (PE). The aim was to assess the prevalence of venous thromboembolic complications in patients with active pulmonary tuberculosis and to reveal the main factors influencing the development of VTEC in this cohort of patients.

Methods A retrospective study of electronic health records of patients with active pulmonary tuberculosis was carried out. Patients: All patients with confirmed active pulmonary tuberculosis and VTEC for the period from January 01, 2020 to December 31, 2022.

Results An overall 214 cases of VTEC were identified. The most significant risk factors for the development of thrombotic complications in tuberculosis patients were human immunodeficiency viruses (HIV) / tuberculosis co-infection (RR, 3.8; 95% CI, 2.7-4.5) and the duration of the disease (according to the criterion of formation of fibrosis foci and/or cavities) (RR, 9.1; 95% CI, 4.7-17.6). The overall prevalence of VTEC in the tuberculosis hospital exceeded the literature data for non-tuberculosis clinics by 3.3 times.

Conclusion Tuberculosis is a major reversible risk factor for the venous thromboembolic events, probably due to impaired coagulation mechanisms, venous stasis and endothelial dysfunction. HIV infection in this context is the second major reversible factor in the development of VTEC.

Keywords: venous thrombosis; tuberculosis; thromboembolism; HIV; hypercoagulation

САЖЕТАК

Увод/циљ Компликације венске тромбоемболије (ВТЕК) укључују: дубоку венску тромбозу (ДВТ), тромбозу површинских вена (ТПВ) и плућну емболију (ПЕ). Сврха: Процена преваленције венских тромбоемболијских компликација код пацијената са активном плућном туберкулозом и откривање главних фактора који утичу на развој ВТЕК-а у овој кохорти пацијената.

Метод Урађена је ретроспективна студија електронских здравствених картона пацијената са активном плућном туберкулозом. Пацијенти: Сви пацијенти са потврђеном активном плућном туберкулозом и ВТЕК-ом за период од 01.01.2020. до 31.12.2022.

Резултати Идентификовано је укупно 214 случајева ВТЕК. Најзначајнији фактори ризика за настанак тромботичких компликација код туберкулозе били су коинфекција ХИВ/туберкулозе (РР, 3,8; 95% ИП, 2,7-4,5) и трајање болести (према критеријуму формирања жаришта фиброзе). и/или шупљине) (РР, 9,1; 95% ИП, 4,7-17,6). Укупна преваленција ВТЕК-а у болници за туберкулозу премашила је литературне податке за нетуберкулозне клинике за 3,3 пута.

Закључак Туберкулоза је главни реверзибилни фактор ризика за венске тромбоемболијске догађаје, вероватно због поремећених механизма коагулације, венске стазе и ендотелне дисфункције. ХИВ инфекција у овом контексту је други велики реверзибилни фактор у развоју ВТЕК.

Кључне речи: венска тромбоза; туберкулоза; тромбоемболија; ХИВ; хиперкоагулација

INTRODUCTION

Tuberculosis and venous thromboembolic complications (VTEC) are two global problems of modern healthcare that receive significant attention both in the scientific literature and in practical guidelines for clinical use. Against the background of a decrease in the basic incidence rate of tuberculosis in the Russian Federation to 33.5 cases per 100,000 people per

year (2021), there is a tendency to increase the number of cases of severe and complicated course of the disease [1, 2]. This situation is largely explained by the development of active tuberculosis in presence of human immunodeficiency viruses (HIV) infection, comorbid diseases (cardiovascular, autoimmune, oncological, etc.), widespread drug resistance of the pathogen and other procoagulant conditions that increase the threat of VTEC [3, 4].

Currently, many risk factors for venous thromboembolic complications are known, which, under certain conditions, trigger the mechanisms of thrombosis described in the classic work of the Austrian pathologist R. Virchow (1856) in the form of a pathogenetic triad: venous stasis, hypercoagulation and injury to the vascular wall [4]. Studies in recent years have shown that tuberculosis, as a chronic infection, is a procoagulant pathological condition due to the synergistic action of several factors affecting the coagulation equilibrium mechanisms [5].

Thus, the research aimed at studying the prevalence of VTEC among hospital patients with active tuberculosis and identifying the main risk factors for thrombosis is of significant practical importance and will further allow to elaborate effective methods for preventing VTEC in this cohort of patients. Moscow is the best place to conduct such a study in the Russian Federation, as a multinational region with a permanent population of more than 13 million people, which has a sufficiently developed system for recording tuberculosis patients.

