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a Danish nationwide cohort study

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Original article

Tuberculosis incidence and mortality in people living with human immunodeficiency virus: a Danish nationwide cohort study

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ABSTRACT

Objectives: To explore changes over time in the epidemiology of tuberculosis (TB) in Denmark in people living with human immunodeficiency virus (HIV) (PLWH).
Methods: In this nationwide, population-based cohort study we included all adult PLWH from the Danish HIV Cohort Study (1995–2017) without previous TB. We estimated TB incidence rate (IR), all-cause mortality rate (MR), associated risk and prognostic factors using Poisson regression.
Results: Among 6982 PLWH (73 596 person-years (PY)), we observed 217 TB events (IR 2.9/1000 PY, 95% CI 2.6–3.4: IR 6.7, 95% CI 5.7–7.9 among migrants and IR 1.4, 95% CI 1.1–1.7 among Danish-born individuals; $p < 0.001$). The IR of concomitant HIV/TB remained high and unchanged over time. The IR of TB diagnosed >3 months after HIV diagnosis declined with calendar time, longer time from HIV diagnosis, and CD4 cell recovery. Independent TB risk factors were African/Asian/Greenland origin (adjusted incidence rate ratio (aIRR) 5.2, 95% CI 3.5–7.6, aIRR 6.5, 95% CI 4.2–10.0, aIRR 7.0, 95% CI 3.4–14.6, respectively), illicit drug use (aIRR 6.9, 95% CI 4.2–11.2), CD4 <200 cells/μL (aIRR 2.7, 95% CI 2.0–3.6) and not receiving antiretroviral therapy (aIRR 3.7, 95% CI 2.5–5.3). Fifty-five patients died (MR 27.9/1000 PY, 95% CI 21.4–36.3), with no improvement in mortality over time. Mortality prognostic factors were Danish-origin (adjusted mortality rate ratio (aMRR) 2.3, 95% CI 1.3–4.3), social burden (aMRR 3.9, 95% CI 2.2–7.0), CD4 <100 cells/μL at TB diagnosis (aMRR 2.6, 95% CI 1.3–4.9), TB diagnosed >3 months after HIV versus concomitant diagnosis (aMRR 4.3, 95% CI 2.2–8.7) and disseminated TB (aMRR 3.3, 95% CI 1.1–9.9).
Conclusion: Late HIV presentation with concomitant TB remains a challenge. Declining TB rates in PLWH were observed over time and with CD4 recovery, highlighting the importance of early and successful antiretroviral therapy. However, MR remained high. Our findings highlight the importance of HIV and TB screening strategies and treatment of latent TB in high-risk groups. **Raquel Martin-Iguacel, Clin Microbiol Infect 2022;28:570**

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Introduction

The use of antiretroviral therapy (ART) has sharply reduced the incidence of tuberculosis (TB) in people living with human immunodeficiency virus (HIV) (PLWH). TB is still the most common AIDS-defining condition, however, and is a leading cause of death among PLWH [1,2].

Identifying risk factors for TB development, treatment failure and death in PLWH is pivotal to achieve the goals of the End TB Strategy [3]. Previous studies have identified immigration from high-burden TB countries and HIV-related immunosuppression as risk factors for development of active TB in low-incidence countries [2,4]. However, improved ART coverage and changing migration dynamics over the last decade may have influenced TB epidemiology in countries with a low TB incidence.

We conducted a Danish nationwide cohort study from 1995 to 2017 among PLWH to estimate the incidence rate (IR) of TB, the associated mortality rates (MR) and the associated predictive and prognostic factors.

Materials and methods

Study design

In this Danish nationwide population-based cohort of HIV-1-infected individuals, we estimated the incidence and prognosis of TB. The study design had two parts. First, we investigated the IR and risk factors for Danish adult PLWH to develop the first TB episode through Danish nationwide prospective cohorts. Second, we evaluated MR and associated prognostic factors in the cohort of patients with HIV/TB co-infection identified as well in the Danish HIV Cohort Study (DHCS) cross-checked with the Danish National Hospital Registry (DNHR) and the Danish Civil Registration System (DCRS).

Infectious diseases physicians reviewed all hospital records from patients coded with a mycobacterial infection in either DHCS (both hospitalized and outpatient diagnosis) or DNHR (according to International Classification of Disease 10th revision codes at discharge, see Supplementary material, Appendix S1). They validated the TB diagnosis and gathered additional information (see Supplementary material, Fig. S1). Both databases were used to improve case detection.

Setting

In May 2017, Denmark had a population of 5.8 million with an estimated HIV prevalence among the adult population of 0.1% [5] and a TB IR of 0.05/1000 person-years (PY) [6]. The Danish healthcare system is universal and tax-payer funded. All PLWH are followed in one of the eight hospital-based specialized departments of infectious diseases. ART and TB therapy are provided according to national guidelines and are free of charge.

Study period

The study ran from 1 January 1995 to 1 May 2017.

Data sources

We used the Danish personal identification number, which is assigned to all individuals at birth or immigration, to link individuals in the following national registries.

The DHCS is an ongoing nationwide, prospective, population-based cohort of all PLWH treated at Danish hospitals since 1 January 1995. Data are updated yearly and include demographics, date of HIV diagnosis, AIDS-defining events, cause/date of death, ART, CD4 cell count and plasma HIV-RNA measurements [7].

The DCRS, established in 1968, contains information on vital status, residency and migration for all residents in Denmark [8]. We extracted data on emigration, immigration and date of death.

The DNHR, established in 1977, contains information about hospitalization in non-psychiatric Danish hospitals, including discharge diagnosis codes according to the International Classification of Disease 10th revision from 1994 onwards [9].

Study population

For TB incidence, from the DHCS, we included all PLWH ≥18 years of age, alive and living in Denmark at study inclusion, followed for HIV care during 1995–2017, and not diagnosed with TB before to study inclusion.

For TB mortality, we included all PLWH diagnosed with TB during the study period.

Outcomes

For TB incidence, the primary outcome measure was time to TB diagnosis.

We classified TB as either diagnosed concomitantly (within 1 month before and up to 3 months after HIV diagnosis) or diagnosed >3 months thereafter. We included both definitive and presumptive TB diagnoses [10]. The diagnosis was classified as definitive when *Mycobacterium tuberculosis* was identified by culture of *M. tuberculosis* complex and/or detection by nucleic acid amplification or in case of detection of acid-fast bacilli by microscopy and compatible TB clinical symptoms. A presumptive diagnosis was based on histopathological, clinical and/or radiographic criteria compatible with TB.

For TB mortality, the primary outcome measures were time to all-cause mortality and to TB-related mortality.

Statistical analysis

Chi-squared test, *t* test, and Mann–Whitney *U* test were used to compare differences between groups.

