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# Collaborative tuberculosis/HIV activities in the European Region

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ABSTRACT

**Introduction:** An estimated 12% of tuberculosis (TB) patients are co-infected with HIV in the World Health Organization European Region (the Region). Reducing morbidity and mortality from HIV-associated TB requires strong collaboration between TB and HIV services at all levels with integrated people-centred models of care.

**Methods:** We collected information on the current models of integration of TB and HIV services in the Region *via* a comprehensive survey among the TB and HIV National Focal Points, and identified challenges and opportunities.

**Results:** 47 out of 55 (85%) countries responded. HIV testing in all TB patients and screening for active TB in all people living with HIV (PLHIV) was recommended in 40 (85%) and 34 (72%) countries, respectively. 30 (64%) countries recommended latent TB infection (LTBI) screening in all PLHIV, while 13 (28%) had a selective approach and four (9%) did not recommend LTBI screening. In most countries, testing for HIV and screening for active TB and LTBI was done by the specialist treating the patient, *i.e.* TB patients were tested for HIV by a TB specialist in 42 (89%) countries and PLHIV were screened for active TB by an HIV specialist in 34 (72%) countries.

**Conclusions:** TB and HIV care are well integrated in policies of especially high TB and high HIV burden countries; however, implementation needs to be improved. Continuous monitoring of TB and HIV services integration enables assessing the quality of TB/HIV care and to identify where further improvements are needed.

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**TB and HIV care are well integrated in policies of especially high TB and high HIV burden countries. Continuous monitoring of HIV and TB service integration enables identification of where further improvements are needed.** https://bit.ly/34ylc8I

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## Introduction

Globally, the interplay between HIV infection and tuberculosis (TB) is well recognised, particularly in certain world regions such as in Eastern Europe [1–4]. During 2007–2016, the World Health Organization (WHO) European Region (the Region) faced an unprecedented increase in the percentage of TB patients co-infected with HIV from 3% to 12% [5]. The growth halted for the following 2 years; in 2018 an estimated 12.0% of incident TB patients were co-infected with HIV, a total 30 000 TB/HIV patients [5]. This TB/HIV co-infection rate is the second highest after the African Region (29%) [1]. The number and proportion of TB patients co-infected with HIV was highest in the Russian Federation (16 000 patients (20.0%)) and Ukraine (8200 patients (23%)) [5], which represented 81% of the total burden of TB/HIV patients in the Region. At the same time, the Region has the highest coverage of HIV testing among TB patients in the world (85% in 2018) [1, 5]. Enrolment into antiretroviral therapy (ART) programmes among TB/HIV patients in the Region remains low at 73%, which is far below the WHO target of universal coverage. The percentage of cases with a successful TB treatment outcome among TB/HIV patients is also low and was 51% for the cohort of patients starting treatment in 2018 [5].

Reducing morbidity and mortality from HIV-associated TB requires strong collaborative activities between TB and HIV programmes and services at all levels with integrated people-centred models of care [6, 7]. The WHO issued policy guidelines on three distinct objectives of collaboration: establishing and strengthening mechanisms for integrated delivery of TB and HIV services, reducing the burden of TB among people living with HIV (PLHIV) and initiating early ART, and reducing the burden of HIV among people with presumptive TB (*i.e.* people with signs and symptoms of TB but not bacteriologically confirmed) by offering regular HIV testing [8].

Legido-Quigley *et al.* [9] described models of collaborative TB and HIV service delivery with increasing levels of integration. Some countries in the Region have reported on successful collaboration and integration of TB and HIV services [7, 10, 11]. However, it is not known what models and levels of integration are applied in the majority of the Region's countries and territories, and how the prevention and care services for the two diseases collaborate.

In 2015, the "Wolfheze Workshops" [12] created a Working Group on TB/HIV collaborative activities to document and promote the best models of integrated care taking into account the specific challenges and opportunities, and to identify and promote TB/HIV research priorities in the Region.

The Working Group conducted a survey to collect information on the current models of TB and HIV services integration in the Region, and to identify specific challenges and opportunities related to their integration and collaboration. Results of the survey are reported in this article together with recommendations on effective models of integrated TB/HIV care.