Purpose. To assess the prevalence of venous thromboembolic complications in patients with active pulmonary tuberculosis admitted in specialized hospitals in Moscow and to identify the main factors influencing the development of VTEC in this cohort of patients.

METHODS

To solve the set tasks, data from the Moscow Tuberculosis Epidemiological Monitoring System (TEMS) were used. The TEMS is an electronic register (based on the Barclay eo software), which contains basic information about patients with diagnosed active tuberculosis

of any localization, confirmed by cultural, bacterioscopic and/or molecular genetic methods. The registers are replenished monthly on the basis of transmitted information from all tuberculosis hospitals in Moscow, regardless of the patient's residence (patients from other regions of the Russian Federation, foreign citizens, persons of no fixed abode) [6]. To assess the prevalence of VTEC, a retrospective study of medical records (electronic medical records of an inpatient) was performed by viewing them, in the course of which all cases of venous thromboembolic complications were detected in all tuberculosis hospitals in Moscow: Moscow Scientific and Practical Center for Tuberculosis Control, Zakhariin Tuberculosis Clinical Hospital No. 3, Rabukhin Tuberculosis Hospital for the period 2020 – 2022.

The study was approved by the Local Ethics Committee of Moscow Research and Clinical Center for TB Control (Protocol No. 11/23, February 6, 2023). All enrolled patients provided written informed consent to the utilization of their anonymized clinical data.

The criteria for inclusion in the analysis were: 1. Age 18 years and older; 2. Active pulmonary tuberculosis confirmed by X-ray, cultural, bacterioscopic and/or molecular genetic method; 3. Deep vein thrombosis of the lower limbs (DVT), superficial vein thrombosis of the lower limbs (SVT) and pulmonary embolism (PE) – confirmed by instrumental methods of examination (ultrasound angiography, computed tomography of the chest organs with intravenous contrast).

Exclusion criteria: patients with iatrogenic thrombosis after the insertion of central and peripheral venous catheters; patients receiving treatment for COVID – 19 (and within 30 days after recovery); patients with inactive tuberculosis who had previously received therapy or admitted for surgical treatment; patients taking combined oral contraceptives.

The following information about patients was available for obtaining from medical records: gender, age, protocol for the diagnosis of "active tuberculosis", HIV status, protocol for ultrasound angiography of the lower limbs veins, protocol for computed tomography of the

chest with intravenous contrast, the fact of taking oral contraceptives and anticoagulants during the month before the detection of active pulmonary tuberculosis.

To assess the duration of the disease, we used the fact of the presence of massive fibrosis and/or caverns in the lungs, which form no earlier than 16–24 months from the onset of the disease [7]. This is because the moment of onset of a chronic infectious disease in most cases cannot be determined due to the paucisymptomatic course at the beginning.

As part of the statistical analysis, extensive indicators and their 95% confidence intervals (95% CI) based on the Wilson's method, relative risk (RR) and its 95% CI (confidence interval) were calculated. For numerical features whose distribution differed from the normal one according to the Shapiro – Wilk's test, we determined the median (Me) and its 95% CI. To test hypotheses about the effect of age, gender, the presence of HIV infection, as well as the duration of the disease (by the criterion of formation of fibrosis and cavities in the lungs) on the risk of developing VTEC, patients were stratified according to appropriate signs, followed by an analysis of statistically significant differences in the frequency of VTEC in strata. Statistical processing of information was carried out using the program support R , version 3.6.2 (2019-12-12) – "Dark and Stormy Night" with the connection of the DescTools library. The value of $p < 0.05$ was considered statistically significant.

RESULTS

According to the data of the Moscow Regional Register (based on Barclay SW), 4,609 patients with detected active pulmonary tuberculosis were admitted in tuberculosis hospitals in Moscow. The majority of these patients were men (2,987; 64.8%), women made up about a third of all patients (1,622; 35.2%). Reviewing the medical records of these patients we found 214 cases of VTEC that met the search criteria. Men prevailed among patients with VTEC ($n = 145$; 67.8%), women accounted for 32.2% ($n = 69$). None of them received anticoagulant

therapy. Among 214 patients, only 4 had anamnestic indications of cancer. In the last 30 days before the diagnosis of VTEC there was no mention of surgical operations.