For TB incidence, the date of study inclusion was defined as the most recent of the following: 1 January 1995 (initiation of DHCS), date of HIV diagnosis, or date of immigration for individuals with a known HIV infection. We calculated the time from study inclusion to TB diagnosis, death, emigration, loss to follow up, or 1 May 2017, whichever occurred first.

We calculated the crude IR per 1000 PY and 95% CI. The TB IR was further assessed by (a) calendar time:1995–2002, 2003–2009, 2010–2014, ≥2015 (time-updated), (b) time after HIV diagnosis (>3 months to 1 year, >1–5 years, >5–10 years, and >10 years, and (c) recovery of the CD4 cell count.

We used Poisson exponential regression analysis to control for the following potential confounders and to explore risk factors for TB: age, gender, continent of birth, race, route of HIV transmission, CD4 cell count and HIV viral load at study inclusion, AIDS-defining events before study inclusion, and not being on ART (time-updated).

For TB mortality, we assessed the time from TB diagnosis to death, emigration, loss to follow up or 1 May 2017, whichever occurred first, and calculated crude MR and 95% CI. Kaplan–Meier analysis was used to estimate survival according to social burden (defined as alcohol consumption >7/14 drinks per week, illicit drug use (IDU), homelessness, stay in shelter or prison facilities, and/or prostitution), TB localization (pulmonary, extrapulmonary and disseminated), and HIV viraemia copy-years before TB diagnosis

(≥5 versus <5 median log_{10} copy-year/mL). Viraemia copy-years is a time-updated measure of cumulative HIV viral load exposure [11]. The definition of social burden included in this study is not a validated definition but summarizes risk factors for TB exposure that reflect the social vulnerability of these patients.

We used Poisson exponential regression analysis to control for the same confounders described above plus: Charlson co-morbidity score, alcohol/tobacco consumption, social burden, TB localization (pulmonary, extrapulmonary and disseminated), calendar time, TB diagnosed >3 months after HIV, and first 6 months after TB diagnosis.

Causes of death were classified as (a) TB-related, (b) HIV-related, (c) neither HIV- nor TB-related, (d) unknown.

The analyses were stratified by known HIV status at TB diagnosis. STATA software (v.16; StataCorp, College Station, TX, USA) was used for data analyses.

The study was approved by the Danish Data protection Agency (2012-41-0005). Ethical approval and individual consent are not required by Danish legislation for this type of research.

Results

From the DHCS, we identified 6982 PLWH followed for HIV care during 1995–2017, giving rise to 73 596 PY (median follow-up time 9.6 years; interquartile range (IQR) 3.8–16.9 years). We observed 217 (3.1%) incident TB cases in the study period, with an IR of 2.9/1000 PY (95% CI 2.6–3.4): 6.7/1000 PY (95% CI 5.7–7.9) for migrants and 1.4/1000 PY (95% CI 1.1–1.7) for Danish-born individuals (excess IR for migrants 5.3/1000 PY, p < 0.001). In the group of patients co-infected with TB and HIV, there were fewer males compared with mono-infected individuals (58.5% versus 75.9%), and a higher percentage of heterosexuals (58.5% versus 34.9%) and non-European individuals (57.6% versus 20.4%, mainly from Africa (39.2%) and Asia (16.1%)). The median time from arrival in Denmark to HIV diagnosis was 5.9 years (IQR 2.8–9.1 years) for the migrants. Additional characteristics are provided in Table 1.

Ninety-nine patients (45.6%) were diagnosed concomitantly with HIV/TB (median time from HIV to TB diagnosis 7.3 days, IQR 0–21.9 days). Of these patients, three-quarters were migrants, and the median time from arrival in Denmark to HIV/TB diagnosis was 2.7 years (IQR 0.5–6.9 years). In contrast, 118 patients (54.4%) with HIV infection were diagnosed with TB > 3 months after the HIV diagnosis (median time from HIV to TB diagnosis 5.1 years, IQR 2.0–9.6 years). These patients were significantly older, more likely to be of Danish origin, with higher social burden, tobacco consumption, CD4 cell count and Charlson co-morbidity scores (mainly driven by liver and other non-TB AIDS illnesses, see Supplementary material, Table S1), and had higher rates of pulmonary TB (Table 1). Only 41.5% of these PLWH with a subsequent diagnosis of TB had HIV viral load <200 copies/mL at the time of TB diagnosis. More of these individuals interrupted the TB treatment compared with those diagnosed concomitantly (5.1% versus 0%, p 0.02) whereas the rate of TB relapse was similar (6.8% versus 8.1%, p 0.72) in the two groups (Table 1). Only 44.9% ($n = 53$) of these patients had either a Mantoux test ($n = 21$) and/or an interferon-γ release assay ($n = 43$) performed before TB diagnosis, mainly migrants (62.3%, $n = 33$), finding a positive result in 53.8% of cases ($n = 35$). However, none of these patients received treatment for latent tuberculosis infection (LTBI) (Table 1).

Fig. 1 shows that concomitant TB/HIV IR remained unchanged throughout the study period (IR 58.1/1000 PY; 95% CI 47.7–70.8). However, a decline was observed for TB diagnosed >3 months after HIV between 1995–2002 and 2015–2017 (p < 0.01). Investigation of time trends in TB IR in PLWH showed a peak during the first 3 months after HIV diagnosis followed by a substantial decline thereafter (p < 0.001). Hence, the risk of TB decreased significantly beyond 3 months from HIV diagnosis (adjusted incidence rate ratio (aIRR) 0.05; 95% CI 0.04–0.08). Following the initiation of ART, TB incidence declined substantially and correlated inversely with CD4 cell recovery (p < 0.001) (Figs. 1a–f; see Supplementary material, Tables S2 and S3).

In multivariate analyses, African/Asian/Greenland origin (aIRR 5.16, 95% CI 3.52–7.57; aIRR 6.49, 95% CI 4.20–10.01; and aIRR 7.03, 95% CI 3.38–14.59, respectively), IDU (aIRR 6.87, 95% CI 4.21–11.24), heterosexual route of transmission (aIRR 2.99, 95% CI 1.88–4.74), CD4 count ≥100–200 cells/μL (aIRR 2.47, 95% CI 1.64–3.72) or <100 cells/μL (aIRR 2.86, 95% CI 2.05–4.05), and not being on ART (aIRR 3.65, 95% CI 2.53–5.26) remained associated with an increased risk of TB (Table 2).

