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HIV, tuberculosis and co-infection among migrant populations living in Portugal

Ana Maria Pinho Tavares

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Autora: Ana Maria Pinho Tavares

Orientadora: Professora Doutora Sónia Dias

Coorientadora: Professora Doutora Ana B. Abecasis

Coorientador: Professor Doutor Miguel Viveiros

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"Wherever you have friends that's your country, and wherever you receive love, that's your home."

Dalai Lama, citing a Tibetan saying

In: *"The Book of Joy: Lasting happiness in a changing world"*

(Thank you, Pia Müller, for such a wonderful book).

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RESUMO

Os migrantes no seu percurso migratório, e no país de acolhimento, são expostos a diversos fatores que podem conferir maior vulnerabilidade ao VIH e à tuberculose (TB). Contudo, a vulnerabilidade a estas infeções nos migrantes tem sido pouco explorada em estudos recentes e em dados oficiais, particularmente no contexto Português.

Esta tese pretende contribuir para o conhecimento sobre a carga das infeções VIH, TB e VIH-TB em populações migrantes em Portugal, e sobre a vulnerabilidade destas populações a estas infeções. Os objetivos específicos estabelecidos são: 1) descrever a prevalência e determinar fatores sociodemográficos, socioeconómicos e comportamentais relacionados com o VIH, TB e coinfecção VIH-TB em migrantes; 2) descrever as características clínicas e genómicas de migrantes com coinfecção VIH-TB; 3) compreender as especificidades e barreiras aos cuidados de saúde da TB em migrantes infetados com TB ou coinfecção VIH-TB. Este trabalho baseia-se numa revisão sistemática da literatura, num estudo transversal de base comunitária, na análise de dados clínicos e genómicos, e num estudo misto com profissionais de saúde.

Em migrantes oriundos da África Subsariana observou-se uma elevada proporção de infeção por VIH (5.4%) e de infeção por TB no passado (4.1%). A revisão sistemática da literatura mostrou também uma maior prevalência de VIH-TB em migrantes face aos nacionais em países Europeus, sobretudo em migrantes da Africa subsariana. Muitos migrantes relataram uso inconsistente do preservativo (82.5%), múltiplos parceiros (23.5%), e sexo comercial (10.8%). Cerca de metade (49.7%) nunca fez teste para o VIH, e mais de um terço (35%) dos VIH-positivos desconhecia o seu estatuto serológico. A infeção por VIH foi associada à idade (1.07 [IC95%:1.03-1.11]), à violência por parte de um parceiro (2.77 [IC95%:1.08-7.10]), e ao uso consistente do preservativo (0.23 [IC95%:0.09-0.58]). Os participantes que tiveram TB no passado foram sobretudo homens (3.42 [IC95%:1.29-9.06]), e VIH-positivos (11.48 [IC95%:4.55-28.94]). Os migrantes co-infetados mais jovens tenderam a ser diagnosticados simultaneamente para as duas infeções, contrariamente aos mais velhos. Nos migrantes co-infetados verificou-se também uma maior proporção de estirpes não-B do VIH comparativamente aos nacionais, relacionadas com uma maior carga viral. Os profissionais dos cuidados de saúde primários relataram que a falta de conhecimento sobre a TB nos migrantes é um obstáculo ao seu diagnóstico precoce. O tratamento é frequentemente interrompido devido a deslocações ao país de origem e à falta de apoio social no país de acolhimento. Também o acesso e uso de cuidados de saúde da TB pelos migrantes são frequentemente dificultados por fatores socioeconómicos, administrativos, e pela reduzida proteção social.

Os resultados deste trabalho mostram que as populações migrantes são vulneráveis ao VIH e à TB em Portugal, particularmente devido ao seu desconhecimento sobre as mesmas e sobre os serviços de saúde, às suas condições económicas, e às dificuldades de acesso à prevenção e a cuidados de saúde. Intervenções futuras são necessárias em proximidade com as comunidades, ao nível da proteção social, da educação para a prevenção, e no acesso aos serviços de saúde, devendo-se também fomentar a cooperação internacional para responder adequadamente a estes problemas de saúde global.

Palavras-chave: VIH; tuberculose; co-infeção VIH-TB; migrantes; vulnerabilidade.

ABSTRACT

Migrant populations are exposed to several factors throughout their migratory journey and at the host country that can render an increased vulnerability to HIV and tuberculosis (TB). However, migrants' vulnerability to these infectious diseases has been little explored in recent studies and in official reports, particularly regarding the Portuguese context.

This thesis aims to contribute to improve knowledge on the burden of HIV, TB and HIV-TB co-infection among migrant populations in Portugal, and on the vulnerability of these populations to these infectious diseases. The specific objectives proposed are: 1) to describe prevalence and determine sociodemographic, socioeconomic and behavioural factors related to HIV, TB and HIV-TB co-infection among migrants; 2) to describe clinical and genomic characteristics of migrants with HIV-TB co-infection; 3) to understand the specificities and barriers to TB care among migrants infected with TB or HIV-TB. The accomplishment of these objectives is based on a systematic review of literature, on a cross sectional community-based study, on the analysis of clinical and genomic data, and on a mixed-methods study with healthcare providers.

High proportion of HIV infection (5.4%) and of a past TB infection (4.1%) were observed among sub-Saharan African migrants. Data from the systematic review of literature have also shown a higher prevalence of HIV-TB among migrants compared to nationals in European countries, particularly among those from sub-Saharan African countries. Many migrants reported inconsistent condom use (82.5%), multiple partners (23.5%) and engagement in commercial sex (10.8%). About half (49.7%) was never tested for HIV. Over a third (35%) of HIV-positive participants were not aware of their HIV status. HIV infection was associated with increasing age (1.07 [IC95%:1.03-1.11]), violence from a partner (2.77 [IC95%:1.08-7.10]), and consistent condom use (0.23 [IC95%:0.09-0.58]). Those who had TB in the past were more likely to be men (3.42 [IC95%1.29-9.06]) and HIV-positive (11.48 [IC95%:4.55-28.94]). Younger co-infected migrants were more likely to be simultaneously diagnosed for both infections, contrarily to older migrants. A higher proportion of non-B HIV strains were also observed among co-infected migrants compared to nationals, which was also related to a higher viral load. Primary healthcare providers referred that migrants' unawareness about TB is an obstacle to its early diagnosis. Treatment is also frequently interrupted due to travels to their country of origin and due to lack of social support in the host country. Access and use of TB care by migrants is also frequently hampered by socioeconomic and administrative hurdles and by limited social protection.

The findings from this work show that migrant populations remain vulnerable to HIV and TB in Portugal, particularly due to their unawareness about these infections and the healthcare services, due to their economic situation, and due to difficulties in accessing preventive measures and health care. Future interventions are needed in proximity with the communities, at social protection level, in the education for prevention, and in the access to healthcare services, also promoting international cooperation to appropriately respond to these global health issues.

Keywords: HIV; tuberculosis; HIV-TB co-infection; migrants; vulnerability.

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LIST OF ABBREVIATIONS

AIDS – Acquired Immunodeficiency Syndrome

AJPAS - *Associação de Intervenção Comunitária, Desenvolvimento Social e de Saúde*

ART – Antiretroviral therapy

BCG - Bacillus Calmette-Guérin

CDC – Centre for Disease Control and Prevention

CDCs – Chest Disease Centres

CI – Confidence Interval

CPBR – Community-based participatory research

CRFs – Circulating recombinant forms

DGS – *Direcção-Geral da Saúde*/ General Health Directorate

DOTS – Directly Observed Therapy Strategy

ECDC – European Centre for Disease Control and Prevention

EU – European Union

EU/EEA - European Union/European Economic Area

FCT – *Fundação para a Ciência e Tecnologia*

GAT-In Mouraria – *Grupo Português de Ativistas sobre Tratamentos VIH/Sida*

HIV – Human Immunodeficiency Virus

HIV-TB - Human Immunodeficiency Virus and tuberculosis co-infection

IGRA - interferon-γ release assay

IPT - isoniazid preventive treatment

LTBI - latent tuberculosis infection

MDR-TB - Multidrug-resistant tuberculosis

MIPEX - Migration Integration Policy Index

MSM – Men who have sex with men

MTB – *Mycobacterium tuberculosis*

NGOs - non-governmental organizations

OR – Odds Ratio

PEO - patient, exposure and outcome

PHCCs - Public Health Care Centres Clusters

PICO - population, intervention, comparison and outcomes

PIO - patient, intervention and outcome

PrEP - pre-exposure prophylaxis

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses

SDG – Sustainable Development Goal

SEM – Social Ecological Model

SER+ - *Associação Portuguesa para a Prevenção e Desafio à Sida*

SIDA – *Síndrome de Imunodeficiência Adquirida*

SPIDER - sample, phenomenon of interest, design, evaluation, research type

STI – Sexually transmitted infections

TB - Tuberculosis

UN – United Nations

UNAIDS - Joint United Nations Programme on HIV/AIDS

URFs - unique recombinant forms

WHO – World Health Organization

XDR-TB - Extensively drug-resistant tuberculosis

I. GENERAL INTRODUCTION

I. GENERAL INTRODUCTION

1. Migration, health vulnerabilities and infectious diseases

International migration is a complex phenomenon with economic and social implications, intertwined with geopolitics, trade and culture [1]. Migration is recognized as one of the key components of population change in Europe [2]. However, it also represents a critical political and policy challenge for all countries regarding integration, displacement, safe migration and border management [1].

The patterns of migration can change greatly over time, reflecting complex and inter-related factors, ranging from geographical, historical, economic, political, environmental and demographic factors [3–5]. The decision to migrate is complex and results from push factors — inconvenient conditions in homeland that impel the decision to migrate — and pull factors — a series of positive attributes perceived to exist at the new location —, that influence the decision to migrate [6]. There is considerable heterogeneity inside the "migrant" category [7], which can include documented migrants, undocumented (or irregular) migrants, refugees, asylum seekers, internal migrants, labour migrants, among others [8]. For the purpose of this research, we adopted the definition of "migrant" provided by the United Nations (UN): "*Any person who lives temporarily or permanently in a country where he or she was not born, and has acquired some significant social ties to this country."* [9].

The number of international migrants worldwide maintained a growing trend over the past seventeen years. From 2010 to 2015, migration increased 2% and the number of migrants reached the 258 million in 2017 [10]. Between 2014 and 2016, the number of migrants in the European Union (EU) increased more than 40% [11], and in 2017, 78 million international migrants were residing in Europe [10]. In Portugal, there was a 13.9% increase in the foreign-born population in 2018 compared with the previous year, with more than 480 thousand foreign-born individuals; most were on their working age (81.1%) [12]. Previous estimations also report that foreign-born individuals are approximately 4% of the population in Portugal, with about 180 different nationalities composing this subgroup of the general population, and with Brazilians being the most represented (20%) [13,14].

Health is one of the most important aspects of migration [15]. More than

traditional management of diseases among mobile populations, migrants' health is intrinsically linked with the broader social determinants of health and their unequal distribution [16]. The migration process itself is increasingly recognized as a social determinant of health for migrants, their families and communities, and various benefits and risk factors at different stages of migration can impact migrants' health [17]. The health outcomes of migrant populations depend on the living conditions in the country of origin (pre-departure), on experiences during the transit, and on the living conditions in the place of destination [15,16,18]. Such experiences can differently affect distinct migrant groups and communities [15,16]. At the country of origin, the physical, socioeconomic environment and political context, among other factors, determine many of the pre-conditions with which people migrate. The transit phase can be particularly challenging for migrants' health, especially for those without legal documents who tend to undergo into dangerous journeys, travelling clandestinely or by inappropriate ways of transportation, and without access to healthcare during their journey [16]. At the country of destination, where new generations are born and newly arrived migrants are reunited with existing communities and family members, their health will be largely influenced by the outcome of the social integration and the success and their migratory project [15]. In Table 1, are listed some of the existing risk factors for migrants' health during the different phases of migration.

Table 1: Main factors affecting health and well-being of migrant populations throughout the different phases of migration.

Before migration

- Pre-migratory events (i.e. trauma, torture, sexual violence, war, human rights violations)
- Biological characteristics
- Local epidemiological characteristics (compared to the profile at destination)
- Environmental factors
- Political and socioeconomic circumstances
- Efficiency of the healthcare system
- Linguistic, cultural and geographical proximity to destination

During transit

- Transports and travel conditions
- Epidemiological characteristics of transit areas
- Traumatic events (abuse, sexual violence)
- Human trafficking
- Duration of journey
- Single or mass movements

At the destination country

- Migration-related policies/health policies
- Social exclusion, discrimination
- Socio-economic deprivation
- Access to care
- Language and cultural values
- Culturally, linguistically, and epidemiologically adjusted services
- Separation from family/partner
- Legal status
- Duration of stay
- Occupational risks and exploitation
- Exposure to risk behaviours (alcohol abuse, injection drug use, criminal organizations)
- Abuse, (sexual) violence
- Living conditions

Return to the country of origin

- Pre-travel advice
- Level of home community services
- Remaining community ties
- Poor medical assistance
- Behavioural and health profile as acquired in host communities (e.g. reduced immunity against local pathogens)
- Duration of absence

Cross-cutting aspects

- Age, gender
- Socio-economic status
- Generic factors

Sources: Dhavan et al., 2017 [8]; Castelli and Sulis, 2017 [18]; Marceca, 2017 [15]; IOM, 2017 [17].

Migratory success also depends on the health, wealth, physical preparedness and psychological strength of the individual [7,15]. Therefore, a good state of health is usually a prerequisite for migration, which causes a self-selection prior to departure [15]. As a consequence of this pre-selection, migrants from poor areas frequently have a better health than expected for their socioeconomic status — the so-called "healthy migrant effect" [19]. However, after arrival, migrants' exposure to social determinants of health in the host country can lead to two possible scenarios: positive health outcomes with granted support and health protection; or difficult socioeconomic integration and social inequalities that render increased health vulnerability [15,20]. In the later cases, the health advantage once had may deteriorate with the increasing time of residence [19,21], leading to the so-called "exhausted migrant effect" [15], corresponding to a lower health status compared with the native populations [7]. In Figure 1, are presented the main social determinants of migrants' health at host countries across the different levels of organization.

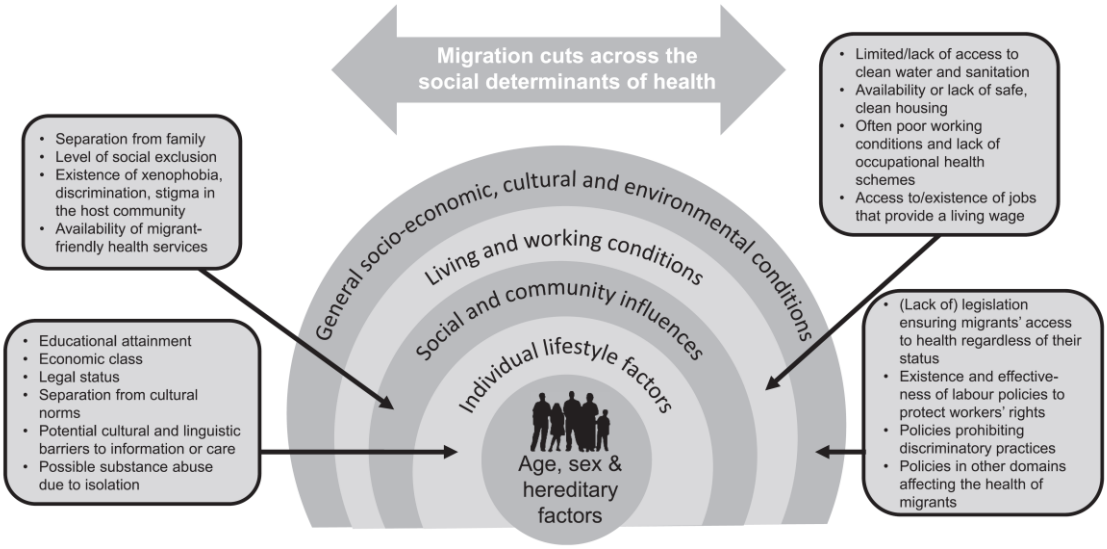

Figure 1: Social determinants of health in migrants. Source: Dhavan P, Dias HM, Creswell J, Weil D. An overview of tuberculosis and migration. Int J Tuberc Lung Dis. 2017, 1;21(6):610–23. doi:10.5588/ijtld.16.0917 [8] (Reprinted with permission of the International Union Against Tuberculosis and Lung Disease. Copyright © The Union.).

At individual level, migrants' health vulnerabilities are often increased by poverty at the destination countries [16], particularly if undocumented or if they are lower skilled workers [5,17]. Their poor economic situation is frequently associated with inadequate

nutrition, precarious housing with poor hygienic conditions [15,22], overcrowded and located in degraded neighbourhoods [20,23]. Moreover, separation from their families and from familiar social norms, alongside with feelings of loneliness might lead them to engage into risky cultural practices or sexual behaviours, increasing their risk for sexually transmitted infections [16,22]. Risky sexual behaviours have also been associated with alcohol consumption, a common practice observed in some migrant workers [24]. Moreover, migrants also frequently experience difficulties in communication and in understanding the functioning of healthcare systems [15,20,22,23]. At social and community level, feelings of failure, discrimination, violence, racism, stigmatization, solitude and anxiety are also commonly experienced by migrants [15,20,22,23]. They are usually more vulnerable for discrimination and bullying at workplace [25]. Additionally, migrants seem to lack control over factors that influence their health, and are limited in making healthy choices [16], namely power to negotiate or a voice in decision-making processes affecting them [5]. At the living and working conditions level, migrants are often exposed to high-risk working and living environments [4]. They usually engage into precarious and/or seasonal jobs [20,23] or exploitation [15], often occupying the so-called 3-D jobs — dirty, dangerous and demeaning [25] —, such as professional activities with higher risk of exposure to dangerous substances [23,25]. Moreover, sexual abuse or sexual exploitation might affect migrant workers, particularly women [16,22]. At the general socio-economic, cultural and environmental conditions level, migrants, particularly those undocumented, may encounter barriers in accessing healthcare services due to restrictive policies, may sometimes have to pay out-of-pocket for health care [5,17], and are frequently excluded from social and healthcare services [4]. Even migrants with a more favourable socioeconomic status may experience challenges in accessing healthcare services related with structural and institutional obstacles [16].

Due to exposure to several of these determinants, migrants might become vulnerable to several health problems, such as diabetes, obesity, psychological diseases, maternal and childhood related health issues, and particularly to infectious diseases such as tuberculosis (TB), Human Immunodeficiency Virus (HIV)/Acquired Immunodeficiency Syndrome (AIDS), hepatitis, and others [22]. In Portugal, data have shown that 37% of foreign-born individuals are at higher risk of poverty and social exclusion compared to nationals (23%) [13,14]. Moreover, despite of their positive

contribution to the country's economy, their salaries are 4.5% lower than salaries of the host population, and those from countries outside the EU have higher unemployment rates (14.4%) compared to nationals (8.9%) [14]. Regardless of such disparities, according to European estimations, immigrants in Portugal perceive themselves as healthier than the native population (59% immigrants reported good health vs. 47% of native-born; adjusted for age), and have lower prevalence of non-communicable diseases [26]. However, infectious diseases remain among the main causes of death in these populations in Portugal [22].

The relation between migration and infectious diseases is complex and difficult to measure [22]. Mobile populations may modify the epidemiology and global distribution of certain infectious diseases. For instance, incidence may increase in the host countries despite of the decline of autochthonous cases [27]. Although there is limited evidence about the transmission of communicable diseases between migrants and native-born citizens [28,29], they can spread within migrant community settings [29], and some might remain asymptomatic for long periods of time without proper care [27].

Infectious diseases among migrants can be categorised according to their distribution. Common diseases comprise respiratory infections and vaccine-preventable diseases. Tropical diseases include typhoid fever, malaria, schistosomiasis, filariasis, cysticercosis and Chagas' disease; and transmissible infections with worldwide distribution include HIV, TB, syphilis [27,30]. Tropical infectious diseases are acquired at the country of origin or during journey, and its transmission cycle is usually interrupted at the host country. However, migrants might remain vulnerable to the acquisition of other types of infections, namely blood-borne viruses during journey and at the host country [31]. Conversely, many migrants outside the EU come from countries where prevention and control of infectious diseases such as HIV and TB is inadequate and exposure to these diseases is higher than in most EU countries [3].

1.1. HIV among migrants

1.1.1. General characteristics of infection and treatment

The first AIDS cases were identified in 1981 and its association with HIV-infection was found in 1983. AIDS was described as a distinct acquired form of immunodeficiency, characterized by a depletion of CD4+ T cells and an expansion of activated CD8+ T cells [32]. Since then, millions of people have died, causing devastation among families and communities in countries of all income levels [30,33].

Viruses HIV-1 and HIV-2 are the causative agents of AIDS [34]. HIV-1 is the most frequent and the main responsible for most cases worldwide [34,35], while HIV-2 has a more regional profile, mostly in Western Africa, and is rare in European countries, except in Portugal due to its historical migration [34].

HIV-1 is characterized by a great genetic diversity [36], being phylogenetically divided into four groups: M, O, N, and P [37]. Groups N and O are largely restricted to Central Africa (essentially Cameroon), but the worldwide pandemic is mainly caused by group M strains, which can be divided into nine genetically distinct subtypes: A to D, F to H, J, and, as well as circulating recombinant forms (CRFs) and unique recombinant forms (URFs) [37–39]. Subtypes A and F can be divided further into sub-subtypes A1, A2, F1 and F2 [40].

Such variability poses challenges to disease control and treatment [36]. It has been argued that different HIV-1 subtypes are characterized by different replication rates and transmission, different susceptibilities to treatment, different viral loads and different degrees of genetic diversity [37,41,42], which can ultimately determine differences in disease progression. The geographic patterns of the M group subtypes are continuously changing in response to human population migrations and active transmission networks [37]. Migration patterns from high prevalence countries have been introducing non-B subtypes, as opposed to subtype B that is predominant in European countries [36,37,40,43].

HIV is mainly transmitted by parenteral or sexual route [32]. The main target of HIV is activated CD4+ T lymphocytes [44], and then is transported to regional lymph nodes where it rapidly replicates and establishes permanent infection. After infection,

non-specific symptoms appear such as fever, malaise, generalised lymphadenopathy, pharyngitis, diarrhoea and rashes. At the primary stage of HIV infection, plasma HIV RNA levels are usually high [32], and the viral load in plasma increase the risk of transmission. This makes acute HIV infection, that occurs in the first few months of infection, an important driver of the epidemic [44]. After primary infection, the viral load decreases [44] causing a chronic asymptomatic phase of variable duration before AIDS onset [32]. This phase causes many HIV-positive individuals to remain unaware of their HIV-status for many years, while the immune system slowly deteriorates [45]. Symptoms develop when CD4+ T cell count falls to lower than 350 cells/mm^3, when several AIDS- or non-AIDS-related events occur [32]. Many diseases are considered as AIDS-related events, including 2 types of cancer (e.g. Kaposi sarcoma) and 10 opportunistic infections, being tuberculosis the most common [46].

Overall, HIV opt-out testing is recommended to: all sexually active individuals who want to perform the test, those who have history of a possible exposure to HIV, those who received transfusions before introduction of routine HIV screening, pregnant women, those who present compatible symptoms with an HIV-infection, those who have past or current history of sexually transmitted infections (STI), and those who seek care in STI/genito-urinary/dermato-venereology [47].

The development of new classes of drugs in 1995-96 allowed the introduction of the combined antiretroviral therapy (ART), and the gradual evolution of HIV infection from a fatal progressive disease into a chronic manageable condition [32,44]. The antiretroviral drugs comprise a variety of compounds that are categorized according to the step they inhibit in the viral life-cycle, namely integrase inhibitors, protease inhibitors, maturation inhibitors, reverse transcriptase inhibitors, and more [32]. ART can stop HIV replication and plasma viral load can become undetectable. Viral suppression allows immune reconstitution to take place, leading to long-term disease remission and prolonged survival [48,49], also preventing disease transmission and the emergence of drug-resistance [50]. Contrarily to previous recommendations to initiate ART when the patient's CD4 cell count drops below 500 cells/mL, current recommendations advise to initiate ART as soon as possible, regardless of the CD4 cell counts for a better public health and prevention coverage [33,51]. These recommendations have been followed by many European Union/European Economic Area (EU/EEA) countries since 2014,

including Portugal [52].

1.1.2. Overall epidemiological context and burden among migrants

HIV continues to be a major global public health issue [53]. Worldwide there were 36.9 million people living with HIV in 2017, of which 1.8 million were newly infected cases. Also, about 940 thousand people died of AIDS-related illnesses in 2017 [54]. The epidemic affects disproportionately the developing world and sub-Saharan Africa bears the greatest burden of the disease [30].

In the EU/EEA, HIV infection remains a significant public health problem [55], as substantial HIV figures are still observed across Europe [56]. A slight decrease from 29 444 to 25 353 new HIV diagnoses was registered in 2017 in the EU/EEA, with a rate of 6.2/100,000 population [53]. However, the World Health Organization (WHO) European Region registered a new increase in the same year, with a total of 159,420 new cases in 50 of the 53 countries, corresponding to an incidence rate of 20.0/100,000 population [56]. Migration is a factor influencing the epidemiology of HIV in Europe [3], and migrants are represented in all risk populations of the EU/EEA— sex workers, injecting drug users, men who have sex with men, (MSM), and prisoners [52]. However, transmission of HIV from migrant to host communities appears to be low [3]. In 2017, 41% of all newly-diagnosed cases of HIV in the EU/EEA were among migrants — 18% were from countries in sub-Saharan Africa, 8% from countries in Latin America and Caribbean, 6% from other countries in central and Eastern Europe, and 4% from other countries in Western Europe [56]. The number of cases among migrants originating from countries with generalized HIV epidemics has been decreasing in the EU/EEA, from 5837 in 2007 to 3388 in 2016. Nevertheless, migrants are still a key population for prevention and control efforts in many countries of the EU/EEA region [57].

The most common transmission mode in the EU/EEA in 2017 was sex between men. Heterosexual intercourse and injecting drug use were the main reported transmission modes in the East part of the Region [56]. The proportion of heterosexually-acquired HIV infections has been decreasing in recent years in the EU/EEA countries [55]. However, migrants originating from countries with generalized HIV epidemics represent a considerable proportion (37%) of the newly diagnosed cases acquired through

heterosexual transmission in EU/EEA [56].

HIV testing uptake increased by 34% in the WHO European Region and by 12% in the EU/EEA [56]. However, very few countries provided data on HIV testing among migrants from high-prevalence countries, of which most reported testing rates below 50% — with the range of testing rates from 3-62% [57].

Late diagnosis remains common in Europe. Over half (53%) of those diagnosed with HIV in 2017 in the WHO European Region were diagnosed at a late stage of infection (CD4 cell count < 350 cells/mm3 at diagnosis), and 49% were diagnosed late in the EU/EEA [56]. Migrants from south and south-east Asia and from sub-Saharan Africa, were among the groups who had higher proportion of late HIV diagnosis in 2016, 53% and 57%, respectively [58].

Undiagnosed HIV continues to be a hindrance to efforts aimed at reducing its incidence. People who remain unaware of their HIV status for a long time have an increased risk of transmitting the virus to others, of not initiating the combined ART timely, and of higher morbidity and mortality (11 times more likely to die within a year after being tested) [59]. Furthermore, an early HIV diagnosis prevents risk behaviours, especially with uninfected individuals [47]. It is estimated that 120 000 people were living with undiagnosed HIV in the EU/EEA in 2015, implying that about 15% of those living with HIV are not aware of their status. Estimates also indicate that it takes 2.9 years from HIV infection to diagnosis in the EU/EEA [56]. This is of particular concern, since it is estimated that people who are unaware of their HIV infection contribute to 50–90% of new HIV infections [48]. However, estimates concerning the fraction of undiagnosed cases among migrants have been receiving little attention in official estimates. One of the specific areas for action proposed by the European Centre for Disease Control and Prevention (ECDC) in their Dublin Declaration Report (2017) was to develop more focused and effective case detection approaches to reach the harder-to-reach[1] undiagnosed individuals within key populations [55]. However, recent studies were still able to find higher proportions of undiagnosed HIV among migrants in Catalonia

[1] Hard-to-reach populations refer to sub-groups of the population that are difficult to reach or to involve in research or public health programmes due to their physical and geographical location or their social and economic situation. These are for instance migrants [215], namely certain groups from sub-Saharan Africa [154].

compared to natives [59].

In 2017, were registered 14 703 new AIDS cases in 47 countries of the WHO European Region — a rate of 2.3 new cases/100,000 population —, and 3130 new AIDS cases in 28 EU/EEA countries — a rate of 0.7 new cases/100,000 population. The number of AIDS-related deaths in the WHO European Region decreased about 14% since 2008, with 4933 related deaths, and also in the EU/EEA with 2147 related deaths. Overall, 89% of these AIDS diagnoses were made within 90 days of the HIV diagnosis, indicating that most AIDS cases in the EU/EEA are due to late diagnosis of HIV infection [56]. However, there is limited official data regarding AIDS cases among migrants in Europe.

In Portugal, from 1999 to 2016 there was a considerable decrease in new HIV cases (61% — from 32.4 cases to 12.7 cases/100,000 population, respectively) [60]. Furthermore, in 2016, 91.7% of the people living with HIV were diagnosed, of which 86.8% were in treatment and of those 90.3% presented viral suppression [61]. However, Portugal was still among the EU/EEA countries with higher HIV incidence rate (10.0/100,000 population) in 2016 [62], and HIV/AIDS was also the disease of compulsory notification with higher number of deaths (334 deaths related to HIV) [22]. In 2017, 1068 new HIV cases were diagnosed in Portugal, with an incidence rate of 10.4/100,000 population, of which 51.5% were diagnosed late [60]. Heterosexual contact was the main mode of transmission, accounting for 59.9% of the cases. Estimations also showed that 33.8% of all new HIV diagnoses in Portugal were among foreign-born individuals [61], of which 57.6% were from sub-Saharan Africa and 32.4% from Latin America [60]. Regarding AIDS, the number of cases has been decreasing since 2008 in natives and migrants. However, although the majority (67.7%) was among native-born persons, most female cases (54.7%) were among women from sub-Saharan African countries [60]. Furthermore, 261 deaths were registered among HIV-infected patients in 2017, 134 among AIDS-patients [60]. Like in European official reports, there is still limited data available regarding the proportion of undiagnosed HIV cases among migrants in Portugal.

1.2. Tuberculosis among migrants

1.2.1. General characteristics of infection and treatment

Tuberculosis infection is likely to have affected humans for most of their history [63]. After more than 100 years since the discovery of its causative agent [64], TB is presently a well-known airborne infectious disease caused by bacteria of the *Mycobacterium tuberculosis* (MTB) complex. This complex is composed of several species of intracellular pathogens fully adapted to the human host [65,66]. MTB can affect any organ (extrapulmonary tuberculosis), although the pulmonary form (pulmonary tuberculosis) is the most common [67,68]. MTB infection is mainly caused by the inhalation of droplets containing bacteria that are spread through cough, speech, or sneezing of a patient with active pulmonary tuberculosis [65,69]. Such aerosol droplets cross the upper airways, overcome barriers along the way and reach the pulmonary alveoli where the infection can be controlled by the immune system or can multiply and spread invading the lung interstitial tissue (cavitation) [65]. The life cycle of MTB is only completed when it causes pulmonary immunopathology, which drives aerosolization and transmission to a new host [70]. The individuals with active TB show symptoms such as sweating, fever, fatigue, lack of appetite, weakness, weight loss, and persistent cough (sometimes producing blood – haemoptysis) [65,69,71]. For extrapulmonary TB, organ-specific signs and symptoms may occur. Some individuals develop active TB-disease without specific signs and symptoms, especially those who are immunocompromised [65,71].