## Methods

The questionnaire for the survey was developed by the members of the Wolfheze Working Group. It was then pre-tested in two countries (Armenia and Ireland), and the Working Group members discussed the results and revised the survey instrument accordingly. The final questionnaire included 31 multiple choice questions on policy and guidelines (*i.e.* on the availability and use of national or international TB/HIV guidelines, national recommendations on HIV testing of TB patients, TB/latent TB infection (LTBI) screening of PLHIV, and ART and co-trimoxazole preventive therapy (CPT) in TB/HIV co-infected persons), diagnosis of TB/HIV co-infection (who is performing the diagnosis of the co-infection and where is it done), treatment and care for TB/HIV co-infected persons (who is/are treating TB/HIV co-infected persons, where does treatment regularly take place, *i.e.* as in-patients or outpatients, and what specific support is given), and surveillance (limited to LTBI screening and treatment in PLHIV) (supplementary material). It was translated into the Russian language to better reach Russian-speaking respondents.

The online questionnaire was sent to the TB Focal Points of the 53 countries and two territories (Kosovo and Liechtenstein) in the Region in December 2016. Two reminders were sent in January and February 2017. The results were presented in May 2017 during the Wolfheze Workshops. After the Wolfheze Workshops, it was advised and decided to collect similar information and views of the HIV Focal Points of the Member States. The same questionnaire was sent to the HIV Focal Points of the 53 countries and two territories in February 2018, and two reminders were sent to nonresponding HIV Focal Points. The answers of countries with both the TB and HIV Focal Points answering the questionnaire were forwarded in July 2018 to the two Focal Points to solve any discrepant results.

All data were entered in SPSS version 22.0 (IBM, Armonk, NY, USA) and analysed using frequency distributions for categories of countries. Countries were stratified by TB and HIV incidence in the year of the study (2016) [13, 14]. Low TB incidence was defined as <10 incident cases per 100 000 population.

TB incidence data were retrieved from the European Centre for Disease Prevention and Control (ECDC)/WHO Regional Office for Europe TB surveillance and monitoring in Europe 2018 report (2016 data) [13]. Low HIV incidence was defined as <10 incident cases per 100 000 population. HIV incidence data were retrieved from the ECDC/WHO Regional Office for Europe HIV surveillance in Europe 2017 report (2016 data) [14].

## Results

47 out of 55 (85%) countries and territories responded, *i.e.* the TB and HIV Focal Points filled in the questionnaire jointly (n=10) or separately (n=12), or they were filled only by the TB Focal Point (n=18) or only by the HIV Focal Point (n=7). No response from the TB Focal Point or the HIV Focal Point was received from eight (15%) countries (figure 1). Of the 47 responding countries, 11 (23%) were classified as high TB and high HIV incidence, two (4%) as low TB and high HIV incidence, 14 (33%) as high TB and low HIV incidence, and 20 (43%) as low TB and low HIV incidence (figure 1 and table 1).

### *Policy and guidelines*

28 (60%) respondents reported having written national guidelines, regulations or strategies on collaboration between TB and HIV programmes and services, while 19 (40%) used other guidelines, such as the WHO policy on collaborative TB/HIV activities (n=10) [10], European AIDS Clinical Society guidelines (n=3) (www.eacsociety.org/guidelines) or other (n=6).

In 40 (85%) countries and territories, guidelines recommended HIV testing in all TB patients; in 34 (72%) countries, screening for active TB in all PLHIV was recommended. The recommendations differed by TB and/or HIV incidence in countries (table 2). All countries with a high HIV incidence (n=13) recommended to test all TB patients for HIV and to screen all PLHIV for TB, irrespective of the country's TB incidence. By contrast, among the countries with a low HIV incidence (n=34), 28 (82%) recommended to test all TB patients for HIV, while six (18%) recommended selective HIV testing of TB patients.