Fifty-five patients (25.4%) died during the study period (27 866 PY, crude all-cause MR 27.9/1000 PY, 95% CI 21.4–36.3). From 2007 to 2017, the mortality rate was 56% higher in PLWH developing TB compared with HIV mono-infected (MR 22.7/1000 PY versus 14.6/1000 PY; IRR 1.56, 95% CI 1.11–2.19, p 0.01). No changes in MR were observed over calendar time in TB/HIV co-infected patients (Table 3), whereas a clear decline was observed for HIV mono-infected patients (from 34.2/1000 PY before 2007 to 14.6/1000 PY from 2007 onwards; IRR 0.43, 95% CI 0.39–0.47, p < 0.01). TB-related deaths accounted for 29% of all deaths (Table 1).

Mortality rates were higher in patients diagnosed with TB > 3 months after HIV diagnosis compared with those diagnosed concomitantly (adjusted mortality rate ratio (aMRR) 4.34, 95% CI 2.17–8.66) despite the higher rates of late HIV diagnosis in the latter (13% versus 36%, p < 0.001) (Table 3). Thirty-three per cent of the deaths in the first group (versus 15% in the latter) occurred within the first 6 months and were mainly TB-related (Table 1).

In multivariate analyses, the following factors remained associated with an increased risk of death: Danish-origin (aMRR 2.34, 95% CI 1.27–4.33), social burden (aMRR 3.87, 95% CI 2.15–6.97), CD4 count <100 cells/μL at TB diagnosis (aMRR 2,57, 95% CI 1.34–4.94), TB diagnosed >3 months after HIV (aMRR 4.34, 95% CI 2.17–8.66), higher HIV viraemia/copy years (aMRR 3.58, 95% CI 1.56–8.22) and disseminated TB (aMRR 3.32, 95% CI 1.11–9.94) (Table 3, Fig. 2). Fig. 2 shows Kaplan–Meier survival curves for all-cause mortality stratified by social burden, HIV viraemia copy-years and TB.

Similar results were found when stratifying analyses by HIV status at TB diagnosis (see Supplementary material, Tables S3 and S4).

Discussion

In this Danish, nationwide population-based cohort study, the risk of concomitant HIV/TB diagnosis remained high and unchanged over calendar time, affecting mainly migrants at an advanced stage of HIV infection at diagnosis. For individuals with known HIV, we observed a steady decline in TB rates over time. Overall, the risk of TB in PLWH was associated with migration, vulnerable subgroups (IDU, social burden, not receiving ART) and with HIV-induced immunosuppression. All-cause mortality in PLWH co-infected with TB remained high over time. HIV-associated immunosuppression, disseminated TB and social burden were found to be significant predictors of death.

Our data suggest that individuals with concomitant HIV/TB are a different population from those with previously known HIV infection who develop TB > 3 months after their HIV diagnosis. Whereas those diagnosed concomitantly were mainly migrants and HIV late-presenters, many of those with a later TB diagnosis had social burden, higher co-morbidity and sub-optimal linkage to care and ART. Patients in the latter group were also more prone to poor

Table 1
Characteristics of the study population

	All HIV-infected individuals without TB ($n = 6765$)	All TB cases 1995–2017 ($n = 217$)	p value	Concomitant TB/HIV $n = 99$	TB diagnosed >3 months after HIV ($n = 118$)	p value
Observation time (years), median (IQR)	9.9 (4.2–17.3)	0.4 (0.03–4.1)		0.02 (0.001–0.06)	4.0 (1.3–8.2)	
Male, *n* (%)	5169 (76.4)	127 (58.5)	<0.0001	60 (60.6)	67 (56.8)	0.57
Age at baseline (years), median (IQR)	37 (30–45)	35 (30–42)	0.08	36 (31–41)	35 (29–42)	0.34
Caucasian, *n* (%)	5224 (77.2)	81 (37.3)	<0.0001	28 (29.5)	53 (45.3)	0.001
Route of HIV transmission, *n* (%)						
MSM	3156 (46.7)	30 (13.8)	<0.0001	14 (14.1)	16 (13.6)	0.90
Heterosexual	2363 (34.9)	127 (58.5)	<0.0001	64 (64.7)	63 (53.4)	0.09
IDU	593 (8.8)	35 (16.1))	<0.0001	8 (8.1)	29 (24.6)	0.001
Unknown	653 (9.7)	23 (10.6)	0.643	13 (13.1)	10 (8.5)	0.27
HCV, *n* (%)	1359 (20.1)	54 (24.9)	0.08	17 (17.2)	37 (31.2)	0.02
HBV, *n* (%)	385 (5.7)	19 (8.8)	0.06	7 (7.1)	12 (10.2)	0.42
HIV diagnosis before 1995, *n* (%)	2010 (29.7)	38 (17.5)	<0.0001	1 (1.0)	37 (31.4)	<0.0001
Non-TB AIDS before inclusion, *n* (%)	463 (6.8)	12 (5.5)	0.449	8 (8.1)	4 (3.4)	0.13
Non-TB AIDS before TB diagnosis, *n* (%)		33 (15.2)		7 (7.1)	26 (22.0)	0.002
$CD4^+$ cell count at study inclusion (cells/μL), median (IQR)	290 (106–499)	190 (65–373)	<0.0001	80 (40–175)	291 (205–522)	<0.0001
HIV VL at study inclusion (log_{10} copies/mL), median (IQR)	4.8 (4.1–5.4)	5.0 (4.5–5.7)	0.002	5.2 (4.9–5.7)	4.6 (4.1–5.2)	0.004
Emigration during the study period, *n* (%)	395 (5.8)	13 (6.0)	0.925	10 (10.1)	3 (2.5)	0.019
Loss to follow-up, *n* (%)	32 (0,5)	2 (0.9)	0.35	2 (2.0)	0	0.12
Region of origin						
Denmark	4745 (70.1)	72 (33.2)	<0.0001	23 (23.2)	49 (41.5)	0.01
Greenland	64 (1.0)	9 (4.1)	<0.0001	3 (3.0)	6 (5.2)	0.6
Europe	510 (7.5)	11 (5.1)	0.17	6 (6.1)1	5 (4.3)2	0.2
Africa	888 (13.1)	85 (39.2)	<0.0001	42 (42.4)	43 (36.4)	0.37
Asia	336 (5.0)	35 (16.1)	<0.0001	23 (23.2)	12 (10.2)	0.009
America	153 (2.3)	5 (2.3)	0.967	2 (2.0)	3 (2.6)	0.51
Unknown	69 (1.0)	0	—			
Age at TB diagnosis (years), median (IQR)				35 (31–41)	40 (33–48)	0.005
Time from arrival in Denmark to TB diagnosis (years), median (IQR)		4.1 (1.2–8.6)		2.7 (0.5–6.9)	5.9 (2.8–9.1)	0.004
Alcohol, *n* (%)		65 (30.0)		31 (31.3)	34 (28.8)	0.69
<7/14 per week		25 (11.8)		16 (16.8)	9 (7.8)	0.05
>7/14 per week		33 (15.6)		14 (14.7)	19 (16.4)	0.69
Unknown		159 (73.3))		69/70.0)	90/76.3)	0.28
Smoking, *n* (%)		98 (45.2)		37 (37.4)	61 (51.7)	0.04
<10 cigarettes/day		8 (3.8)		5 (5.3)	3 (2.6)	0.33
10–20 cigarettes/day		34 (16.2)		10 (10.6)	24 (20.7)	0.04
>20 cigarettes/day		24 (11.4)		7 (7.5)	17 (14.7)	0.09
Unknown		151 (69.6)		77 (77.8)	74 (62.7)	0.02
Social burden[a]		71 (32.7)		26 (26.3)	45 (38.1)	0.06
$CD4^+$ cell count, at TB diagnosis (cells/μL), median (IQR)		170 (70–371)		80 (40–175)	260 (140–460)	<0.0001
Viral load at TB diagnosis (log_{10} copies/mL), median (IQR)		4.9 (1.8–5.3)		5.2 (4.9–5.7)	3.0 (1.3–5.0)	<0.0001
Virological suppression at TB diagnosis (<200 copies/mL), *n* (%)		51 (23.5)		2 (2.0)	49 (41.5)	<0.0001
Viraemia copy-years from HIV diagnosis to TB diagnosis (log_{10} copy-years/mL), median (IQR)		4.9 (4.2–6.0)		4.0 (3.9–4.2)	5.0 (4.2–6.0)	0.06
On ART at TB diagnosis, *n* (%)		61 (28.1)		0	61 (51.7)	<0.0001
Charlson co-morbidity score at TB diagnosis						
0		135 (62.2)		75 (75.8)	60 (50.9)	<0.0001
1		31 (14.3)		14 (14.1)	17 (14.4)	0.96
2–5		16 (7.4)		3 (3.0)	13 (11.0)	0.03
≥6		35 (16.1)		7 (7.1)	28 (23.7)	0.001
TB diagnosis, *n* (%), based on						
Microbiology (PCR or culture)		180 (83.7)				
Histopathology		33 (15.4)				
Clinical suspicion		2 (0.9)				
Autopsy		2 (0.9)				