Based on statistical calculations, the rate of venous thromboembolic complications among 4,609 tuberculosis patients was: 4.6% (95% CI; 4.1-5.3), where deep vein thrombosis was detected in 3.5% (95% CI; 3 - 4.1), superficial vein thrombosis – in 1.5% (95% CI; 1.2-1.9), and PE – in 0.6% (95% CI; 0.4-0.8) (Figure 1). A combination of DVT and SVT was registered in 16 patients (7.5%; 95% CI 4.7-11.8), all cases of PE (n = 26) were combined with DVT (12.2%; 95% CI 8.4-17.2), and in 2 cases a combination of PE and SVT was noted (0.9%; 95% CI 0.3 - 3.3).

In the course of the study, it was necessary to discover the factors influencing the rate of VTEC, among which we considered age, gender, the presence of HIV infection with any immune status and the disease duration to be the most significant. Analyzing the influence of the patient's age and gender on the frequency of venous thromboembolic events, no statistically significant differences were obtained, they occurred with approximately the same frequency in both men and women (Table1). Relative risk (RR) of VTEC development in admitted men and women with tuberculosis was 1.14 (95% CI; 0.86 - 1.51); (p = 0.2).

According to multivariate analysis, statistically independent predictors of venous thromboembolic complications were: HIV infection and the duration of the disease (after development of fibrous and/or cavernous processes in the lungs). Thus, according to our data, the incidence of VTEC was 3.8 times higher in patients with HIV/TB co-infection than in patients with active tuberculosis without HIV infection. There was a statistically significant age difference in patients with HIV/TB (Me = 40; 95% CI 38 - 41 years) and TB (Me = 43; 95% CI 41-47 years) (p = 0.0003; Mann – Whitney test). For this reason, we stratified patients by age groups with a 10 - year interval and determined the frequency of VTEC in strata (Table 2).

The results obtained allow us to reject the null hypothesis and accept an alternative one, according to which HIV infection (even when receiving antiretroviral therapy) increases the risk of developing VTEC in admitted patients with active pulmonary tuberculosis, regardless of their age.

Another factor affecting the frequency of acute venous thrombosis is the duration of the disease. Unfortunately, since we cannot have data about the moment of onset of the disease (as a rule, patients don't have these data due to the paucisymptomatic course of the disease), we used the criterion of the presence of fibrosis foci and/or cavities, which don't form earlier (and, most often, later) 16-24 months from the onset of the disease.

CT showed that the relative risk of developing VTEC in patients with fibrous and/or cavernous changes in the lungs compared with patients with pulmonary tuberculosis without these changes was 9.08 (95% CI; 4.7-17.5). Thus, the presence of fibrosis foci and cavitary necrosis, which in this case are noted in every fourth patient, significantly increases the risk of developing VTEC. The age of patients with VTEC and fibrous-cavernous changes in the lungs (Me = 49; 95% CI; 25-78 years) didn't differ much from the age of patients with VTEC but without fibrous-cavernous changes in the lungs (Me = 43; 95%; CI 41-47 years) ($p = 0.9$). Acute venous thrombosis was almost as frequent in patients under the age of 45 with active tuberculosis and fibrous-cavernous changes in the lungs as in patients over 45 years of age; 33.3% vs. 23.5% ($p = 0.9$).

To compare the frequency of VTEC among admitted patients with active pulmonary tuberculosis and patients in non-tuberculosis hospitals, we used expert estimates in scientific publications of the European Union and the United States over the past 10 years (Table 3) [8,9,10].

The analysis allows us to reveal the main patterns affecting the frequency of acute venous thrombosis and embolism in patients admitted in tuberculosis hospitals for active pulmonary

tuberculosis. A comparison of our data and expert estimates of the frequency of venous thromboembolic events in the hospital allowed us to assert that, in general, the frequency of VTEC in patients of tuberculosis dispensaries is 3.3 times higher than in patients in non-tuberculosis hospitals. Interestingly, the incidence of DVT is 2.9 times higher in patients with active pulmonary tuberculosis, while the rate of PE is approximately equal in both groups (Figure 2).

DISCUSSION

For a long time, the relationship between chronic infectious processes and VTEC was considered as an accidental phenomenon, so that only rare instances of DVT and PE in active tuberculosis were discussed in the literature [11]. At the same time, as early as 1948, there were reported cases of deep vein thrombosis and pulmonary embolism in tuberculosis patients without concomitant blood clotting disorders [12]. Subsequently, it was noted that according to the results of autopsies and screening ultrasound examinations, VTEC occur in patients of tuberculosis clinics in Europe, North America and the Middle East with a fairly high frequency exceeding 2.5% [12]. Based on a meta-analysis by Dentan S. et al. (2014), hospital mortality in patients with active tuberculosis and VTEC (15%) was 5 times higher than mortality among tuberculosis patients without VTEC (2.7%) or patients in general hospitals with VTEC (2.5%) ($p < 0.001$) [13]. In the multifactorial analysis model, adults with active tuberculosis had a higher risk of VTEC than patients without tuberculosis, but with a risk of VTEC due to oncology [14].