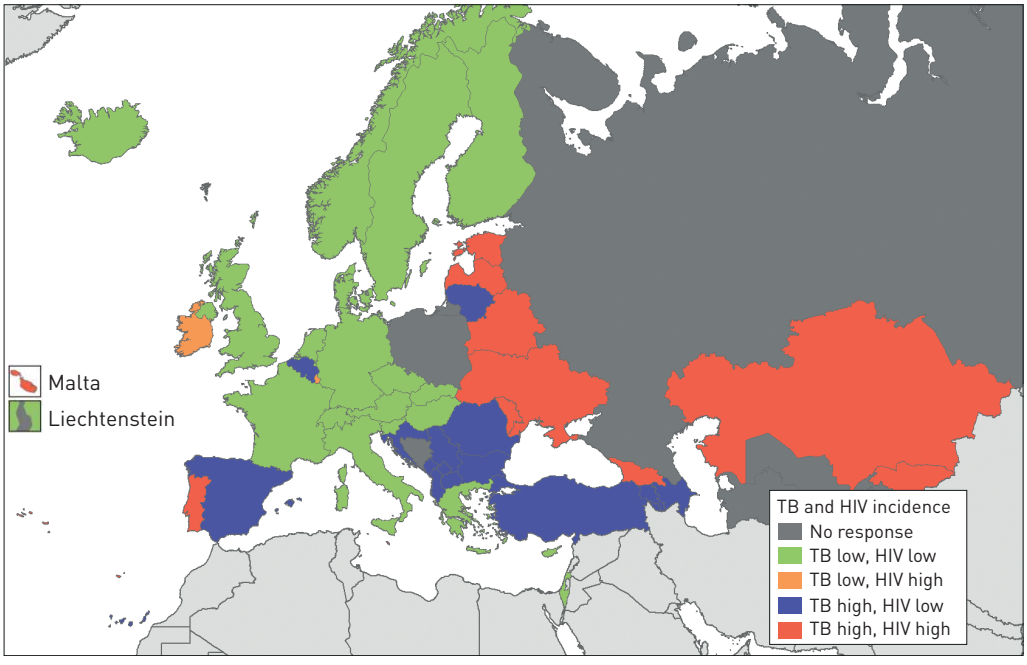


FIGURE 1 Tuberculosis (TB) and HIV incidence in responding countries. TB low, HIV low (<10 cases per 100 000 population): Austria, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Israel, Italy, Monaco, the Netherlands, Norway, Slovakia, Slovenia, Sweden, Switzerland, the UK. TB high, HIV low (<10 cases per 100 000 population): Albania, Armenia, Azerbaijan, Belgium, Bulgaria, Croatia, Kosovo, Lithuania, Macedonia, Montenegro, Romania, Serbia, Spain, Turkey. TB low, HIV high (⩾10 cases per 100 000 population): Ireland and Luxembourg; TB high, HIV high (⩾10 cases per 100 000 population): Belarus, Estonia, Georgia, Kazakhstan, Kyrgyzstan, Latvia, Malta, Moldova, Portugal, Ukraine, Uzbekistan. No response from: Andorra, San Marino (TB low, HIV low), Bosnia and Herzegovina, Poland (TB high, HIV low), Tajikistan (TB high, HIV high), Liechtenstein (no TB incidence, HIV low), Russian Federation, Turkmenistan (TB high, no HIV incidence). Map produced on December 14, 2018. Administrative boundaries: EuroGraphics and United Nations Food and Agriculture Organization.

TABLE 1 Overview of respondents to the survey among TB and HIV Focal Points

| | TB Focal Points | HIV Focal Points | Total |
|---|---|---|---|
| **Separate responses by TB and HIV Focal Points[#]** | 12 | 12 | 12 |
| **Joint response by TB and HIV Focal Points** | 10 | 10 | 10 |
| **Response by TB Focal Point only** | 18 | | 18 |
| **Response by HIV Focal Point only** | | 7 | 7 |
| **No response** | | | 8 |
| **Total** | 40 | 29 | 55 |

Data are presented as n. [#]: discrepant results were identified by the authors and aligned by the responding Focal Points.