(*continued on next page*)

Table 1 (*continued*)

	All HIV-infected individuals without TB ($n = 6765$)	All TB cases 1995–2017 ($n = 217$)	p value	Concomitant TB/HIV $n = 99$	TB diagnosed >3 months after HIV ($n = 118$)	p value
Performance of interferon-γ release assays, *n* (%)	na	67 (30.9)		24 (24.2)	43 (36.4)	0.05
Positive	na	40 (59.7)		15 (62.5)	25 (58.1)	0.25
Negative	na	25 (37.3)		9 (37.5)	16 (37.2)	0.30
Performance of Mantoux test, *n* (%)	na	32 (14.7)		11 (11.1)	21 (17.8)	0.17
Positive	na	21 (65.6)		7 (63.6)	14 (66.7)	0.23
Negative	na	11 (34.4)		4 (36.4)	7 (33.3)	0.53
TB localization, *n* (%)						
Pulmonary		102 (47.0)		34 (34.3)	68 (57.6)	0.001
Extrapulmonary		47 (21.7)		21 (21.2)	28 (22.0)	0.88
Disseminated		68 (31.3)		44 (44.4)	24 (20.3)	<0.0001
Treatment outcome[b], *n* (%)						
Cure		5 (2.3)		1 (1.0)	4 (3.4)	0.25
Treatment completed		187 (86.2)		94 (95.0)	93 (78.8)	0.001
Died in the study period	1772 (25.4)	55 (25.4)	0.991	13 (13.1)	42 (35.6)	<0.0001
Treatment failure		0		0	0	—
Treatment interrupted		6 (2.8)		0	6 (5.1)	0.02
Relapse		16 (7.4%)		8 (8.1)	8 (6.8)	0.72
Time from TB to death (years), median (IQR)		2.1 (0.3–8.4)		5.8 (1.4–8.7)	1.8 (0.1–7.3)	0.16
Causes of death, *n* (%)		total	first ½ year	beyond ½ year	first ½ year	beyond ½ year
TB-related		16 (29.0)	2[c]	0	12[d]	2[e]
HIV-related		3 (5.5)	0	1	0	2
Not TB- or HIV-related[f]		27 (49.1)	0	9	2	16
Unknown		9 (16.4)	0	1	0	8

Abbreviations: ART, antiretroviral therapy; HBV, hepatitis B virus infection; HCV, hepatitis C virus infection; HIV, human immunodeficiency virus; IDU, illicit drug use; IQR, interquartile range; MSM, men having sex with men; NA, data not available; TB, tuberculosis; VL, viral load.

[a] Social burden defined as alcohol consumption >7/14 drinks per week, injection drug use (IDU), homelessness, stay in shelter or prison facilities, and/or prostitution.

[b] Outcome for TB treatment according to WHO guidelines [10].

[c] Due to disseminated TB.

[d] Six cases of pulmonary TB, one extrapulmonary TB and five disseminated TB.

[e] One pulmonary and one disseminated.

[f] Five due to malignancies (two lung, one oropharynx, one breast, one anal cancer), five other infections (one aspergillus, three pneumonia sepsis, one staphylococcal sepsis), one terminal liver disease, one terminal chronic obstructive pulmonary disease, three ischaemic heart disease, one bleeding from liver biopsy, one fire accident and ten drug abuse.