Notably, not all infected individuals develop TB disease [72]. Only 10% of the infected individuals will develop the active disease in their lifetime [67,68,70]. The risk of developing TB is higher in the first 12 to 18 months following the acquisition of infection, but activation of disease can occur decades after [63]. Individuals who mount an effective immune response leading to successful containment of MTB growth (the majority) remain with the latent form of the disease (latent TB-infection - LTBI) [69]. This is the most common outcome, and can be maintained for life without symptoms manifestation, and with inability to transmit the disease [63,65,73,74]. The reactivation of TB can be averted by preventive treatment [75].

TB control and elimination rely on an early detection of active TB cases, prompt anti-TB treatment, identification of persons at risk of exposure and infection, and

prevention of secondary TB cases [76]. All persons presenting characteristic signs and symptoms of TB, that have unexplained productive cough for >2 weeks, have contacted with a TB case, live with HIV, present lymphadenopathy, or pleural effusion, are considered as "presumptive TB" cases, and should be evaluated for pulmonary and/or extrapulmonary tuberculosis [77]. Moreover, all persons with chest radiographic findings suggestive of pulmonary tuberculosis should also be tested [71]. Other groups with risk-related comorbidities will be further described (see 2.2), and should be also systematically screened for TB-infection [74]. Chest radiography, Mantoux tuberculin skin test and/or interferon-γ release assay (IGRA) are some of the commonly used tests [67]. Confirmation of diagnosis and the profile of susceptibility to anti-tuberculous drugs allows the appropriate therapy choice [67]. Some forms of TB are intrinsically difficult to diagnose, namely child TB, extrapulmonary TB, TB in HIV/AIDS patients and drug-resistant TB. HIV-counselling and testing should be recommended to all patients with or presumed to have tuberculosis [73].

The discovery and wide use of antimicrobials effective against TB in the 20th century allowed dramatic reductions in TB mortality [63]. Standard treatment for drug-susceptible TB consists of a six-month regimen with four first-line drugs in the first 2 months — isoniazid, rifampicin, ethambutol and pyrazinamide –, followed by isoniazid and rifampicin in the subsequent 4 months [65,67,68,71,78]. Daily dosage is strongly recommended [71]. This treatment regimen has an 85% success rate [67,68], and after two weeks the likelihood of transmission is reduced [72]. Still, those who are cured from TB can be left with sequelae that substantially reduce their quality of life [63]. Treatment regimens for LTBI include isoniazid from 6 to 9 months, rifampicin for 4 months, isoniazid and rifampicin from 3 to 4 months, or isoniazid and rifapentine once a week for 3 months [78]. Preventive treatment of LTBI is recommended for high risk groups [75].

An important consequence of the prolonged treatment scheme is poor patient compliance [79]. Thus, the introduction of the first anti-TB drugs was soon followed of emerging drug resistance [63]. Previous TB treatment, poor adherence or inadequate treatment regimens are some of the risk factors to develop drug-resistant TB [80]. Drug resistant-TB require longer treatments with more drugs and are associated with lower success rates [67,68]. In multidrug-resistant TB (MDR-TB) bacilli strains are resistant to both isoniazid and rifampicin. Extensively drug-resistant tuberculosis (XDR-TB) is

defined as MDR-TB with further resistance to any fluoroquinolones and to at least one of the second-line injectable drugs (amikacin, capreomycin, and kanamycin) [81].

The Directly Observed Therapy Strategy (DOTS) was launched in 1994 in order to disseminate a new standard approach for TB control [63,82]. DOTS is a patient-centred approach to treatment, based on the patient's needs and mutual respect between the patient and the provider. This approach includes observation of medication ingestion by a healthcare provider and it may include identification and training of a treatment supporter acceptable and accountable to the patient and to the health system. It may also include incentives and enablers, including financial, social and psycho-social support in order to promote adherence [71].

1.2.2. Overall epidemiological context and burden among migrants

TB was declared a Global Health Emergency by the WHO in 1993 after a period of prolonged neglect [78,81] and is still considered a worldwide health concern [64]. Currently, TB is one of the top 10 causes of death globally, and the leading cause of death from a single infectious agent (above HIV/AIDS). The global number of new TB cases has remained stable since the beginning of the 21st century [83]. About 1.7 billion (23%) of the world's population is infected with MTB [78], and the WHO estimated that 10 million people developed TB disease in 2017, of which 6% were in the WHO European Region [83]. There is about 30 high-burden countries worldwide identified for TB for the period 2016-2020, of which several are the main countries of origin of most migrants [8]. Much TB burden is concentrated in Africa and Asia (28 and 58%, respectively), where it still causes a high morbidity and mortality [73]. Migrants contribute disproportionately to the burden of TB in low incidence countries, representing a challenge for TB control programs and a public health concern [84–86].

The WHO European Region was the WHO region showing fastest declines in TB incidence (on average, 5% per year), and in mortality (11% per year) between 2013 and 2017 [83]. In 2017, 55 337 cases of TB were reported in 31 EU/EEA countries, with a notification rate of 10.7 cases per 100,000 population, and continuing the downward trend observed since 1996. Between 2013−2017, the average annual decline in the notification rate in EU/EEA was 4.5% [87]. There were 29 000 estimated TB-related deaths in the European Region of the WHO in 2017, equivalent to 3.1 deaths/100,000

population, and there were 4000 deaths in the EU/EEA, a decrease compared to the 4200 estimated for 2016 [87].

Currently, most EU/EEA countries are low-incidence countries [87], and some countries are progressing towards the pre-elimination phase (<1 case per 100,000 inhabitants) [71,86]. In these countries, high TB incidence has been associated with people living in disadvantaged regions or settings [84]. However, there is currently few surveillance and survey data available for tuberculosis in hard-to-reach populations, which are more likely to acquire or carry TB than the general population [88]. TB cases among migrants represented 33.1% of all TB cases in the EU/EEA, and in many countries, it represented a large majority — Malta (92.9%), Sweden (90.0%), Norway (88.5%), Israel (81.2%), Switzerland (79.8%), Luxembourg (78.1%), the Netherlands (74.5%) and Cyprus (71.7%) [87]. The annual number and proportion of native TB cases has declined since 2013 to 2017 (from 45 162 to 35 446, and from 68.7% to 64.1% respectively) in the EU/EEA, whereas the proportion of TB cases of foreign origin increased over the same period (from 27.1% to 33.1%) [87]. The increase in the proportion of TB among foreign-born populations can result from a decrease of TB notifications among native populations [89,90]. A systematic review by Odone and colleagues (2015) suggested that the overall increase of foreign-born subjects among notified TB cases in the EU/EEA is both due to a real increase, and due to the sizeable drop in native cases in certain countries [91]. Conversely, the increase in the absolute number of foreign-born TB notifications has been suggested to be caused by the increased immigration from TB-endemic countries, with TB burden reflecting the incidence in their countries of origin [68,90,92].

In Portugal, the number of cases has been consistently decreasing [93], and by 2014, Portugal became for the first time a low incidence country (incidence rate <20 new cases per 100,000 population). However, some regions such as Porto, Lisbon and Setubal still presented intermediate incidence (20-50 cases per 100,000 population) [94,95]. Although, there was 40% decrease in TB notification rate and incidence in the last 10 years [67], in 2017 Portugal was still one of the EU/EEA countries with highest notification rates [87] — 1741 TB cases of which 1607 were new cases (notification rate of 17.8/100,000 population and incidence rate of 16.4/100,000 population), and a substantial concentration of TB cases is still observed in Porto and Lisbon areas (57.3% of all cases) [67]. New cases among migrants in Portugal increased in number and

proportion, from 336 (18.3%) in 2016 to 351 (19.5%) in 2017, with an estimated incidence rate of 83.7/100,000 population, 5.4-fold higher than the general population estimate [67,87]. In 2017, 77 people died of TB in Portugal [87], and in 2016 more than a considerable proportion (12%) of all deaths caused by pulmonary TB were among foreign-born individuals living in Portugal [22].

1.3. HIV-TB co-infection among migrants

1.3.1. General characteristics of infection and treatment

HIV-infection is the most important risk factor to develop active TB, as it dramatically increases the susceptibility to primary infection, reinfection, or reactivation in patients with LTBI. TB is also the major opportunistic disease in HIV/AIDS patients [35]. Although incidence of active TB is higher among HIV-patients with lower CD4+ T cell count [76], TB infection or reactivation can occur almost immediately after HIV infection, even when CD4+ T cell counts are still high [65], contrarily to other HIV opportunistic infections that only occur at low CD4+ T cell counts [96,97]. The clinical presentation of TB among HIV-TB co-infected patients may be atypical [46,98], differing according to the degree of immunosuppression [96,99]. In patients with CD4+ T cell count above 200/mm^3, pulmonary TB is more common [96,99], with similar TB-related symptoms to those observed among HIV-negative patients [100]. As immunosuppression progresses, extrapulmonary TB becomes more common [96], as a consequence of the immune system failing to contain the bacteria within the lungs, causing its dissemination to extrapulmonary sites [100]. TB may also induce retroviral replication [101], which favours viral growth [97], accelerates HIV disease progression, and reduces HIV treatment efficacy [102].

The WHO recommends HIV testing for all patients with known or suspected TB, regardless of the stage of the country's HIV epidemic [95]. However, these recommendations are not followed in every setting. Screening for active TB is not done in all low-incidence countries and, even among high-risk groups, LTBI screening is not widely implemented. Moreover, diagnosing LTBI in HIV-positive patients can be difficult, as diagnostic tests for LTBI are less sensitive at low CD4+ T cell counts [96].

Treatment for both conditions can be quite problematic due to drug-drug

interactions, to overlapping toxicity, to the possibility of developing an immune reconstitution inflammatory syndrome, and due to a higher tablet burden required to treat both diseases that may reduce adherence [74,103,104]. The absence of appropriate treatment for HIV and TB in these patients significantly reduces survival [81] and without preventive treatment about 13% of the people living with HIV will develop TB [105]. The risk for active TB-infection in persons living with HIV is strongly reduced by early ART [106]. However, the risk remains considerably higher, with worse TB treatment outcomes and higher mortality rate compared with HIV-negative patients [100,107,108]. There is a lot of debate on the ideal timing of ART initiation and concomitant administration with anti-TB medication [97]. For HIV-positive patients, with or without active TB, anti-TB treatment should start immediately, and the antiretroviral treatment should be prescribed as soon as possible. In order to reduce the risk of adverse reactions, a delay of at least 14 days is suggested by the 2017 WHO treatment guidelines between the initiation of anti-TB therapy and the initiation of ART [71]. However, recently, the early initiation of ART during treatment for tuberculosis has shown successful results in reducing HIV-TB related morbidity and morbidity [76]. The WHO also recommends the "Three I's for HIV-TB" strategy for reducing the burden of TB among HIV-seropositive individuals, which includes: 1) isoniazid preventive treatment (IPT) – for those who do not report symptoms for at least 6 months; 2) intensified case finding; and 3) infection control for TB at all clinical encounters [109].

1.3.2. Overall epidemiological context and burden among migrants

The influence of HIV and TB on each other's natural history and pathogenesis has contributed to enhance the magnitude of HIV-TB epidemic [99]. HIV and TB are global public health problems with considerable interaction [103], causing an immense burden on healthcare systems of high burden countries [99].

Since the 1990s, the HIV/AIDS epidemic has been one of the main causes of the slow decline, if not of increase, of TB incidence worldwide [81]. In 2017, there were 464,633 reported cases of TB among people living with HIV (51% of the estimated 920,000 new cases in the same year), corresponding to approximately 9% of the incident TB cases in 2017. Surprisingly, about 84% of these cases were on ART. The proportion

of TB cases co-infected with HIV was highest in countries in the WHO African Region, exceeding 50% in parts of southern Africa [83]. TB caused an estimated 300,000 deaths among HIV-positive people in 2017. However, the number of TB deaths among HIV-positive people has fallen by 44% since 2000 [83].

In the WHO European Region, a total of 25,153 TB cases (12.8% of the total HIV cases) were detected among HIV-positive individuals in 2017, and the highest proportions were observed in Ukraine (22.4%), the Russian Federation (19.3%), Portugal (10.9%) and Latvia (10.8%). In the EU/EEA, 1006 cases of HIV (3.9% of the total TB cases with known HIV status) were detected in the same year, and the highest proportions were observed in Estonia (8.6%), Latvia (11.0%) and Portugal (11.4%) [87]. Although the proportion of HIV co-infected TB cases has been decreasing in later years [68,87], notification of prevalence is still compromised by sub-optimal reporting, a persistent issue in several countries [71,87]. There is a close link between the global HIV and TB situation and the situation in the EU/EEA as 27% of all TB cases and 37% of new HIV cases in the EU/EEA are among migrants [108]. Globalization and migration from endemic zones continue to be major forces in the global spread of this co-infection [60,110]. In low TB incidence countries, the changing epidemiology of TB has led to a concentration of disease in high-risk groups [111]. Previous studies observed that HIV-positive migrants had higher rates of AIDS-defining illnesses compared to natives, being TB the most common in this population [112]. Moreover, a systematic review by Pimpin et al. (2011), have also shown increasing co-infection trends in EU/EEA countries related with increased HIV among foreign-born populations [103]. However, the epidemiology of HIV-TB co-infection among migrant populations has been receiving little attention in official surveillance publications and research studies.

Official Portuguese data from 2016 have shown that HIV status was known among 86.7% of the TB-patients in Portugal, of which 10.9% were HIV-positive [67]. Moreover, in 2017, and keeping the trend observed since 2008, the most frequent AIDS-defining illness was pulmonary tuberculosis (11.6%), followed by extrapulmonary TB (8.6%) [60]. However, in Portugal, official data on prevalence of HIV-TB co-infection among migrants is, to our knowledge, still absent, and this topic has been also poorly explored in recent national studies.

2. Factors related to migrants' vulnerability to HIV and tuberculosis

Several individual, behavioural, social, economic, cultural and environmental determinants are implicated in migrants' vulnerability to HIV and TB [69,113]. The Social Ecological Model (SEM) is a framework that represents the interactions between determinants [114] and is useful in the creation of sustainable solutions for at-risk individuals and societies [115]. There are several variations of the model according to the studied outcome and the organizations that use it. The Centres for Disease Control and Prevention (CDC) preferably uses a four-level model [115,116]. Each level overlaps with other levels, and the best public health strategies are those that encompass and target a wide range of perspectives [115]. The first level — individual— identifies biological, behavioural and personal history factors associated with vulnerability to acquire or transmit illness or infection, such as age, education level, sexual orientation and economic status. The second level — interpersonal — examines close relationships and social networks that directly influence health and health behaviours in multiple ways, such as family, friends, neighbours and others. The third level — community — explores the settings, such as schools, workplaces, and neighbourhoods, in which social relationships occur and seeks to identify the characteristics of these settings. The fourth level — societal — looks at the broad societal factors, including health, economic, educational and social policies that maintain economic or social inequalities between groups in society [115–117]. In Figure 2, we present a four-level socio-ecological model with some of the main groups of factors related with migrants' vulnerability to HIV and TB.

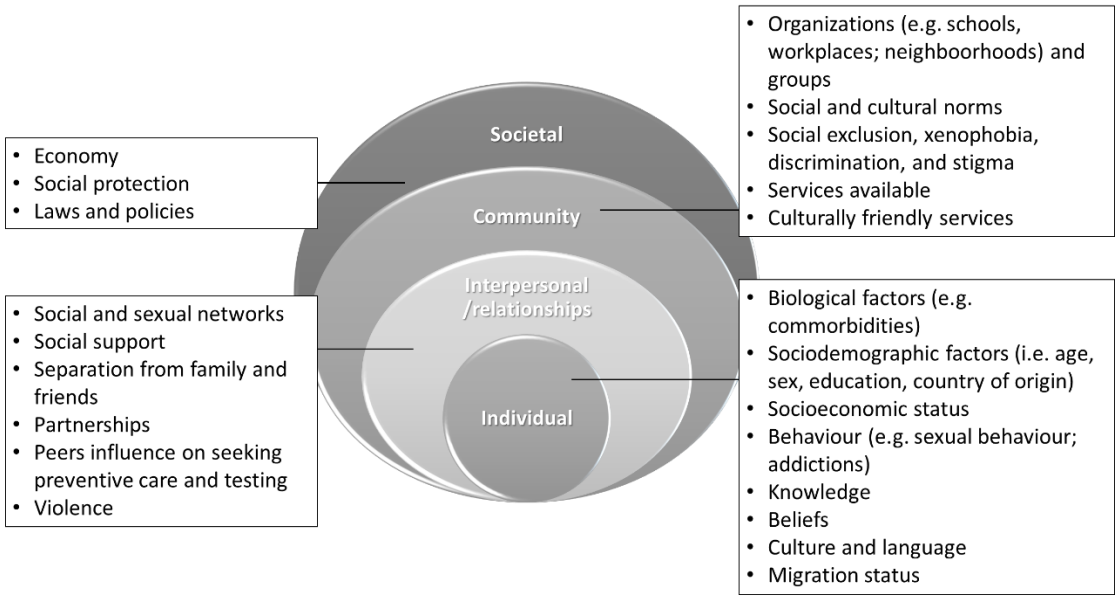

Figure 2: Representation of the socio-ecological model of factors related to migrants' vulnerability to HIV and TB (author's own elaboration with information from the sources: Dyson et al., 2018 [114]; Baral et al., 2013 [117]; Pan American Health Organization, 2017 [118]; Kaufman et al., 2014 [119]; and Olayiwola and Raffoul, 2016 [120]).

2.1. Factors related to migrants' vulnerability to HIV

Individual factors

The presence of other STI — syphilis, herpes, chlamydia, gonorrhoea, bacterial vaginosis, among others —, is a well-known risk factor for acquiring HIV [53]. The epidemiology of STI serves as a proxy for the level of HIV infection among populations, due to similarities in behavioural patterns of people afflicted with STI and HIV [121]. One of the reasons for this linkage between STI and HIV is the fact that pre-existing STI can form ulcerative/inflammatory lesions in the genitalia, increasing the chances of HIV during sexual contact [121]. Moreover, the occurrence of STI can indicate, for instance, previous unprotected sex, and consequently the potential for HIV to spread and increase prevalence within a population [122]. Another relevant factor is the presence of TB infection. As previously mentioned, TB increases the chances of poor disease outcomes in HIV-positive patients [102], and increase the risk of HIV-related mortality by 4.5-fold [103].

Sociodemographic factors, such as age, gender, education and country of origin have been implicated in migrants' vulnerability to HIV. Gender has been reported to

moderate the relationships between acculturation, and multiple partnerships and unsafe sex [123]. Women's reproductive system has a larger surface area of mucosal exposure. In addition, they are also more likely to experience tissue injury during sex, which increase their vulnerability [124]. According to a recent integrative review, the distribution of HIV between genders is different according to geographical contexts, for instance being more prevalent among men from the EU and Latin America, and more prevalent among women from African countries. In sub-Saharan Africa there is a feminization of the epidemic as a reflection of a range of biological, socioeconomic and cultural risk factors that increase the vulnerability of women to HIV [124]. On the other hand, a previous study with Polish migrants living in the UK have also shown that being a male was associated with greater odds of unprotected sex, of having multiple partners, and of sex after the use of alcohol [125], being the later also known to impair judgment and increase the chances of engaging into sexual risk behaviours [24,126]. Previous studies on migrants have also shown differences between sexes regarding HIV testing, mainly explained by the fact that migrant women tend to use more healthcare services for antenatal care, which also includes HIV counselling and testing [59,127].

Regarding age, the same integrated review observed that all analysed studies converged to a higher prevalence of HIV among adults aged 20 to 49 years old [124]. Sexual behaviour at a young age poses multiple risks including prolonged exposure to risk and higher probability of sexual risk behaviours [128]. However, among older groups, condom use is also less frequent, as many believe to be immune to sexually transmitted diseases [124].

A higher education has been associated with more HIV knowledge, awareness of availability of healthcare services and HIV testing [127,129], being also considered as the so-called "vaccine" against HIV [33]. In fact, a study by Dias and colleagues (2014) in Portugal have shown higher rates of sexual risk behaviours among less educated and older migrants, including having multiple sexual partners and unprotected sexual intercourse [130].

The country of origin is another important sociodemographic factor. Overall, most HIV diagnoses among migrants are made for the first time in Europe. Despite of that, acquisition is predominantly assumed to have occurred in their countries of origin,

particularly if migrants originate from high incidence regions [30,36,48,131]. However, increasing evidence has been showing that HIV acquisition at the host countries is a reality [30,36,48,55]. A study by Desgrees-du-Lou and colleagues (2015), have shown high levels of HIV acquisition after migration [132]. Another study by Alvarez del-Arco and colleagues (2017) also estimated that about 63% of HIV-positive migrants living in Europe acquired HIV after migration, and that the probability of acquiring the disease at the host country increases overtime [131]. These evidences suggest that, although migrants from countries with generalized HIV epidemic have an increased risk of acquiring HIV before migration, this risk remains as individuals migrate to the host country. There, they become sexually active and engage into sexual risk behaviours within migrant communities where HIV prevalence is higher than among the receiving country population [133,134].

Regarding sexual risk behaviours, the correct and consistent use of condom is the foundation of HIV risk prevention approaches [135]. However, studies have referred inconsistent condom use among migrants [130,136]. Previous research has also shown that a considerable proportion of migrants engaged into inconsistent condom use either with regular or occasional partner, and in other sexual risk behaviours such as having multiple partners [137–140].

Socioeconomic factors, such as poverty, can lead migrants to engage in sexual risk behaviours, namely engaging in casual and concurrent partnerships [134]. Migrants also frequently engage in commercial sex when facing situations of income and housing insecurity and homelessness [48]. Furthermore, poverty can also cause migrants' isolation from social support systems that increases the chances of exposure to forced sex and domestic violence [141], both associated with high risk for HIV infection [142,143]. Socioeconomic factors have been also associated with barriers to healthcare. In a study by Ndumbi and colleagues (2018), HIV-infected migrants who experienced food insecurity reported barriers in seeking healthcare and also delayed treatment due to medication costs [144].

Other individual factors also determine health-seeking behaviours and HIV testing among migrants. Cultural differences, legal issues, and social inequalities may hamper preventive behaviours and HIV testing by posing barriers to seek care

[131,145,146]. Studies have suggested that many undocumented migrants fear deportation based on a HIV diagnosis, which hinders them to use health services and uptake the test [147]. Other studies have also shown that residence issues and traumatic experiences during the migration process also pose barriers in accessing preventive measures and healthcare services [148]. Additionally, a recent systematic review also showed that some sub-Saharan African migrants still prefer traditional medication and expressed mistrust towards "Western Medicine" [149]. Migrants also often lack knowledge about the health system and about sexual and reproductive health services [4]. They are often not aware of the HIV risk factors, with a significant negative impact on their perception of risk [127]. In a study by Fakoya and colleagues (2017), about 10% of migrants did not have basic knowledge about HIV and about half did not know where to access free condoms [150].

Interpersonal/relationship factors

To better understand the vulnerabilities of migrants to HIV, it is important to explore the social contexts in which HIV risk behaviours among migrants are shaped [151]. In the country of destination, migrants face long periods away from family and partners, leading to a sense of solitude, isolation and stress [130,134,152–154]. Additionally, migrants are exposed to different behaviours and norms, with limited social control [155]. In these circumstances, relationships that are prohibited at home are often possible abroad, such as extramarital relations, same sex relations [126,155], and risky sexual practices — multiple partners, sex without condom, concurrent sexual partners and sex under the influence of alcohol or drugs [130,134,152–154]. Previous research has also highlighted the importance of a partner and social networks in providing emotional and material support, in promoting treatment adherence, and in avoiding sex work, alcohol consumption and sexual risk behaviours [124].

Relationships not always have positive effects on migrants' vulnerability to HIV. Migrants may face sexual violence, as well as gender-based exploitation during migration and in host countries [126]. Sexual violence is an important determinant of post-migration acquisition of HIV [142], and affects particularly migrant women, engaged in domestic work [126] and undocumented [141]. In a study by Pannetier and colleagues (2018), sub-

Saharan African women living in Paris were regularly exposed to forced sex in their lifetimes. Forced sex after migration was also associated with post-migration acquisition of HIV and with being hosted by family and friends [142], who sometimes are the perpetrators of sexual violence in migrant women [141]. One of the consequences of sexual violence is victims' social isolation and separation from partners, possibly creating conditions for further engagement in sexual risk behaviours [143]. Furthermore, literature has shown that abused women and their abusive partners are more likely to engage in sexual risk behaviours, increasing their chances of becoming infected with HIV [143,156,157]. Also important is the fact that those who have been abused or live in fear of violence, have also limited capacity to refuse sex or negotiate condom use, due to fear of further violence [143,158]. Fear of violence from a partner can also prevent the victims from disclosing their HIV status and seeking HIV testing [159], with health consequences for the victims and partners.

Community factors

Community environments can either promote health and well-being or can be sources of stigma [117]. Despite of significant improvements in HIV/AIDS prevention and care, the disease is still associated with negative social representations [37]. The social and health inequities resulting from HIV-related stigma continue to be a significant barrier in an effective global response to the HIV/AIDS epidemic [160] and, in the case of migrants, stigma is often exacerbated by marginalisation [48].

In certain cultures and countries of origin, HIV is considered a shameful disease and portrayed as a condition that afflicts only men who have sex with men or drug addicts [126]. Migrants from these countries tend to believe they do not need to practice safe sex since they do not engage in such practices, which increase their risk of HIV [126]. On the other hand, high levels of perceived, anticipated or internalized stigma among those who are living with HIV yield lower levels of HIV status disclosure, denying the individual the beneficial impact in terms of greater social support, adoption of preventive behaviours and involvement in HIV care [48,148,149,161–163]. Nevertheless, due to existent HIV-related stigma, the disclosure of HIV status might not be always beneficial and those living with HIV might face adverse outcomes such as blame, discrimination, rejection,

loss of financial support, marital conflicts, as well as physical and emotional violence. These outcomes are particularly worrisome for migrants considering that some have issues with their legal status, lack of health insurance, or financial or job insecurity [163].

Healthcare providers may be influential in encouraging individuals to HIV testing [127]. However, stigma and discrimination can also be present at healthcare services, preventing migrants from seeking care. Migrants' experiences of language barriers and of lower standards of care compared to natives lead them to decrease adherence to treatment and to engage in self-medication [160]. Lack of cultural sensitivity of healthcare providers towards communication issues about sexuality and patients' privacy can limit migrants' uptake of HIV testing. Furthermore, the location of testing also has implications; namely those performed at hospitals were referred not to offer enough privacy, posing an obstacle to HIV testing for migrants [129].

Societal factors

Currently in some countries worldwide there are still certain immigration policies and practices that exacerbate vulnerability to HIV [33]. Migrants' administrative insecurity, such as lack of a residence permit, has been associated to situations of sexual violence and engagement in sexual risk behaviours [142]. Moreover, in many countries, undocumented migrants still face complex obstacles, such as lack of access to healthcare services or lack of social protection, namely health insurance and other social security benefits [153]. Mullerschon and colleagues (2019) have shown that absence of regular health insurance by migrants from sub-Saharan African countries increased the odds of no contact with the healthcare system, and that these migrants were less likely to have been tested for HIV than insured patients [148]. Furthermore, migrants' employers may also exercise considerable power over their employees by refusing their sick leave and enforcing long work shifts, making it extremely challenging to access HIV services [153]. Regarding HIV treatment, in the EU/EEA many countries still do not provide ART for undocumented migrants [55]. In some cases, the limited offer of healthcare services available for migrants working in more remote regions can also pose challenges to treatment adherence [153].

In Portugal, vulnerable populations such as migrants are one of the priorities of

the National HIV Program [23]. HIV testing can be done for free, anonymously and confidentially, and in case of positive result individuals are entitled to free treatment and care regardless of their legal status [147]. HIV-positive patients are also exempt of user fees [164]. However, official data reported that the majority of EU/EEA countries, Portugal included, still face major gaps in HIV prevention services for migrants from high-prevalence countries, particularly for those undocumented [55,57]. Therefore, current HIV prevention efforts are still inadequate for migrant populations in Portugal [57].

2.2. Factors related to migrants' vulnerability to tuberculosis

Individual factors

Several individual factors increase the risk for TB infection or reactivation at several stages of the migration process, and can vary greatly between different migrant groups and also between migrants and nationals [90].

Several comorbidities such as HIV, diabetes, chronic kidney disease, silicosis, cancer, and also immunosuppressive therapies (e.g. for rheumatic disease, anti-tumour necrosis factor treatment, dialysis or preparation for organ or haematological transplantation) can impair the immune system, favouring TB infection and reactivation [65,69,73,74,76,81,165,166]. Globally, people living with HIV have 26–31 times higher risk of TB than people without HIV infection living in the same country, and have a risk of reactivation of 10% per year of life [73,111,166]. Moreover, the genetic heterogeneity of HIV viruses, and the differences between strains regarding disease progression and clinical outcomes [37,41,42], might influence the susceptibility to TB.

Sociodemographic factors like age, sex, and country of origin can also determine migrants' vulnerability to TB. The increasing age has been referred as an important factor for TB disease activation. With the increasing age, the immune system becomes more compromised, either by age-related immune-senescence, either by the onset of comorbidities that impair immunity [167]. However, when compared with host populations, migrants usually tend to be affected by TB disease at a younger age, as a result of a higher exposure to other risk factors compared to natives [92]. Gender is also

an important factor, since it is recognized from early ages of TB epidemiology that men are disproportionately more affected by TB than women. Several hypotheses have been proposed to explain such disproportion between sexes (globally an average of 2 men per each woman): different physiological/immune responses, different behaviours, or even differences in reporting and diagnosis between men and women. However, scientific literature is still inconclusive regarding the true reasons for this discrepancy and remains an unsolved mystery [168]. Such disproportion of TB disease between sexes has been also observed among migrants. A comprehensive literature review on TB among migrant populations in the EU/EEA described more TB reports among male migrants, with a male: female sex ratio of 1.5:1 [91].

The country of origin is also a relevant factor for TB. In countries with a high incidence of TB the entire population can be at risk, even those who are wealthier and highly educated. The high burden of TB observed among migrants from TB-endemic countries can result from: 1) arrival in the host country with active TB; 2) entering the host country with LTBI that reactivates after arrival; 3) new TB infection acquired in the host country; or 4) acquired TB infection when travelling to the country of origin and vice-versa [90]. Migrants from high incidence countries usually have higher rates of TB than native European populations [92], which is often attributed to the reactivation of an "imported" LTBI [72]. The risk of disease development is higher in the first few years after arrival for migrants from endemic countries, which reflects a previous infection acquired at the country of origin [169,170] and then, the notification rate among these new arrivals decrease with time after migration. However, not all TB cases among migrants is due to an infection at a high incidence country [90], but rather a result of a complex interplay of other factors that can influence susceptibility for TB [169].

The conditions faced during transit from country of origin to host country are also important. Migrants often face dangerous, crowded and unsafe travel conditions that might increase the risk of acquiring TB [8]. These precarious travel conditions are usually worse for undocumented migrants [73], frequently involving poorly ventilated spaces that favour transmission [72,171]. Moreover, modern migration patterns also mean frequent post-resettlement travels, increasing the risk of acquiring TB infection, of transmitting the disease, and of interrupting treatment [8,169]. These risks are proportional to the duration of travel and to the existing burden at the country visited [169].