TABLE 2 Country policies and recommendations on HIV testing, tuberculosis (TB) screening, latent TB infection (LTBI) testing, antiretroviral treatment (ART) and co-trimoxazole preventive treatment (CPT) based on the responses from 47 countries

| | TB incidence | HIV incidence | | Total |
|---|---|---|---|---|
| | | High | Low | |
| **All countries** | High | 11[+] | 14[§] | 25 |
| | Low | 2[f] | 20[##] | 22 |
| **Policies and recommendations** | | | | |
| HIV test in TB patients[#] | | | | |
| All patients | High | 11 (100) | 13 (93) | 24 |
| | Low | 1 (50) | 15 (75) | 16 |
| Selected patients | High | 0 (0) | 1 (7) | 1 |
| | Low | 0 (0) | 5 (25) | 5 |
| TB screening in PLHIV | | | | |
| All patients | High | 11 (100) | 11 (79) | 22 |
| | Low | 2 (100) | 10 (50) | 12 |
| Selected patients | High | 0 (0) | 3 (21) | 3 |
| | Low | 0 (0) | 10 (50) | 10 |
| LTBI screening in PLHIV | | | | |
| All patients | High | 5 (45) | 13 (93) | 18 |
| | Low | 2 (100) | 10 (50) | 12 |
| Selected patients | High | 3 (27) | 1 (7) | 4 |
| | Low | 0 (0) | 9 (45) | 9 |
| Not recommended | High | 3 (27) | 0 (0) | 3 |
| | Low | 0 (0) | 1 (5) | 1 |
| Start of ART in TB/HIV patients | | | | |
| All patients | High | 11 (100) | 13 (93) | 24 |
| | Low | 1 (50) | 18 (90) | 19 |
| Selected patients | High | 0 (0) | 1 (7) | 1 |
| | Low | 1 (50) | 2 (10) | 3 |
| CPT of TB/HIV patients[¶] | | | | |
| All patients | High | 8 (73) | 8 (57) | 16 |
| | Low | 0 (0) | 3 (15) | 3 |
| Selected patients | High | 2 (18) | 0 (0) | 2 |
| | Low | 1 (50) | 4 (20) | 5 |
| Not recommended | High | 0 (0) | 6 (43) | 6 |
| | Low | 0 (0) | 10 (50) | 10 |

Data are presented as n or n (% of total number of countries in the category). PLHIV: people living with HIV. [#]: one country did not respond to this question. [¶]: five respondents were not familiar with their country's recommendation for CPT. [+]: high TB, high HIV: Belarus, Estonia, Georgia, Kazakhstan, Kyrgyzstan, Latvia, Malta, Moldova, Portugal, Ukraine, Uzbekistan. [§]: high TB, low HIV: Albania, Armenia, Azerbaijan, Belgium, Bulgaria, Croatia, Kosovo, Lithuania, Macedonia, Montenegro, Romania, Serbia, Spain, Turkey. [f]: low TB, high HIV: Ireland, Luxembourg. [##]: low TB, low HIV: Austria, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Israel, Italy, Monaco, the Netherlands, Norway, Slovakia, Slovenia, Sweden, Switzerland, the UK.

In these low HIV incidence countries, 21 (62%) recommended to screen all PLHIV for TB, while 13 (38%) recommended selective TB screening. The criteria used for selecting PLHIV for TB screening were (more than one answer was possible): contact with an infectious TB patient (n=12), TB symptoms (n=11), previous TB (n=9) and PLHIV with a low CD4 cell count (<350 cells·mm$^{-3}$) (n=5).

30 (64%) countries recommended LTBI screening in all PLHIV, while 13 (28%) had a selective approach and four (9%) did not recommend LTBI screening. Of the 11 countries with a high incidence for both diseases, five (45%) recommended LTBI screening in all PLHIV, three (27%) followed a selective LTBI screening approach and three (27%) did not recommend LTBI screening. 13 out of the 14 (93%) countries with a high TB incidence and a low HIV incidence recommended LTBI screening in all PLHIV. Of the 20 countries with a low incidence of both diseases, 10 (50%) recommended LTBI screening in all PLHIV, nine (45%) followed a selective approach and one (5%) did not recommend LTBI screening in PLHIV. The selection criteria for LTBI screening most often mentioned were: PLHIV from high TB incidence countries (n=10), PLHIV who have been in contact with infectious TB patients (n=10) and PLHIV with a low CD4 cell count (<350 cells·mm$^{-3}$) (n=4). The tests and algorithms used for LTBI testing included the tuberculin skin test (TST) (n=12), interferon-γ release assay (IGRA) (n=11), TST and IGRA simultaneously (n=9) and TST followed by IGRA if positive (n=4), and other (n=6). One country did not provide information on tests and algorithms used.