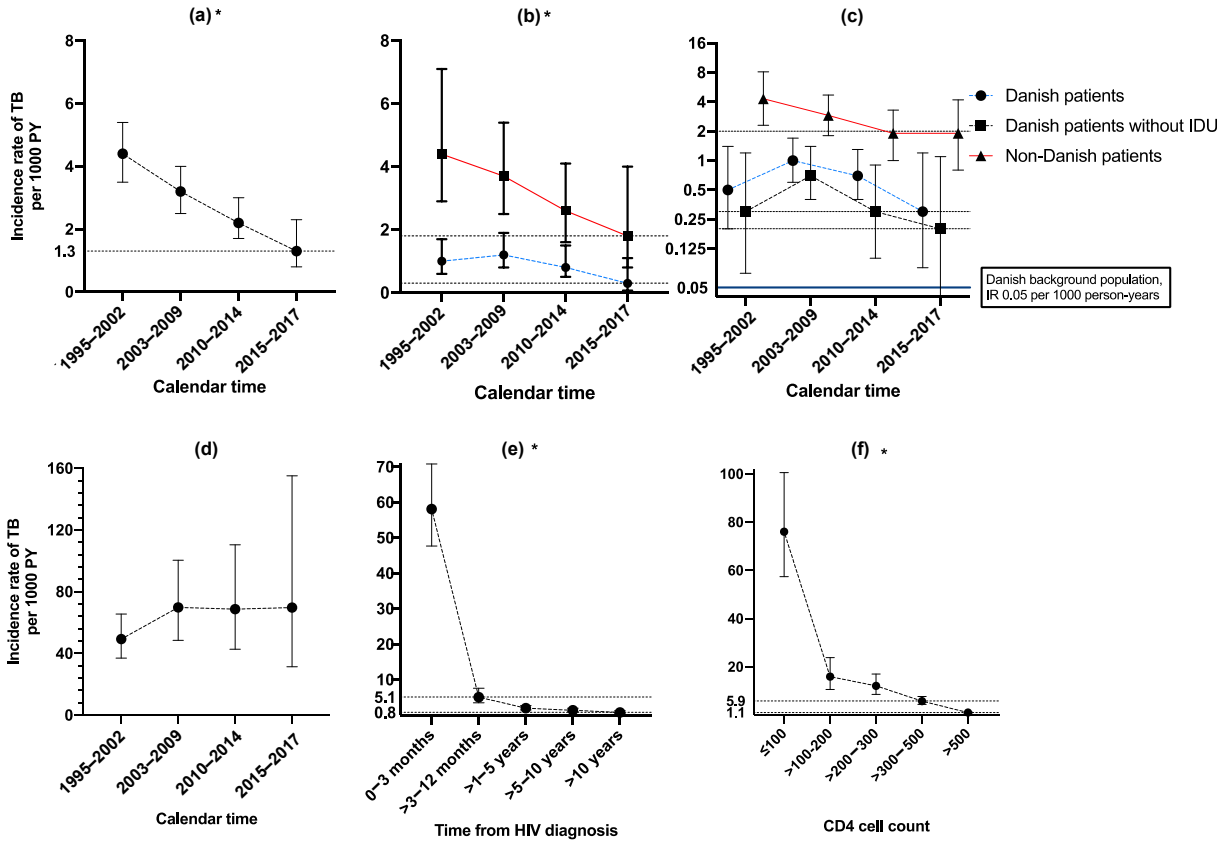

Fig. 1. Incidence rates of tuberculosis (TB) stratified by calendar time, time after human immunodeficiency virus (HIV) diagnosis, and CD4 cell count recovery. Incidence rates of TB are defined as incident TB cases per 1000 person-years (PY) of follow up. IDU, illicit drug use. (a) Incidence rates of TB over calendar time. (b) Incidence rates of TB in patients with known HIV infection over calendar time stratified by Danish origin. (c) Incidence rates of TB in patients with known HIV infection on antiretroviral therapy over calendar time stratified by Danish origin (incidence rate in log scale base 2). The blue line represents TB incidence in the Danish background population (source www.ssi.dk). (d) Incidence rates of TB diagnosed concomitantly with HIV infection over calendar time. (e) Incidence rates of TB by time after HIV diagnosis. (f) Incidence rates of TB by CD4 cell count recovery (time updated). The dotted grey lines in every figure represent the point incidence rate in the recent calendar period. * Statistically significant test for trend (<0.001).

TB treatment outcomes and death, suggesting that individualized care programmes are still needed for this subset.

The IR for concomitant HIV/TB diagnosis remained high and showed no significant changes over time. This trend is in line with high and persistent rates of late HIV presentation worldwide. This has a negative impact on morbidity and survival for the individual and fuels ongoing transmission of both TB and HIV at the population level [12–15]. These findings highlight the importance of timely HIV diagnosis by improving awareness of HIV risk and effectiveness of TB screening strategies. Three-quarters were migrants, mostly from countries with high HIV and TB incidence, which in itself should have triggered a proactive HIV and TB screening upon immigration.

We observed a statistically significant decline in TB IR over time among individuals with known HIV. The improved ART coverage and earlier ART initiation [16] might have contributed to this decline. The risk of TB also declined progressively with time from HIV diagnosis and paralleled CD4 recovery in those successfully treated for HIV.

The interaction between social burden and lack of adherence to ART/TB-treatment and health-care follow up may explain the increased TB IR and MR seen in a subset of Danish-born patients with previously known HIV infection. This vulnerable and difficult-to-treat population should probably be the focus of targeted public health strategies to encourage relinkage to care and treatment.

Current guidelines recommend systematic testing for and treatment of LTBI in PLWH once active TB is excluded, as PLWH have a lifelong risk of developing active TB [17–19]. Treatment of LTBI is estimated to reduce the overall risk of developing active TB by around 33%, up to 64% in those with positive screening tests [19]. Although the level of evidence is high for middle and high TB burden countries [20], the evidence for low-incidence countries with good access to ART is less robust [21–26]. With the high efficacy and immediate ART initiation, the benefit of treating LTBI is perceived as less important. For these reasons, the implementation of these guidelines is poor in Denmark and in many European countries with low TB incidence [27]. This is demonstrated by the low rates of LTBI screening and the absence of LTBI treatment despite positive screening tests in our population. The low awareness among physicians of the *a priori* risk of TB development in PLWH was more pronounced for patients of Danish origin, as shown by the lower rates of LTBI screening among Danish-born individuals.

Although the rate of active TB disease in PLWH declined over the study period, it remained 16-fold higher than in the background Danish population. Although the absolute country incidence remains low, the incremental relative risk is high. Our results support the ongoing need for intensified routine targeted screening and treatment of LTBI in PLWH, the last especially in those with the highest risk, i.e. migrants and individuals with IDU, low CD4 counts, social risk factors, irregular follow up and poor ART adherence.

Main strengths of our study include the design, a population-based, nationwide HIV cohort with high coverage, long observation time and almost complete follow up with a linked review of

Table 2
Predictive factors for developing tuberculosis in Danish HIV-infected patients