Socioeconomic factors deeply influence TB epidemiology in all stages of its pathogenesis (risk of exposure, susceptibility to progression of disease, time to diagnosis and treatment, compliance and treatment success) [76]. Poverty in general can increase the probability of contacting with a person with active TB [67,76]. This is due to the fact that poverty is related with sub-standard living and working conditions, namely high incidence settings, poor, crowded and badly ventilated places [76]. Therefore, socially disadvantaged migrants are themselves a risk group for TB [172]. Undocumented migrants face even worse situations and higher risks for TB, since their entry in the host country is more recent [73], and their living conditions are usually worse [73]. In Portugal, data have shown that 27.2% of migrants were living in overcrowded houses in 2015, while only 9.7% of nationals lived in the same conditions (9.7%) [22]. A spatial analysis conducted by Couceiro and colleagues (2011) identified greater TB risk in some municipalities in Portugal, mostly with high TB incidence, where populations lived in poor and overcrowded houses. These populations were mainly unemployed, had history of imprisonment and also included immigrants from high incidence countries [173]. Moreover, a study from Paulino and colleagues (2016) has shown that foreign-born TB patients in Portugal were more likely to be younger, HIV-positive, homeless or living in shelters [174]. Migrants at an economically disadvantage situation also have higher likelihood of suffering malnutrition [65,76,165], which weakens their immune system increasing the probability of developing active TB [81]. Socioeconomic factors also impact migrants' health-seeking behaviours as those more disadvantage have low health-related spending capacity [175], increasing the probability of worse clinical outcomes [86].

Less healthy behaviours and addictions, which can be also linked to socioeconomic disadvantage, such as smoking, alcohol abuse and drugs, can lead to poor disease outcomes and lower compliance with treatment [65,76,165]. Smoking and excessive alcohol consumption have been associated with higher TB-related death, worse radiological presentation of the disease and higher risk of disease reactivation [76]. Alcoholism has been also linked to other socioeconomic determinants of TB, such as homelessness and malnutrition [76]. Additionally, increased indoor and outdoor pollution, for instance caused by smoking environments, negatively affects the immune system and favours TB infection and reactivation [81].

Several other individual factors determine migrants' health-seeking behaviours, access to TB care and treatment adherence. Those who are still undocumented may fear being arrested and deported, causing delays in the diagnosis [176], and also difficulties for the contact tracing [69]. Migrants' limited knowledge on TB causes, symptoms, transmission and treatment can also limit their health-seeking behaviours [8]. For instance, some migrants may erroneously perceive that the high risk of TB was "left behind" in their country of origin, where the disease was also more severe [69]. Moreover, cultural and linguistic differences can pose limitations to access information on TB prevention and transmission [175], and can also cause delays in TB diagnosis [92]. Some migrant communities may also follow closely sociocultural beliefs, sometimes distrusting public services in favour of traditional healers, which may also delay health care seeking [8,69].

Interpersonal/relationship factors

Social support and its complex interactions with migrants' susceptibility for TB, healthcare seeking behaviours and adherence to TB treatment are still poorly explored in the literature. However, social support is a crucial factor for migrants at host countries in order to overcome personal and structural barriers [177]. Migrants who are separated from their families and friends to provide them protection, may fall into alcohol and/or substance abuse [178], which, as previously mentioned, are well-known risk factors for TB [65,76,165]. Moreover, the lack of a supporting network might cause mental health issues such as psychological stress and depression, which in turn can have negative effects on their immune system and increase the risk of progression to active TB [69].

Healthcare seeking behaviours and adherence to TB treatment are also determined by the presence of social support [179]. It has been described that, in the absence of a social network, migrants' health status can become weakened without any family member or friend to encourage them to go to a healthcare centre when necessary [178]. Moreover, a previous systematic review has described the importance of families' support and of a more "personal touch" from healthcare providers in overcoming migrants' fear of TB disease, and in promoting long-term adherence to TB treatment and treatment success [72]. However, sometimes family members might also negatively

influence migrants' adherence to TB treatment due to their attitudes or by neglecting their supervision to the patient [177].

Community factors

Isolation, stigma and discrimination are also important factors for TB among migrants [72,76]. In low TB incidence countries, migrants may face stigma given the exaggerated and false public perception of the risk posed by migrants in increasing TB transmission in host communities [8]. Moreover, for some cultures, TB is perceived as sinful and dirty, causing feelings of guilt and shame, which can lead to avoidance of disease disclosure, hampering the identification of contacts and disease control [69]. Such perceptions may contribute to increase disease transmission, morbidity and mortality among migrants [180], and can even contribute to increase drug resistance [92]. In fact, a study by Baussano and colleagues (2013) observed that socially marginalized immigrants in Italy were key reservoirs of TB infection, with substantial ongoing transmission in the first few years after arrival [170].

Migrants-unfriendly services and xenophobic attitudes can negatively impact TB outcomes in these populations. For instance, the attitudes of healthcare providers towards TB-infected migrants can influence adherence to TB treatment, and treatment outcomes [8]. A study by Zelnick and colleagues (2016) with healthcare providers from New York City reported barriers to TB care among migrants mainly related to social and economic issues, but providers' commitment to the foreign-born communities was a significant resource to tackle TB in these populations [181].

Societal factors

Factors such as income levels per capita, income inequality and spending on social protection have been associated with TB burden in European countries [86,90]. A TB diagnosis often implies individuals' reduced productivity, which can hamper their socioeconomic status [76,182]. Migrants faced with a TB diagnosis might be subjected to catastrophic financial burden due to direct (e.g. transport to and from the healthcare facilities, medication, exams or consultations incurred by individuals) and indirect costs

(e.g. illness-related work absences) of anti-tuberculosis treatment if policies for free TB treatment for migrants are not adopted or implemented [8,182]. Co-payments, even if relatively small can constitute financial barriers for some migrants [183]. Even in countries where TB diagnostics and treatment are free for all, these populations might incur in costs associated with complementary tests, supplements and lost livelihood that might become unaffordable [8]. Such significant social and economic burdens make patients less likely to complete TB testing and treatment [180]. The absence of labour and social policies can have negative TB outcomes in these populations. For instance, poor working benefits, such as lack of sick leave benefits for health care visits, can lead to poor or late health-seeking behaviours and TB detection, as well as poor treatment adherence [8]. Moreover, for migrants on treatment, the rigid opening hours for medication often do not fit with the working hours of patients, leading to poor compliance to treatment [69]. Furthermore, those co-infected with HIV often have to visit several health-care institutions to obtain treatment for both diseases since services are disintegrated in many European countries [184]. The lack of entitlements to care, namely medical insurance among migrants is another factor contributing to diagnostic delay observed when compared to native populations [73], and can also cause poor adherence to treatment, consequently increasing the chances of disease transmission to the community and of acquiring drug resistances [92]. Some low-incidence countries do not provide free TB care to all, and marginalised groups, such as undocumented migrants, may be excluded from national health services or insurance schemes [183]. Moreover, limited access to care can also prevent migrant populations from accessing information that would enable them to avoid TB or to obtain early diagnosis and treatment [3]. Migrants also frequently face several legal and administrative hurdles, and health systems are often unprepared to provide information on how the system works [8,185]. Although supportive health policies are in place in several countries, the problems faced by migrants persist due to low awareness and poor enforcement capacity with administrative challenges. Moreover, during periods of economic crisis, targeted funding cuts are frequently made in prevention or treatment programmes for non-nationals, causing additional risks for migrant populations [8].

In Portugal, TB patients are diagnosed and treated free of charge, regardless of the country of origin and legal status [186]. A study in Portugal, by Paulino and colleagues

(2016) have shown no delay in TB diagnosis in foreign-born patients when compared to native-born patients [174]. However, a more recent study by Linhas and colleagues (2018), highlighted that despite of the theoretically non-existent legal barriers, migrants at high risk of TB in Portugal still have difficulties in accessing healthcare services [187]. Therefore, further research is needed to provide more information on the barriers related to access and use of TB care among migrants in Portugal.

3. Contextualization within the Sustainable Development Agenda, and the HIV and TB global health targets

The UN General Assembly in 2015 launched the 2030 Agenda for Sustainable Development with 17 Sustainable Development Goals (SDGs) that must be accomplished globally by 2030, based on the principle of "leaving no one behind" [188]. The relationship between migration and health was recognized as an important aspect to take into account within the 2030 Agenda [189] and, for that reason, several targets within the 17 SDGs are explicitly or indirectly related to migration [188]. The SDG 3 — "Ensure healthy lives and promote well-being for all at all ages" [189] — addresses specifically the issue of HIV/AIDS and tuberculosis in target 3.3 — "End epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, waterborne diseases and other communicable disease" [188]. Aligned with the Sustainable Development Agenda for 2030, the global health programmes for HIV/AIDS and TB acknowledged that only targeting vulnerable populations such as migrants it is possible to achieve national and global targets [17].

The Joint United Nations Programme on HIV/AIDS (UNAIDS) settled the 2016-2021 Strategy, a bold call to front-load investment, to achieve the 90-90-90 treatment targets by 2020 — 90% of people living with HIV know their HIV status, 90% with HIV diagnosis receive ART, and 90% have viral suppression, meaning that 73% of all people living with HIV would have supressed viral load — and also to close gaps in HIV testing and treatment [33,190]. UNAIDS also advocated the expansion of migrants' access to HIV related services, to HIV testing and treatment, and also the reduction of social inequalities for these populations [190]. Similarly to UNAIDS, the WHO also created The End TB Strategy covering the period of 2016-2035 [63], and anchored on three

pillars: 1) integrated, patient-centred TB care and prevention (including collaborative TB/HIV activities and management of comorbidities); 2) bold policies and supportive systems (including universal health coverage, social protection and action on TB determinants); and 3) intensified research and innovation [78,81,82,191]. The End TB strategy also specifically addresses the needs of migrants and calls for adaptation at the country level and collaboration with the migration sector [17]. For 2035 there must be a reduction in TB deaths by 95%, in TB incidence rates by 90% (<10 cases per 100 000), and no affected families facing catastrophic costs due to TB [78].

Considering the ambitious targets for the global burden of HIV and TB, and the importance of addressing migrants' vulnerabilities to achieve these goals, the topic and objectives of this work are well contextualized within these global efforts. In this sense, this work ultimately seeks to contribute for the accomplishment of these global health targets by providing evidence that can be a base for future measures to tackle migrants' vulnerability to HIV and TB.

4. Objectives

The overall aim of this research is to contribute to improve knowledge on the burden of HIV, TB and HIV-TB co-infection among migrant populations in Portugal, and on the vulnerability of these populations to these infectious diseases.

The specific objectives established for this research are the following:

1) Describe prevalence and determine sociodemographic, socioeconomic and behavioural risk factors related to HIV, TB and HIV-TB co-infection among migrants
   Study I: "HIV and tuberculosis co-infection among migrants in Europe: A systematic review on the prevalence, incidence and mortality"

   Study II: "Are there opportunities being missed? Burden of HIV, STI and TB, unawareness of HIV and testing among SSAMs" (submitted)

2) Describe clinical and genomic characteristics of migrants with HIV-TB co-infection
   Study III: "HIV and tuberculosis co-infection among migrants in Portugal: sociodemographic, clinical and genomic characteristics" (short communication; submitted)

3) Understand the specificities and barriers related to TB care among migrants with TB or HIV-TB
   Study IV: "Tuberculosis care for migrant patients in Portugal: a mixed methods study with primary care providers"

5. Methodological approaches

This PhD research was based on a multidisciplinary approach to the vulnerabilities of migrant populations in Portugal to HIV, TB and HIV-TB co-infection. In order to accomplish the specific objectives proposed, we relied on different methodologies and sources of data to collect epidemiological, behavioural, clinical, and genomic data, as well as perceptions from primary healthcare providers. Figure 3 briefly summarizes all the methodological approaches used in this research.

MAIN OBJECTIVE:
Contribute to improve knowledge on the vulnerability of migrant populations in Portugal regarding tuberculosis, HIV and HIV-TB co-infection.

	SPECIFIC OBJECTIVE 1 Describe prevalence and determine sociodemographic, socioeconomic and behavioural risk factors related to HIV, TB and HIV-TB co-infection among migrants		**SPECIFIC OBJECTIVE 2** Describe clinical and genomic characteristics of migrants with HIV-TB co-infection	**SPECIFIC OBJECTIVE 3** Understand specificities and barriers related to TB care among migrants with TB or HIV-TB
Studies conducted	**Study 1:** ***"HIV and tuberculosis co-infection among migrants in Europe: A systematic review on the prevalence, incidence and mortality"***	**Study 2:** ***"Are there opportunities being missed? Burden of HIV, STI and TB, unawareness of HIV and testing among SSAMs"***	**Study 3:** ***"HIV and tuberculosis co-infection among migrants in Portugal: sociodemographic, clinical and genomic characteristics"***	**Study 4:** ***"Tuberculosis care for migrant patients in Portugal: a mixed methods study with primary care providers"***
Research strategies used	• Systematic review of observational studies	• Application of a structured questionnaire and of a rapid test for HIV	• Analysis of routine clinical information of HIV-positive patients in Portugal	• Application of a structured questionnaire and semi-structured interviews with primary healthcare providers dedicated to TB care
Sources of data	• Electronic literature databases: MEDLINE®, Web of Science®, Scopus®	• Project "Imigrantes e VIH/SIDA" – financed by Direcção-Geral da Saúde and Programa Nacional para a Infecção VIH/SIDA	• Project "BEST HOPE" (HIVERA/0001/2011) • Project "MigrantHIV" (PTDC/DTP-EPI/7066/2014) • Patients' database from *Laboratório de Microbiologia Clínica e Biologia Molecular, Serviço de Patologia Clínica, CHLO - Hospital Egas Moniz*	• The study was designed, implemmented and data was collected specifically for this research
Outcomes assessed	• Prevalence • Incidence • Mortality	• Sociodemographic characteristics • Sexual practices • HIV serostatus • Self-reported HIV, STIs and TB	• Sociodemographic characteristics • Clinical data • Viral genetic sequences	Perspectives on: • Stage of TB disease upon migrants' arrival to healthcare services • Migrants' difficulties in adherence to TB treatment • Barriers to access and use of TB care by migrants

Figure 3: Methodological approaches to the specific objectives of research.

5.1. Systematic review of literature

A systematic review is a type of literature review with a clearly formulated research question, to which are used explicit methods to identify, select, critically appraise, collect and analyse data from included studies [192]. Systematic reviews have gradually earned importance in biomedical research [193], providing a more scientific and rigorous approach compared to the traditional reviews [194]. A systematic review often includes seven steps: 1) defining a research question; 2) searching and identifying relevant literature; 3) data screening; 4) quality assessment; 5) data extraction; 6) data synthesis; and 7) writing the report [194]. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Statement is the most widely used guideline for systematic reviews [195] and aims to help authors improve the reporting of systematic reviews and meta-analyses. It includes a 27-item checklist and a four-phase flow diagram [192]. It also recommends creating a systematic review protocol that describe the rationale, the hypothesis, and the plan of the review [195].

When defining the research question, one must keep in mind that it must be focused, not too general that makes it difficult to examine such vast amount of literature, and not too narrow that might limit the generalisability of findings [194]. There are several models that can be used to appropriately formulate the research question, such as PICO (population, intervention, comparison and outcomes) and other models such as PEO (patient, exposure and outcome), PIO (patient, intervention and outcome), and SPIDER (sample, phenomenon of interest, design, evaluation, research type) [194,196].

The literature search must be as comprehensive as possible and involve multiple resources [194], in order to minimize bias [193]. However, the resources available to conduct a systematic review are limited, and it is always necessary to find a compromise between a high sensitivity and a low “number needed to read”. Electronic databases are the source of the largest number of articles included in any systematic review on health-related topics [193]. MEDLINE®, Web of Science® or Scopus®, provide an extensive coverage of bibliographic references related to medical fields [197–199]. When conducting searches in several databases, one must take into account that each database has different search fields and indexation keywords, which requires that the search expressions are adjusted to each source. A detailed description of the search expression used in each database must be available to be replicable by others [193].

The screening of reference lists obtained from different sources should be based in clear and sound criteria defined *a priori* in order to guarantee the validity of the review [193]. Therefore, the criteria for inclusion and exclusion in the systematic review must be explicitly stated and consistently implemented such that the decision to include or exclude particular studies is clear [195]. Articles screening must be performed by two independent reviewers [194]. A quantitative measure of agreement between reviewers may be reported; Cohen's kappa is one of the most appropriate statistics for this purpose [195]. Usually a three-step approach to the screening is recommended (Figure 4). The first and second steps are based on the same set of criteria [193]. In the first step only titles and abstracts are screened [193,194]. If the studies are potentially eligible for inclusion in the review, they move to the second step when the full-text version of the study is analysed [193,195], and definite decision on its inclusion or exclusion is made [193]. Step three is based on full reports and involves the assessment of the availability of data in the appropriate format for data synthesis [193]. Data extracted can include title, study purpose, design, main findings, and more details. After data extraction, data synthesis is performed, with tabulation of the studies characteristics [194].

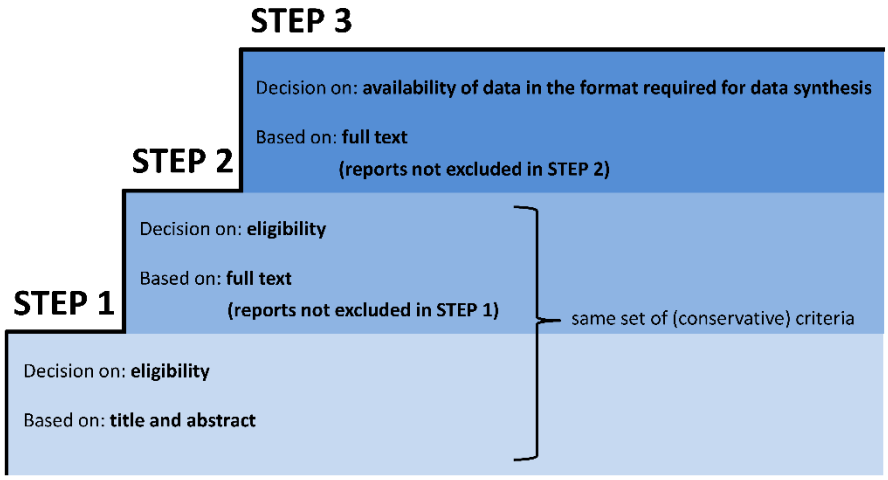

Figure 4. A three-step approach to the screening of bibliographic references in the context of a systematic review [193] (This is an open access article distributed under the terms of the Creative Commons Attribution 3.0 License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited).

As recommended by the PRISMA Statement [192], best practice for systematic reviews is to present a flow diagram to summarize all the process — identification, screening, eligibility, and included studies —, providing a succinct summary of the

number of studies included and excluded at each stage of the process [195]. Statistical methods — meta-analysis — may or may not be used to analyse and summarize the results of the included studies [192]. Frequently, systematic reviews use meta-analysis, combining studies that address the same question, intervention or outcome through statistical methods [194]. However, when participants' characteristics, study designs, exposures/interventions, or measure of outcomes differ meaningfully across studies, the combined estimates are likely to be meaningless, and an analytical rather than synthetic approach is required [193].

5.2. Community-based participatory study with sub-Saharan African migrants

This study was conducted using secondary data from the Research Project "*Imigrantes e VIH/SIDA*" — sociodemographic and socioeconomic characteristics, sexual practices, HIV serostatus, self-reported HIV, self-report of others STI and of TB —, and in collaboration with the research team.

"Imigrantes e VIH/SIDA" Project

The "*Imigrantes e VIH/SIDA*" Project was developed by the Institute of Hygiene and Tropical Medicine (IHMT) with the coordination of Doctor Sónia Dias, and funded by the General Health Directorate (DGS - Direcção-Geral da Saúde) through the National Program for HIV/AIDS infection. This Project consisted of a bio-behavioural study with the application of a structured questionnaire and of a rapid test for HIV. Overall, this research project aimed to: a) estimate the prevalence of HIV among migrant populations; b) identify relevant behaviours for HIV-infection; and c) characterize access and use of healthcare services in the context of HIV/AIDS by migrant populations.

To accomplish the research objectives, a participatory-based approach was used in order to reach sub-Saharan African migrants living in Lisbon region. The community-based participatory research (CPBR) involves equitable collaborative partnerships between researchers and non-academic stakeholders, such as community members, representatives of governmental and non-governmental organizations, incorporating their different perspectives and experiences. By combining research and capacity building strategies, CPBR allows to translate knowledge into interventions that improve

populations' health [200,201]. Furthermore, this close collaboration with community members increase population's adhesion to the study, even the most vulnerable groups. These features make CPBR a useful method to be applied in hard-to-reach populations, as observed in previous studies [34,147]. In the "*Imigrantes e VIH/SIDA*" Project, partnerships were made with non-governmental organizations (NGOs) dedicated to HIV prevention, testing and counselling: the Association for Community Intervention, Social Development and Health (AJPAS – *Associação de Intervenção Comunitária, Desenvolvimento Social e de Saúde*), The Portuguese Association for Prevention and Challenge to AIDS (SER+ - *Associação Portuguesa para a Prevenção e Desafio à Sida*), and The Portuguese Group of Activists for HIV/AIDS treatment (GAT-In Mouraria – *Grupo Português de Ativistas sobre Tratamentos VIH/Sida*).

After performing a geographical mapping to identify possible recruitment sites, a venue-based sampling method was used to recruit participants, including documented and undocumented migrants, as there was no sampling frame allowing us to draw a representative sample [202].

5.3. Cross-sectional study on clinical and genomic characteristics among migrants with HIV-TB co-infection

This study used secondary data from the Research Projects "BEST HOPE" and "MigrantHIV", and from the patients' database of *Laboratório de Microbiologia Clínica e Biologia Molecular, Serviço de Patologia Clínica, Centro Hospitalar Lisboa Ocidental*. A research protocol including background, description of the study objectives and methodologies to be applied was submitted to the Ethics Committee of Centro Hospitalar de Lisboa Ocidental and received ethical approval. Only HIV-positive patients who had a TB diagnosis between 2010 and 2018 were selected, and data on sociodemographic characteristics, clinical data and viral genomic sequences were analysed in collaboration with the research team.

Projects "BEST HOPE" and "MigrantHIV"

The "BEST HOPE" Project (HIVERA/0001/2011) - Harmonizing, Integrating and Vitalizing European Research on HIVAIDS — was funded by the ERA-Net HIVERA (https://www.fct.pt/apoios/cooptrans/eranets/hivera) and conducted between 2014 and 2017. IHMT was one of the partner institutions, and Doctor Ana B. Abecasis was the responsible investigator of the research conducted at IHMT, in particular of work packages (WP) 1 and 5:

- WP1 – "Analyses of HIV-1 transmission chains": provide additional data on recent HIV-1 transmission dynamics in Europe primarily by investigating transmission chains using a highly innovative method;
- WP5 – "Socio-behavioural analysis of transmission dynamics of HIV and hepatitis": collection of socio-behavioural data to analyse patterns of spread and acquisition of HIV and hepatitis co-infection.

Continuing the work performed in the "BEST HOPE" Project, "MigrantHIV" Project (PTDC/DTP-EPI/7066/2014) ― Genomics, socio-behavioural and clinical data to prevent HIV transmission in migrants: an innovative approach" ― was developed at the IHMT under the coordination of Doctor Ana B. Abecasis and was funded by the Portuguese Foundation for Science and Technology (FCT - Fundação para a Ciência e Tecnologia). This Project is a prospective study on HIV newly diagnosed migrants living in Portugal, aiming to understand, model and predict patterns of HIV transmission in migrants, with or without transmission of drug resistance. The Project started in 2016 and is currently ongoing. Data collection on socio-behavioural characteristics and genomic HIV-1 sequences is being performed in collaboration with Hospitals from all over the country.

5.4. Mixed methods study on perspectives from healthcare providers regarding TB care for migrants

Study design

A study on the perspectives of healthcare providers dedicated to TB care was

designed and implemented specifically for the purpose of this research. The study objectives were: 1) characterize specificities regarding TB care to migrant patients with TB or HIV-TB compared to national patients with the same pathologies; and 2) identify barriers to TB care for migrant patients with TB or HIV-TB, namely related to access, provision of care, and healthcare services functioning.

In Portugal, the National TB Program action is mainly in primary care, with Chest Disease Centres (CDCs) — specific facilities for the treatment of respiratory diseases, including TB — as the main primary care facilities involved [203,204]. Therefore, the participants in our study were healthcare providers dedicated to TB care in primary care settings, namely CDCs.

A mixed methods approach was the chosen methodology. The combination of quantitative and qualitative methodologies in a single study is increasingly common [205], being able to enhance and enrich the meaning of a singular perspective, providing a more complete understanding of a problem or complex health topic [205,206]. For the quantitative approach, an online structured, self-administered questionnaire was constructed, introduced in the online platform Survey Monkey®, and was accessible by the participants through a web link. For the qualitative approach, semi-structured interviews were conducted. This type of interviews is frequently used in health related research, and have the advantage of balancing between structure and flexibility; the pre-developed questions are open-ended specifically to the studied topics, but also allow to explore other emerging topics and are flexible regarding the timing when they can be asked [205]. The interviews may be based on an interview guide. These include a brief introduction of the interviewer, of the study, and of the procedures applied; it includes primary open-ended questions organized from the most general to more specific and secondary questions also called "probe questions" intended to explore in-depth the emerging topics — e.g. "Can you talk a little more about your experience?" or "What did you mean by 'xxx'?" [205].

Implementation

A study protocol containing background information, research questions, objectives and the description of the methodologies to be applied was submitted to the Ethics

Committees for Health of the Regional Administrations of Portugal. The quantitative approach was conducted in North, Central, Lisbon, and Alentejo regions of Portugal, after obtaining the approval from the Ethics Committees of the respective Regional Health Administrations. The qualitative approach was conducted in Lisbon region and approval was obtained from the Ethics Committee of Lisbon Regional Health Administration.

In Portugal, primary healthcare services are organized into clusters – Public Health Care Centres Clusters (PHCCs) – that also include the CDCs. Each PHCC is administered by an Executive Director. For implementation of the study, the Executive Directors were contacted through institutional contacts (phone, email, mail) and the study was introduced. The study protocol and the report of approval from the respective Ethics Committees were also provided. A written permission was solicited from the Executive Director allowing the implementation of the study. The study was only implemented at primary care facilities to which permission was granted by the respective Executive Director.

5.5. Analysis of data

Analysis of quantitative data

Quantitative data analysis procedures are essential to determine our study findings. In experimental and survey research, data analysis usually begins with descriptive statistics, followed by inferential statistical tests to examine the research questions or hypotheses [201].

In descriptive statistics, data is usually summarized in three different forms: frequencies (number of occurrences and percentages), measures of central tendency (mean, median, mode), and measures of dispersion (e.g. standard deviation). Inferential statistics usually test the significance of null hypothesis, with significant results providing a p-value under 0.05. Chi-square (χ^2) is an example of a test of significance based on the null hypothesis, used to test the association between two categorical variables [201]. Although with Chi-square we can infer if the variables are dependent or independent of each other, it is not possible to infer the degree of association between the variables [207].

The logistic regression is the most popular multivariable method used in health science [208]. It has become an integral component of any data analysis that aims to describe the relationship between a response variable and one or more explanatory variables (usually called covariates) [209,210], and also enables to calculate the probability of occurrence of an event [208]. The goal of any regression model is to find the best fitting and most parsimonious, clinically interpretable model [210]. The impact of independent variables is usually explained in terms of odds of an event. The odds ratio (OR) is a comparative measure of two odds relative to different events, being OR a measure of association between an exposure and an outcome: OR=1 indicates that exposure does not affect the odds of outcome; OR>1 indicates that exposure is associated with higher odds of outcome; and OR<1 indicates that exposure is associated with lower odds of outcome. The 95% confidence interval (CI) is used to estimate the precision of the OR. A large CI indicates a low level of precision of the OR, whereas a small CI indicates a higher precision of the OR. The 95% CI does not report a measure of statistical significance; however, it can be used as a proxy for the presence of statistical significance if it does not overlap the null value (e.g. OR=1) [208]. To perform a proper logistic regression analysis, some requirements are needed: a) the dependent variable must be discrete, mostly dichotomous; b) the desired outcome should be coded to be 1; c) the model should be fitted correctly, not including meaningless variables, and not excluding meaningful variables; d) variables must not be linear functions of each other; e) the independent variables must be linearly related to the log odds of an event; f) it requires large sample sizes [208].

Analysis of qualitative data

The process of qualitative data analysis is to assemble or reconstruct the data in a meaningful or comprehensible manner, in a way that is transparent, rigorous and thorough, while remaining ‘true’ to participants’ accounts [211]. Thematic analysis approach offers an accessible and accurate form of analysis, without requiring extensive expertise in qualitative research [212]. Overall, the process of thematic analysis can be divided into six phases:

- Familiarization with the data: researchers read through the entire data set at least once before beginning coding;
- Generating initial codes: initial production of codes; requires the researcher to keep revisiting the data and will allow the simplification of data. In this phase is also possible to use a code manual with defined codes prior to the in-depth analysis, which is common when conducting a deductive thematic analysis;
- Searching for themes: sorting and collating all the potentially relevant coded data extracts into themes; if conducting a deductive thematic analysis, coding will be determined by the researchers' theoretical or analytical interest;
- Reviewing themes: researchers review the coded data extracts for each theme to consider whether they appear to form a coherent pattern;
- Defining and naming themes: theme names need to be illustrative of what the theme is about;
- Producing the report [212].

Integration of quantitative and qualitative data

Integration is a key process when using mixed-methods [213]. One of the most difficult challenges is how to integrate different forms of data. The basic concept is that integration of quantitative and qualitative data maximizes the strengths and minimizes the weaknesses of each type of data [214]. Three approaches are possible:

- Merging data: reporting results together in a section of a study, such as reporting first the quantitative statistical results followed by qualitative quotes or themes that support or refute the quantitative results (e.g. using tables or figures that display both the quantitative and the qualitative results);
- Connecting data: involves analysing one dataset (e.g. a quantitative survey), and then using the information to inform the subsequent data collection (e.g., interview questions, identification of participants to interview);
- Embedding data: a dataset of secondary priority is embedded within a larger, primary design (e.g. the collection of supplemental qualitative data about how participants are experiencing an intervention during an experimental trial) [214].

In this research, qualitative data (from study IV) was analysed through Thematic Analysis and further integrated with the quantitative data from the online survey following the "connecting data" approach.

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II. RESULTS

1. HIV and tuberculosis co-infection among migrants in Europe: a systematic review on the prevalence, incidence and mortality

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RESEARCH ARTICLE

HIV and tuberculosis co-infection among migrants in Europe: A systematic review on the prevalence, incidence and mortality

Ana Maria Tavares*, Inês Fronteira, Isabel Couto, Diana Machado, Miguel Viveiros, Ana B. Abecasis, Sónia Dias*

Global Health and Tropical Medicine, GHTM, Instituto de Higiene e Medicina Tropical, IHMT, Universidade Nova de Lisboa, UNL, Lisboa, Portugal

* SFDias@ihmt.unl.pt (SD); ana.tavares@ihmt.unl.pt (AMT)

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Abstract

Background

International human migration has been rapidly growing. Migrants coming from low and middle income countries continue to be considerably vulnerable and at higher risk for infectious diseases, namely HIV (Human Immunodeficiency Virus) and tuberculosis (TB). In Europe, the number of patients with HIV-TB co-infection has been increasing and migration could be one of the potential driving forces.

Objective

This systematic review aims to improve the understanding on the burden of HIV-TB co-infection among migrants in Europe and to assess whether these populations are particularly vulnerable to this co-infection compared to nationals.

Design

MEDLINE®, Web of Science® and Scopus® databases were searched from March to April 2016 using combinations of keywords. Titles and abstracts were screened and studies meeting the inclusion criteria proceeded for full-text revision. These articles were then selected for data extraction on the prevalence, incidence and mortality.