43 (91%) countries recommended starting ART for all TB/HIV co-infected patients and four (9%) advised ART below a specific CD4 cell count (range <200 to <500 cells·mm$^{-3}$). 19 (40%) countries recommended CPT for all TB/HIV co-infected patients, seven (15%) recommended CPT when the CD4 cell count was below a certain level (<200 cells·mm$^{-3}$), 16 (34%) did not recommend CPT (all countries with low HIV incidence) and five respondents were not familiar with their country's recommendation for CPT.

### *Management of TB/HIV collaborative activities*

Most respondents reported that testing for HIV and screening for active TB and LTBI was done by the specialist treating the patient, *i.e.* TB patients were tested for HIV by a TB specialist in 42 (89%) countries and PLHIV were screened for active TB by an HIV specialist in 34 (72%) countries (figure 2). In 27 (57%) countries, PLHIV were tested for LTBI by a HIV specialist. Two countries reported that TB and LTBI screening was done by a visiting TB specialist to the AIDS centre.

In most countries, TB/HIV co-infected patients were initially hospitalised in an infectious diseases hospital/department (n=21 (45%)) or in a TB hospital/department (n=19 (40%)) and continued ambulatory treatment as soon as possible. In seven (15%) countries, TB/HIV co-infected patients were hospitalised for the entire duration of treatment in a TB hospital/department (n=3) or infectious diseases hospital/department (n=4).

During ambulatory treatment (40 countries), patients were treated in three (8%) countries for both diseases by the TB specialist, in 16 (40%) countries by the HIV/infectious diseases specialist, and in 21 (52%) countries TB was treated by the TB specialist and HIV by the HIV/infectious diseases specialist (figure 2). Monitoring and follow-up of patients treated by two specialists was often (52%) done at the same facility (figure 2).

TB/HIV patients collected their TB and HIV medication mostly in one place, either in the treatment facility or at the pharmacy (33 (72%) countries), while in 13 (28%) countries patients received their TB and HIV medication at different places. One country did not indicate where patients receive their medication.

### *Surveillance and monitoring of TB and HIV co-infections*

In the survey, we asked for the (estimated) national coverage of LTBI screening of PLHIV newly enrolled in care in 2015, the proportion of LTBI diagnosis among tested PLHIV and the proportion of PLHIV with an LTBI diagnosis starting treatment. Three (6%) respondents provided an (estimated) coverage for their country of 0%, 30% or 80% and seven (15%) reported a coverage of ⩾90%. The other 37 (79%) respondents could not provide information on LTBI screening coverage in PLHIV in their countries. Four countries reported on the (estimated) proportion of LTBI diagnosis among tested PLHIV (*i.e.* 11%, 30%, 50% and 100%). These countries also knew the (estimated) proportion that started LTBI treatment (*i.e.* 90%, 50%, 25% and 100%, respectively). In one other country, all PLHIV were offered 6-month isoniazid prophylaxis (without LTBI testing) every 2 years. The estimated percentage of those accepting the prophylaxis was <10% in this country.

## Discussion

This study provides an overview of policies and regulations for the management of TB in PLHIV and HIV in TB patients, as well as TB/HIV collaborative activities and their implementation in the Member States