	TB events	PRY	IR per 1000 pyr (95% ci)	IRR (95% CI)	aIRR[a] (95% CI)
Total	217	73 595.8	2.9 (2.6–3.4)		
Demographic factors					
Gender					
Female	90	18 954.7	4.7 (3.9–5.8)	ref (1)	ref (1)
Male	127	54 641.1	2.3 (2.3–2.8)	0.49 (0.37–0.64)	1.44 (1.05–1.97)
Age (time-updated)[b]					
≥40 years	93	47 428.5	2.0 (1.6–2.4)	ref (1)	ref (1)
<40 years	124	26 167.3	4.7 (4.0–5.7)	2.42 (1.85–3.16)	1.06 (0.78–1.43)
Region of birth					
Denmark	74	52 237.9	1.4 (1.1–1.8)	ref (1)	ref (1)
Europe	11	4772.0	2.3 (1.3–4.2)	1.63 (0.86–3.07)	1.69 (0.89–3.18)
Africa	82	9944.5	8.2 (6.6–10.2)	5.82 (4.25–7.97)	5.16 (3.52–7.57)
Asia	36	3644.5	9.9 (7.1–13.7)	6.97 (4.68–10.38)	6.49 (4.20–10.01)
Greenland	8	743.4	10.8 (5.4–21.5)	7.60 (3.66–15.75)	7.03 (3.38–14.59)
Other	6	2253.5	2.7 (1.2–5.9)	1.88 (0.82–4.32)	2.15 (0.93–4.96)
Route of HIV transmission					
MSM	30	34 911.0	0.9 (0.6–1.2)	ref (1)	ref (1)
IDU	37	6128.6	6.0 (4.4–8.3)	7.03 (4.34–11.37)	6.87 (4.21–11.24)
Heterosexual	127	27 489.3	4.6 (3.9–5.5)	5.38 (3.61–8.00)	2.99 (1.88–4.74)
Other	23	5067.0	4.5 (3.0–6.8)	5.28 (3.07–9.09)	2.62 (1.48–4.64)
HIV factors					
CD4 cell count at baseline					
CD4 cell count ≥200 cells/μL	138	58 040.3	2.4 (2.0–2.8)	ref (1)	ref (1)
CD4 cell count <200, ≥100 cells/μL	30	6539.3	4.6 (3.2–6.6)	1.93 (1.30–2.86)	2.47 (1.64–3.72)
CD4 cell count <100 cells/μL	48	9016.2	5.4 (4.1–7.2)	2.29 (1.65–3.17)	2.86 (2.05–4.05)
VL ≥ 100 000 copies/mL at study inclusion					
No	60	19 726.9	3.0 (2.4–3.9)	ref (1)	
Yes	67	12 411.5	5.4 (4.2–6.9)	1.78 (1.25–2.51)	
Baseline VL, $\log_{10}$ copies/mL				1.23 (1.06–1.43)	
Non-TB AIDS before inclusion					
No	205	70 514.3	2.9 (2.5–3.3)	ref (1)	
Yes	12	3081.5	3.9 (2.2–6.9)	1.34 (0.75–2.40)	
ART initiation (time-updated)					
Time before ART initiation	133	15 963.0	8.3 (7.0–9.9)	5.72 (4.35–7.51)	3.65 (2.53–5.26)
Time after ART initiation	84	57 632.8	1.5 (1.2–1.8)	ref (1)	ref (1)
Time-related factors					
Calendar time (time-updated)					
1995–2002	82	18 786.4	4.4 (3.5–5.4))	3.25 (1.84–5.72)	0.91 (0.49–1.68)
2003–2009	75	23 613.0	3.2 (2.5–4.0)	2.36 (1.34–4.18)	1.34 (0.74–2.42)
2010–2014	46	20 781.7	2.2 (1.7–3.0)	1.65 (0.91–3.00)	1.34 (0.73–2.44)
2015–2017	14	10 414.7	1.3 (0.8–2.3)	ref (1)	ref (1)
HIV status at TB diagnosis					
Concomitant diagnosis[c]	99	1703.6	58.1 (47.7–70.8)	ref (1)	ref (1)
Known HIV infection[d]	118	71 892.2	1.6 (1.4–2.0)	0.03 (0.02–0.04)	0.05 (0.04–0.07)

Abbreviations: aIRR, adjusted incidence rate ratio; ART, antiretroviral therapy; HIV, human immunodeficiency virus; IDU, illicit drug use; IR, incidence rate; IRR, incidence rate ratio; MSM, men having sex with men; PYR, person-years at risk; TB, Tuberculosis, VL, viral load.
[a] Adjusted for gender, age, race (Caucasian versus non-Caucasian), route of HIV transmission, CD4 cell count at study inclusion, ART initiation during the study period (time-updated), calendar time (time-updated), and HIV status at TB diagnosis.
[b] Age ≥40 years versus <40 years at time of study inclusion (time updated).
[c] TB was diagnosed up to 1 month before or within 3 months after HIV diagnosis.
[d] TB was diagnosed >3 months after HIV diagnosis.

validated national databases. We had full access to Danish registries providing high-quality, individual-level data on vital status, residency and migration. This allowed the estimation of longitudinal trends in TB incidence and survival. Moreover, all medical records coded with any mycobacterial infection were reviewed by specialists to confirm TB diagnosis and cause of death. An additional strength is the high number of definitive TB cases included in the study.

Fifty-nine medical records of patients coded with mycobacterial infection had been sent to shredding from the archives, 78% of these before the year 2000. Forty-six of them were coded as atypical mycobacterial infection, but misclassification cannot be ruled out. This could have led to underestimation of the TB incidence in the first period (1995–2002), and thus the real decline over time in TB incidence could have been steeper.

In conclusion, we observed declining rates of TB in PLWH over time, which paralleled CD4 cell recovery. This highlights the importance of early and successful ART. Late HIV presentation with concomitant TB diagnosis remained a challenge with persistently high rates, underlining the need for intensified strategies to ensure earlier diagnosis of HIV and TB. Migration, IDU and HIV-induced immunosuppression were identified as important risk factors for TB, supporting the need for routine screening and treatment of LTBI in these high-risk groups in countries with low TB incidence. Finally, mortality in TB/HIV co-infected individuals remained unchanged over time, and immunosuppression and social burden had an important impact on prognosis.