Results

The majority of HIV-TB prevalence data reported in the analysed studies, including extrapulmonary/disseminated TB forms, was higher among migrant vs. nationals, some of the studies even showing increasing trends over time. Additionally, while HIV-TB incidence rates have decreased among migrants and nationals, migrants are still at a higher risk for this co-infection. Migrants with HIV-TB co-infection were also more prone to unsuccessful treatment outcomes, death and drug resistant TB. However, contradicting results also showed lower mortality compared to nationals.

prevent HIV transmission in migrants: an innovative approach' (PTDC/DTP-EPI/7066/2014). This study was supported by funds of the GHTM, through the project "Characterization of Drug-Resistant TB and HIV, and Associated Socio-Behavioural Factors Among Migrants in Lisbon, Portugal". AMT and DM were supported by FCT: grants PD/BD/105916/2014 and SFRH/BPD/100688/2014, respectively. ABA was funded by the Investigador FCT programme. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

Conclusions

Overall, a disproportionate vulnerability of migrants to acquire the HIV-TB co-infection was observed across studies. Such vulnerability has been associated to low socioeconomic status, poor living conditions and limited access to healthcare. Adequate social support, early detection, appropriate treatment, and adequate access to healthcare are key improvements to tackle HIV-TB co-infection among these populations.

Introduction

The number of international human migratory movements worldwide has been growing over the past fifteen years, reaching 244 million in 2015 [1]. Since the 1960s, a steady increase in the number of international migrants coming to and living in Europe has been recorded [2]. Migration is, therefore, recognized as a key component of population change in Europe [3]. In 2015, 1,046,599 migrants arrived to Europe [2], and 76 million international migrants were residing in Europe, a huge increase compared with the year 2000 (56 million) [1].

Due to these increasing numbers, and regardless of the abiding movements and recent social awareness for the human crisis affecting Europe, migrants remain among the most vulnerable members of the European societies [1], and can be at risk for diseases, including infectious diseases, due to poor living conditions or other disparities [3]. In fact, in the European Union, migrant populations are at a greater risk of HIV and/or TB acquisition than the general population [4].

HIV and TB have been influencing each other's natural history and pathogenesis over time, enhancing the magnitude of HIV-TB co-infection epidemic [5]. HIV infection is the strongest known risk factor for developing active TB, which is also the most common opportunistic disease among HIV-infected patients [6]. People living with HIV/AIDS (Acquired Immunodeficiency Syndrome) and infected with *Mycobacterium tuberculosis* (latent TB) are at twenty-times greater risk of developing active TB [6,7], and the intersection of both diseases contributes to a significant higher morbidity and mortality [6].

Globalization and migration from endemic zones have been considered a major drive in the global spread of HIV-TB co-infection [8]. In the European Region of the World Health Organization (WHO), the number of patients with HIV-TB co-infection increased between 2008 and 2014 [9], which some authors attributed partially to migration [10]. Social, economic and political factors in the origin and destination countries influence the risk of migrant populations to HIV acquisition—poverty, separation from sexual partners, different social and cultural norms, language barriers, substandard living and exploitative working conditions, including sexual violence—force many migrants to engage into risky behaviours, increasing the risk for acquiring the infection. Moreover, living and working conditions in the host country (access to health services and social protection), travelling journey to Europe (higher risk in crowded transport vehicles with poorly ventilated spaces plus unhealthy conditions in many migrant camps across the journey), TB incidence in their country of origin and previous contact with an infectious case, are determinant factors for TB infection among migrants [11].

Many countries have made considerable progress in addressing HIV-TB co-infection, but many global targets have not been reached yet [5]. Despite the importance of TB and HIV as public health problems in the European Region of the WHO [7,12], data available is limited on the risk factors for HIV-TB co-infection [12] and the case-reporting is often incomplete [13]. The available information on the HIV-TB co-infection burden among migrants living in

Europe is still limited. This information is crucial to provide a comprehensive view to inform policies and improve adequate care and support to these populations. In this study, a systematic review of literature was conducted aiming to improve the understanding of the burden of HIV-TB co-infection among migrants in Europe and to compare the prevalence, incidence and mortality in this population with nationals in Europe. This systematic review is one of the first addressing specifically on the burden of this co-infection among migrants and the results obtained clearly demonstrate the importance for the national HIV-TB programs to address this reality systematically in order to control the predicted impact on these vulnerable populations and on the national control programs.

Materials and methods

A combination of key words and/or Medical Subject Headings (MeSH) terms was used to find relevant studies. Our search was defined, using specific tools available in the searched databases, to retrieve publications between 2000 and 2016. Only articles with abstracts and written in English, Spanish, French or Portuguese were considered. Books or book chapters, comments, editorials, reviews, guidelines, reports, newspaper articles and case-studies were not included.

The electronic databases MEDLINE®, Web of Science® and Scopus® were systematically searched between March and April 2016 for original articles using search terms presented in S1 Table. MEDLINE® was the first choice since it is one of the largest bibliographic databases focused on medical related fields [14,15]. Scopus® was also searched as it includes also EMBASE® database additionally to MEDLINE® content, plus other journals indirectly related to the medical field [16]. Web of Science® (via https://www.webofknowledge.com) was also included due to its coverage on medical or medically related journals missed by Pubmed and EMBASE® [17].

The titles and abstracts of all documents retrieved were screened by one main reviewer (Ana Maria Tavares—AMT). A second reviewer (Inês Fronteira—IF) performed screening in a random sample of retrieved documents—the minimum sample size was calculated in OpenEpi platform (in www.openepi.com) using an anticipated frequency of 7.6%, for a 95% Confidence Interval (CI)—, in order to access sensibility and specificity of the inclusion criteria [18]. Disagreement between reviewers concerning this sample of documents was solved through reanalysis of the respective titles/abstracts and consensus.

Only the scientific papers meeting the following inclusion criteria were selected: 1) the studied population includes migrant subjects infected with HIV and TB, 2) it provides measures of prevalence, incidence and/or mortality; 3) the study and/or studied population was sampled in one or more European countries (of the 51 independent states [19]); 4) it is an observational study. The following exclusion criteria were defined: 1) articles in which the studied population does not mention human migrants (immigrants, emigrants and others); 2) articles with migrants not living in European countries; 3) articles about infectious diseases other than HIV and/or pulmonary tuberculosis; 4) articles about HIV or TB only, separately; 5) articles about co-infections other than HIV-TB co-infection; 6) articles without the outcomes of interest (prevalence, incidence and/or mortality).

After screening for titles and abstracts, the selected articles proceeded for fulltext review, in which, only articles meeting all inclusion criteria and not meeting any exclusion criteria were considered for data extraction. The data extraction process was performed by one researcher (AMT). Data on the prevalence, incidence and mortality associated with co-infection in migrants and nationals (when available) were extracted. Prevalence of extrapulmonary and/or

disseminated TB and drug resistant TB among HIV-TB co-infection cases were also considered, as well as measures of risk and association related to HIV-TB co-infection in migrants.

For this systematic review no protocol was registered and no quality scoring system was applied.

Results

A total of 746 articles were retrieved from databases (S1 Table) and, after removing duplicates (n = 251), 495 articles remained for title and abstract screening by one main reviewer (AMT). Of these, a sample of 214 articles was randomly selected for titles and abstracts screening by a second reviewer (IF).

During screening, 453 articles were excluded: 292 articles were eliminated after applying the inclusion and exclusion criteria, 54 articles were written in other foreign languages not considered, 85 documents were publication types not considered for this review, and 22 documents lacked an abstract available for screening. After screening, 42 articles remained for full-text revision and, after applying inclusion and exclusion criteria, only 27 articles were retrieved for data extraction. The full details of the articles selection process is summarised in Fig 1.

Characteristics of the studies

The studies included were published between 2003 and 2016, while the sampling for those studies was conducted between 1984 and 2013. Eight European countries were represented: eleven studies conducted in Spain [20–30], five studies in Italy [31–35], three studies in France [36–38], two studies in Portugal [39,40], Germany [41,42], and United Kingdom (UK) [43,44], and one study in Switzerland [45] and The Netherlands [46] (Table 1).

The main study design was retrospective—eight studies [22–24,28,29,39,40,42]—followed by six prospective/cohort studies [34,36,37,41,45,46] (one of them also multicentric [34]), two population-based studies [31,43], one quasi-experimental study [26] and one multicentric study [35]. The remaining studies did not mention the adopted study design [20,21,25,27,30,32,33,38,44] (Table 1). Four studies provided data from national registries [28,33,39,43].

The sample size ranged between studies from 69 [22] to 72580 subjects [36,37]. The included subjects varied between studies: some studies included patients diagnosed with TB [27,28,32,38–40], HIV/AIDS [20,24,36,37,41,46], or HIV-TB co-infection [30,33,34,43]. Other studies included immigrant patients [21,35], immigrant/foreign-born TB patients [26,29,39,42], immigrant/foreign-born HIV patients [22,23,25,45,46], and immigrant/foreign-born HIV-TB patients [42].

Considering the region of origin, Africa was predominant, with higher percentages of immigrants born in Africa in 10 retrieved studies [25,30,33,35–37,39,40,42,46], followed by Latin America [20–22,26,27], and Western/Eastern Europe [38,45] (Table 1).

Prevalence of HIV-TB co-infection among migrants

Prevalence measures of HIV-TB co-infection were reported in 20 of the 27 studies selected in this review (Table 2).

Among these, 10 studies reported prevalence numbers of HIV-TB co-infection in immigrants and nationals [20,21,24,27,32,37–40,44]. Prevalence of co-infection was higher among immigrants than among nationals in 7 studies conducted in France, Portugal, Spain and UK [20,24,37–40,44]—range of 2.8%-85% among migrants vs. 2.3%-30.8% among nationals (Table 2)—, of which, one study was based on national registries from Portugal (2008–2012)

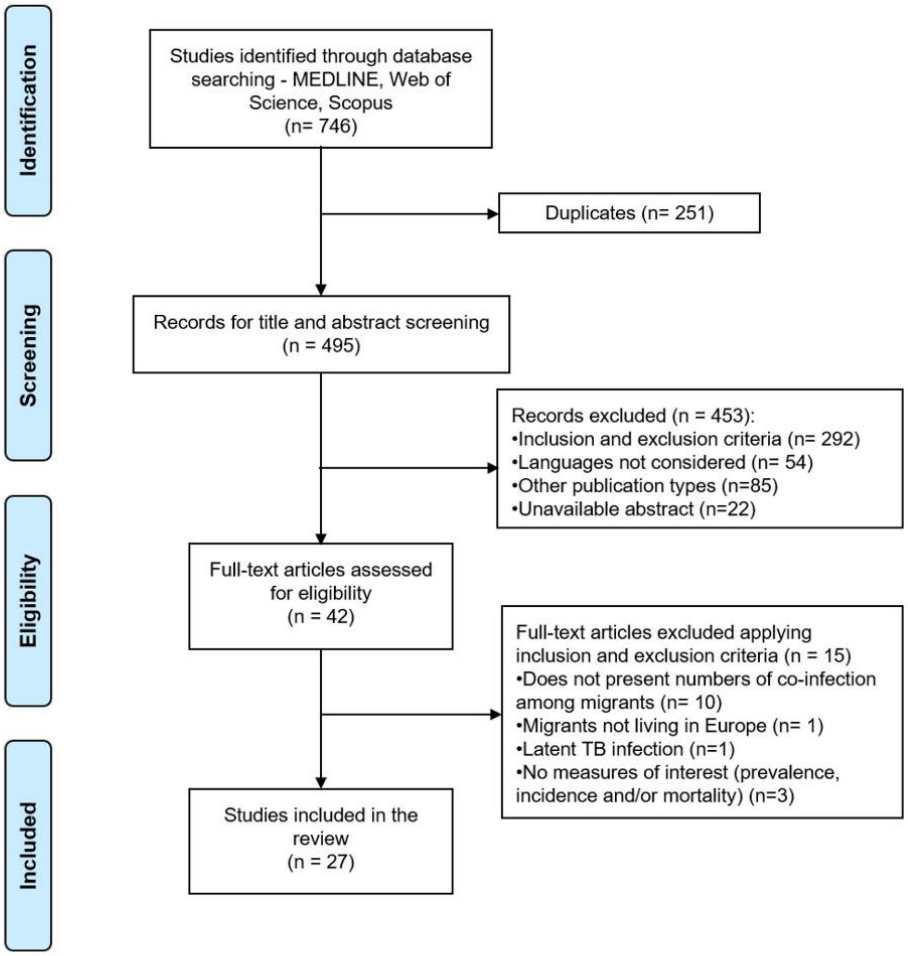

Fig 1. PRISMA flow diagram.

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[39]. Contradictory results were observed in 3 studies [21,27,32]—ranging between 6%-6.8% among migrants vs. 2.3%-37% among nationals (Table 2). Studies including only migrant patients, most conducted in Spain, showed prevalences of HIV-TB co-infection ranging from 1% to 76.6% [22,23,25,26,29,31,35,42,45,46] (Table 2).

Increases in prevalence of HIV-TB co-infection among migrants during data collection periods were reported in 3 studies. In the city of Barcelona, a significant increase was observed in the prevalence of HIV-TB co-infection in migrants, from 6.5% in 1994 to 37.1% in 2004, contrarily to nationals, in which a significant decrease has been observed [24]. Another study in Barcelona also reported a small increase in the prevalence of HIV-TB co-infection among migrants from 8.6% in 2000–2002 to 9.3% in 2003–2005 [26]. This increasing trend was also

Table 1. Main characteristics of the studies included in the review.

First author	Year	Year of data collection	Country	Sample			Type of study
				Type	Nr. Of subjects	Origin	
Abgrall et al. (a) [37]	2010	1997–2008	France	HIV patients	72580	France: 58 089 (80%); SSA: 9095 (12.5%); Others: 5396 (7.5%)	Prospective cohort study
Abgrall et al. (b) [36]	2010	1997–2008	France	HIV patients	72580	France: 58 089 (80%); SSA: 9095 (12.5%); Others: 5396 (7.5%)	Prospective cohort study
Baussano et al. [31]	2006	2001	Italy	New TB immigrant patients	640	EE: 43 (25%); Africa: 89 (52%); LA: 20 (12%); Asia: 13 (8%)	Population-based study
Brindicci et al.[32]	2016	2005–2013	Italy (BAT Province)	TB patients	129	Italy: 85; Immigrants: 44 immigrants [EE: 25 (22.7%); SSA: 10 (22.7%); NA: 6 (13.6%)]	-
Camoni et al.[33]	2012	1993–2010	Italy	HIV-TB patients	4075	Italy: 2685 (65.9%); Immigrants: 1390 (34.1%) (Africa: 55.3%; SA: 29.0%; EE: 7.9%; Asia: 5.7%; Others: 2.1%	-
Caro-Murillo et al. [20]	2009	2004–2006	Spain	HIV patients	2507	Spain: 1793 (71.5%); WE: 93 (3.7%); EE: 42 (1.7%); SSA: 145 (5.8%); NA: 34 (1,4%); LA/Caribbean: 400 (16.0%)	-
Diz et al.[21]	2007	1990–2002	Spain	Immigrant patients	1353	LA: 55%; Africa (37%).	-
Ennemoser et al. [42]	2015	1994–2013	Germany	HIV-TB/TB immigrant patients	47; 46	Africa: 53; Asia: 34; EE: 6	Retrospective study
Eszol et al.[22]	2009	2000–2006	Spain (Alicante)	immigrant HIV patients	69	LA: 38; SSA: 23; EE: 7; NA: 1	Retrospective study
Girardi et al.,[34]	2012	-	Italy	HIV-TB patients	246	Italy: 162; Foreign-born: 84	Multicenter prospective study
Karo et al.[41]	2014	2001–2011	Germany	HIV patients	11693	-	Cohort study
Kesselring et al. [46]	2010	1996–2008	Netherlands	Foreign-born HIV patients	6057	WE/North America: 3947 (65%); SSA: 989 (16%); Southeast Asia: 237 (4%); LA/Caribbean: 695 (11%); Others: 189 (3%)	Cohort study
Llenas-Garcia et al.[23]	2012	1992–2009	Spain (Madrid)	Immigrant HIV patients	371	LA: 197 (53.1%); SSA: 91 (24.5%); Caribbean: 32 (8.6%); EE/Central Asia: 20 (5.4%); Central-WE: 20 (5.4%); NA/Middle East: 9 (2.4%); North America: 1 (0.3%); South and Southeast Asia: 1 (0.3%)	Retrospective study
Martin et al.[24]	2011	1994–2005	Spain (Barcelona)	AIDS patients	3600	Spain: 3279; Immigrants: 321	Retrospective study of prevalence
Meyssonier et al. [38]	2012	1995–2008	France	new TB patients	14610	France: 7481; Foreign-born: 7129 [SSA: 2770 (39%); Maghreb: 2101 (30%); Asia: 1243 (17%); Europe: 695 (9.8%) (EE/Balkans: 308 (44%); Central Europe: 53 (8%); WE: 334 (48%))].	-
Ortega et al.[25]	2007	2001–2005	Spain (Madrid)	Foreign-born HIV patients	78	SSA: 41 (56.9%); SA: 19 (26.4%); Others: 18 (16.7%)	-
Ospina et al.[26]	2012	2000–2002 and 2003–2005	Spain (Barcelona)	Foreign-born TB patients	572 (2000–2002); 388 (2003–2005)	2000–2002 –LA: 202 (35.3%); India/ Pakistan: 136 (23.8%); NA: 92 (16.1%); Others: 142 (24.8%). 2003–2005 –LA: 152 (39.2%); India/ Pakistan: 112 (28.9%); NA: 42 (10.8%); SSA: 16 (4.1%); Others: 66 (17%)	Quasi-experimental study
Paulino et al.[39]	2016	2008–2012	Portugal	native-born TB patients; foreign-born TB patients	4131; 2009	Nationals: 4131; Foreign-born: 2009 [Africa: 1484 (73.9%); SA: 209 (10.4%); EE: 197 (9.8%); Asia: 104 (5.2%); Others: (0.7%)]	Retrospective study

(*Continued*)

Table 1. (*Continued*)

First author	Year	Year of data collection	Country	Sample			Type of study
				Type	Nr. Of subjects	Origin	
Rajamanoharan et al.[44]	2004	2001–2002	United Kingdom	Persons with insecure immigration/ seeking asylum	-	-	-
Ramos et al.[27]	2004	1999–2002	Spain (Elche)	TB patients	105	Nationals: 83; Immigrants: 22 [Morocco: 5 (22.7%); SA: 9 (40.9%); EE: 4 (18,2%); SSA: 4 (18,2%)]	-
Rice et al.[43]	2013	2002–2010	England and Wales	HIV-TB patients	45322	Foreign-born: 3163 (96% - 3163/in 3310 patients co-infected)	Population-based register
Rifes and Villar [40]	2003	1996–2000	Portugal (Amadora)	TB patients	1013	Nationals: 765; Immigrants: 248 [Cape Verde: 107 (43,1%); Angola: 60 (24,2%); Guinea: 40 (16,1%); S.Tome and Principe: 21 (8,5%); Mozambique: 12 (4,8%); Timor: 1 (0,4%); Others: 7 (2,8%)	Retrospective study
Rodriguez-Valin et al.[28]	2015	2012	Spain	TB patients	5880	Nationals: 3992; Foreign-born: 1888	Retrospective study
Scotto et al.[35]	2006	2003	Italy	immigrant patients	2392	Africa: 145 (48.3%); Asia: 60 (20%); EE: 61 (20.3%); SA: 34 (11.3%)	Multicentric study
Staehelin et al. [45]	2003	1989–2001	Switzerland	HIV immigrant patients	11872	Northwestern Europe: 9420 (79%); SSA: 671 (6%); Others: 1781 (15%).	Prospective national cohort study
Supervía et al. [29]	2015	2006–2012	Spain (Barcelona)	new TB immigrant patients	94	Asia: 49; LA: 45	Retrospective descriptive study
Velasco et al.[30]	2008	1984–2000	Spain (Madrid)	HIV-TB patients	1284	Nationals: 1185; Immigrants: 99 [Africa: 62.6%; Central/SA: 16.2%; EE: 4%; WE: 14%; Asia: 3%].	-

BAT—Barletta-Andria-Trani; EE- Eastern Europe; LA—Latin America; NA—North Africa; SA—South America; Sub-Saharan Africa—SSA; WE—Western Europe

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observed in the UK in the number of HIV-TB cases either among persons with insecure immigration or seeking asylum, from 45 in 2001 to 78 in 2002 [44].

Ten studies reported prevalence of HIV-TB co-infection per migrants' region of origin [20–24,29,35,42,45,46], namely African [20–24,35,42,45,46], Latin American [20–24,29,35], European [20,22,23,35], and Asian regions [24,35]. The highest HIV-TB percentages were observed in migrants from African regions (range 1%-76.6%) [42,45], particularly migrants from SSA (range 1%-50% [24,45]), followed by migrants from Europe [3.2% (Western Europe) - 42.8% (Eastern Europe) [20,22]], from Asia (36.4% from South Asia/East Asia/Pacific [24]), and from Latin America (range 2% to 31.7% [21,24]) (Table 2).

Concerning the prevalence of various TB forms among HIV infected patients, seven studies reported extrapulmonary and/or disseminated TB cases [20–23,25,30,35], of which, three, all conducted in Spain, compared prevalence between migrants and nationals. Higher percentage of extrapulmonary TB was reported among HIV-infected migrants (75.8% vs. 68.4% in nationals) from 1984 to 2000, however non-significantly [30]. Contradictory results were observed between 1990 and 2002, with a higher rate of disseminated TB among HIV-infected nationals (33%) [21]. However, between 2004 and 2006 a significantly higher percentage of extrapulmonary TB was observed among HIV-infected migrants from Eastern Europe/Russia, Sub-

Table 2. Prevalence of HIV-TB co-infection among national and migrant patients.

References	Year	Country	Sample	Prevalence of HIV-TB cases	
				Nationals—n (%)	Migrants—n (%)
Abgrall et al. (a) [37]	2010	France	HIV patients	1394 (2.4%)	1231 (8.5%)
Baussano et al.[31]	2006	Italy	New TB immigrant patients	NA	32 (5%)
Brindicci et al.[32]	2016	Italy (BAT Province)	TB patients	9.4% HIV-TB (p>0.05)	6.8% HIV-TB (p>0.05)
Caro-Murillo et al. [20]	2009	Spain	HIV patients	41 (2.3%)	4 (2.8%) from SSA; 12 (3%) from LA/Caribbean; 3 (3.2%) from WE
Diz et al.[21]	2007	Spain	Immigrant patients	37%	6% (p<0.001) (14% from Africa, 2% from LA)
Ennemoser et al. [42]	2015	Germany	HIV-TB and TB immigrant patients	NA	47 (51%): (higher proportion of patients from Africa [36 (76.6%]
Eszol et al.[22]	2009	Spain (Alicante)	Immigrant HIV patients	NA	8 (11.6%): 4 (17.4%) from SSA, 1 (2.6%) from LA, 3 (42.8%) from EE.
Kesselring et al. [46]	2010	Netherlands	Foreign-born HIV patients	NA	58 (1%): (higher proportion in patients from SSA vs. WE/North America—3.0% vs. 0.4%)
Llenas-Garcia et al. [23]	2012	Spain (Madrid)	Immigrant HIV patients	NA	36 (9.7%): 13.2% from SSA, 33.3% from North Africa/Middle East, 6.1% from LA, 6.3% from Caribbean, 20% from Central/ WE, 10% from EE/Central Asia
Martin et al.[24]	2011	Spain (Barcelona)	AIDS patients	30.8% (p = 0.02)	37.1% (p = 0.02): 50% from North Africa/Middle East, 50% from SSA, 31.7% from LA/Caribbean, 36.4% from South Asia/ East Asia/Pacific, 29.9% from WE/North America, 45.5% from Europe/Central Asia
Meyssonier et al. [38]	2012	France	New TB patients	6.5%	11%
Ortega et al.[25]	2007	Spain (Madrid)	Foreign-born HIV patients	NA	16 (20.5%)
Ospina et al.[26]	2012	Spain (Barcelona)	Foreign-born TB patients	NA	49 (8.6%) in 2000–2002, 36 (9.3%) in 2003–2005
Paulino et al.[39]	2016	Portugal	Native and foreign-born TB patients	671 (16%)	452 (22%)
Rajamanoharan et al.[44]	2004	United Kingdom	Persons with insecure immigration/ seeking asylum	15% (p<0.001)	85% (p<0.001)
Ramos et al.[27]	2004	Spain (Elche)	TB patients	12 (14.5%) (p = 0.4)	2 (9.1%) (p = 0.4)
Rifes and Villar[40]	2003	Portugal (Amadora)	TB patients	182 (18%)	66 (26.6%)
Scotto et al.[35]	2006	Italy	Immigrant patients	NA	31 (10.3%): 18 from Africa, 8 from LA, 3 from EE, 2 from Asia,
Staehelin et al.[45]	2003	Switzerland	HIV immigrant patients	NA	7 (1%) (from SSA)
Supervía et al.[29]	2015	Spain (Barcelona)	New TB immigrant patients	NA	5 (11.1%) (from LA)

BAT—Barletta-Andria-Trani; EE- Eastern Europe; NA- not applicable; SSA- Sub-Saharan Africa; LA—Latin America; WE—Western Europe

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Saharan Africa, Western Europe, North Africa, and Latin America/Caribbean (9.5%, 5.5%, 4.3%, 2.9%, and 2%, respectively vs. 2.5% in nationals) [20].

In Italy, a study including only migrants reported 13% of lymph node TB, 9.7% of multiple localization TB; 3.2% of osteoarticular TB, 3.2% of central nervous system TB, and 3.2% of intestinal TB in 2003 among HIV-TB infected migrants [35]. In Spain, studies performed in Alicante and Madrid, reported similar figures of disseminated TB—5.8% and 7.7%,

respectively—, from 2000 to 2006 [22,25]. Another study in Madrid reported 37.1% cases of disseminated TB, 14.3% cases of ganglionar TB, 5.7% cases of tuberculous meningitis and 2.9% cases of pleural TB from 1992 to 2009 [23].

Among the included studies, 4 analysed proportion of migrants among co-infected cases [30,33,41,43]: two showing higher percentages of immigrants among co-infected patients [41,43], and two showing increasing trends in the proportion of migrants among co-infected patients during data collection [30,33].

Only a study in France reported prevalence of drug resistant TB among HIV-TB co-infected migrants and nationals, with a significantly higher percentage of resistance to streptomycin, isoniazid, rifampicin among foreign born patients compared to nationals (12.5%, 10.4% and 3.6%, vs. 8.0%, 6.7% and 1.2%, respectively) [38].

Incidence of HIV-TB co-infection among migrants

Incidence rates of HIV-TB co-infection among migrants were reported in 6 studies [24,33,36,37,41,46]. Two studies conducted in France by the same authors on the same patients' cohort reported a higher incidence rate among migrants—1.03/100 person-years; 95% CI: 0.95–1.11 vs. 0.28/100 person-years; 95% CI: 0.26–0.30 in nationals [36,37], despite of a significantly higher proportion of incident cases among nationals—564 (55.6%) vs. 330 (48.6%) in migrants—observed between 1997 and 2008 in one of the studies [37]. In the same two studies, the adjusted incidence rates showed an increase in the incidence of HIV-TB co-infection either among migrants (0.77/100 person-years in 1997; 1.60/100 in 2000; 1.24/100 person-years in 2002; 1.94/100 in 2008) and among nationals (0.46/100 person-years in 1997 person-years; 0.57/100 in 2000; 0.64/100 in 2002; 0.86/100 in 2008) during the study period [36,37]. Similarly, in Italy a higher incidence rate was observed among migrants—2.97/100 000 person years vs. 0.11/100 000 person years among nationals—, with a decrease over time among migrants (5.16/100 000 person-years in 1993 to 1.20/100 000 person-years in 2010) and nationals (0.17 /100 000 person-years in 1993 to 0.05/100 000 person-years in 2010) [33]. In England and Wales, HIV-TB incidence was higher among foreign-born patients in 2002 (42.5/1000 person-years vs. 8.6/1000 person-years among nationals) and 2010 (10.9/1000 person-years vs. 83.3/1000 person-years among nationals), also showing a decline in the HIV-TB incidence between 2002 and 2010 either for foreign-born (decline in 74.3%) or national patients (decline in 61.2%) [43]. A study conducted in Barcelona also showed higher incidence rates among male immigrants aged 29–49 years (15.8 vs. 12.7/100000 national inhabitants aged 20–29 years; 41.8 vs. 37.5/100000 national inhabitants aged 30–39 years; 33.4 vs. 14.7/100000 national inhabitants aged 40–49 years) and female immigrants aged 40–50 years old (7.9 vs. 1.3/100000 national inhabitants aged 40–49 years; 4.7 vs. 0.4/100000 national inhabitants aged 50–59 years), with an average rate decrease of 20% per year between 1994 and 2005 among both nationals and immigrants [24].

Three studies compared the incidence rates within migrants' region of origin. A study conducted in Germany reported a significantly higher incidence density rate of HIV-TB co-infection in patients from Sub-Saharan Africa (1.20/100 vs. 0.21/100 person years in nationals) and other countries (0.52/100 vs. 0.21/100 person years in nationals) between 2001 and 2011 [41]. Similarly, in a study conducted in The Netherlands, the cumulative TB incidence after 7 years of combined antiretroviral therapy (cART) treatment was higher among HIV-positive patients from Sub-Saharan Africa compared with HIV-TB patients from Western Europe/North America (4.5% vs. 0.5%) [46]. A study conducted on the region of Piedmont, Italy, with new cases of TB among immigrant patients, showed annual incidence rate ratios of HIV-TB co-infection among patients from low prevalence countries of 179.3/100 000; 95% CI: 88.7–269.9

population among patients < 50 years, and 681.6/100 000; 95% CI: 212.7–1150.5 population among patients ≥50 years. Among patients from higher prevalence countries the annual incidence rate ratios were of 1139.5/100 000; 95% CI 403.1–1857.9 population among patients <50 years, and no incident cases among patients ≥50 years [31].

Mortality and survival among HIV-TB infected migrants

Mortality and survival measures were reported in four studies [28,30,34,41], all with data on migrants and nationals. A study conducted in Germany from 2001 to 2011 observed a significantly lower survival in co-infected patients from Sub-Saharan Africa, compared to co-infected nationals (93% vs. 99% among nationals) [41]. However, contrasting results were shown previously in a study conducted in Spain from 1984 to 2000, with a significantly better survival of co-infected immigrants (median 8.7 vs. 5.4 years among nationals) and also a significantly lower mortality rate (0.42 vs. 0.45 among nationals) [30]. Another study conducted in Spain in 2012 also showed lower percentage of deaths among immigrant HIV-TB patients (6.99% vs. 8.79% among nationals) [28]. Similarly, a study from Italy reported a lower percentage of deaths among co-infected foreign-born patients (8.3% vs. 17.9% among nationals), however without statistical significance [34].

Indicators and trends of risk and association

Eleven studies reported measures of risk and/or association [22,24,28,31,34,36–39,41,46]. Two studies performed in France between 1997 and 2008 using the same patients' cohort observed twice more risk of TB among HIV-infected migrants—adjusted risk ratio (aRR) = 2.01; 95% CI: 1.79–2.26 [36,37]. An increased risk of HIV-TB from 2000/2001 to 2008 among nationals and migrants was also observed in one of the studies—aRR = 1.85; 95% CI: 1.27–2.70 [37]. Also, a non-significant 21% risk increase among nationals (aRR = 1.21, 95% CI: 0.86–1.70) and a significant 49% risk increase among migrants (aRR = 1.49, 95% CI 1.04–2.14) were observed from 2002–2003 to 2008 in the other study [36].