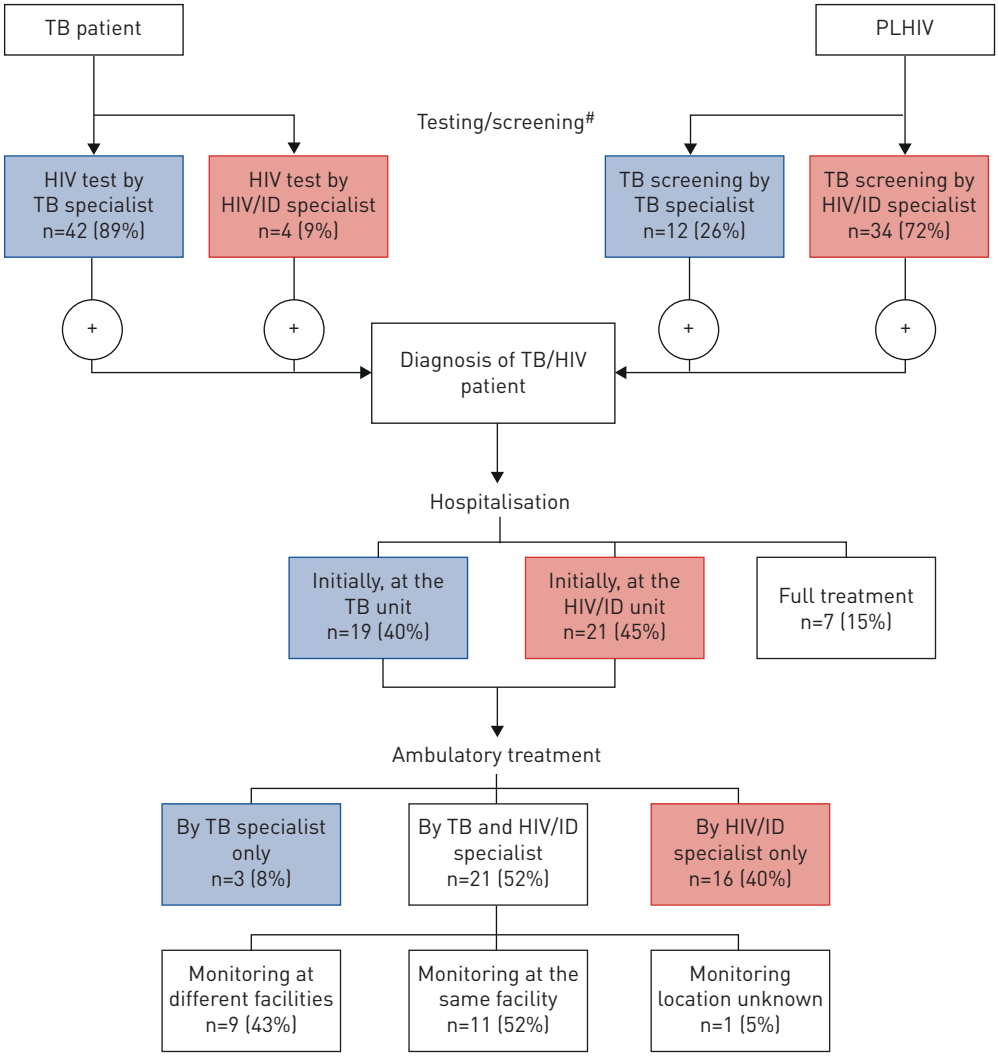


FIGURE 2 Overview of treatment providers and locations for the diagnosis and ambulatory treatment of tuberculosis (TB)/HIV patients. ID: infectious diseases; PLHIV: people living with HIV. #: one country did not provide the HIV testing and TB screening location.

and territories of the Region. All respondents reported availability of written national guidelines or the use of international guidelines for TB/HIV collaborative activities in their countries, including the management of co-infections. In general, most countries recommend screening for HIV in all TB patients and screening for active TB in all PLHIV. This was different in some low-incidence countries, where policy on screening for the two diseases was selective rather than routine, which is different from the WHO policy on collaborative TB/HIV activities. Screening policies for LTBI were more diverse; countries with a high incidence of both diseases seem to be more prone to screen all PLHIV for LTBI.

While surveillance data show a high uptake of HIV testing among TB patients in the Region (91.5% having a known HIV status) [15], there is a lack of surveillance data on TB screening among PLHIV. The increase of TB/HIV co-infection in the Region reflects ongoing transmission of both infections, late diagnosis or suboptimal management of HIV infection, where active TB develops due to progression of immunodeficiency. This underlines the need for intensive case finding and measures to prevent the development of TB. Given the close synergy between TB and HIV it is important that routine bidirectional testing is undertaken when a patient is identified with TB or HIV. One simple method would be for physicians to offer opt-out, routine testing at the same healthcare facility where a patient was identified with the first condition [16–18]. Referral to a different healthcare unit and complicated legislative procedures may contribute to increased risk of test refusal and missing patients with co-infection.