Transparency declaration

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted

Table 3
Prognostic factors for mortality in HIV-infected patients developing TB

	Deaths	PYR	MR per 1000 PYR (95% CI)	MRR (95% CI)	aMRR[a] (95% CI)
Total	55	27 866	27.9 (21.4–36.3)		
Gender					
Female	15	851.7	17.6 (10.6–29.2)	ref (1)	ref (1)
Male	40	1122.1	35.6 (26.1–48.6)	2.02 (1.12–3.66)	1.26 (0.66–2.39)
Age (time-updated)[b]					
≥40 years	38	1248.4	30.4 (22.1–41.8)	ref (1)	ref (1)
<40 years	17	725.3	23.4 (14.6–37.7)	1.30 (0.73–2.30)	1.08 (0.58–2.02)
Migrants					
No	38	607.6	62.5 (45.5–86.0)	5.03 (2.84–8.90)	2.34 (1.27–4.33)
Yes	17	1366.2	12.4 (7.7–20.0)	ref (1)	ref (1)
IDU					
No	31	1803.8	17.2 (12.1–24.4)	ref (1)	
Yes	24	170.0	141.2 (94.6–210.7)	8.22 (4.82–14.00)	
High alcohol consumption[c]					
No	40	1751.9	22.8 (16.7–31.1)	ref (1)	
Yes	15	221.8	67.6 (40.8–112.2)	2.96 (1.64–5.36)	
High tobacco consumption[d]					
No	32	1496.8	21.4 (15.1–30.2)	ref (1)	
Yes	23	477.0	48.2 (32.0–72.6)	2.26 (1.32–3.85)	
Social burden[e]					
No	21	1541.7	13.6 (8.9–20.9)	ref (1)	ref (1)
Tes	34	432.1	78.7 (56.2–110.1)	5.78 (3.35–9.95)	3.87 (2.15–6.97)
CD4 cell count at TB diagnosis					
≥200 cells/μL	25	836.9	29.9 (20.2–44.2)	ref (1)	ref (1)
<200, ≥100 cells/μL	10	462.9	21.6 (11.6–40.1)	0.72 (0.35–1.51)	1.17 (0.55–2.48)
<100 cells/μL	20	673.9	29.7 (19.1–46.0)	0.99 (0.55–1.79)	2.57 (1.34–4.94)
Viraemia copy-years from HIV to TB, median log_{10} copies/mL[f]					
≥log_{10} 5 copy-years/mL	19	307.0	61.9 (39.5–97.0)	2.27 (1.03–5.02)	
<log_{10} 5 copy-years/mL	9	353.2	25.5 (13.3–49.0)	ref (1)	
Charlson co-morbidity score					
0	29	1371.4	21.1 (14.7–30.4)	ref (1)	
1	9	221.3	40.7 (21.2–78.2)	1.92 (0.91–4.06)	
2–5	5	97.2	51.4 (21.4–123.6)	2.43 (0.94–6.28)	
≥6	12	283.8	42.3 (24.0–74.4)	2.0 (1.02–3.92)	
Non-TB AIDS before TB diagnosis					
No	45	1691.0	26.6 (19.9–35.6)	ref (1)	
Yes	10	282.8	35.4 (19.0–65.7)	1.33 (0.67–2.64)	
ART initiation (time-updated)					
Time before ART initiation	11	126.8	86.7 (48.1–156.7)	3.64 (1.88–7.05)	
Time after ART initiation	44	1847.0	23.8 (17.7–32.0)	ref (1)	
Calendar time (time–updated)					
1995–2002	9	269.3	33.4 (17.4–64.2)	ref (1)	
2003–2009	23	701.4	32.8 (21.8–49.3)	0.98 (0.45–2.12)	
2010–2014	15	661.5	22.7 (13.7–37.6)	0.68 (0.30–1.55)	
2015–2017	8	341.5	23.4 (11.7–46.8)	0.70 (0.27–1.82)	
HIV status at TB diagnosis					
Concomitant diagnosis[g]	13	1044.8	12.4 (7.2–21.4)	ref (1)	ref (1)
Known HIV infection[h]	42	928.9	45.2 (33.4–61.2)	3.63 (1.96–6.77)	4.34 (2.17–8.66)
Time from TB diagnosis (time-updated)					
First 6 months	16	101.7	157.3 (96.3–256.7)	7.54 (4.22–13.51)	5.37 (2.92–9.84)
Beyond 6 months	39	1872.0	20.8 (15.2–28.5)	ref (1)	ref (1)
TB localization					
Extrapulmonary	4	511.5	7.82 (2.9–20.8)	ref (1)	ref (1)
Pulmonary	31	819.6	37.8 (26.6–53.8)	4.84 (1.71–13.70)	2.74 (0.94–8.05)
Disseminated	20	642.7	31.1 (20.1–48.2)	3.98 (1.36–11.64)	3.32 (1.11–9.94)
Recurrence of TB during the study period					
No	47	1829.1	25.7 (19.3–34.2)	ref (1)	
Yes	8	144.7	55.3 (27.7–110.6)	2.15 (1.02–4.55)	

Abbreviations: aMRR, adjusted mortality rate ratio; ART, antiretroviral therapy; HIV, human immunodeficiency virus; IDU, illicit drug use; MMR, mortality rate ratio; MR, mortality rate; PYR, person-years at risk; TB, tuberculosis.

[a] Adjusted for age, gender, migrant, social burden, CD4 cell count, HIV status at TB diagnosis, first half year from TB diagnosis (time-updated), and TB localization. Same results were found when age and gender were not included in the final model.

[b] Age, ≥40 years versus <40 years at time of TB diagnosis (time updated).

[c] Alcohol consumption defined as >7/14 drinks per week for women and men respectively.

[d] Tobacco consumption defined as ≥10 cigarettes daily.

[e] Social burden defined as alcohol consumption >7/14 drinks per week, illicit drug use, homelessness, stay in prison or shelter and/or prostitution.

[f] Viraemia copy-years from HIV to TB diagnosis, median Log_{10} copies/mL in those patients with known HIV infection, ≥ log_{10} 5 copy-years/mL versus < log_{10} 5 copy-years/mL.

[g] TB was diagnosed at up to 1 month before or within 3 months after HIV diagnosis.

[h] TB was diagnosed >3 months after HIV diagnosis.

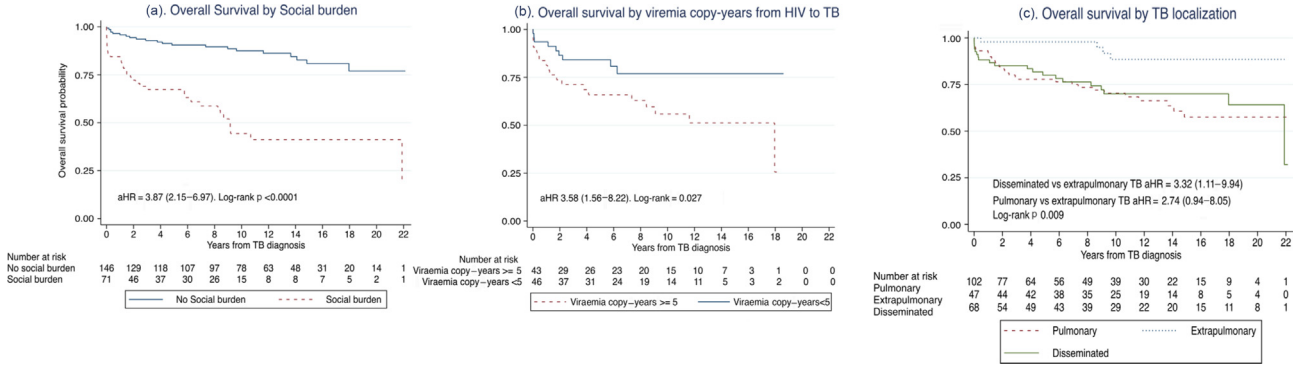

Fig. 2. Kaplan–Meier curves for overall survival after tuberculosis diagnosis in human immunodeficiency virus (HIV) -infected individuals stratified by social burden, viraemia copy-years and tuberculosis (TB) localization. (a) Overall survival by social burden. Social burden was defined as alcohol consumption >7/14 units per week, illicit drug use, homelessness, stay in shelter or prison, and/or prostitution. (b) Overall survival by HIV viraemia copy-years to TB diagnosis in patients with previously diagnosed HIV. Viraemia copy-years ≥ 5 $\log_{10}$ copy-years/mL versus <5 $\log_{10}$ copy-years/mL. Adjusted hazard ratio (aHR) 3.58 (model adjusted for age (time-updated), gender, social burden, viraemia copy-years, HIV status at TB diagnosis and TB localization). (c) Overall survival by TB localization.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2021.07.036.