Three studies evaluated the risk of HIV-TB acquisition considering the regions of origin [31,41,46]. A study conducted in The Netherlands between 1996 and 2008 observed a 5-fold higher risk of HIV-TB among immigrants born in Sub-Saharan Africa compared to immigrants from Western Europe or North America (Hazard ratio (HR) = 5.08, 95% CI: 2.22–11.60) [46]. Similarly, a study conducted in Germany between 2001 and 2011 showed that being born in Sub-Saharan Africa significantly rendered a higher risk for HIV-TB [HR = 4.05; 95% CI: 1.87–8.78 among patients who never started combination antiretroviral therapy (cART) and HR = 5.15; 95% CI 2.76–9.60 among patients on cART], as well as being born in other countries than Germany (HR = 2.22; 95% CI 1.18–4.20 among patients on cART) [41]. A study in the Italian region of Piedmont referred that an HIV-positive status appeared to promote TB among immigrants from low and high prevalence countries, with a higher risk among those originating from low prevalence countries—incidence rate ratio of 51.9; 95% CI: 30.2–89.4 vs. 11.4; 95% CI 5.8–22.5 among those originating from high prevalence countries [31].

Four studies reported associations between migration and HIV-TB co-infection. A study conducted in Barcelona from 1994 to 2005 observed an association between being born in Sub-Saharan Africa and having TB and AIDS defining illness—adjusted odds ratio (aOR) = 2.2; 95% CI: 1.2–4.6 [24]. However, another study from Spain, performed between 2000 and 2006, showed a strong significant association of HIV-TB co-infection with being born in Eastern Europe—OR = 8.55; IC 95%: 1.5–49.4—and a negative association with being born in Latin America—OR = 0.09; 95% CI: 0.01–0.89 [22]. In a study in Portugal conducted between

2008 and 2012, the odds of being a foreign-born TB case among the HIV-positive population was approximately double compared to nationals—OR = 2.137; IC 95%: 1.65–2.77 [39]. Moreover, the abovementioned study conducted in France from 1997 to 2008 observed a higher risk for HIV-TB co-infection among migrants from Sub-Saharan Africa—adjusted risk ratio (aRR): 2.16 (95% CI: 1.88–2.48)—and other regions—aRR: 1.83 (95% CI 1.57–2.14)—, compared to nationals [37].

A study conducted in Italy referred an association between being a migrant with HIV-TB and unsuccessful treatment outcomes (i.e. lost to follow-up, failure, being transferred out, default)—OR = 3.38, 95% CI 1.38–8.29) [34]. Similarly, in a study in Spain a higher association with potentially unsuccessful outcomes and death was observed among co-infected foreign-born patients than in nationals (OR = 1.7; 95% CI: 1.15–2.60 vs. OR = 1.6; 95% CI: 1.09–2.29 and OR = 3.2; 95% CI: 1.53–6.76 vs. OR = 2.7; 95% CI: 1.63–4.54, respectively) [28]. In a study conducted in France, an association between being a migrant with HIV-TB and having TB resistance to streptomycin (OR = 1.6; 95% CI: 1.3–2.0), isoniazid (OR = 1.6; 95% CI: 1.3–2.1) and rifampicin (OR: 2.9; 95% CI: 1.9–4.6) was also observed, whereas co-infection in French-born patients was only associated with rifampicin resistance (OR: 4.7; 95% CI: 2.1–10.5) [38].

Discussion

In this systematic review we investigated the burden of HIV-TB co-infection among migrants comparatively to national populations.

The results have shown that migrant populations are disproportionately affected by HIV-TB co-infection when compared to nationals. The majority of the studies reporting prevalence of HIV-TB co-infection showed significantly higher values among migrants compared to nationals, and some studies also showed a higher prevalence of extrapulmonary/disseminated TB among HIV-infected migrants. Moreover, in all the studies in which prevalence fluctuations of HIV-TB co-infection were shown, most of them conducted in Spain, a more pronounced increasing trend was observed among migrants, whereas a decreasing pattern was observed in some national populations. These results are in line with a 2017 ECDC report, describing an increase in the absolute number of patients with HIV-TB co-infection in the European Region of the WHO from 11652 cases in 2011 to 16380 in 2015 [47]. As previously described in a systematic review conducted in 2011, the increasing trends of HIV-TB co-infection might be related to migration, especially in countries such as Spain and Italy [10], which were also the countries of the majority of our studies. Nevertheless, considering that the comparison of HIV-TB prevalences between nationals and migrants was only performed in 10 of the 20 articles reporting prevalence of HIV-TB co-infection, such findings must be interpreted with caution, as we cannot disregard that different findings could be observed if more studies compared prevalence between the two populations.

When considering the country of origin, the highest prevalences were observed in migrants originating from African regions. It has been documented that HIV epidemic among the communities of sub-Saharan African migrants in Europe partially resembles the magnitude of the HIV epidemics in their home countries [48]. Also, the described reasons underlying the burden of TB among migrants are the interaction of migration from high TB burden countries and the reactivation in host countries [49]. Therefore, these prevalences might be related with origin from high HIV and TB prevalence countries in Africa, especially those from Sub-Saharan region. However, more data regarding regions of origin could provide a clearer view.

The incidence rates of HIV-TB were also shown to be significantly higher among migrant populations, as well as the risk for co-infection, affecting especially those from high prevalence regions, such as Sub-Saharan Africa. In fact, Africa is still the most common origin of

migration to Europe and since the late 1980s there has been a hastening of emigration from this region to Europe [50]. Moreover, the prevalence of HIV-TB co-infection is the highest in the African region [51]. Therefore, it is not unexpected that migrants from Sub-Saharan Africa were observed to be at higher risk of co-infection in the analysed studies, since HIV co-infection has been found to be more likely in TB cases originating from Africa [47].

In this review, many studies reported a decrease in the incidence of HIV-TB co-infection over the data collection period among migrants and nationals. These promising findings may be interpreted as a success of control and prevention measures in Europe. However, a report from WHO refers that the incidence of HIV-TB co-infection has been slowly increasing since 1990 in the WHO European Region, being 2.2/100000 population in 2014 [51]. Therefore, no firm conclusions can yet be drawn based on these findings.

Being a migrant infected with HIV-TB was also associated with unsuccessful outcomes (treatment failure, being transferred out, and others), death and drug resistant TB, the later also observed in a previous review by Hargreaves et al. (2016) [52]. These findings are possibly related with factors influencing patients' adherence to treatment, such as financial and social support, medication burden, side effects, stigma, beliefs and poor communication with health professionals [53]. Some of the studies [28,30,34] also referred that migrants co-infected with HIV-TB seemed to have lower mortality than nationals with the same co-infection. These results are quite contradictory in the light of the disproportionate vulnerability of migrants to HIV-TB observed in the previous results. Similar findings have been documented in a review by Domnich et al. (2012) and associated with the not yet fully understood and paradoxical "healthy migrant" effect—migrant populations may present a better health compared to nationals—, caused by a previous self-selection process prior to migration, in which only healthier and younger subjects are fit for emigration [54]. This effect would cause better chances of survival in case of infection, what could explain the lower mortality rates observed among migrants. However, according to Domnich et al. (2012), the "healthy migrant" effect is a temporary state that diminishes as time passes after immigration, possibly due to the disparities in the access to healthcare, and in the socioeconomic status [54]. These are factors that also might negatively impact the unsuccessful outcomes and TB resistance observed in our study. Although better survival was observed among migrants in this systematic review, Europe is one of the world's regions with higher mortality rates caused by HIV-TB co-infection [55] and, therefore, it is important to understand the role of migration in HIV-TB associated mortality in European countries.

Methodological heterogeneity was observed in analysed studies, especially regarding study design, sample size, sampling procedure and epidemiological outcomes. Such differences rendered a challenging interpretation and comparison between studies.

Limitations of this systematic review must be acknowledged. Given the vast existing number of articles on the HIV, TB and/or migrants subjects, a narrow search strategy was used, very focused on the objectives of this review. MeSH terms were criteriously selected to be used in the MEDLINE® database search, as well as restrictions for titles and abstracts search at Scopus® database. Broader search terms could have also been used in the search expressions, such as "vulnerable populations" and "Europe". We acknowledge that such methodological choices may imply a loss of comprehensiveness in our search. Also, the outcomes observed in the selected studies comprised different data collection periods, some of them taking place before the dawn of the combined antiretroviral therapy in 1996 [56]. In such studies, no distinction was made between data from pre and post-HAART period. No differences were observed when comparing the data from studies conducted before and after the introduction of HAART. Even so, we cannot exclude potential bias in the outcomes assessed in this review. Moreover, many retrieved studies were conducted on a specific region or city and, therefore,

lack epidemiological representativeness of the problem in a certain country. In such cases, only a descriptive synthesis of evidence was possible and the findings must be interpreted only in the context of the represented region.

In this work we have been able to highlight the disproportionate vulnerability of migrants to acquire HIV-TB compared to nationals, a clear trend in the majority of the studies included. Higher prevalence, incidence, unsuccessful outcomes and drug resistance figures were observed among migrants living in European countries. The low socioeconomic status, the poor and overcrowded living and working conditions, malnutrition, substance use induced by marginalization, social exclusion [57], and barriers in the access to health care [58], are well described factors that may contribute for this disproportion between migrants and nationals. In order to tackle such inequities, European health systems must keep their efforts on the early detection and appropriate treatment of these infections among these populations, as well as to guarantee an adequate access to healthcare and efficient social support. Moreover, policies of inclusion and integration of these populations in the host society are of utmost importance in the preventive care of these diseases. Further research should continue on data collection from national registries on the HIV-TB co-infection among migrants, providing information on the epidemiological situation of each European country, and also in interventions to improve the main barriers to health care perceived by migrant patients infected with HIV-TB. Information on length of stay among migrants was also poorly explored in the included studies of this Systematic Review. Therefore, future research should also take into account this variable in order to allow better understanding of how the burden of HIV-TB co-infection varies with time of residency in the host country. This work highlights the importance for the national HIV-TB programs to thoroughly address this problem in order to mitigate the impact on these vulnerable populations and on the national control programs.

Supporting information

S1 Table. Database searches.
(DOCX)

S2 Table. PRISMA checklist.
(DOC)

Author Contributions

Conceptualization: Ana Maria Tavares, Inês Fronteira, Sónia Dias.

Investigation: Ana Maria Tavares, Inês Fronteira.

Methodology: Ana Maria Tavares, Inês Fronteira, Miguel Viveiros, Ana B. Abecasis, Sónia Dias.

Supervision: Sónia Dias.

Visualization: Ana Maria Tavares.

Writing – original draft: Ana Maria Tavares, Inês Fronteira, Sónia Dias.

Writing – review & editing: Ana Maria Tavares, Inês Fronteira, Isabel Couto, Diana Machado, Miguel Viveiros, Ana B. Abecasis, Sónia Dias.

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2. Are there opportunities being missed? Burden of HIV, STI and TB, unawareness of HIV and testing among sub-Saharan African migrants

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Are there opportunities being missed? Burden of HIV, STI and TB, unawareness of HIV and testing among SSAMs

Sónia Dias [1,*], Ana Gama [2], Ana Maria Tavares [3], Vera Reigado [3], Daniel Simões [4], Emília Carreiras [5], Cristina Mora [5] and Andreia Pinto Ferreira [6]

[1] Escola Nacional de Saúde Pública, Centro de Investigação em Saúde Pública, Universidade NOVA de Lisboa; Global Health and Tropical Medicine, GHTM, Instituto de Higiene e Medicina Tropical, IHMT, Universidade Nova de Lisboa, UNL; sonia.dias@ensp.unl.pt; smfdias@yahoo.com
[2] Escola Nacional de Saúde Pública, Centro de Investigação em Saúde Pública, Universidade NOVA de Lisboa; ana.gama@ensp.unl.pt; anafgama@gmail.com
[3] Global Health and Tropical Medicine, GHTM, Instituto de Higiene e Medicina Tropical, IHMT, Universidade Nova de Lisboa, UNL; ana.tavares@ihmt.unl.pt; vaapareigado@gmail.com
[4] GAT - Grupo de Ativistas em Tratamentos; danielsimoes@gatportugal.org
[5] AJPAS - Associação de Intervenção Comunitária, Desenvolvimento Social e de Saúde; ec@ajpas.pt; cm@ajpas.pt
[6] Ser + - Associação Portuguesa para a Prevenção e Desafio à Sida; andreiapferreira@sermais.pt
* Correspondence: smfdias@yahoo.com; Tel.: 00351 217 512 100

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Abstract: Sub-Saharan African migrants (SSAMs) have been disproportionately affected by infectious disease burden. We aimed to identify correlates of HIV, past STI and past TB, as well as examine HIV seropositivity awareness and testing history among SSAMs. A venue-based sample of 790 SSAMs completed a cross-sectional biobehavioral survey on sexual practices, HIV testing and self-reported infectious diseases; a HIV rapid test was offered. Overall, 5.4% of participants were HIV-positive and 16.7% reported a past STI. Odds of being HIV positive or having a past STI were higher among participants with low socioeconomic status and who experienced violence from a partner. Increased odds of having a past STI were also found among long-term migrants and those who reported sexual risk behaviors. In total, 4.1% of participants had TB in the past; these were more likely male and HIV positive. Unawareness of HIV-positive status was notably high (35%). A half of the participants had never been tested for HIV before, including over a third of those who had STI or TB in the past. Efforts are needed to reduce missed opportunities for HIV/STIs prevention and uptake of HIV testing among SSAMs through more integrated care, while addressing social determinants of infectious diseases.

Keywords: sub-Saharan African migrants; HIV; STI; TB; awareness of HIV; HIV testing

1. Introduction

Increased rates of migration to and within Europe in recent years has made migrant health a priority for the region [1,2]. In 2017, 78 million international migrants were residing in Europe [3], and 9 million were originated from African countries [4]. In a number of EU/EEA Member States, subgroups of migrant populations including those originated from African countries are disproportionately affected by infectious diseases as HIV, other STIs and TB [1,5–8]. Due to historical reasons, Portugal has been host country of sub-Saharan African migrants (SSAMs) [9], mostly from Portuguese-speaking African countries [10]. In 2017, a third of the HIV cases diagnosed in the country

(340/1064) were among foreign-born individuals; SSAMs represented 57.6% of those cases (n=196) [11]. Recent data on TB have also shown that the proportion of TB cases among foreign-born individuals in Portugal has been increasing (19% in 2017 vs. 15.9% in 2014) [8,12], yet with no information available on the countries or regions of origin.

The vulnerability of migrant populations to infectious diseases is likely shaped by multilevel factors that increase exposure to risk through their migratory environments [13,14]. The prevalence of infectious diseases as HIV, other STIs and TB has been associated with the high disease burden at the countries of origin [14–16]. Other factors manifest in the host countries and include the poor socioeconomic conditions frequently faced by migrant populations upon arrival and during their stay [11,12,17,18]. The context of socioeconomic disadvantage may also pose barriers to access health services for information, prevention and care, delaying diagnosis and treatment, and increasing the risk for transmission, morbidity and mortality [19–21]. During migration, the separation from partners and the sense of solitude and isolation experienced by many migrants may favor the engagement in risky sexual practices, putting them particularly at increased risk for HIV and STIs [22]. The migration process may also expose individuals to sexual and gender-based violence, often involving unprotected sexual contact [23]. Additionally, having an infectious disease may increase the risk for acquiring other infectious diseases. This is the case of syphilis and gonorrhea that increase the risk of HIV infection [24], and also the case of HIV/AIDS that increase the risk of TB infection, activation or reactivation [25].

Research on infectious diseases and related factors among migrant populations is critical to further understand these populations' health vulnerabilities and inform prevention strategies. However, migrants are often underrepresented in national statistics and research studies [26]. The burden of infectious diseases and related factors among migrants from sub-Saharan African countries in particular has been understudied. This study aimed to identify correlates of HIV, past STI and past TB among a population of SSAMs living in Lisbon, as well as examine awareness of HIV seropositivity and testing history in this population.

2. Materials and Methods

2.1. Study design and participants

A cross-sectional bio-behavioral study was conducted with SSAMs in the Lisbon Metropolitan Area. According to official data, this is the region with the highest concentration of immigrants in the country [10]. A participatory approach was adopted with the active collaboration of non-governmental organizations (NGOs) with years of community work experience in different phases of the study [27].

A venue-based sampling method [28] was used to recruit participants. Methods and procedures used are described in detail elsewhere [29]. Through a formative research in partnership with community members, a geographic and social mapping was developed in Lisbon region to systematically identify and list venues commonly frequented by SSAMs (e.g. associations, neighborhoods, events). Recruitment teams of outreach workers from partner NGOs and migrant peers attended the listed venues to approach potential participants and to invite them to participate in the study. The inclusion criteria were being ≥ 18 years old, being a SSAM, residing in Portugal, and having initiated sexual activity. A total of 790 SSAMs were enrolled in the study.

2.2. Data collection

In brief, data were collected at recruitment sites, in appropriate spaces providing privacy and comfort to the participants. An anonymous structured questionnaire was applied by interviewers. Interviewers were recruited from community-based organization partners and received specific training on the study purpose, data collection procedures and ethical considerations.

After the questionnaire, a finger-stick whole-blood HIV-rapid test was offered to all participants, which was performed by qualified technicians of the partner NGOs. Those with a reactive test were referred to healthcare services for confirmatory testing and linkage to care.

Anonymous participation and confidentiality of data were guaranteed. Informed consent was obtained from all participants. Participants received free condoms and leaflets with information on prevention, testing and treatment. The study was approved by the Ethics Committee of Instituto de Higiene e Medicina Tropical, Universidade Nova de Lisboa.

2.3. Measures

The questionnaire included close-ended questions on sociodemographic characteristics, sexual practices, HIV testing and self-reported infectious diseases. Sociodemographic characteristics included sex, age, educational level, occupation, perceived income and length of stay in Portugal.

Participants who were sexually active in the last 12 months (n=656) were inquired about their sexual practices for this reference period. Sexual practices assessed were number of sexual partners, condom use ("consistent" included the option "always used condom"; "inconsistent" included the options "sometimes" and "never" used condom) and engagement in commercial sex (defined as having received or paid money/goods in exchange for sexual services as a sex worker or as a client). Participants were also asked about experience in their lifetime of physical/emotional violence from a partner and of forced sexual relations.

Participants were asked if they ever tested for HIV and about their current status for HIV infection based on the last HIV testing result. Participants were also asked if they ever had or had not been diagnosed with other sexually transmitted infections (than HIV) and TB in their lifetime. Unawareness of HIV infection was defined as having a reactive HIV rapid test and either reporting a negative or an unknown prior HIV test result in the survey. Those not reporting a positive HIV-status were asked about how they perceived their risk for HIV infection and if they knew where they could get tested.

2.4. Data analysis

Data analysis was performed using IBM SPSS Statistics v.24. Categorical variables were compared using Pearson's $\chi 2$ or Fisher's Exact test when appropriate. Continuous variables were compared using ANOVA test. Bivariable regression analyses were performed to estimate the crude odds ratios (OR) and 95% confidence intervals (CI) of factors associated with having a reactive test for HIV, with having other STI in the past and with having TB in the past. Variables significantly associated ($P<0.05$) were included in the multivariable analyses. Multivariable logistic regression analyses were performed to estimate the adjusted odds ratios (aOR) and 95% CI of factors associated with HIV reactive test, with past STI and with past TB.

3. Results

3.1. Description of the study participants

The characteristics of the participants are presented in Table 1. Overall, 58.0% of participants were male and the mean age was 38.4 years. Most participants perceived their income as insufficient (77.3%), were non-employed (64.3%) and about 46% had intermediate education (5th-9th grade). Almost 35% were living in the country for 6-15 years.

Of the participants who were sexually active in the last 12 months (n=656, 83.2% of the total sample), the great majority used inconsistently condom (82.5%) (Table 1). Almost a fourth reported ≥3 sexual partners and 10.8% engaged into commercial sex (Table 1). Inconsistent condom use was more frequent among women (89.7% vs. 77.7% among men, $p<0.001$), those reporting only one sexual partner (84.8% vs. 76.6% among those reporting ≥3 partners, $p<0.1$), and those who did not engage in commercial sex (84.3% vs. 67.6% among those who engaged in commercial sex, $p<0.001$) (data not shown in table). Inconsistent condom use was independent of age, educational level, occupation, length of stay in Portugal, experience of violence and experience of forced sex.

Overall, 21.9% of the participants reported experience of violence from a partner and 9.6% reported forced sex (Table 1). Reported violence was significantly more prevalent among women (30.4% vs. 15.7% among men, $p<0.001$), those with insufficient income (24.9% vs. 11.7% among those with sufficient income, $p<0.001$), with ≥3 sexual partners (27.9% vs. 18.4% among those with one

142 sexual partner, p=0.037), and who engaged in commercial sex (31.0% vs. 19.3% among those who did
143 not engage in commercial sex, p=0.022). Half of participants (49.4%, n=376) did not perceive being at
144 risk for HIV infection (data not shown in table).
145 Overall, 49.7% of participants were never tested for HIV (Table 1); of these, almost three quarters
146 (72.6%, n=275) did not know where they could get tested (data not shown in table).

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Table 1. Bivariable analysis of sociodemographics, sexual behaviors and infections correlated with HIV reactive test, past STI and past TB.

		HIV reactive (n=790)			Past STI (n=790)			Past TB (n=790)		
	n (%)	n (%)	OR (95% CI)	P	n (%)	OR (95% CI)	P	n (%)	OR (95% CI)	P
		43 (5.4)			132 (16.7)			32 (4.1)		
Sociodemographics										
Age (years, mean ± SD) (n= 790)	38.4 ± 14.5	50.2 ± 11.2	**1.06 (1.03-1.08)**	**<0.001**	40.6 ± 13.6	1.01 (0.99-1.03)	0.063	46.3 ± 13.5	**1.04 (1.01-1.06)**	**0.002**
Sex (n= 790)										
Male	458 (58.0)	20 (4.4)	1		82 (17.9)	1		26 (5.7)	1	
Female	332 (42.0)	23 (6.9)	1.63 (0.88-3.02)	0.120	50 (15.1)	0.81 (0.55-1.19)	0.291	6 (1.8)	**0.31 (0.12-0.75)**	**0.010**
Educational level (n= 790)										
Secondary/Higher	219 (27.7)	5 (2.3)	1		39 (17.8)	1		10 (4.6)	1	
Intermediate	361 (45.7)	14 (3.9)	1.73 (0.61-4.86)	0.301	58 (16.1)	0.88 (0.57-1.38)	0.586	9 (2.5)	0.72 (0.31-1.69)	0.457
Primary/no education	210 (26.6)	24 (11.4)	**5.52 (2.07-14.8)**	**0.001**	35 (16.7)	0.92 (0.56-1.52)	0.754	13 (6.2)	1.87 (0.75-4.68)	0.180
Occupation (n=790)										
Employed	282 (35.7)	9 (3.2)	**1**		39 (13.8)	1		5 (1.8)	1	
Non-employed	508 (64.3)	34 (6.7)	**2.18 (1.03-4.60)**	**0.042**	93 (18.3)	1.40 (0.93-2.10)	0.107	27 (5.3)	**3.11 (1.18-8.17)**	**0.021**
Perceived income (n= 790)										
Sufficient	179 (22.7)	4 (2.2)	1		14 (7.8)	1		5 (2.8)	1	
Insufficient	611 (77.3)	39 (6.4)	**2.98 (1.05-8.46)**	**0.040**	118 (19.3)	**2.82 (1.58-5.04)**	**<0.001**	27 (4.4)	1.61 (0.61-4.24)	0.336
Length of stay in the country (n= 790)										
≤ 5 years	155 (19.6)	7 (4.5)	1		14 (9.0)	1		2 (1.3)	1	
6-15 years	276 (34.9)	10 (3.6)	0.80 (0.30-2.13)	0.648	49 (17.8)	2.17 (1.16-4.08)	0.016	11 (4.0)	3.18 (0.70-14.5)	0.136
16-25 years	91 (11.5)	3 (3.3)	0.72 (0.18-2.86)	0.641	9 (9.9)	1.10 (0.46-2.67)	0.823	3 (3.3)	2.61 (0.43-15.9)	0.299
>25 years	268 (33.9)	23 (8.6)	1.99 (0.83-4.74)	0.123	60 (22.4)	**2.90 (1.56-5.40)**	**0.001**	16 (6.0)	**4.86 (1.10-21.4)**	**0.037**
Sexual practices										

Number of sexual partners (last 12 months; n=655)										
1	376 (57.4)	18 (4.8)	1		53 (14.1)	1				
2	125 (19.1)	3 (2.4)	0.48 (0.14-1.69)	0.258	24 (19.2)	1.45 (0.85-2.46)	0.172	-	-	-
≥3	154 (23.5)	6 (3.9)	0.81 (0.31-2.07)	0.655	42 (27.3)	**2.28 (1.44-3.61)**	**<0.001**	-	-	-
Condom use (last 12 months, n= 656)										
Consistent	115 (17.5)	10 (8.7)	1		12 (10.4)	1		-	-	-
Inconsistent	541 (82.5)	17 (3.1)	**0.34 (0.15-0.76)**	**0.009**	107 (19.8)	**2.12 (1.12-3.99)**	**0.021**	-	-	-
Engaged into commercial sex (last 12 months; n= 656)										
No	585 (89.2)	22 (3.8)	1		99 (16.9)	1		-	-	-
Yes	71 (10.8)	5 (7.0)	1.94 (0.71-5.29)	0.196	20 (28.2)	**1.93 (1.10-3.37)**	**0.022**	-	-	-
Experience of violence from partner ever (n= 790)										
No	617 (78.1)	28 (4.5)	1		83 (13.5)	1		-	-	-
Yes	173 (21.9)	15 (8.7)	**2.00 (1.04-3.83)**	**0.037**	49 (28.3)	**2.54 (1.70-3.81)**	**<0.001**	-	-	-
Experience of forced sexual relations ever (n= 789)										
No	713 (90.4)	37 (5.2)	1		105 (14.7)	1		-	-	-
Yes	76 (9.6)	6 (7.9)	1.57 (0.64-3.84)	0.327	27 (35.5)	**3.19 (1.91-5.33)**	**<0.001**	-	-	-
HIV testing										
HIV reactive (n=790)										
No	747 (94.6)	-	-	-	124 (16.6)	1	0.732	21 (2.8)	1	
Yes	43 (5.4)	-	-	-	8 (18.6)	1.15 (0.52-2.54)		11 (25.6)	**11.9 (5.29-26.7)**	**0.001**
Ever tested for HIV (n=763)										
Yes	384 (50.3)	36 (9.4)	-		80 (20.8)	**1**		17 (4.4)	1	
No	379 (49.7)	6 (1.6)	-	-	49 (12.9)	**0.56 (0.38-0.83)**	**0.004**	12 (3.2)	0.71 (0.33-1.50)	0.365

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149 *3.2. HIV, other STI and associated factors*

150 Forty-three (5.4%) participants had a reactive test for HIV and 132 (16.7%) reported a past STI
151 (Table 1). Of the HIV-positive participants, 8 (18.6%) had other STI in the past.
152 In the bivariable analysis, prevalence and odds of being HIV positive increased by age (OR 1.06,
153 95%CI 1.03-1.08; p<0.001), were higher among those with primary/no education (OR 5.52, 95%CI 2.07-
154 14.8; p=0.001), non-employed (OR 2.18, 95%CI 1.03-4.60; p=0.042), with insufficient income (OR 2.98,
155 95%CI 1.05-8.46; p=0.040), and those who experienced violence from a partner (OR 2.00, 95%CI 1.04-
156 3.83; p=0.037) (Table 1). The prevalence and odds of being HIV positive were lower among
157 participants who reported inconsistent condom use (OR 0.34, 95%CI 0.15-0.76; p=0.009) (Table 1). In
158 the multivariable analysis (Table 2), being HIV positive remained associated with increasing age and
159 experience of violence from a partner. Inconsistent condom use was less likely to be reported by HIV-
160 positive participants.
161 The bivariable analysis showed that prevalence and odds of having other STI in the past were
162 higher among those with insufficient income (OR 2.82, 95%CI 1.58-5.04; p<0.001) and those living in
163 Portugal for >25 years (OR 2.90, 95%CI 1.56-5.40; p=0.001) (Table 1). Of sexual risk factors, participants
164 who reported ≥3 sexual partners (OR 2.28, 95%CI 1.44-3.61; p<0.001), inconsistent condom use (OR
165 2.12, 95%CI 1.12-3.99; p=0.021) and engagement in commercial sex (OR 1.93, 95%CI 1.10-3.37; p=0.022)
166 were almost twice as likely to have past STI, and participants who experienced violence from a
167 partner (OR 2.54, 95%CI 1.70-3.81; p<0.001) and forced sexual relations (OR 3.19, 95%CI 1.91-5.33;
168 p<0.001) were almost three times as likely to have past STI (Table 1). After adjustment, odds of having
169 other STI remained higher among participants with insufficient income, living in the country for >25
170 years, having ≥3 sexual partners, reporting inconsistent condom use, having experienced violence
171 from a partner and having had forced sexual relations (Table 2).

172 **Table 2.** Factors associated with HIV reactive test and past STI.

	HIV reactive		Past STI	
	Adjusted OR (95% CI)	P	Adjusted OR (95% CI)	P
Age (years)	**1.07 (1.03-1.11)**	**<0.001**	1.01 (0.99-1.03)	0.310
Sex				
Male	1		1	
Female	1.83 (0.70-4.74)	0.215	0.96 (0.57-1.61)	0.865
Education				
Continued education	1			
5th-9th grade	2.19 (0.58-8.37)	0.250	-	-
Elementary school or less	1.12 (0.33-3.83)	0.860	-	
Occupation				
Employed	1		-	-
Non-employed	1.98 (0.67-5.86)	0.220	-	
Perceived income				
Sufficient	1		1	
Insufficient	0.62 (0.19-2.07)	0.439	**2.86 (1.48-5.56)**	**0.002**
Length of stay in the country				
≤ 5 years	-		1	
6-15 years	-	-	1.54 (0.77-3.10)	0.221
16-25 years	-	-	0.99 (0.38-2.61)	0.987
>25 years	-	-	**2.16 (1.06-4.38)**	**0.033**
Number of sexual partners (last 12 months)				

1	-		1	
2	-	-	1.50 (0.85-2.65)	0.165
≥3	-	-	**2.06 (1.14-3.70)**	**0.016**
Engaged into commercial sex (last 12 months)				
No	-		1	
Yes	-	-	0.98 (0.49-1.98)	0.965
Condom use (last 12 months)				
Consistent	1		1	
Inconsistent	**0.23 (0.09-0.58)**	**0.002**	**2.61 (1.32-5.17)**	**0.006**
Physical and/or emotional abuse from partner				
No	1		1	
Yes	**2.77 (1.08-7.10)**	**0.034**	**1.80 (1.09-3.00)**	**0.022**
Forced sexual relations				
No	-		1	
Yes	-	-	**2.57 (1.33-4.96)**	**0.005**

3.3. TB and associated factors

Thirty-two (4.1%) participants reported having had TB in the past. Of the HIV-positive participants, a quarter (25.6%, n=11) reported past TB (Table 1).

In the bivariable analysis, prevalence and odds of past TB increased by age (OR 1.04, 95%CI 1.01-1.06; p=0.002), were higher among non-employed participants (OR 3.11, 95%CI 1.18-8.17; p=0.021), those living in Portugal for >25 years (OR 4.86, 95%CI 1.10-21.4; p=0.037) and being HIV positive (OR 11.9, 95%CI 5.29-26.7; p=0.001), and were lower among women (OR 0.31, 95%CI 0.12-0.75; p=0.010) (Table 1). After adjustment, HIV-positive participants and those male remained more likely to have had TB in the past (Table 3).

Table 3. Factors associated with history of TB disease.