It has been found that tuberculosis, as a chronic infection, has a direct impact on the processes leading to hypercoagulation. According to Turken O. et al. (2002) this is directly manifested by an increase in the level of fibrinogen, factor VIII in blood plasma, as well as a decrease in the synthesis of antithrombin III and inhibition of protein C [15]. Another

observation showed that in the case of active tuberculosis, antiphospholipid antibodies are often found in the blood of patients, which inhibit the activation of proteins S and C, inhibit the functions of antithrombin III and the fibrinolysis system (decrease in the tissue plasminogen activator function), increase the expression of tissue factor (TF) on immune cells and increase platelet aggregation (due to active synthesis of thromboxanes) [16]. These processes seem to be associated with high cytokine activity in tuberculosis, which leads to endothelial dysfunction. Indeed, back in 1991, Japanese scientists studies showed high production of interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-alpha) by monocytes of patients with active tuberculosis of various localizations [17]. Additionally, it is possible to note the progressive effect of *Mycobacterium tuberculosis* itself on the expression of TF on cell membranes, which is currently considered as the main triggering factor of thrombosis [18].

It is no secret that tuberculosis patients, both pulmonary and extrapulmonary, as a rule, suffer from weight loss and hypodynamia due to various reasons: against the background of intoxication and weakness, after surgical interference, long stay in intensive care units, skeletal muscles hypotrophy [19]. The combination of these factors creates prerequisites for the occurrence of venous stasis in the deep veins of the lower extremities. Thus, tuberculous inflammation determines all three interrelated components of the Virchow's triad: inflammatory endothelium damage, venous stasis and hypercoagulation.

HIV infection plays another but not less important role in the processes of thrombosis formation. According to the results of the conducted studies, HIV – positive people, regardless of antiretroviral therapy (ART), had an increase in the frequency of VTEC due to immune system dysregulation and the development of chronic inflammation. HIV infection is recognized as a prothrombotic disease, while the incidence of VTEC among HIV – infected patients vary from 0.19% to 7.63% per year [20]. The relationship between HIV infection and VTEC was first reported by Hassell K. et al. in 1994: according to the authors, the incidence

of DVT among HIV-infected patients reached 18% in the Denver County Hospital, and researchers associated this phenomenon with the detected deficiency of protein S and antiphospholipid antibodies [21]. A protein S concentration decrease in people living with HIV was subsequently proved in a series of works by American and Dutch scientists, a clear correlation having been observed in an concentration increase of factor VIII and fibrinogen in blood plasma [22]. It is assumed that the synthesis of protein S in endothelial cells, hepatocytes and megakaryocytes is suppressed due to the activity of TNF-alpha and/or the HIV virus itself [23]. The Funderburg N. et al (2010) research group found a significantly higher incidence of TF – expressing monocytes in fresh blood samples in HIV-infected patients than in uninfected control groups. Presumably, various ligands of bacterial Toll – like receptors are translocated through the damaged intestinal wall in chronic HIV infection and stimulate immune activation (in addition to HIV virus replication) and TF expression by monocytes [24]. The increased TF expression in HIV infection is indirectly confirmed by high plasma levels of D-dimers and the correlation between TF expression and D-dimer levels. HIV replication and systemic translocation of microbial products from the damaged intestine and subsequent immune activation contribute to the procoagulant state in HIV-infected patients.

Changes in the hemostasis system towards procoagulant activity are associated with the severity of immunosuppression, determined by the number of CD4+ lymphocytes [25]. Thus, Feffer S. et al. found a statistically significant difference in the levels of D-dimer, proteins C and S, antigens to proteins C and S, and Von Willebrand factor in individuals with CD4+ levels below 200 cells/ μ l and above 400, which suggested a tendency to thrombosis in HIV – infected patients with deep immunosuppression [26]. The cause of the relationship between HIV infection and VTEC development has not yet been definitively clarified, but it seems to be of a multimodal nature, while all three links of the Virchow's triad are involved. For example, it has been proven that the virus primarily infects endothelial cells, which leads to increasing

plasma concentration of such factors of endothelial dysfunction as thrombomodulin, Von Willebrand factor and E-selectin [27]. The concentration of the latter ones increases by more than 60% and is in inverse proportion to the number of CD4+ lymphocytes, that is, it directly depends on the availability and effectiveness of ART [28]. The concentration of the latter ones increases by more than 60% and is in inverse proportion to the number of CD4+ lymphocytes, that is, it directly depends on the availability and effectiveness of ART [28].