References

[1] Suthar AB, Lawn SD, del Amo J, Getahun H, Dye C, Sculier D, et al. Antiretroviral therapy for prevention of tuberculosis in adults with HIV: a systematic review and meta-analysis. PLoS Med 2012;9.
[2] Taarnhøj GA, Engsig FN, Ravn P, Johansen IS, Larsen CS, Røge B, et al. Incidence, risk factors and mortality of tuberculosis in Danish HIV patients 1995–2007. BMC Pulm Med 2011;11:26.
[3] World Health Organization. The end TB strategy—2015. World health organization. Available at: https://www.who.int/tb/End_TB_brochure.pdf. [Accessed 29 June 2021].
[4] Moreno S, Jarrin I, Iribarren JA, Perez-Elías MJ, Viciana P, Parra-Ruiz J, et al. Incidence and risk factors for tuberculosis in HIV-positive subjects by HAART status. Int J Tuberc Lung Dis 2008;12:1393–400.
[5] Populations and elections: population in Denmark. 2020. Available at: http://www.statistikbanken.dk. [Accessed 30 November 2020]. n.d.
[6] Tuberculosis—2018 report on disease occurrence. 2020. p. 1–8. Available at: https://en.ssi.dk/surveillance-and-preparedness/surveillance-in-denmark/annual-reports-on-disease-incidence/tuberculosis-2018.
[7] Omland LH, Ahlstrom MG, Obel N. Cohort profile update: the Danish HIV cohort study (DHCS). Int J Epidemiol 2014;43:1769. 1769e.
[8] Schmidt M, Pedersen L, Sørensen HT. The Danish Civil registration system as a tool in epidemiology. Eur J Epidemiol 2014;29:541–9.
[9] Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol 2015:449.
[10] World Health Organization. Definitions and reporting framework for tuberculosis - 2013 revision (updated Dec 2014 and Jan 2020). Available at: https://apps.who.int/iris/handle/10665/79199. [Accessed 29 June 2021].
[11] Cole SR, Napravnik S, Mugavero MJ, Lau B, Eron J, Saag MS. Copy-years viremia as a measure of cumulative human immunodeficiency virus viral burden. Am J Epidemiol 2010;171:198–205.
[12] Mocroft A, Lundgren JD, Sabin ML, d'Arminio Monforte A, Brockmeyer N, Casabona J, et al. Risk factors and outcomes for late presentation for HIV-positive persons in europe: results from the collaboration of observational HIV epidemiological research europe study (COHERE). PLoS Med 2013;10:e1001510.
[13] May M, Gompels M, Delpech V, Porter K, Post F, Johnson M, et al. Impact of late diagnosis and treatment on life expectancy in people with HIV-1: UK Collaborative HIV Cohort (UK CHIC) Study. BMJ 2011;343:d6016.
[14] Montaner JSG, Lima VD, Barrios R, Yip B, Wood E, Kerr T, et al. Association of highly active antiretroviral therapy coverage, population viral load, and yearly new HIV diagnoses in British Columbia, Canada: a population-based study. Lancet 2010;376:532–9.
[15] Martin-Iguacel R, Pedersen C, Llibre JM, Søndergaard J, Ilkjær FV, Jensen J, et al. Prescription of antimicrobials in primary health care as a marker to identify people living with undiagnosed HIV infection, Denmark, 1998 to 2016. Euro Surveill 2019;24:1–12.
[16] The INSIGHT START Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection. N Engl J Med 2015;373:795–807.
[17] Centers for Disease Control and Prevention (CDC). Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV. MMWR Recomm Rep 2020:424. Available at: https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/Adult_OI.pdf. [Accessed 29 June 2021].
[18] Getahun H, Matteelli A, Abubakar I, Abdel Aziz M, Baddeley A, Barreira D, et al. Management of latent *Mycobacterium tuberculosis* infection: WHO guidelines for low tuberculosis burden countries. Eur Respir J 2015;46:1563–76.
[19] World Health Organization. Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. 2011. Available at: https://apps.who.int/iris/handle/10665/44472. [Accessed 29 June 2021].
[20] Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons (review). Cochrane Database Syst Rev 2010;2010:CD000171.
[21] Lin AWC, Lau SKP, Woo PCY. Screening and treatment of latent tuberculosis infection among HIV-infected patients in resource-rich settings. Expert Rev Anti Infect Ther 2016;14:489–500.
[22] Norrby M, Wannheden C, Ekström AM, Berggren I, Lindquist L. Incidence of tuberculosis and the need of prophylactic treatment in persons living with HIV in Stockholm during the era of anti-retroviral therapy 1996–2013. Infect Dis (Auckl) 2018;50:807–16.

[23] Brassard P, Hottes TS, Lalonde RG, Klein MB. Tuberculosis screening and active tuberculosis among HIV-infected persons in a Canadian tertiary care centre. Can J Infect Dis Med Microbiol 2009;20:51–7.
[24] Elzi L, Schlegel M, Weber R, Hirschel B, Cavassini M, Schmid P. Reducing tuberculosis incidence in HIV-infected patients by tuberculin skin testing, preventive treatment, and antiretroviral therapy in an area of low tuberculosis transmission. Clin Infect Dis 2007;44:94–102.
[25] Aichelburg MC, Rieger A, Breitenecker F, Pfistershammer K, Tittes J, Eltz S, et al. Detection and prediction of active tuberculosis disease by a whole-blood interferon-γ release assay in HIV-I-infected individuals. Clin Infect Dis 2009;48:954–62.
[26] Sester M, Van Leth F, Bruchfeld J, Bumbacea D, Cirillo DM, Dilektasli AG, et al. Risk assessment of tuberculosis in immunocompromised patients: a TBNET study. Am J Respir Crit Care Med 2014;190:1168–76.
[27] Evenblij K, Verbon A, Van Leth F. Intention of physicians to implement guidelines for screening and treatment of latent tuberculosis infection in HIV-infected patients in The Netherlands: a mixed-method design. BMC Public Health 2016;16:1–9.