	Past TB	
	Adjusted OR (95%	**P**
Age (years)	1.01 (0.99-1.04)	0.349
Sex		
Female	1	
Male	**3.42 (1.29-9.06)**	**0.014**
Occupation		
Employed	1	
Non-employed	1.92 (0.68-5.38)	0.217
Length of stay in the country		
≤ 5 years	1	
6-15 years	2.96 (0.62-14.16)	0.173
16-25 years	2.56 (0.40-16.46)	0.322
>25 years	2.58 (0.54-12.32)	0.235
Reactive test for HIV		
No	1	
Yes	**11.48 (4.55-28.94)**	**<0.001**

3.4. Awareness of HIV status and testing history

Of the HIV-positive participants, 35% (n=15) were unaware of their HIV infection (8 reported not to be infected based on the result of their last HIV test and 7 had never been tested) and 65% (n=28) reported being infected based on the result of their last HIV test. Most of the participants unaware of their HIV-positive status were female (n=8), reported inconsistent condom use (n=9), had only one sexual partner (n=8) and perceived not being at risk for HIV (n=8). Over a third were living in Portugal for ≤5 years (n=6) and the same proportion were living for >25 years (n=6).

Of the HIV-positive participants who reported not to be infected based on their last HIV test, 75% (n=6) reported that their last HIV test was preformed over 12 months prior to the survey, while a quarter (n=2/8) had their last test in the previous year, suggesting a recent infection.

Around 37% (n=49) of participants who had other STI were never tested for HIV; of these, 69.4% (n=34) reported not knowing where to perform the test. Similarly, 37.5% (n=12) of participants who had TB in their lifetime had never been tested for HIV and 58.3% (n=7) of them did not know where to get tested (data not shown in table).

4. Discussion

This study provides valuable data on the burden of infectious diseases and associated factors among sub-Saharan African migrants (SSAMs) in Portugal. Overall, 5.4% of the participants were HIV positive, 16.7% had other STI in the past and 4.1% had TB in their lifetime. The proportion of HIV found among SSAMs in this study was nine times higher than the estimates for the general Portuguese population (0.6%) [30], and was in line with the HIV prevalence observed among SSAMs in other research in Europe [31]. Of the HIV-positive participants, a quarter (25.6%, n=11) reported past TB, which is not surprising considering that HIV is the main risk factor for TB-disease [25]. As shown in previous research, migrant populations are disproportionately affected by HIV-TB co-infection when compared to nationals, with the highest prevalence being observed in migrants originating from African regions [32]. In our study, almost a fifth of HIV-positive participants (18.6%, n=8) had also other STI in the past.

Overall, unprotected sex along with multiple sexual partnerships and engagement in commercial sex were reported by a high proportion of participants. Simultaneous risk behaviors were considerably common among those previously diagnosed with STI. The fact that these participants still engage in risky sexual behaviors, use inconsistently condom and over a third perceived themselves not being at risk for HIV indicate that there may be missed opportunities for prevention of risk behaviors and counselling for behavior change when they are diagnosed with STI.

Even though underreporting cannot be excluded, the fact that over a third of participants with a reactive HIV test result did not report being HIV-positive suggest a high unawareness of HIV serostatus among SSAMs in this study, surpassing some of the EU/EEA countries estimations for undiagnosed HIV in the general population [33]. A small group of HIV-positive participants unaware of their status had been tested for HIV in the previous year, suggesting recent HIV infection. People who are unaware of their HIV infection are estimated to contribute up to 50-90% of new HIV infections [34]. The proportion of study participants who ever tested for HIV was notably low (50.3%) and almost a half of the participants unaware of their HIV-positive status had never tested for HIV. These findings are in line with literature documenting high rates of undiagnosed infection and low rates of HIV testing among migrants [35,36], particularly those from sub-Saharan Africa [31,34]. Overall, our findings reflect insufficient testing, potential barriers to testing or testing services not reaching those most at risk [33]. In this community-based participatory research, the community partners' active involvement in the participants' recruitment, collection of data and provision of HIV rapid test in migrant-friendly community-based settings contributed to a total of 379 out of 790 SSAMs taking the HIV test for the first time and out of 43 participants with reactive test result, 15 became aware of their HIV-status and were referred to health services. This shows that there are

alternative approaches, such as community-based participatory outreach initiatives, with potential to reduce barriers to HIV testing and encourage uptake of testing among these populations, and therefore should be promoted [37]. The high proportions of participants with past STI and past TB never tested for HIV and not knowing where to test indicate that considerable opportunities have been missed for early HIV detection and treatment during contacts with health services, and that integrated care of infectious diseases should be strengthened.

Structural factors related to poor living conditions in the host country were found to influence SSAMs vulnerability to infectious diseases. High proportions of primary/no educational level, non-employed status and low income were found among the study participants and were significantly associated with HIV, past STI and past TB. These findings are consistent with the extensive literature describing the great influence of social and economic vulnerability in the susceptibility to infectious diseases such as STIs [19,38]. Indeed, socioeconomically vulnerable individuals are positioned in society such that they experience a variety of economic, social, gender, and ethnic-based discriminations that constrain individual agency for sexual decision-making. As a result, structurally vulnerable individuals are likely to have more exposure to HIV/STI and a lower capacity to protect against infection [39]. In addition, structural factors have also been documented as hindering healthcare services seeking and access. Structurally vulnerable populations often experience co-occurring mutually reinforcing disadvantages, such as limited access to steady employment, and affordable, quality education, which can be barriers in access to health services and trigger limited opportunities to seek healthcare [39,40].

In this study, experience of violence from a partner and forced sex were persistently associated with HIV infection and past STI. The intersection between intimate partner violence and HIV infection has long been documented [41,42]. We found that suffering from intimate partner violence was more prevalent among women, as also evidenced in other research [43]. It has been demonstrated that gender norms and relational factors, together with fear of suffering further violence can limit a woman's ability to refuse sex or negotiate safer sexual behavior [42,44,45]. Indeed, a significant group of HIV-positive participants unaware of their status were female, had only one sexual partner and had unprotected sex, indicating that their vulnerability is intrinsically connected to their intimate partners' risk behavior. Social hardships can aggravate women's vulnerability by limiting their power and control in the relationship and the use of condom [44]. Women with reduced socioeconomic resources may depend on partners for economic support, which favors exploitative or abusive situations, sometimes comprising sexual violence, including among female SSAMs [46]. Indeed, participants with lower income reported more frequently having experienced violence from a partner. In addition, a significantly higher proportion of study participants who ever experienced violence had multiple partners and engaged into commercial sex. In fact, studies have shown that abused women are more likely to engage in risky sexual behaviors, increasing their chances of becoming infected with STIs [45,47,48].

The length of stay in Portugal was found to be associated with sexually transmitted infections, with migrants residing for longer time being more likely to report past STI, as found in other studies [49,50]. Of the 43 HIV-positive participants, over a half (n=23) were residing in Portugal for ≥25 years. Migration to the countries of destination usually occur at young and active age [51]. Therefore, older migrants are usually living in the host country for a longer time, experiencing long-term exposure to risk factors [52]. Consistently, in other studies, acculturation throughout length of stay was associated with adoption of risky sexual behaviors [53]. But our study also shows that a relevant proportion of the HIV-positive participants (7/43; 16.3%) were residing in Portugal for ≤5 years, and over a third of the HIV-positive participants unaware of their positive status were similarly recent migrants. These findings show that there are migrant subgroups with disparate levels of vulnerability to infectious diseases associated with multiple interrelated factors. While burden of infectious diseases among recent migrants may partially be due to the endemicity in their origin countries, among long-term migrants it may be strongly related to adverse social and living conditions faced during their stay in the host countries [16]. This highlights the complexity of the debate concerning where infectious diseases are acquired, reinforcing that attention must be given to both origin and host countries as

contexts of vulnerability to infectious diseases for migrant populations. In Europe, HIV epidemic among migrants, particularly among those from sub-Saharan African countries, was long assumed to be imported from origin countries with generalized HIV epidemics, which made prevention efforts mostly focused on promotion of HIV testing and early linkage to care [15,31,54]. But as highlighted by other authors, this perception recently changed with increasing evidence of HIV acquisition in Europe [15,31,49]. In the aMASE study, conducted in nine European countries including Portugal, 31% of HIV-infected Africans acquired HIV while living in European host countries, emphasizing the renewed need for primary prevention [55].

In our study, we were also able to identify risk factors associated with TB. Men were more likely to report having had TB in the past, which is consistent with the broad literature on sex differences in TB prevalence [56,57]. In our study, non-employed participants reported more frequently having had TB in the past. Indeed, the poor socio-economic conditions that many migrants face in host countries can increase risk exposure and contribute to differential treatment-seeking behavior, with impact on TB acquisition/reactivation within these communities [58]. In the context of continuing intense migration flows in Europe and given the estimates of high TB incidence in foreign-born populations compared to native populations [56], it has been claimed that migrants and ethnic minorities 'import' TB into the European host countries, being often labelled as carriers of infectious agents [58,59]. In contrast, our findings highlight the influence of complex socio-structural factors to increased vulnerability of migrants to TB, reinforcing that European health systems must keep their efforts to guarantee effective social support, besides adequate access to healthcare, in order to strengthen prevention.

Limitations of this study must be mentioned. As the study sample was not randomly recruited, the results may not reflect the situation of SSAMs in general. Notwithstanding, the recruitment strategy used allowed us to gather a large and diverse sample of SSAMs residing in Lisbon. As the data are drawn from a cross-sectional survey, any inferences about causality are not possible. Participants were asked to report on behaviors over a long duration of time, with possible risk for recall bias. In addition, the use of face-to-face interviews, given the low literacy rate among the study population, may have led to misreporting due to social desirability bias. Nevertheless, in order to minimize potential biases, all interviewers were systematically trained on interview techniques and ethical principles. Self-reported data, in particular on sensitive issues such as HIV status, past STI, past TB and sexual behavior may have potentially resulted in bias. In a worst-case scenario, our data underestimate the burden of infectious diseases and sexual risks among SSAMs.

5. Conclusions

This study demonstrates a high burden and vulnerability to infectious diseases among a SSAM population, and high rates of HIV-infection unawareness. Knowledge of HIV status could help protect people from transmitting HIV unknowingly, from suffering unnecessarily from opportunistic infections, and from dying prematurely with no access to treatment [60]. Further efforts are needed to reduce missed opportunities for HIV/STIs prevention and uptake of HIV testing through community-based outreach initiatives and more integrated care of infectious diseases among SSAMs. Social inequalities are persistently a major factor affecting risk for HIV, STIs and TB, and thus addressing social determinants of infectious diseases must continue a public health priority.

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3. HIV and tuberculosis co-infection among migrants in Portugal: sociodemographic, clinical, and genomic characteristics (short communication)

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Complete List of Authors:	Tavares, Ana; Global Health and Tropical Medicine, GHTM, Instituto de Higiene e Medicina Tropical, IHMT, Universidade Nova de Lisboa, UNL, Rua da Junqueira 100, 1349-008 Lisboa, Portugal Pingarilho, Marta; Global Health and Tropical Medicine, Instituto de Higiene e Medicina Tropical - Universidade Nova de Lisboa Batista, Judite; Laboratório de Microbiologia Clínica e Biologia Molecular, Serviço de Patologia Clínica, Centro Hospitalar Lisboa Ocidental-Hospital Egas Moniz, R. da Junqueira 126, 1349-019 Lisboa, Portugal Study Group, BEST-HOPE Study Group, Portuguese HIV-1 Resistance Viveiros, Miguel; Global Health and Tropical Medicine, GHTM, Instituto de Higiene e Medicina Tropical, IHMT, Universidade Nova de Lisboa, UNL, Rua da Junqueira 100, 1349-008 Lisboa, Portugal Dias, Sónia; Global Health and Tropical Medicine, GHTM, Instituto de Higiene e Medicina Tropical, IHMT, Universidade Nova de Lisboa, UNL, Rua da Junqueira 100, 1349-008 Lisboa, Portugal; Escola Nacional de Saúde Pública, Centro de Investigação em Saúde Pública, Universidade NOVA de Lisboa, Av. Padre Cruz, 1600-560 Lisbon, Portugal Toscano, Cristina; Laboratório de Microbiologia Clínica e Biologia Molecular, Serviço de Patologia Clínica, Centro Hospitalar Lisboa Ocidental-Hospital Egas Moniz, R. da Junqueira 126, 1349-019 Lisboa, Portugal Gomes, Perpétua; Laboratório de Microbiologia Clínica e Biologia Molecular, Serviço de Patologia Clínica, Centro Hospitalar Lisboa Ocidental-Hospital Egas Moniz, R. da Junqueira 126, 1349-019 Lisboa, Portugal; Centro de Investigação Interdisciplinar Egas Moniz (CiiEM), Instituto Universitário Egas Moniz, Caparica, Portugal. Abecasis, Ana; Global Health and Tropical Medicine, GHTM, Instituto de Higiene e Medicina Tropical, IHMT, Universidade Nova de Lisboa, UNL, Rua da Junqueira 100, 1349-008 Lisboa, Portugal
Keywords:	migrants, HIV-TB co-infection, HIV-1 clades, viral load

Table 1. Sociodemographic, clinical and viral genomic characteristics among migrants and natives with HIV and TB diagnoses.

	Total N (%)	Migrants n (%)	Natives n (%)	P-value
Age at TB diagnosis (median (IQR); N=65)	43.0 (35.0-50.5)	42.5 (32.8-53.8)	42.5 (38.0-49.0)	0.989
20-35	17 (26.2)	8 (36.4)	9 (21.4)	
35-50	32 (49.2)	6 (27.3)	26 (61.9)	**0.029**
>50	16 (24.6)	8 (36.4)	7 (16.7)	
Gender (N=67)				
male	48 (71.6)	13 (54.2)	34 (81.0)	**0.021**
female	19 (28.4)	11 (45.8)	8 (19.0)	
Transmission group (N=39)				
Heterosexual	28 (71.8)	15 (88.2)	13 (59.1)	
Homosexual	6 (15.4)	1 (5.9)	5 (22.7)	0.170
IDUs	5 (12.8)	1 (5.9)	4 (18.2)	
CD4+ T cell count (median (IQR); N=67)	123.0 (53.0-285.0)	168.5 (89.8-256.5)	106.5 (49.5-324.5)	0.655
<200 cells/µL	40 (59.7)	13 (54.2)	26 (61.9)	
200-350 cells/µL	14 (20.9)	7 (29.2)	7 (16.7)	0.483
>350 cells/µL	13 (19.4)	4 (16.7)	9 (21.4)	
Viral load (log_{10} copies/mL; median (IQR); N=67)	5.23 (4.66-5.71)	5.25 (4.64-6.03)	5.22 (4.61-5.62)	0.603
HIV strains (N=66)				
B	24 (36.4)	2 (8.7)	13 (31.0)	**0.042**
Non-B[a]	42 (63.6)	21 (91.3)	29 (69.0)	
HIV and TB diagnoses (N=66)				
TB diagnosis before HIV	5 (7.6)	0 (0.0)	5 (11.9)	
Simultaneous diagnoses	42 (63.6)	17 (73.9)	24 (57.1)	0.227
TB diagnosis after HIV	19 (28.8)	6 (26.1)	13 (31.0)	
Had initiated ART at the time of TB diagnosis; N=58)[a]				
Yes	14 (24.1)	5 (22.7)	9 (25.7)	0.799
No	44 (75.9)	17 (77.3)	26 (74.3)	

[a] Includes subtypes A, C, G, F and recombinant forms.
TB – Tuberculosis; IQR – Interquartile Range; HIV – Human Immunodeficiency Virus; ART – Antiretroviral Treatment;

HIV and tuberculosis co-infection among migrants in Portugal: sociodemographic, clinical, and genomic characteristics

A. M. Tavares[1], M. Pingarilho[1], J. Batista[2], BEST HOPE Study Group, Portuguese HIV-1 Resistance Study Group, M. Viveiros[1], S. Dias[1,3], C. Toscano[2], P. Gomes[2,4], A. B. Abecasis[1].

1 Global Health and Tropical Medicine, GHTM, Instituto de Higiene e Medicina Tropical, IHMT, Universidade Nova de Lisboa, UNL, Rua da Junqueira 100, 1349-008 Lisboa, Portugal.

2 Laboratório de Microbiologia Clínica e Biologia Molecular, Serviço de Patologia Clínica, Centro Hospitalar Lisboa Ocidental-Hospital Egas Moniz, R. da Junqueira 126, 1349-019 Lisboa, Portugal

3 Escola Nacional de Saúde Pública, Centro de Investigação em Saúde Pública, Universidade NOVA de Lisboa, Av. Padre Cruz, 1600-560 Lisbon, Portugal.

4 Centro de Investigação Interdisciplinar Egas Moniz (CiiEM), Instituto Universitário Egas Moniz, Caparica, Portugal.

Correspondence: Ana Maria Tavares, Global Health and Tropical Medicine, GHTM, Instituto de Higiene e Medicina Tropical, IHMT, Universidade Nova de Lisboa, UNL, Rua da Junqueira 100, 1349-008 Lisboa, Portugal; Tel: 351 213 652 600; email: ana.tavares@ihmt.unl.pt

Abstract

Objectives: This study aimed to describe sociodemographic, clinical and genomic characteristics of HIV-TB co-infected migrants living in Portugal and to compare with the characteristics of HIV-TB co-infected natives.

Methods: Data from HIV-positive patients diagnosed with a TB infection between 2010 and 2018 in Portugal were accessed from HIV patients databases. HIV-1 subtypes and recombinant forms were determined using genotyping tools. Descriptive statistical analyses were performed, and differences between groups were analyzed through Chi-square or Fisher's Exact tests for categorical variables, and through Kruskal-Wallis or Mann-Whitney tests for continuous variables.

Results: A higher proportion of HIV-TB co-infection was observed among migrant patients (5.7%) compared to natives (4.7%), of which the majority were from sub-Saharan African countries (83.3%). HIV and TB diagnoses were simultaneous for most patients (63.6%), most (73.8%) presenting CD4+ T cell counts below 200 cells/μL. Younger migrants were more likely

to be diagnosed simultaneously for HIV and TB than older migrants. There was a significantly higher proportion of non-B HIV-1 strains among migrants (91.3%) compared to natives (69.0%). A significantly higher viral load was also observed among patients with non-B strains.

Conclusions: Our findings highlight differences in HIV-1 infecting strains when comparing HIV-TB co-infected natives and migrants. Particularly, the differences identified in the HIV-1 viral load can have an important impact on disease transmissibility and pathogenicity. Future studies should continue to investigate the interaction between different HIV strains and Mycobacterium tuberculosis and the consequences for transmission and disease outcomes.

Keywords: migrants; HIV-TB co-infection; HIV-1 clades; viral load

Introduction

The Human Immunodeficiency Virus (HIV) and tuberculosis (TB) are known to be among the ten leading causes of death worldwide. When concurrent infection occurs, both pathogens can potentiate each other's disease progression, substantially contributing to their high incidence and mortality (bell). HIV infection is the greatest risk factor for developing active TB (Kwan), and *Mycobacterium tuberculosis* also accelerates the progression of HIV infection to AIDS [1,2].

In 2017, about 3.9% of those living with HIV in the EU/EEA were infected with TB, of which Portugal was one of the countries with highest proportions of co-infection (11.4%) [3]. Globalization and migration from endemic zones have been referred as important drivers of the global spread of HIV-TB co-infection [2]. However, studies and surveillance data are still scarce on the epidemiology of HIV-TB co-infection among migrant populations.

HIV-1 presents an extraordinary degree of genetic diversity and has been classified based on phylogenetic clustering into groups (M, N, O and P), M group subtypes (A-D, F-H, J and K), sub-subtypes (i.e. A1, A2, F1 and F2), and recombinant forms. Each can present different antiretroviral treatment (ART) response, different disease progression or transmission rates [4,5]. Since its introduction in Europe, the HIV geographical distribution has become quite heterogeneous, with subtype B prevailing in most Western and Central European countries. However, prevalence of non-B viruses has been increasing, mainly due to travel and migration, particularly from sub-Saharan African countries [4]. Despite of this evidence, literature is still scarce on the susceptibility of specific HIV clades to TB and on clinical outcomes in cases of a concurrent TB infection. In this study, we aimed to compare sociodemographic, clinical, and genomic data of HIV-positive migrants and natives with a TB diagnosis.

Methods

Data collection

This study was based on data from the Portuguese HIV-1 database RegaDB from Laboratory of Molecular Biology, Centro Hospitalar de Lisboa Ocidental (CHLO), and on the HIV-1 patients cohort collected during projects BEST HOPE (HIVERA/0001/2011) and MigrantHIV (PTDC/DTP-EPI/7066/2014). RegaDB contains anonymized information of adult HIV-positive patients (≥18 years old), including sociodemographic, clinical and genomic viral data collected

during routine care between May 2001 and December 2018 [6]. The BEST HOPE and MigrantHIV patients database contains information from adult HIV-positive patients, including sociodemographic, clinical and treatment data, data on co-infections such as TB, and genomic viral sequences.

All patients from both databases who had a diagnosis of *Mycobacterium tuberculosis* between 2010 and December 2018 were included in the study. Since RegaDB does not contain information on co-infections, patients from RegaDB with a TB diagnosis were selected by crossing patients' information with data from the *Laboratório de Microbiologia Clínica e Biologia Molecular*, CHLO, in collaboration with the in-house professionals.

For each HIV patient diagnosed with TB within the studied period, the following data was registered: age, gender, country of origin, risk group of HIV transmission, date of HIV diagnosis, date of TB diagnosis, date of ART initiation, HIV-1 partial pol genomic sequence and CD4+ T cell count and viral load measured at the time of the routine resistance test.

This study was approved by the Ethical Committee of Centro Hospitalar de Lisboa Ocidental (302/CES-2018).

Subtyping

HIV-1 subtypes and recombinant forms were determined using Rega HIV-1 Subtyping Tool - Version 3.0 (REGA Institute, Katholieke Universiteit Leuven, Belgique) (http://dbpartners.stanford.edu:8080/RegaSubtyping/stanford-hiv/typingtool/), COMET HIV-1 Version 2.2. (Luxembourg Institute of Health, Stassen, Luxembourg) (https://comet.lih.lu/), and jpHMM (Institute of Microbiology and Genetics, University of Gottingen, Germany) (http://jphmm.gobics.de/) genotyping tools.

Statistical analysis

Descriptive statistical analyses included frequencies and percentages of continuous variables, and median and interquartile ranges (IQR: 25%-75%) of continuous variables. Chi-square and Fisher's Exact tests were used whenever appropriate to compare proportions between categorical variables. Kruskal-Wallis and Mann-Whitney U tests were used whenever appropriate to

compare differences between categorical and continuous variables. All analyses were conducted using IBM SPSS Statistics version 24.

Results

Between 2010 and 2018, 2545 HIV-positive patients were followed in 17 Hospitals. Of these, 1311 provided information on country of origin — 419 were migrants and 892 were born in Portugal. Within this period 67 HIV-positive patients had a TB diagnosis (67/2545, 2.6%). Country of origin was known for 66 patients: 24 were migrants (24/419, 5.7%) and 42 were natives (42/892, 4.7%). Characteristics of the HIV-positive patients with a TB diagnosis are presented in Table 1.

The majority of patients was male, and median age was 43 years (IQR: 35.0-50.5 years) (Table 1). Over a third (n=24; 36.4%) of the patients were migrants, mostly from sub-Saharan African countries (n=20, 83.3%; data not shown in table). A significantly higher proportion of natives were aged 35-50 years old, while a higher proportion of migrants was young (20-35 years old) or aged over 50 (P=0.029). A significantly higher proportion of migrants were also female (P=0.021). Most patients acquired HIV infection through heterosexual intercourse, and this was similar between migrants and natives (Table 1).

Overall, CD4+ T cell counts assessed were low (<200 cells/μL) in the majority of patients (59.7%), with a median of 123.0 cells/μL (IQR: 53.0-285.0 cells/μL). The overall median of viral load was 5.23 $\log_{10}$ copies/mL (IQR: 4.66-5.71 $\log_{10}$ copies/mL). No significant differences were observed regarding CD4+ T cell counts and viral load between migrants and natives (Table 1).

HIV and TB diagnoses were simultaneous for most patients (63.6%), without significant differences between migrants and natives (Table 1). The majority of those who were simultaneously diagnosed for HIV and TB presented CD4+ T cell counts <200 cells/μL (n=31, 73.8%; P=0.006). Among migrants, a significantly higher proportion of simultaneous diagnosis was observed at younger ages (n=8, among those aged 20-35 years; P=0.045) compared with those aged over 35 (n=5) and over 50 (n=4). Natives showed no differences regarding age and the time of TB diagnosis (data not shown in table).

Most patients (75.9%) in our study were not undergoing ART at the time of TB diagnosis. No significant differences were observed between migrants and natives regarding ART at the

time of TB diagnosis (P=0.799). Despite undergoing ART, still 24.1% (n=14) were diagnosed with TB (Table 1).

Most patients in our study were infected with HIV non-B strains (n=42, 63.6%; Table 1). Of these, subtype G was the most frequent (n=24, 57.1%), followed by recombinant forms (n=17, 40.5%) and by subtype C (n=15, 35.7%). Subtype A was the least frequent (n=4, 9.5%) (data not shown in table). Migrants had significantly higher prevalence of non-B viruses compared to natives (P=0.042; Table 1). A significantly higher viral load was observed among patients presenting non-B strains (median of 5.37 $\log_{10}$ copies/mL [IQR: 4.82-5.99]) compared with those with B subtype (median of 5.04 $\log_{10}$ copies/mL [IQR: 3.37-5.41 $\log_{10}$ copies/mL]) (P= 0.017; data not shown in table).

Discussion

In this study, we report a higher proportion of TB diagnosis among HIV-positive migrants, the majority originating from sub-Saharan African countries. Our findings are in line with previous research showing a disproportionate higher burden of HIV-TB co-infection among migrants, particularly among those from sub-Saharan African countries [7], possibly reflecting the epidemiology in their countries of origin [8–10] or, alternatively, higher rates of transmission in their communities in Portugal [11,12].

CD4+ T cell count is a strong predictor of the risk of death in HIV patients with pulmonary complications [13]. In our study, most patients had TB as an AIDS-defining event, as most presented CD4+ T cell counts below 350 cells/μL [14]. Furthermore, the majority was also diagnosed simultaneously for HIV and TB, suggesting that most patients only sought healthcare when TB symptoms appeared. Our findings were similar for migrants and natives concerning the timing of HIV and TB diagnoses. However, simultaneous diagnosis was more frequent among younger migrants. These findings suggest that younger migrants possibly arrived more recently to the country, which has been associated with low access and use of healthcare services [15]. Furthermore, the fact that no differences were observed between younger and older natives regarding the timing of HIV and TB diagnoses also supports this hypothesis. Also noteworthy was the fact that some patients were already on ART when acquired TB infection, and that some also had high CD4+ T cell counts at the time TB infection. These findings highlight the fact that TB disease can also develop among less immunosuppressed HIV-positive patients [16].

Most patients were infected with HIV viruses from non-B strains (63.6%), which is consistent with the overall HIV epidemiology in Portugal, where non-B clades account for about 63% of all HIV infections [4]. Migrants had a significantly higher proportion of non-B strains compared to natives. Attending to HIV-1 world geographical distribution, these findings could lead us to speculate a possible infection at the country of origin, considering that non-B viruses predominate among non-Europeans in Western Europe. However, compared to other European countries, Portugal is quite an exception with evidence of non-B infections transmission within local sexual networks [4]. Therefore, in our study it is not clear whether the infection occurred at the country of origin or within sexual networks in the country of destination. More studies, namely using phylogenetic approaches, are needed to know more about the transmission dynamics of non-B strains among migrant populations in Portugal.

Non-B strains were also more likely to cause higher viral loads in our study, which can increase disease progression and higher probability of transmission [17]. In addition, literature has been also referring the negative effects of TB infection in the rapid HIV disease progression to AIDS, namely by increasing viral genetic heterogeneity, viral load in the blood, and by decreasing CD4+ T cell counts [1,18]. Particular attention is needed for patients infected by non-B viruses, namely migrants and with TB co-infection, as these can have an impact on patients' disease transmission, morbidity and mortality [18,19]. However, more research is still needed on the interaction of HIV genetic variability and TB infection on the disease outcomes among migrants and natives.

Some limitations in our study must be acknowledged. First, the main limitation of this study was the relatively small sample size, which may have limited the extent of our findings. However, considering the small number of patients with HIV-TB co-infection in Portugal [20], we can still provide new evidence on HIV-TB co-infection among natives and migrants; a topic that so far received limited attention in the literature. Second, the cross-sectional nature of our data did not allow us to provide a representative view of the Portuguese context. Lastly, some of the HIV-positive subjects from the accessed databases might have been lost to follow-up or diagnosed with TB disease in other healthcare facilities and, therefore, were not included in this study. Thus, we cannot exclude the possibility that the number of HIV-positive patients with a TB diagnosis is underestimated.

Our study indicates differences in the transmission dynamics of HIV-1 among migrants with HIV-TB in Portugal. Future efforts should continue to investigate the link between different

HIV strains and *Mycobacterium tuberculosis* and the consequences for transmission and disease outcomes.

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4. Tuberculosis care for migrant patients in Portugal: a mixed methods study with primary healthcare providers

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RESEARCH ARTICLE Open Access

Tuberculosis care for migrant patients in Portugal: a mixed methods study with primary healthcare providers

Ana Maria Tavares[1*], Ana Cristina Garcia[1,3], Ana Gama[2], Ana B. Abecasis[1], Miguel Viveiros[1] and Sónia Dias[1,2]

Abstract

Background: Tuberculosis (TB) is still a major global health problem. The increasing number of cases observed among foreign-born populations contrasts with the decreasing trends observed in later years in some high-income countries. Healthcare providers are key interveners in the control of TB and HIV-TB infections. In this study, we aimed to explore the perspectives of healthcare providers working in primary care in Portugal about the provision of TB care for migrant patients with TB or HIV-TB co-infection.

Methods: We applied a mixed-methods approach using an online survey and semi-structured interviews with primary healthcare providers. A total of 120 Portuguese healthcare providers participated in the survey, and 17 were interviewed. Survey and interview data were analysed applying descriptive statistics and thematic analysis, respectively.

Results: Migrants' lack of knowledge on TB disease and its symptoms was the main reason for advanced-stage presentation of cases. Their high mobility and social isolation affect adherence to treatment. The providers also listed several barriers to migrants' access and use of TB care. The most frequently referred were limited socioeconomic resources, complex bureaucracy at the point of access and registration for healthcare services, especially for undocumented migrants, and obstacles for social protection. Providers also advocated more training initiatives on migrants' health, social and cultural contexts, on HIV and TB integrated care, and on TB scientific update for general practitioners and nurses working at primary healthcare centres.

Conclusions: Future efforts should provide measures to overcome social, economic and administrative obstacles to care for TB-infected migrants, and promote regular training initiatives for national healthcare providers in order to raise awareness and facilitate better care to culturally diverse populations with TB.

Keywords: Migrants, Tuberculosis, HIV-TB, Healthcare providers, Mixed methods research

Background

Tuberculosis is one of the top ten causes of death worldwide, causing disease in millions of people each year. In 2017, TB incidence rate in the European Region of the World Health Organization (WHO) was 30/100,000 population [1]. In the context of high-income countries, the number of TB cases has stabilized or even decreased among native-born populations in the last decade. However, among the foreign-born, the number of cases has decreased more slowly or even increased in some countries [2].