Although policies in 91% of responding countries in our study recommended initiation of ART treatment of all TB/HIV co-infected patients regardless of CD4 cell count, only 73% of TB/HIV patients in the 27

countries providing data on ART enrolment started ART in 2018 [5]. The WHO recommends to initiate ART in all TB patients living with HIV, regardless of their CD4 cell count, within the first 8 weeks of TB treatment, and for HIV-positive TB patients with profound immunodepression (CD4 count <50 cells·mm$^{-3}$) and patients with HIV and drug-resistant TB within the first 2 weeks of initiating TB treatment and not later than 8 weeks [19, 20].

Identifying and treating LTBI is an additional method to reduce the risk of TB-associated morbidity and mortality in PLHIV [21–23]. Therefore, the WHO recommends that PLHIV, with unknown or confirmed LTBI, should receive preventive treatment for TB after exclusion of active disease [24, 25]. In our study, most high TB incidence countries followed this recommendation, while 45% of the low TB incidence countries were recommending selective LTBI screening, *e.g.* prioritising PLHIV from countries with a medium and high TB incidence [26, 27]. It is important to bear in mind that actual practice on the ground may vary substantially from the recommendations, as was seen in the Netherlands and the UK [28, 29]. Furthermore, it is notable that few countries have data on the cascade of LTBI care in PLHIV, such as the number actually screened, diagnosed with LTBI, and starting and completing TB preventive treatment. Nine Member States provided information on LTBI treatment to the Joint United Nations Programme on HIV/AIDS (UNAIDS) reporting system in 2018 (aidsinfo.unaids.org). Azerbaijan, Kazakhstan, Kyrgyzstan, the Russian Federation and Ukraine reported that >50% of PLHIV received LTBI treatment. No relevant data were available in the UNAIDS database for any European Union/European Economic Area Member State in 2016.

Our survey shows that almost all TB/HIV co-infected patients are hospitalised either partially or for the entire period of TB treatment, which is a high burden for both the health system and patients. The WHO recommends using ambulatory care rather than models of care based on hospitalisation of patients with TB, including rifampicin-resistant/multidrug-resistant TB and TB/HIV co-infection [20]. The evidence shows that community or home-based TB treatment has higher rates of treatment success and lower rates of mortality and unfavourable outcomes compared with treatment in a health facility. We did not ask for the duration of partial hospitalisation for TB treatment, and it might just have been for a short period to complete the diagnostic process and to start patients on treatment.

Our study had several strengths and limitations. First, the response rate was high. Unfortunately, no response was received from the Russian Federation, the country with the highest number of TB/HIV patients [15]. One of the Working Group members approached one of the oblasts to fill in the survey. Answers were in line with most of the answers from countries in the Region. One of the weaknesses in our study was the low response rate of HIV Focal Points of Eastern European and Central Asian countries. Furthermore, the TB Focal Point respondents were from national TB programmes and obsequiousness bias can be present, especially in large countries where the situation may differ between regions. Whether the policies are equally implemented and uniformly interpreted across the country is unknown. Our results are, however, consistent with data from a recently published survey among clinicians involved in the care of HIV and TB patients across Europe [3, 30].

National policy needs to be translated into practice by secured funding, developing and implementing effective, integrated patient-centred care models aligned with health workforce task shifting and capacity building and improving health information systems. Screening and treatment of LTBI is becoming more important in eliminating TB worldwide, and therefore surveillance systems should be able to capture relevant data to measure progress [6, 11]. We further recommend research on the effectiveness and efficiency of different models of integrated TB/HIV service provision, *e.g.* to measure the impact on the (perceived) quality of care and treatment outcomes and of selective testing and screening for HIV and TB/LTBI. Finally, the lessons learned from TB/HIV collaborative activities can be extended to integrated care for other comorbidities and conditions such as hepatitis B and C viral infections, alcohol and drug abuse, and diabetes [31, 32].

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