Currently available epidemiological data indicate that HIV infection is interlinked with an increased risk of VTEC by 2-10 times compared with the general population of the same age [29]. Some risk factors, such as low CD4+ lymphocyte count, protein S deficiency, and protein C deficiency, have shown the strongest association with VTEC. Other risk factors are still controversial, for example, protease inhibitor therapy, the presence of active opportunistic infections, and the presence of antiphospholipid antibodies, including antibodies to cardiolipin and lupus anticoagulant.

Finally, pulmonary tuberculosis patients with acute respiratory failure who are in a state of chronic hypoxia (for example, with cavernous and/or fibrous changes in the lung parenchyma) are also at the greatest risk of developing VTEC, which is probably due to a decrease in the concentration and synthesis of protein S by the liver against the background of oxygen deficiency. The mechanism of this effect hasn't been fully studied yet, but it is assumed that it is related with the expression of certain genes that respond to hypoxia and regulate a decrease in protein S levels and an associated increase in serum thrombin levels [29].

CONCLUSION

Based on the data obtained, it can reasonably be assumed that tuberculosis is a major reversible risk factor for venous thromboembolic events, probably due to impaired coagulation mechanisms, venous stasis and endothelial dysfunction. HIV infection in this context is the

second major reversible factor in the development of VTEC. It is logical to assume a synergistic effect of both factors on the incidence of thrombotic events, which makes patients with pulmonary tuberculosis and patients with HIV/TB co-infection, along with cancer patients and patients in traumatology departments, the most vulnerable group with a high risk of developing VTEC. The phenomena of chronic hypoxia expand the threat and risks of acute venous thrombosis in patients with severe lung damage (fibrous and/or cavernous) and also determines the high frequency of VTEC in this part of patients. This fact dictates the need to elaborate systems for assessing the risk of VTEC in patients with pulmonary tuberculosis, specific prevention measures and effective treatment regimens.

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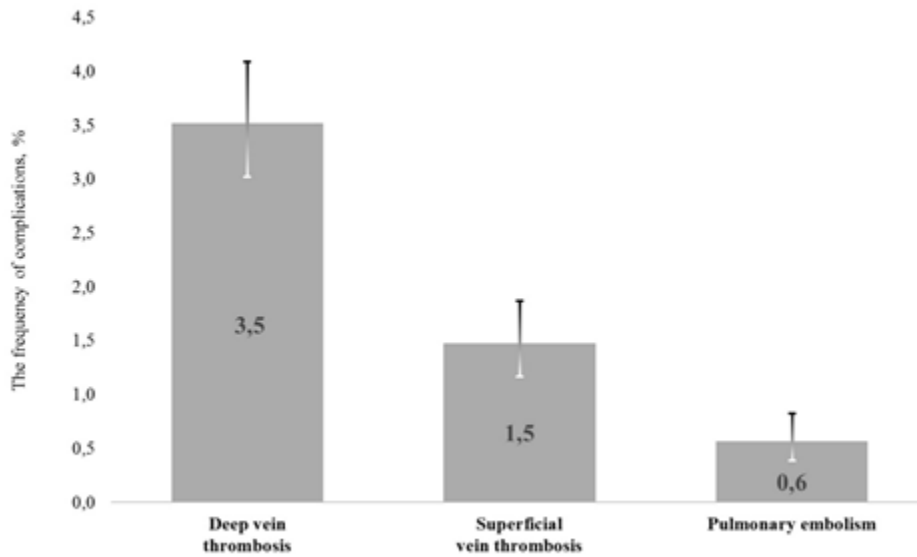


Figure 1. The frequency of certain forms of venous thromboembolism complications in patients with active pulmonary tuberculosis, admitted in tuberculosis hospitals in Moscow (2020–2022); horizontal segments show the boundaries of 95% CI