In Portugal, 1741 TB cases were notified in 2017, maintaining a trend of 5% decrease per year. The proportion of TB cases among foreign-born individuals has been increasing over the last years: 19% of the total TB cases in 2017 occurred in foreign-born individuals vs. 15.9% in 2014 [3, 4]. In 2016, the proportion of TB cases co-infected with HIV in Portugal was one of the highest within the European Union/European Economic Area [5], and 10.9% of all TB patients tested for HIV were positive [3]. Previous studies in Portugal reported a higher risk for TB infection within areas of greater density of migrants,

* Correspondence: ana.tavares@ihmt.unl.pt
[1]Global Health and Tropical Medicine, GHTM, Instituto de Higiene e Medicina Tropical, IHMT, Universidade Nova de Lisboa, UNL, Rua da Junqueira 100, 1349-008 Lisbon, Portugal
Full list of author information is available at the end of the article

of high prevalence of HIV/AIDS, and of poor living conditions [6]. Furthermore, the foreign-born population living in Portugal increased 6% in 2017 compared to the previous year [7], which raises particular concern in terms of TB control due to migrants' vulnerability to TB and HIV-TB infections [8–10].

Healthcare providers play a critical role in the control of TB and HIV-TB infections, providing close support and supervision to the patients [11]. Previous research on perceptions from healthcare providers about the difficulties in the provision of care to migrant populations described structural disorganization, high workload [12–14], and lack of knowledge about migrants' health issues [13, 15]. In addition, the lack of services adapted to the needs of migrant patients [16], their limited access to care [17, 18], the communication and cultural barriers [12, 14, 18], their low socioeconomic status, and the lack of knowledge about the functioning of healthcare services [18], have been highlighted in the literature. Previous studies addressing the Portuguese healthcare system have also explored perceptions of healthcare providers regarding the delivery of care to migrant patients [19, 20]. However, studies on TB care for migrant patients in Portugal are still lacking. In this study, we aim to explore and describe the perspectives of primary healthcare providers in Portugal and to gain an understanding about the current provision of TB care for migrant patients with TB or HIV-TB co-infection. The findings obtained in this study are expected to contribute to improve the provision of TB care for migrant patients.

Methods

Design and setting

A mixed-methods study was used to obtain an enriched knowledge on the healthcare providers' perspectives and experiences about TB care for migrant patients. The quantitative approach allowed to obtain measurable evidence on providers' perspectives, and the qualitative approach provided a deeper understanding of their perceptions [21]. The study comprised an online survey and semi-structured interviews conducted with healthcare providers working on TB care at primary care services in Portugal, namely at Chest Disease Centres (CDCs).

The National Tuberculosis Program (NTP) regulates and coordinates activities for health promotion and prevention of TB disease, and plans technical requirements for an adequate provision of care. The NTP activities are mainly facilitated in primary care, with CDCs being the main facilities involved in the routine practice [22, 23]. CDCs are healthcare units exclusively dedicated to the diagnosis and treatment of respiratory diseases and are included within Primary Healthcare Centres Clusters (PHCCs). In Portugal, TB treatment procedures are based on the current WHO recommendations [24, 25]: patients follow a daily Directly Observed Therapy (DOT) approach – daily uptake of medication under supervision of a healthcare provider – for a minimum period of 6 months [26]. The healthcare services must ensure the patient receives TB treatment at the healthcare unit closer to his residency, at home, at CDCs, other healthcare facilities, or other location agreed with the patient [27].

Online survey

Sample and data collection

The online survey enrolled healthcare providers working on TB care at primary care services in Portugal, namely at CDCs, in Lisbon, North, Centre, and Alentejo Regions of Portugal. About 84% of the total foreign-born population residing in Portugal in 2017 lived in these regions (over 350 thousand foreign-born individuals) [28]. The studied regions comprised approximately 60 CDCs. In each CDC work 3–4 healthcare providers. A total of 120 healthcare providers were included in the sample, comprising nurses, medical doctors, and diagnosis and therapy technicians [a.1]

The questionnaire was provided through an online survey platform. Intending to reach as much healthcare providers as possible, we sent an email to healthcare services inviting the providers to participate in the study. The providers were asked to access the web link of the survey and to complete the questionnaire. Participants were also asked to forward the email to peers. Out of a total of 185 providers who accessed the survey link, 120 completed the questionnaire. No significant differences were observed between respondents and refusals regarding sociodemographic characteristics (gender, $P = 0.490$; age, $P = 0.693$; occupation, $P = 0.304$; country of origin, $P = 0.610$; experience in TB care, $P = 0.120$; experience with migrant patients, $P = 1.000$).

The instrument included 19 multiple choice items, namely questions on sociodemographic characteristics (gender, age, country of birth), occupational history (occupation, years of professional experience in providing TB care, years of professional experience with migrant patients), practice with migrant patients (proportion of migrant patients consulted daily, stage of TB disease upon arrival to healthcare services, frequency of treatment interruption, difficulties in treatment adherence compared to nationals), barriers to access and use of TB care (cultural and language differences, migrants' knowledge on their rights and duties, socioeconomic status, health services functioning and networking), and perceived competences and needs for training on the provision of TB care for migrant patients, and on planning strategies for treatment adherence. Reminders were sent to the

healthcare services to promote participation. Data were collected from October 2016 to February 2018.

Data analysis

Descriptive statistical analyses were performed to describe healthcare providers' sociodemographic characteristics, occupational history, migrants' TB disease stage upon arrival to healthcare services, their adherence to TB treatment, perceived barriers to access and use of TB care, as well as perceived competences and training needs. Analyses were performed using SPSS Statistics v.24 software (IBM Corporation, New York, USA).

Semi-structured interviews

Sample and recruitment procedure

Semi-structured interviews were conducted with healthcare providers working on TB care at primary care services, namely CDCs, in Lisbon Region. This region was inhabited by more than 182 thousand foreign-born individuals in 2017 (about 43% of the total foreign-born population in Portugal) [28].

A purposive sample of healthcare providers was obtained through snowball sampling [29]. The first contacts were provided by one researcher (ACG) from her network. The healthcare providers were then contacted via phone call or email, informed about the objectives and details of the study and invited to participate on a face-to-face interview. Interviewees were asked to identify other eligible peers. Participants included 17 healthcare providers: 11 nurses and 6 medical doctors (14 women and 3 men).

Data collection

Interviews were conducted from October to December 2017 in primary healthcare facilities or other public locations according to providers' preference and availability. The interview guide included questions about the perceptions on migrants' stage of TB disease upon arrival to healthcare services, adherence to TB treatment and related factors, barriers to access and use of TB care, and perceived competences and training needs to provide TB care to migrant patients. Interviews were audio-recorded upon participants' agreement and informed consent. Each interview was conducted by one researcher (AMT) and lasted on average 45 min. Data collection was conducted until data saturation was reached. All participants were invited to complete a brief questionnaire for sociodemographic characterization.

Data analysis

The interviews were analysed using a thematic analysis approach [30]. Each interview was transcribed and analysed by one researcher (AMT) and whenever doubts emerged during analysis, a discussion was held between two researchers until consensus was reached. The initial categories for the qualitative data analysis were defined based on a preliminary literature review and descriptive analysis of the survey data. These categories further evolved and changed during the analysis of the interviews. Data were converted into segments of relevant information and concepts, then organized into the categories, and the results were analysed and interpreted. Quotes were chosen to illustrate the topics, meanings and contexts provided by the interviewees. To maintain participants' confidentiality, the names of the interviewees and of other providers/institutions were removed from the transcripts. The interviewees were identified in the text by their occupation and their years of professional experience in TB care.

Ethical considerations

Participation was voluntary and informed consent was obtained from all enrolled participants. All information was handled with confidentiality. Each interview was given an anonymised coding number. This study was approved by the Ethics Committees of the Regional Health Administrations of each region where the study was implemented.

Results

The characteristics of the surveyed participants are presented in Table 1. Most participants were women (78.3%), born in Portugal (88.3%) and had 10 years or less (65.0%) of experience in TB care. There were equal proportions (46.7%) of medical doctors and nurses.

Of the 17 interviewees, 14 (82.4%) were women. Ages ranged from 38 to 67 years (mean 53.4 ± 2.3 years). Six providers had 10 years or less of professional experience in TB care, 4 providers had 11 to 20 years of experience and 6 providers had more than 20 years of experience. Three providers had 10 years or less of experience working with migrant patients, 7 providers had 11 to 20 years of experience and 7 providers had more than 20 years of experience.

Migrants' TB disease stage upon arrival to the healthcare services

More than one third of the surveyed participants considered that migrants arrive at healthcare services at an intermediate (39.6%) or advanced stage of TB disease (36.9%), while 23.5% considered that migrants arrive at an early stage. Migrants' unawareness of TB disease and its symptoms was the main factor referred for presentation of advanced disease stage: the interviewees stated that migrants frequently neglect initial symptoms, associating, for example, cough and fatigue with smoking habits and their life style. The patients were also referred to arrive at an advanced stage of disease as a result of

Table 1 Sociodemographic and professional experience characteristics of the surveyed participants

Total		
Characteristic	n	%
Gender ($N = 120$)		
Male	26	21.7
Female	94	78.3
Age (years; $N = 120$)		
20–30	8	6.6
31–40	44	36.7
41–50	30	25.0
> 50	38	31.7
Country of birth ($N = 120$)		
Portugal	106	88.3
Other	14	11.7
Occupation ($N = 120$)		
Medical Doctor	56	46.7
Nurse	56	46.7
Diagnosis and therapy technicians	8	6.6
Professional experience in TB care (years; $N = 117$)[a]		
0–10	76	65.0
11–20	17	14.5
> 20	24	20.5
Professional experience with migrant patients (years; $N = 113$)[a]		
0–10	51	45.1
11–20	30	26.5
> 20	32	28.4
Approximate amount of migrant patients consulted daily[‡] ($N = 120$)		
None	19	15.8
Few (approx. 1 third)	95	79.2
Some (approx. half)	6	5.0
Many (more than half)	0	0.0

[a]Missing values corresponding to non-responses; [‡]Compared with the proportion of patients consulted daily from the general population
TB tuberculosis

being tested first for other pathologies with similar initial symptoms:

> *"Tuberculosis symptoms are similar to other pathologies, thus they first test to see if it is cancer, or something else. They only think of tuberculosis when they have exhausted all hypotheses (…)"* (Nurse, 37).

Some interviewees considered that migrant-specific factors were related to presenting advanced TB disease. Among migrants who develop TB disease prior to migration, the poor living conditions and precarious healthcare services in the country of origin were indicated as responsible for the advanced disease upon arrival to services. Conversely, among settled migrants, the experience of social and economic adversities in the host country, namely poor and/or overcrowded housing, lack of knowledge on hygiene, nutritional deprivation, and limited access to care, may also contribute to an advanced stage of TB disease upon arrival to healthcare services:

> *"Jobs for nationals are so few, even less for these people [migrants], which makes it difficult for them to settle, or when they do, they settle within communities of 50 to 60 people living in apartments intended for 4 (…) so it is a risk. Wet places, poorly ventilated, attics (…)"* (Nurse, 38).

Migrants' adherence to TB treatment

The perceptions of the surveyed providers on migrants' adherence to TB treatment are described in Table 2. Migrant-specific factors, namely the mobility of the patients and their social isolation, were considered by the interviewees as the main reasons for non-adherence to treatment. The return to the country of origin and internal mobility, with frequent changes in addresses and

Table 2 Perceptions on migrants' adherence to TB treatment and on their experienced difficulties compared to nationals

Variables related to TB treatment adherence among migrant patients	Total	
	n	%
Frequency of non-adherence to TB treatment among TB-infected migrants ($N = 88$)[a]		
Rare	24	27.3
Occasional/Frequent	44	50.0
Do not know	20	22.7
Frequency of non-adherence to TB treatment among HIV-TB infected migrants ($N = 88$)[a]		
Rare	26	29.5
Occasional/Frequent	38	43.2
Do not know	24	27.3
Difficulty to complete TB treatment among TB-infected migrants compared to TB-infected nationals ($N = 89$)[a]		
Same/less difficulty	41	46.1
Higher difficulty	31	34.8
Do not know	17	19.1
Difficulty to complete TB treatment among HIV-TB infected migrants compared to HIV-TB infected nationals ($N = 89$)[a]		
Same/less difficulty	37	41.6
Higher difficulty	27	30.3
Do not know	25	28.1

[a]Missing values corresponding to non-responses
HIV Human Immunodeficiency virus, *TB* tuberculosis, *HIV-TB* HIV and TB co-infection

phone contacts, were referred to cause difficulties in follow-up, possibly leading to treatment default:

> *"Since it is a long-term treatment, sometimes they are not able to stay as long as necessary and they leave treatment early. (...) and for us it is a little difficult, since we cannot manage this kind of treatment from the distance (...). They are a little constrained in their ability to stay for the time needed for the treatment."* (Doctor, 15).

The consequent social isolation and lack of family support were referred to hamper treatment adherence and the correct follow-up of the treatment plan:

> *"Without support [from family], or somebody saying 'It is better if you take it [TB medication]', I think it can happen [interruption of treatment]. (...) If the person lives alone (...) maybe will make more mistakes (...), ends up being sloppier."* (Nurse, 12).

Some interviewees reported migrants' difficulties in understanding the treatment plan, sometimes taking the multiple drug therapy throughout the day instead of early in the morning, as recommended. Treatment characteristics and its side effects were also referred to hinder adherence, namely the high pill burden and the long period of treatment. The side effects and the relief of symptoms after initiating treatment were also referred to favour self-perception of cure and uselessness of continuing treatment. Some patients were also referred to interrupt treatment due to incompatibilities of DOT appointments with their working hours.

According to our quantitative findings, the participants did not consider HIV-TB infected migrants more prone to occasional/frequent non-adherence to treatment than those with only TB (43.2% vs. 50.0% among those with only TB, Table 2). In contrast, the interviewees considered that having HIV co-infection can impair treatment adherence as patients have to deal with more time-consuming medical consultations, more tests, and frequent treatment side effects. Noteworthy, some interviewees also perceived treatment adherence to be related with personal and behavioural factors, namely having a non-cooperating personality or addictions (i.e. drugs, alcohol). Moreover, some interviewees mentioned religious constraints to treatment adherence. For instance, motivating Muslim patients to comply with treatment during the fasting hours of Ramadan was particularly difficult.

Some interviewees expressed the need of a legal framework obliging patients to comply with treatment, enabling, for instance, compulsory in-patient care or deportation in cases of continuous non-adherence to treatment.

Barriers to access and use of TB care by migrant patients

Barriers to migrants' access and use of TB care perceived by the surveyed providers are represented in Fig. 1. The most frequently perceived barrier by the surveyed participants was the limited socioeconomic resources of migrant patients (44.4%; Fig. 1). In fact, half of the interviewees considered out-of-pocket payments related to

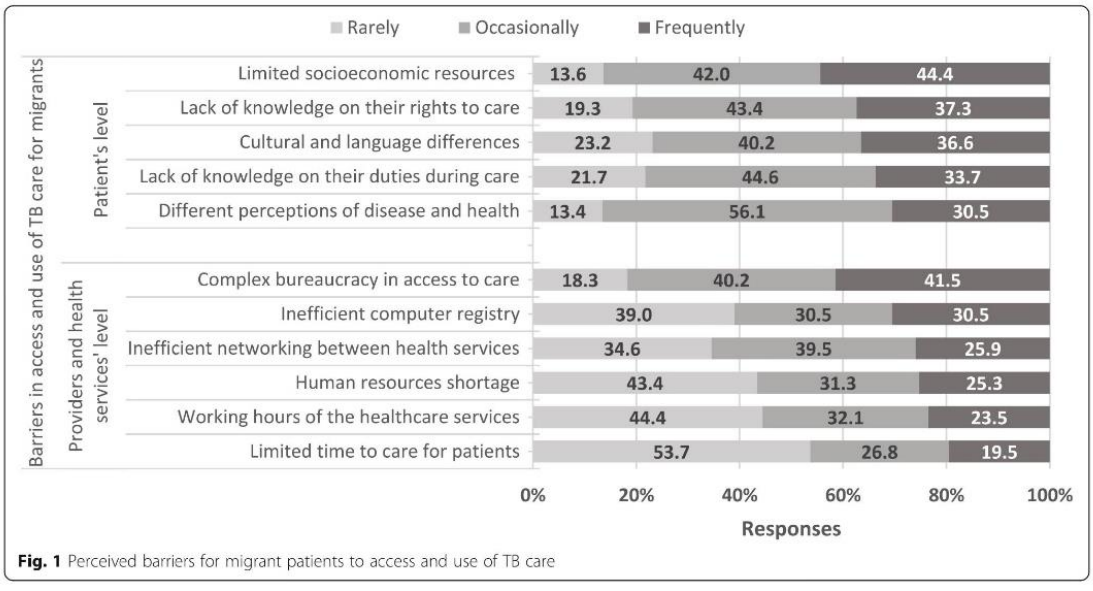

Fig. 1 Perceived barriers for migrant patients to access and use of TB care

transportation as a financial burden for migrant patients. This was particularly burdensome for those with HIV-TB co-infection, who also travel to the hospital for HIV medical appointments. Examples:

> *"These people often have no means to buy anything. We have experienced situations in which they come to take medication and have no money for breakfast. They have no income at all. (…) In many cases, we had to go buy some food and make a basket of goods until the patient received the minimum subsistence"* (Nurse, 8).

> *"Although everything is free of charge, merely travelling to the hospital [for HIV medical appointments] (…) is quite expensive, and sometimes patients have no money for food and even less for treating themselves."* (Nurse, 9).

Also, some interviewees referred patients' concerns related to costs with work absences and delays or with becoming unemployed while on sick leave, particularly among those with unstable non-licensed jobs. The absence of social support mechanisms preventing unemployment and loss of income lead these patients to prioritize their subsistence over their health by returning to work early:

> *"When a patient with an unstable job arrives [at the CDC], we do not let him return to work because he is contagious and might infect other people. We put him on DOT but the State fails to keep his job. It's in the law, but in practical terms, the patient loses his job, and it's not only one case or two (…), they are many! (…) The law exists, but its application doesn't."* (Nurse, 30)

> *"Many of these patients have a job but have never payed contributions [to social security]. So, they have to work to make a living. If they are on sick leave they do not earn any money, and cannot pay their bills (…)".* (Nurse, 9)

A great proportion of the surveyed providers considered the complexity of the bureaucratic procedures a frequent barrier for migrants' access and use of TB care (41.5%; Fig. 1). Most interviewees described difficulties with the bureaucratic procedures during registration at PHCCs, the first step to access primary health care in Portugal. Whenever a patient arrived at a CDC without previous registration at a PHCC, CDC's providers had difficulties in prescribing exams, tests and home health care. The procedures of registration, access and entitlement to co-payments were considered timely and requiring several forms from different public services. Such administrative processes were referred to be difficult for migrants, particularly for those undocumented, since many lack the required elements for the computer-based registration. Accordingly, 30.5% of the surveyed participants considered the computer-based registry a frequent barrier (Fig. 1). These constraints were even observed for undocumented migrants living in Portugal for many decades. Examples:

> *"Everything is increasingly electronic and it is getting more and more complicated to register a patient. We need a VAT number, ID number (…)."* (Doctor, 30).

> *"There is this neighbourhood where we used to provide home health care, people live here [in Portugal] for more than 30 years and are still undocumented. The doctor needed to prescribe an X-ray and she just couldn't."* (Nurse, 3).

One of the most frequently perceived barriers was migrants' lack of knowledge on their rights to health care (37.3%, Fig. 1). Interviewees considered such health illiteracy as an obstacle for recently arrived migrants to navigate through the healthcare system, and was also referred as an obstacle for undocumented migrants to seek health care. Healthcare providers also stated that some migrants needlessly feared being reported to Immigration Services or being deported to their country of origin.

Cultural and language differences were less frequently perceived as barriers by the surveyed participants (Fig. 1). However, most interviewees reported existing communication barriers with migrant patients, sometimes even with migrants from other Portuguese-speaking countries due to linguistic variations of the Portuguese language. Some interviewees described barriers related to social and cultural perceptions of the disease, and stigma towards TB disease among patients and the community.

At healthcare providers' level, workload and understaffing were referred to hamper the accomplishment of relevant tasks, including the provision of home visits to patients. The providers working on TB care at other primary care units than CDCs were referred to have an increased workload, compared to those at CDCs, due to conciliating TB care activities with other routine work tasks:

> *"We feel that healthcare centres lack human resources, there are many tasks to accomplish and they have to care for a variety of situations and pathologies (…) sometimes they are less alert to these kind of situations [TB disease]. I know, for instance, that healthcare*

centres' nurses in charge of TB care have other thousand things to do. (…) Here [CDC] I can provide response because this [TB care] is all I do." (Nurse, years of experience not provided by this participant)

At the healthcare services' level, about half of the interviewees reported increasing barriers for the provision of social protection to TB patients and the need for more social workers placed at the healthcare units. Policy measures implemented during the Portuguese financial crisis were also referred to have reduced the support provided by the social services:

"Our patients used to be much more supported [by the social services]. There used to be specific subsidies for TB patients (…). Almost all patients were entitled to a public transport pass. (…) Even at food level (…) there were institutions helping us to provide food. (…) Now, we are more depending on the goodwill. Do you understand?" (Nurse, 37).

Moreover, inefficient organization of healthcare services and low problem solving capacity, were also reported. Interviewees also stated that communication problems between hospitals and primary care centres, during enrolment and referral, frequently lead to loss of follow-up.

In general, human resources constraints were not perceived as a frequent barrier by many surveyed providers (Fig. 1). However, a significantly higher proportion of providers who do not work with migrants on their daily practice (n = 19, Table 1), perceived human resources shortage as a frequent barrier (54.5%, P = 0.008, data not shown).

Some interviewees expressed the need for more psychological support services for migrant patients, especially for those with HIV-TB co-infection. More pulmonologists at primary care units, as well as adapted in-patient facilities to allow isolation of TB patients, were also suggested.

Competences and training

Perceived competences and training needs of the surveyed providers related with providing TB care to migrant patients are described in Table 3. More than one fifth of the surveyed participants considered their competences and training insufficient to provide adequate and up to date TB care to migrants or to define a treatment adherence strategy for these patients (Table 3). Moreover, when asked about the level of agreement with the following statement: "There is a higher probability of making a mistake when providing care to migrant patients than to the general population"; one third (33.3%) of the surveyed participants agreed, 28.6% provided a neutral response and 38% disagreed (data not shown in table).

Table 3 Competences and training needs perceived by the healthcare providers

Total		
Perceived competences and training needs	n	%
Competences/training to provide TB care for migrant patients (N = 84)[a]		
Insufficient	20	23.8
Neither sufficient or insufficient	14	16.7
Sufficient	50	59.5
Competences/training to define a strategy for treatment adherence in migrant patients (N = 82)[a]		
Insufficient	17	20.7
Neither sufficient or insufficient	17	20.7
Sufficient	48	58.6
Relevance of receiving training about migrants' health (N = 82)[a]		
Relevant	65	79.3
Moderately relevant	7	8.5
Irrelevant	10	12.2
Relevance of receiving training on strategies to improve TB treatment adherence in migrants (N = 82)[a]		
Relevant	64	78.0
Moderately relevant	5	6.1
Irrelevant	13	15.9

[a]Missing values corresponding to non-responses
TB tuberculosis

About half of the interviewees emphasised the relevance of increasing training initiatives for the healthcare workers dedicated to TB care, namely: actions that improve cross-cultural competencies, as well as knowledge on migrants' social and health contexts; training on HIV and TB integrated care for healthcare providers from both specialties; and language training in order to assure providers' proficiency in at least one foreign language. Healthcare providers working on TB care at other primary care units than CDCs were referred to have less experience with TB patients, consequently having a higher perception of TB disease as a hazard to other patients or healthcare providers. Therefore, interviewees considered important to increase updating training and raise awareness to TB disease among all providers in general.

Some interviewees also showed willingness to know more about institutions and public services to which they can refer migrant patients for support. However, scientific update and training initiatives were also considered costly, non-sponsored, and often restricted to certain professional groups — usually the superiors rather than routine service providers in close contact with the patients.

Noteworthy, a significantly higher proportion of providers who do not work with migrants on a daily basis (n = 19, Table 1) considered training on migrants' health

(44.4%, $P = 0.023$), and on strategies to improve treatment adherence in migrants (44.4%, $P = 0.028$) as irrelevant (data not shown in table).

Discussion

This mixed-methods study allowed to gain insight into the perspectives of primary healthcare providers on current provision of TB care for migrants in Portugal. Our findings highlighted several factors hampering the provision of TB care to these populations that need to be addressed. These included factors related to the specific context of migration and also factors affecting the provision of TB care to all patients in general.

Over a third of the surveyed providers referred that migrants entering the healthcare system are frequently in an advanced stage of TB disease, mainly due to their unawareness of the disease and its symptoms. This is in line with the existing literature showing that limited knowledge and understanding about TB causes, symptoms, modes of transmission and treatment deeply influences migrants' health-seeking behaviours [31]. Migrant patients may have differing values, beliefs and concepts of disease and health based on their ethnic and cultural background [32]. The preventive care culture varies from country to country, being sometimes weak or even absent in the countries of origin of many migrants [32]. These cultural factors can shape how people understand signs and symptoms and perceive healthcare needs, delaying care-seeking behaviour [20]. Such delays in prompt TB diagnosis and/or treatment can contribute to onwards transmission of TB within migrant communities [33]. Health campaigns targeted to migrant communities should be promoted to raise awareness towards TB disease and increase health literacy.

In our study, the healthcare providers referred that many migrants struggle to comply with TB treatment, mainly due to their frequent mobility and the absence of family support. Modern migration patterns involve recurrent travels between origin and destination countries, which can increase risk of treatment interruption [31]. This is particularly worrying, given that suboptimal adherence to TB treatment may cause drug resistance [33] and consequently compromise treatment and disease outcomes. In addition, previous studies described the importance of social, emotional and financial support from families and communities on treatment adherence and good treatment outcomes [34–37]. Our findings reinforce that optimal adherence to treatment among migrant patients requires increasing support from family and community members in the treatment process.

Limited socioeconomic resources of migrant patients were referred by the healthcare providers as the main barrier to TB care. Previous studies in Portugal have reported lower access and use of healthcare services among migrants in disadvantaged socioeconomic situation [38, 39]. Other studies on TB care concluded that even when diagnosis and treatment are free of charge, indirect costs, namely related to transportation, loss of income, and productivity, hinder prompt uptake of treatment [37]. Our findings also indicate that the effect of economic constraints for migrants may be exacerbated by the lack of social protection while on treatment. Moreover, political measures taken in the context of the financial crisis in Portugal were referred to impair mechanisms of social protection that used to be available for TB patients with low socioeconomic status. Budget-balancing measures introduced into the social protection system during the financial crisis have tightened the eligibility for social assistance, unemployment benefit, and other protection mechanisms, increasing poverty rates [40]. These constraints surely affected migrant populations disproportionally as they are often socioeconomically more vulnerable [41]. Increasing social protection spending can contribute to reduce loss of income and poverty, improving access and use of TB care and consequently clinical outcomes [42, 43]. In this work, we propose that social protection for migrants must be strengthened and linked to healthcare services. Future political measures aiming to improve TB care efficacy among migrant populations must also target financial support to migrant patients with low socioeconomic status.

In our study, another significant barrier was the complexity of bureaucratic procedures required for migrants to access primary care services, particularly for those with undocumented status. Portugal has been recognized for implementing migrant-friendly policies [41]. By law, migrants in Portugal have the same access to the healthcare system as Portuguese citizens once they obtain a residence permit. Free access to health care is guaranteed in situations of urgent and vital care, communicable diseases, among others. Fees exemption is also granted in situations of public health threat, such as TB or HIV, including for undocumented migrants [41, 44]. However, our study indicates a discrepancy between legislation and its application to health practice. As observed in our study, despite of being entitled to care, some migrants are unaware of their rights and some also fear being deported or reported to Immigration Services, leading to underuse of TB care. These findings are consistent with other studies [45].

Appropriate access to TB care, regardless of the legal status, is crucial for individual's and community's health [33]. With this in mind, barriers should be reduced in order to improve access to the healthcare system and thus ensure prompt diagnosis and treatment. Specifically, the information system should be simplified in order to enable migrants' registration in a more

straightforward and flexible manner and, especially, to ensure compliance with the current legislation. These measures might also improve general patient satisfaction and healthcare providers´ efficiency.

In this study, many healthcare providers perceived having limited competences and training about the social, cultural and health context of migrant patients. In addition, a considerable proportion of the surveyed participants reported low self-confidence in providing TB care for migrants, which can be partially explained by the low number of migrant patients consulted daily. Providers also referred that colleagues working at primary care units other than CDCs often face high workload, conciliating TB care with other routine tasks, and that they could benefit from further training in TB care. Our findings suggest that training on provision of TB care to culturally diverse populations should be supported in the future, in order to enhance optimal performance of healthcare providers [12, 46].

Reaching the global TB targets aligned with the 2030 Agenda for Sustainable Development and as part of the End TB Strategy requires universal health coverage of essential health services, and social protection mechanisms to prevent TB patients from suffering catastrophic costs [47]. The WHO and the International Organization for Migration proposed actions that support personnel cultural competence, culturally sensitive healthcare services, including HIV-TB management, and the implementation of policies that aim to improve migrants' access to health services and to eliminate legal and administrative barriers [31]. Although political measures in Portugal have attempted to follow those recommendations, our study revealed that several barriers to TB care still prevail for migrants. These barriers may compromise migrants´ health, as well as ongoing public health control measures [48–50], and therefore should be mitigated in the future.

We acknowledge some limitations of our study. The limited response rate may have possibly introduced a nonresponse bias. However, similar reduced response rates are commonly observed in studies involving healthcare providers, particularly medical doctors [51]. Likewise, in a recent systematic review on response rates of general practitioners from primary care in Portugal, an average response rate of 56% (95%CI 47–64%) was observed [52]. Furthermore, no significant differences were observed between respondents and refusals concerning their sociodemographic characteristics. Another limitation was the inability to include providers from all regions of Portugal. However, it was possible to include providers from regions in which overall inhabit about 84% of the total foreign-born population [28]. Additionally, we also acknowledge the possibility that providers who agreed to participate in the study shared a particular interest in this research topic, introducing a self-selection bias. Nevertheless, considering the limited number of healthcare providers dedicated to TB care in some of the enrolled primary care settings, the sampling methods used in this study allowed us to reach these providers and to obtain their valuable views.

A strength of this study was the use of a mixed methods approach, which allowed to gain a deeper, broader and richer understanding of the providers' perceptions, compared with either quantitative or qualitative methods alone [53]. This type of approach was particularly valuable for our study considering the reduced number of providers dedicated to TB in primary care, and, most of all, allowed us to collect relevant perspectives from those who are key interveners in the control of TB disease. Moreover, the anonymity and confidentiality guaranteed throughout the study rendered the necessary comfort to participants go deeper into their opinions.

The main relevance of this study is its contribution to increase scientific evidence on the underexplored theme of TB care for migrant patients in the Portuguese context, identifying existing obstacles and highlighting targets for future improvement measures.

Conclusions

This study was, to our knowledge, the first to explore the difficulties faced by TB-infected migrants in Portugal to seek TB care, comply with TB treatment and access and use healthcare services for TB care. Such insight was gained through the perspectives of healthcare providers in close contact with the patients. Our findings suggest that future efforts should focus on measures to overcome social, economic and administrative obstacles to care for TB-infected migrants. Training initiatives for healthcare providers should also be promoted in order to improve TB care to culturally diverse populations.

Endnotes

[1]Provider who uses scientifically based techniques for health promotion aimed at prevention and diagnosis. Develops activities with autonomy and complementarity with other professional groups. Examples: Clinical and Public Health Analysis Technician; Radiology Technician [54].