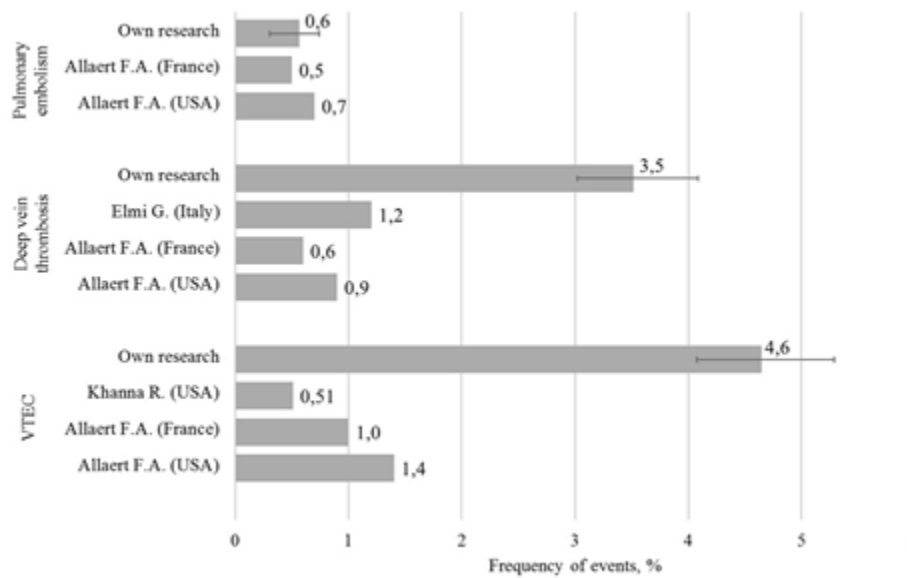


Figure 2. The incidence of venous thromboembolism complications (VTEC), deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients with active pulmonary tuberculosis in comparison with expert estimates; the vertical segments show the boundaries of 95% CI

Table 1. The frequency of venous thromboembolism complications in admitted patients with active pulmonary tuberculosis depending on gender

Parameter	n	sample	%	95% CI	p
Venous thromboembolism complications frequency	214	4609	4.6	4.1–5.3	
Men	145	2987	4.9	4.1–5.7	0.2
Women	69	1622	4.3	3.4–5.3	
Young (< 45 years old) men	89	1757	5.1	4.1–6.2	0.7
Young (< 45 years old) women	47	1004	4.7	3.5–6.2	
Over 45 years old men	56	1230	4.6	3.5–5.9	0.4
Over 45 years old women	22	618	3.6	2.4–5.3	

Table 2. The frequency of venous thromboembolism complications (VTEC) in different age groups among admitted patients with human immunodeficiency viruses (HIV) co-infection/TB and HIV – negative tuberculosis patients

HIV status, age	The number of VTEC, abs.	Group size, abs.	% (95% CI)	p
HIV+, total	98	904	10.8 (9–13)	< 0.001
HIV-, total	116	3705	3.1 (2.6–3.7)	
HIV+, 18–24	0	10	0 (0–27.8)	< 0.001
HIV-, 18–24	1	455	0.2 (0–1.2)	
HIV+, 25–34	18	191	9.4 (6.2–14.4)	< 0.001
HIV-, 25–34	19	819	2.3 (1.5–3.6)	
HIV+, 35–44	58	458	12.7 (9.9–16)	< 0.001
HIV-, 35–44	40	828	4.8 (3.6–6.5)	
HIV+, 45–54	18	196	9.2 (5.9–14)	0.01
HIV-, 45–54	28	657	4.3 (3–6.1)	
HIV+, 55–64	4	45	8.9 (3.5–20.7)	0.08
HIV-, 55–64	14	493	2.8 (1.7–4.7)	
HIV+, 65 and older	0	4	0 (0–49)	0.07
HIV -, 65 and older	14	453	3.1 (1.8–5.1)	
HIV+, 45 and older	22	245	9 (6–13.2)	< 0.001
HIV-, 45 and older	56	1603	3.5 (2.7–4.5)	

Table 3. Expert assessments of the frequency of venous thromboembolism complications (VTEC) in admitted patients in non-tuberculous hospitals

No	Author	Year	Country	VTEC frequency	Note
1	Allaert F.A.	2016	USA	VTEC – 1.4% DVT – 0.9% PE – 0.7 %	Non-tuberculous hospitals
2	Allaert F.A.	2016	France	VTEC – 1% DVT – 0.6% PE – 0.5 %	Non-tuberculous hospitals
3	Elmi G.	2020	Italy	DVT – 1.2%	Non-tuberculous hospitals
4	Khanna R.	2014	USA	VTEC – 0.51%	Non-tuberculous hospitals

DVT – deep vein thrombosis; PE – pulmonary embolism