Abbreviations

ABA: Ana B. Abecasis; ACG: Ana Cristina Garcia; AIDS: Acquired Immunodeficiency Syndrome; AMT: Ana Maria Tavares; CDC(s): Chest Disease Centre(s); DOT: Directly Observed Therapy; HIV: Human Immunodeficiency Virus; HIV-TB: HIV and Tuberculosis co-infection; NTP: National TB Programme; PHCC(s): Primary Healthcare Centres Cluster(s); SD: Sónia Dias; TB: Tuberculosis; WHO: World Health Organization

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Availability of data and materials
The dataset used during the current study is available from the corresponding author on reasonable request.

Authors' contributions
AMT, ACG and SD contributed to the design and implementation of the study, and provided input and recommendations at all stages of the study. Data collection and analysis was performed by AMT. AMT and SD were the major contributors in organizing and presenting the study findings. AMT wrote the first draft of the manuscript. All authors participated in the writing, reviewing and editing of the manuscript. All authors approved the final version.

Ethics approval and consent to participate
Participation was voluntary, informed consent was obtained from all enrolled participants and verbal consent was recorded for each interview. Ethical approval for the online survey was granted from the Ethics Committees for Health of *Administração Regional de Saúde de Lisboa e Vale do Tejo (ARSLVT)*, of *Norte (ARSNorte)*, of *Alentejo (ARSAlentejo)*, and *Centro (ARS Centro)*. Ethical approval for the semi-structured interviews was granted by the Ethics Committee for Health of ARSLVT.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Author details
[1]Global Health and Tropical Medicine, GHTM, Instituto de Higiene e Medicina Tropical, IHMT, Universidade Nova de Lisboa, UNL, Rua da Junqueira 100, 1349-008 Lisbon, Portugal. [2]Escola Nacional de Saúde Pública, Centro de Investigação em Saúde Pública, Universidade NOVA de Lisboa, Av. Padre Cruz, 1600-560 Lisbon, Portugal. [3]Departamento de Epidemiologia, Instituto Nacional de Saúde Dr. Ricardo Jorge (INSA), Av. Padre Cruz, 1649-016 Lisbon, Portugal.

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III. GENERAL DISCUSSION AND CONCLUSIONS

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In this work, we were able to explore the burden of HIV, TB and HIV-TB co-infection among migrants and the factors responsible for their higher vulnerability. In this section, we summarize and discuss the main findings of this research and propose some topics for future studies. We also provide an insight into possible implications for public health intervention and discuss the limitations and strengths of our work.

1. Discussion of the main findings

One of the specific objectives of this PhD thesis was to describe the prevalence of HIV, TB and HIV-TB co-infection among migrants, as well as to determine sociodemographic, socioeconomic and behavioural factors related to these infections. The occurrence of HIV and TB was explored, as well as related risk factors, among a community of sub-Saharan African migrants living in Lisbon (study II). HIV was prevalent in 5.4% of the participants, a proportion 9 times higher than the UNAIDS estimates for the general population in Portugal in 2017 (0.6% for ages 15-49 years) [1]. A past TB infection was also reported by 4.1% of the participants. A considerable proportion (25.6%) of HIV-positive participants also had a TB infection in the past.

In study I, a systematic review of relevant studies allowed to observe a disproportionately higher burden of HIV-TB co-infection among migrants living in European countries. Higher prevalence and higher incidence of HIV-TB were reported among migrants compared to nationals in most reporting studies. Moreover, when considering migrants' region of origin, those from sub-Saharan African countries had the highest prevalence, incidence, and risk of acquisition of HIV-TB. Our findings were consistent with recent estimates referring that HIV in the EU/EEA is more likely among TB cases originating from Africa [2]. However, indicators on the burden of HIV-TB co-infection among migrants in Europe has been receiving little attention in recent official reports. The provision of accurate and updated data on HIV-TB in the European context is still a challenge due to the persistent sub-optimal reporting observed in many countries [3,4]. Therefore, considering that HIV-TB co-infection and migration are closely linked [5,6], this systematic review provided a relevant contribution to systematize evidence on migrants' disproportionate vulnerability.

Regarding our findings from studies I and II, the heightened vulnerability to HIV, TB and HIV-TB co-infection could be related with to a previous acquisition at a high burdened country of origin [7–14]. However, as further discussed, it has been demonstrated that these infectious diseases can be also acquired within migrant communities at the host country due to experienced social inequalities, limited access to prevention and care services [15–17]. In a study by Desgrees-du-Lou and colleagues (2016), social hardships affected a large proportion of sub-Saharan migrants in France during their settlement process, being associated with sexual risk behaviours that in turn appeared to be related to HIV acquisition in France [18]. Furthermore, a recent study by Pereira and colleagues (2019) on the genetic profiles of *Mycobacterium tuberculosis* isolates from foreign-born individuals in Portugal, suggested a high degree of transmission of Portuguese endemic strains to migrant population rather than strains importation from other Portuguese speaking countries [19].

Sexual risk behaviours, such as inconsistent condom use and multiple partners, as well as experiences of intimate partner violence were referred by a considerable proportion of sub-Saharan African migrants in study II. Those who had STI in the past were more likely to have multiple sexual partners and to use condom inconsistently, and they also had a low risk perception regarding HIV. This findings reflect persistent exposure to sexual risk behaviours in this population that can put them at a higher risk for acquiring HIV in the future [20,21]. In fact, previous research has shown higher risk of STI among migrants compared to natives [22]. Our findings suggest that counselling for behavioural changes is not yet reaching these populations.

Over a third of the HIV-positive participants were unaware of their HIV infection. It is plausible that some of our participants have chosen not to disclose their status perceiving possible negative consequences during the study or in their social context. Nevertheless, the high unawareness observed in our study surpasses some of the EU/EEA countries estimations for undiagnosed HIV in the general population [23]. Our findings are particularly worrisome considering the increased risk for morbidity and mortality among undiagnosed individuals [24], and also their substantial contribution for the occurrence of new HIV cases [25]. Furthermore, remaining undiagnosed can substantially increase their risk for a future TB disease, posing challenges to the control of HIV-TB co-infection [26]. Presently, official statistics show promising results for Portugal in

achieving the UNAIDS 90-90-90 treatment targets for 2020, with 91.7% of people living with HIV in Portugal being diagnosed in 2016 [18]. However, the undiagnosed cases among migrant populations might undermine the achievement of relevant goals, as they reflect limited awareness and difficult access to prevention and care [27].

High rates of undiagnosed infection and low testing rates among sub-Saharan African migrants have been described in the literature [25,28–30]. In our study, only half of the participants was ever tested for HIV, which suggests the existence of potential barriers for testing or that the testing services are not reaching those most at risk. Among those who were never tested, about three quarters did not know where they could get tested. Such lack of knowledge about the available healthcare services and about the disease, may also affect their risk perception and their HIV-testing [31,32]. Previous research has shown that even migrants from sub-Saharan African countries with good knowledge on HIV-transmission had knowledge gaps regarding HIV/STI-testing services [33]. Data from a recent ECDC report have also shown that migrants from high prevalence countries are among the groups with lower HIV testing rates in EU/EEA countries due to fear of knowing one's status, to denial of risk behaviours, stigma, discrimination, and low risk perception [23]. In our study, 37.5% of migrants who had STI in the past were never tested for HIV. Considering that recent HIV testing guidelines advocate that everyone with STI should be proposed for HIV testing [34], these findings possible indicate missed opportunities for early HIV detection and treatment during contact with healthcare services. In fact, a recent study by Dias and colleagues (2019) in Portugal has shown that HIV-prevention interventions, especially regarding HIV testing, are not reaching migrant groups that are most at risk [35].

One of the factors associated with HIV infection was the experience of violence from a partner. The correlation between HIV and intimate partner violence is well-known from the literature [36], and can be explained by the direct transmission through traumatic lesions inflicted during sexual violence, or by the indirect correlation between violence and sexual risk behaviours [37]. In fact, it has been documented that those who experience violence from their partners are less able to negotiate condom use, and more likely to engage in sexual risk behaviours [37,38]. Another possible explanation for our findings is the occurrence of violence from partners as a consequence of their HIV-positive status [37]. For instance, disclosure of HIV-positive status in certain socio-cultural contexts may

imply discrimination, rejection, loss of financial support, marital conflicts, physical and emotional violence [39]. Previous studies have shown that women living with HIV are also more likely to have experienced intimate partner violence than their HIV-negative female counterparts [40,41]. In the overall sample, those who reported violence from a partner were more likely to be female, with low income, multiple sexual partners, and to have engaged in commercial sex; all these are well-known factors that have been associated with violence [22,42–45]. Furthermore, the higher proportion of violence experiences among women reflect possible gender inequalities or particular gender norms in these populations that favour gender-based violence and increased risk for HIV prior to migration or in the host country [45–47].

The oral pre-exposure prophylaxis (PrEP) has been emerging as a considerable promise to overcome many of the barriers of traditional HIV prevention method for women in violent relationships [48]. It brings the advantages of not being partner dependent, not requiring partners' knowledge or consent, it does not require to be taken at the time of the sexual encounter, can be taken at a time or location inaccessible for the abusive partner, and can promote more connection with medical and social services [48]. However, recent research has shown that intimate partner violence can also undermine the adherence to PrEP and leave people vulnerable to HIV acquisition [36,38]. For instance, partners may become aware of their partner's use of PrEP reacting with more violence. Gendered norms regarding sexuality might also suggest that women who use PrEP are not perceived as respectful or worthy [48]. However, literature on this topic is still scarce, especially in the Portuguese context, where the application of PrEP is still at its infancy [23,49]. Therefore, more studies will be needed to explore the benefits and barriers of the use of PrEP as a preventive HIV measure for migrants in Portugal.

Another factor associated with HIV infection was the increasing age of migrants, which contrasted with the relatively young age of the overall participants — mean age of 38.4 years old. These findings can be explained by the fact that migrants tend to migrate at a younger and active age and, therefore, those who are older possibly have been exposed to risk factors for HIV infection for a longer time at the host countries [20].

Contrasting with the behavioural patterns of the overall participants, those with HIV infection were more likely to use condoms consistently, and no associations with

other sexual risk behaviours were observed. These findings suggest a distinct behavioural pattern, possibly adopted after HIV notification. This was also supported by the fact that those who were unaware of their HIV-positive status reported using condom inconsistently. Our findings possibly reflect the benefits of HIV counselling and follow-up provided at healthcare services in terms of behavioural change in HIV-positive migrants. In fact, previous studies have shown behavioural and relational changes after notification of an HIV-positive status, for instance by reducing the number of sexual partners [50].

When analysing the factors associated with TB, those who were male and who were HIV-positive were more likely to report a past TB infection. These results were quite expected considering the well-known higher susceptibility for TB among men [51], and among those living with HIV [26,52,53]. Those who were non-employed were also more likely to report a past TB infection, what was consistent with previous studies describing the impact of difficult socioeconomic conditions experienced at the host countries on the risk for infection or reactivation [54,55]. However, probably due to small numbers this association did not remain after adjustment for other variables.

In the second specific objective of this research, we aimed to describe clinical and genomic characteristics among migrants with HIV-TB co-infection (study III). By accessing databases of HIV-positive patients followed-up in Hospitals in Portugal, we observed a higher proportion of TB diagnosis among HIV-positive migrant patients compared to no native-born patients (5.7% vs. 4.7% among native-born patients). Most migrants with HIV-TB in our study were from sub-Saharan African countries, in line with the findings from study I. Most patients, migrants and natives, had CD4+ T cell counts <350 cells/μL and were diagnosed simultaneously for both infections, suggesting that patients sought care when TB symptoms appeared. Younger migrants were more likely to be diagnosed simultaneously compared with other age groups, which can be possibly related with a short stay in the country, and consequently to a low access and use of healthcare services [56]. This hypothesis is consistent with the absence of significant differences regarding diagnosis between age groups among native-born patients. Therefore, our findings indicate that more active case finding is needed for HIV infection among younger and recently arrived migrants in order to early initiate HIV treatment and prevent TB disease.

HIV non-B clades were the most prevalent among all patients (63.6%), and the proportion was similar to the overall proportion of non-B viruses in Portugal (63% of all HIV infections) [57]. Nevertheless, non-B viruses were also significantly higher among migrants compared with native-born patients. These findings are in line with literature referring an increased emergence of non-B subtypes in European countries possibly related with migration events, in particular from African countries [13,57–59]. The fact that non-B viruses in Western Europe are predominant among non-Europeans [57] could lead us to infer that migrants in our study possibly acquired the infection at the country of origin. However, the Portuguese context is one of the exceptions where evidence of non-B infections transmission within local sexual networks was demonstrated [57].

Non-B strains also caused significantly higher viral loads in patients, which is known to increase the likelihood of disease transmission [60]. It is also important to consider that HIV patients with a TB infection might have a more rapid progression to AIDS, due to TB-driven increased viral genetic heterogeneity, increased viral load in the blood, and decreased CD4+ T cell counts [61,62]. Therefore, in the future, possible synergistic effects between non-B HIV strains and TB infection should be explored, especially considering migrant populations, who are more vulnerable to co-infection and have higher rates of non-B strains.

The third specific objective proposed for this work was to understand the specificities and barriers related to TB care among migrants with TB or HIV-TB in Portugal (study IV). According to many primary care providers, migrants seek TB care at an advanced stage of the disease, mainly due to their unawareness about TB disease and its symptoms. Similar unawareness was also observed among migrants in study II regarding HIV testing services. These findings suggest that migrants' health illiteracy hampers their health-seeking behaviours, contributing to onwards transmission within the community [27,63]. Low health literacy was also one of the barriers most referred to hamper migrants' access and use of TB care in our study. It has been documented that migrants' limited health literacy often correlates with a lack of access to health services, limited ability to effectively self-manage health, to understand available and relevant information, and also to make health-related decisions [64]. This lack of health literacy is usually associated with economic and social barriers for migrants to access educational resources and information programs [64]. Furthermore, different cultural and social

backgrounds can also shape migrants' notions of disease and health needs, and in some countries of origin preventive care medicine is sometimes weak or even absent, possibly influencing their health-seeking behaviours [65].

Interruption of TB treatment was also considered frequent among migrants. The constant mobility within the country or to the country of origin, the inherent difficulties for medical follow-up in these circumstances, and their social isolation throughout the treatment process, were the main causes referred for non-compliance. Although limited research has been dedicated to evaluate the effects of social support in TB disease outcomes, it is known that family and/or friends support during TB treatment is important for treatment success [66]. Therefore, promoting family and community support to migrant patients during treatment is crucial, and may also prevent those on treatment to urge for family support abroad. Nevertheless, increased social support is only possible by increasing knowledge about the disease within the community, in order to tackle the inherent fear and stigma associated to this infection [14,55].

Socioeconomic barriers were referred to frequently prevent migrants from accessing and using TB care, namely due to limited economic resources for transportation, no sick leave benefits from work, and fear of unemployment during sick leave. In these situations, migrants might avoid complying with treatment to avoid incur in indirect costs [67], and might continue to work even sick [68]. Another important barrier for migrants was their difficulties in obtaining financial help from the social services, and the fact that some of these financial incentives were made shorter during the period of austerity in Portugal. This barrier is particularly relevant since an adequate social protection is one of the cornerstones of TB prevention and care [17], enabling to reduce vulnerability to poverty, economic shocks caused by illness [69], the risk of TB transmission and activation [17], and treatment default and therapeutic failure among the poorest populations [70].

Another relevant barrier was the complexity involved in the administrative processes during migrants' access to primary care, namely the documents required and the complex computer registration system. Such administrative hurdles may lead migrants to resort to informal/traditional healing care, or to seek care only in acute situations, mostly to emergency care services, what might ultimately hamper their

engagement in preventive care [63,71,72]. Our findings are consistent with evidence that despite of the legal access to care for all migrants in Portugal, there are still administrative barriers hampering their access and rights to universal healthcare [73]. Therefore, besides providing financial and social support for migrants, their access and use of services must also be simplified in order to prevent them from postponing fundamental care.

Regarding providers' competences and training, overall most healthcare providers perceived themselves as prepared and trained to provide TB care for migrants. Still, most considered relevant to receive more training on migrants' health and on strategies to promote migrants' adherence to treatment. Noteworthy was the fact that a considerable proportion of providers (22.7%) did not know how migrants comply with TB treatment. This unawareness among healthcare providers can be due to the low number of migrant patients visiting primary care services dedicated to TB. Nevertheless, previous research has shown the importance of culture diverse training for healthcare providers in order to optimize their performance [74,75]. Therefore, measures to increase providers' awareness and cultural competences must be considered in order to converge to an increasingly patient-centred approach for migrants.

2. Recommendations for future research

In this research we were able to explore migrants' vulnerability to HIV, TB and HIV-TB in Europe with a main focus in the Portuguese situation, through different approaches and perspectives. Our study findings contributed to the overall knowledge about this still poorly explored global health topic and highlighted several possible topics for future research.

Until now, most literature has been looking at migrants within specific and homogeneous categories, which means that the existing diversity among migrants and minorities goes unnoticed [76,77]. However, migrant populations are quite heterogeneous [17], and each migrant sub-group intrinsically bear specific levels of vulnerability to health issues [77]. In this sense, future studies should consider the particularities of different migrant sub-groups in terms of their specific vulnerability factors for HIV and TB, and their access and use of HIV and TB-related healthcare services.

Regarding complementary preventive measures, more evidence is needed on the benefits and barriers of the use of PrEP among high risk groups of migrants in Portugal. These studies should explore the users' experiences in order to describe methods to overcome barriers for those in violent relationships or facing other vulnerabilities.

Future molecular epidemiology approaches might provide an understanding about sexual networks and existing vulnerabilities in specific migrant communities and sub-groups of migrants in Portugal. These studies might also contribute to know more about the transmission dynamics and the places of acquisition of HIV and TB — e.g. country of origin vs. host country — in order to provide future targeted interventions. These studies might also provide insight into the role of HIV subtypes on the susceptibilities for other infectious diseases such as TB.

The patterns of health-seeking behaviours should be also explored in the future, in order to identify the underlying factors related to the poor health literacy among migrants in Portugal and its relationship with low risk perception and low health-seeking behaviours. More studies on this topic will also provide responses targeted to increase education and awareness among migrant communities that promote preventive behaviours, early diagnosis and treatment.

In addition, studies on healthcare providers' cultural competences involving more participants, for instance using representative samples, are also important to provide evidence for future improvements at providers and healthcare system's level [78]. In the Portuguese specific context, little is still known regarding the healthcare providers' cultural competences, and therefore, more research should be promoted under the scope of specific health programmes and health authorities to enable prompt changes within the training initiatives proposed for the sector.

3. Implications for public health intervention

The findings observed throughout this research suggested several implications for public health intervention and policy. Overall, we observed that migrants are disproportionately vulnerable to HIV, TB, and HIV-TB co-infection, adopt sexual risk behaviours, and have limited health literacy to perceive the risk for infection and the

importance of seeking prevention, testing and care. Moreover, we also observed that the Portuguese health system is not yet adequately prepared to promote change of risk behaviours, to prevent and early detect these infectious diseases, and to promptly start treatment to avoid transmission.

In order to address migrants' vulnerability to HIV, individual-level interventions must include behavioural integrated approaches aiming at delivering a clear message on the risk of HIV transmission and strategies for HIV prevention [39]. At interpersonal level, interventions should focus on tackling intimate partner violence through promoting behavioural change using communication strategies, namely through the media, and programs with peer groups to explore attitudes, behaviours and values of sexuality and gender relations [37]. These interventions should also encourage critical reflection on gender and sexual norms, gendered power inequalities, and the ways that these contribute to violence and HIV risk [48].

Community involvement is critical in the uptake of strategies to improve access to sexual health services and to address unique barriers [79]. Community and religious leaders must be involved in the delivery of sexual education and in addressing stigma and judgment associated with HIV. Partnerships between communities, healthcare services and health promotion organisations must be also established in order to develop trust and facilitate access to relevant services by migrants. Education on sexual and health-seeking behaviours should be promoted at schools, social and ethnic media and community events, and throughout the settlement process [79].

At societal level, it is imperative to have a good understanding of the populations most at risk of and affected by HIV infection, so as to inform and evaluate the public health response to epidemic, including prevention efforts and adequate fund for treatment and healthcare services [30]. The ECDC in their Dublin Declaration Special Report (2016) has proposed priorities for action, namely to strengthen the targeted HIV prevention programmes for migrants from high-HIV-prevalence countries, and to develop more focused case detection to reach the hard-to-reach undiagnosed individuals within key populations [23]. Social protection programmes should also ensure the reduction of disadvantages that put people at high risk of HIV infection, helping overcome barriers to HIV prevention and treatment, and mitigating the overall effect of HIV on households [80]. Moreover, future policy measures should be also strengthened against domestic

violence [37]. At healthcare services, providers must also be able to routinely screen for intimate partner violence as a part of HIV prevention and screening [48].

Previous studies have suggested that given the complexity of HIV prevention, a single strategy alone is not enough and that future interventions should integrate behavioural, biomedical and structural approaches [81]. For instance, biomedical interventions such as PrEP may be a more effective way in HIV prevention than behavioural approaches in contexts of violent relationships [36]. Until now, protection against HIV has been mainly relying on consistent condom use, which is the most effective method to prevent transmission and acquisition of HIV [81]. However, the WHO recommends PrEP as part of a comprehensive HIV prevention package for people at substantial risk of HIV infection [82]. Only recently EU/EEA have started to consider PrEP for populations at higher risk of acquiring HIV [23], and in Portugal in 2018 PrEP was only available in some hospitals and only 50 persons were on PrEP [49]. In the future, interventions should complement the promotion of consistent condom use with an increased offer of PrEP as a biomedical approach to protect high risk groups in Portugal [49,81].

Overall, it is important to shift from a disease-management framework to a well-being perspective, in order to emphasize HIV as an infectious disease with a long progression and to destigmatize the disease [81], particularly among migrants populations.

Achieving the milestones and targets of the End TB Strategy will require further efforts addressing the most vulnerable and hard-to-reach groups such as migrants [2]. Individual-level interventions should promote health education and awareness raising programmes as part of the TB services for migrants [63].

At community-level, empowerment and social mobilisation of migrant communities for overall well-being is equally important in tackling TB, and should include capacity building of migrant worker associations and community leaders, engaging social or medical workers from migrant communities, and enabling community patient support groups, as appropriate to the context [63].

At societal level, social policy strategies must be implemented to protect migrants from the financial shock caused by the disease, in order to avoid further impoverishment that can trigger a downward spiral of worsening health, ongoing tuberculosis

transmission, and crippling medical expenses which can further entrench poverty [67].

Following the recommendations of the End TB Strategy, the systematic screening of active TB and LTBI in migrants from high-TB-burden countries should be promoted, particularly among those living with HIV [83]. However, consensus must be reached on the best approach for screening and care, which is dependent on the available resources, as well as on health system organization and government commitment [27]. Consensus is also needed on the threshold for what is considered a "high burden" country [84]. Low TB incidence countries should consider harmonisation of screening protocols, along with contact tracing, in-country follow-up of migrants, and migrant-sensitive screening services. TB screening programmes for migrants should address barriers faced by migrants to access health services after arrival, being linked with parallel regulatory efforts for migrants' inclusion in the national health system, ensuring timely and equitable TB diagnosis, treatment and care [63]. Targeted TB screening policies for migrants should also respect public health ethics and human rights principles for screening for infectious diseases [63,83].

TB elimination in low-incidence countries is closely linked to global TB prevention [17]. Therefore, only with a Global approach is possible to accomplish the goals of the End TB Strategy. Changing TB rates in the source countries, which are slowly falling in most places, also influence TB rates in migrants. Unless global efforts are accelerated, TB in migrants will remain a challenge in low-incidence countries for a long time to come. Therefore, low-incidence countries need to continue and extend their support to global efforts [17]. It is recommended that high-income countries and their institutions cooperate in the near future with high-burden countries [52]. Cross-border collaboration should be promoted, and should address not only health sector policies, but also improve the overall living and working conditions of migrants. Such international collaboration should also encompass well-functioning cross-border referral systems with contact tracing, information sharing and harmonisation of treatment protocols to ensure continuity of care and monitoring outcomes [63]. These measures will be meeting the key components included in the second pillar of the End TB Strategy, that recommends political commitment with adequate resources for TB care and prevention, universal health coverage and actions on the social determinants of TB such as poverty alleviation and social protection [85]. The latter is particularly important to prevent TB-related

catastrophic costs for migrants and their families, considering that these often do not benefit from social protection mechanisms when they are sick [63].

Without a systematic implementation and improvement of migrant-friendly health services, any intervention would be useless and mostly short-sighted [27]. The healthcare systems must adapt to changes in migratory flows and to changes in the population, adjusting to the health needs and cultural diversity of the new elements that now compose the general population [73]. This is particularly important at primary care level considering its important role in providing accessible and cultural-competent care for the most vulnerable [86]. Although Portugal was one of the best scored European countries in the Migration Integration Policy Index (MIPEX), when considering migrants' health, the scores were quite low despite of their legal access to care. Therefore, MIPEX recommended to invest in cultural competences and to sensitize the healthcare providers to increase their ability to respond to the specific health needs of migrant patients. For instance, it might be beneficial the inclusion of cross-cultural thematic contents within their academic training and throughout their professional advanced training [78].

As migration is an ever-changing dynamic process, generating and maintaining timely and comparable migration data and improving relevant information systems is important [77]. There is currently no international standardised approach for monitoring data variables and indicators related to the health of migrants, and many countries do not include migrant status variables in their health statistics, which makes tracking outcomes very difficult, and this is a problem observed even among wealthier countries [87]. More and better-quality surveillance data on human mobility and on the burden of HIV and TB among these populations are needed, also taking into account specific vulnerable subgroups [17].

It is important to refer that migrant populations are still frequently and erroneously portrayed as biological threats that introduce infectious diseases in the host countries [27]. However, evidence from the literature and in our work has shown otherwise, with HIV and TB largely reflecting the impact of social and structural factors on migrants' vulnerability, and therefore these infections are likely to remain confined within migrant communities without spreading to the host population [27]. Efforts to identify and treat diseases through a non-discriminatory and health promotion approach not only benefits migrants themselves, but also their families, host communities and the overall public

health [88]. Interventions must aim to reach the recommendation of the 2030 Agenda for Sustainable Development that identifies migrants, refugees and internally displaced people as vulnerable populations that "must be empowered", protected from financial risk and provided with access to quality essential health-care services [87]. Considering our research findings, efforts in Portugal still fall short in order to achieve these recommendations, as migrants still present limited awareness regarding HIV and TB risks, have poor health-seeking behaviours and still struggle to access and use care despite of their free access to HIV and TB diagnosis and treatment.

Considering the European and Portuguese demographic projections, increased immigration will be needed in the next decades to move against the increasing aged populations and low fertility rates [73,89]. Therefore, investing in the health needs of migrants and mobile populations protects global public health, facilitates social integration and contributes to economic prosperity [65,88]. Such investment requires broader multisector engagement, as well as coherent and coordinated policies [88]. Policy makers must also keep in mind that migration is not a problem to be solved; rather it is an opportunity to be managed with political commitment at the highest national and international levels in order to achieve the ambitious goals of the SDGs era [63].

4. Limitations and strengths

Some limitations must be acknowledged in our research. In study I, the large extent of the existing literature on topics related to HIV, TB and migrants led us to choose to use a search expression more focused on the objectives of the study. Therefore, although we aimed to make our literature search as comprehensive as possible, we cannot exclude that in restricting our search strategy we might have lost some comprehensiveness that possibly affected our study findings. Another important limitation was the considerable heterogeneity observed among the selected studies, which limited our ability to summarize the results in a more analytical way. Moreover, few studies were conducted nation-wide, and therefore few were representative of the epidemiological context of a country. Nevertheless, in such cases we were still able to make a descriptive synthesis of the findings, that although must not be generalized to the whole country situation.

In studies II and IV, the non-random recruitment methodologies used might have

led to a higher participation of individuals who shared certain demographic and behavioural characteristics, or a particular interest on the topics being studied. Therefore, due to this possible selection bias, the presented findings might not reflect the overall migrants' situation (study II) or the perspectives of the healthcare providers enrolled (study IV). Notwithstanding, the recruitment strategy used in study II allowed us to gather a large and diverse sample of sub-Saharan African migrants residing in Lisbon, and in study IV we were able to gather the perspectives of healthcare providers from the limited number of primary care units dedicated to TB care in Portugal.

In study II, a considerable amount of data was collected based on participants' self-report. Considering the sensitive nature of the topics approached in the questionnaire, such as sexual behaviours and HIV status, that are closely related with social stigma and judgment, it is possible that some responses were provided according to social desirability. Moreover, considering that some questions were on past events or behaviours, we must also consider the possibility of recall bias. Therefore, it is possible that the burden of HIV and TB and the reported sexual risk behaviours were underestimated among the study participants. However, we are confident that the training received by the interviewers on interviewing techniques and ethical principles have contributed to minimize such potential biases. Another limitation of study II was its cross-sectional design, which did not allow us to make inferences about causality between variables.

In study III, the small sample size limited our statistical analysis, and therefore, associations between variables were not possible to measure. However, the small sample size was quite expected considering the small number of cases of HIV-TB co-infection registered in Portugal each year. Nevertheless, we were able to collect sociodemographic, clinical and viral genomic data of HIV-TB co-infected migrants followed at hospitals from all over the country.

In study IV, one of the main limitations was the reduced response rate observed in the online survey. Although such reduced response rates are quite common in studies involving healthcare providers [90,91], a possible nonresponse bias must be considered in our study. Another limitation of the online survey was also the inability to include healthcare providers dedicated to TB care from all regions of Portugal. However, we were

still able to include providers working in regions where most of the foreign-born population in Portugal (76.5%) were residing in 2018 [92].

Despite of the abovementioned limitations, in this PhD thesis we must also consider some strengths. The main strength of this research was the way that migrants' vulnerability to HIV and TB was approached through different perspectives, using different methodologies and data sources. These methodologies allowed us to identify several different areas at all levels of society that can be the focus for future interventions aiming to improve migrants' health status and decrease their vulnerability to HIV and TB. This research was also able to provide increased new evidences on poorly researched topics in the Portuguese context, particularly those regarding HIV-TB co-infection among migrants, which is even under-researched in international survey and surveillance literature.

5. Conclusions

In this PhD thesis, we provided an innovative insight into the vulnerabilities of migrant populations in Portugal to HIV and TB, using different methodological approaches to different levels of related factors. Our findings have contributed to increase knowledge on this relatively understudied topic, and also provided evidence that can be the base for future interventions at the different levels of society.

The main conclusion of this research is that despite of the increasing legal efforts taken over the years in Portugal to increase migrants' access to HIV and TB prevention, diagnosis and treatment, these populations are still highly vulnerable to these infectious diseases. Despite of the existing belief that these infections are acquired mainly at highly burdened countries of origin, what we observed in this research is that in fact migrants are exposed to socioeconomic disadvantages and sexual risk behaviours at the host country. In addition, it was evident that migrants still face difficulties in accessing and using healthcare services despite of their entitlements and free access. The main factors involved were the lack of social protection to alleviate indirect-costs and financial deprivation, the administrative hurdles, and the lack of health literacy that leads to low health-seeking behaviours.

Future efforts should focus on strengthening social protection policies for migrant

populations. Community-based interventions acting on sexual violence, on promoting sexual education, health literacy and access to healthcare services for migrants should be implemented. Furthermore, at healthcare services level, sexual violence should be included as part of HIV screening protocols, initiatives increasing providers' cross-cultural competences should be implemented, and the administrative processes should be simplified in order to allow an easier access to care for all migrants.

In this work, we addressed several aspects recommended for intervention within the UNAIDS targets [93], and within the pillars of End TB Strategy [85], that are ultimately connected with the accomplishment of the targets established in 2030 Agenda for Sustainable Development. International collaboration and harmonization must go hand-in-hand with national efforts to move towards the accomplishment of such targets, and this work reminds us that only with global responses it is possible to tackle global health problems.

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