Changes in the epidemiology and clinical manifestations of human immunodeficiency virus–associated tuberculosis in Hong Kong

Alan CK Chan *, SS Huang, KH Wong, CC Leung, MP Lee, TY Tsang, WS Law, LB Tai

ABSTRACT

Introduction: Human immunodeficiency virus (HIV)–associated tuberculosis (TB) remains an important health challenge worldwide. Although TB prevalence has decreased in the general population, there is limited information regarding temporal trends in the incidence of HIV-associated TB in Hong Kong. There are also insufficient data regarding changes in clinical manifestation patterns among HIV-associated TB patients over time. This study aimed to describe temporal trends in the epidemiology and clinical manifestations of HIV-associated TB in Hong Kong.

Methods: We retrospectively reviewed data regarding HIV-associated TB patients that were reported to the TB-HIV Registry of the Department of Health during the period 2007 to 2020. Trends of TB as a primary acquired immunodeficiency syndrome (AIDS)–defining illness, as well as changes in demographic features and clinical manifestations of HIV-associated TB during this period were examined using Cochran–Armitage trend test.

Results: A decreasing trend was observed in the proportion of all reported cases of AIDS in which TB was a primary AIDS-defining illness during the study period. The proportions of female patients and patients with extrapulmonary involvement significantly increased, whereas the proportions of ever-smokers and patients with sputum smear positivity significantly decreased during the same period. A decreasing trend was observed in the proportion of patients with pulmonary TB in which the lower zone was the predominant site of lung parenchymal lesions. Among patients with a diagnosis of HIV infection before TB, an increasing trend was observed in the proportion of patients receiving antiretroviral therapy.

Conclusion: Important temporal changes were observed in the epidemiology and clinical manifestations of HIV-associated TB. These results highlight the need for continued surveillance regarding the patterns of demographic features and clinical manifestations to inform policymakers when planning control strategies for HIV-associated TB.

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New knowledge added by this study

- Tuberculosis (TB) has assumed a less important role as a primary acquired immunodeficiency syndrome–defining illness in Hong Kong over the 14 years of the study period.
- Significant temporal changes were observed in the clinical manifestations of human immunodeficiency virus (HIV)–associated TB.

Implications for clinical practice or policy

- Knowledge of the changing patterns of demographic features and clinical manifestations will help policymakers plan control strategies for HIV-associated TB.
- Recognition of changes in clinical manifestations will also help optimise TB and HIV management and improve treatment outcome.

香港人類免疫力缺乏病毒相關結核病的流行病學和臨床表現變化

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引言：人類免疫力缺乏病毒相關結核病仍然是全球重要健康挑戰。儘管整體人口的結核病患病率有所下降，但有關香港人類免疫力缺乏病毒相關結核病發病率變化趨勢的資料有限，人類免疫力缺乏病毒相關結核病患者的臨床表現變化趨勢數據也不足。本研究旨在探討香港人類免疫力缺乏病毒相關結核病的流行病學和臨床表現的變化趨勢。

方法：我們就2007至2020年期間衞生署結核病／人類免疫力缺乏病毒資料庫收集有關人類免疫力缺乏病毒相關結核病患者的數據進行回顧性檢視，以Cochran-Armitage趨勢檢定審視研究期間結核病作為後天免疫力缺乏症（愛滋病）主要界定疾病的趨勢，以及人類免疫力缺乏病毒相關結核病的人口特徵和臨床表現的變化。

結果：在研究期間所有報告的愛滋病病例中，結核病作為愛滋病主要界定疾病的比例呈下降趨勢。研究期間女性患者和肺外受累患者的比例顯著增加，而曾吸煙者和痰塗片陽性患者的比例顯著下降。肺實質病變以下區為主的結核病患者比例呈下降趨勢。在結核病之前被診斷出感染人類免疫力缺乏病毒的患者中，正接受抗病毒治療的患者比例呈上升趨勢。

結論：人類免疫力缺乏病毒相關結核病的流行病學和臨床表現在研究期間發生了重要變化。研究結果顯示有需要持續監測人類免疫力缺乏病毒相關結核病的人口特徵和臨床表現，以便為政策制定者制定控制策略時提供所需依據。

Introduction

The advent of highly active antiretroviral therapy (HAART) in 1996 led to a substantial decrease in the incidence of opportunistic infections among people living with human immunodeficiency virus (HIV) in many regions.[1-3] Nonetheless, HIV-associated tuberculosis (TB) remains an important global health challenge. The World Health Organization estimated that 10.6 million people were living with TB worldwide in 2021, 6.7% of whom were living with HIV.[4] In the same year, 1.6 million people died of TB, including 187 000 people who were living with HIV.[4] The burden of HIV-associated TB considerably varies across countries and regions.[5,6] The prevalence of HIV-associated TB in individual areas reportedly changes over time.[7-9] Awareness of changes in the epidemiology and clinical manifestations of patients with HIV-associated TB can help policymakers formulate timely relevant prevention and control measures. It can also help improve treatment outcomes for patients with HIV-associated TB.

In Hong Kong, the TB case notification rate has exhibited an overall decreasing trend over the past few decades.[10] In 2021, the provisional number of TB cases reported to the Department of Health was 3741.[11] The corresponding TB notification rate was 50.5 per 100 000 inhabitants, a substantial decrease from 84.1 per 100 000 inhabitants in 2006.[11] The overall prevalence of HIV infection in the general adult population has remained low (<0.1%).[12] The epidemiology and clinical manifestations of HIV-associated TB during the period 1996 to 2006 in Hong Kong have been reported.[13] Notably, the report showed that TB had become an increasingly important acquired immunodeficiency syndrome (AIDS)–defining illness in Hong Kong, surpassing *Pneumocystis jirovecii* pneumonia as the most common primary AIDS-defining illness in 2005; the two illnesses represented 39% and 31% of all such illnesses, respectively, in 2005.[13] The presentation of HIV-associated TB is often atypical.[13] Considering the declining prevalence of TB in the general population and accompanying decrease in TB transmission in Hong Kong, the implementation of strategies to enhance screening for latent TB infection, the increased use of molecular tests for TB diagnosis, and the expansion of HAART in recent years, we conducted a retrospective review of data regarding patients with HIV-associated TB that were reported to the TB-HIV Registry of the Department of Health during the period 2007 to 2020. We aimed to identify temporal trends in the epidemiology and clinical manifestations of HIV-associated TB during that period.

Methods

We retrospectively reviewed data contained within the TB-HIV Registry, which captured information regarding nearly all cases of HIV-associated TB diagnosed in the Tuberculosis and Chest Service and Special Preventive Programme (SPP) under the Department of Health, as well as cases referred from regional hospitals of the Hong Kong Hospital Authority, during the period 2007 to 2020. The details of data contained in the TB-HIV Registry, along with the criteria for TB as a primary AIDS-defining illness, were described in a previous report.[13] There have been no changes in the criteria for TB as a primary AIDS-defining illness since the last report. Where necessary, both clinic records and hospital discharge records were reviewed. All data were imported into Epi Info[14] and exported to statistical software SPSS (Windows version 26.0; IBM Corp, Armonk [NY], US) for analysis. The Cochran–Armitage trend test in XLSTAT software (Lumivero, Denver [CO], US) was used to identify trends in the proportion of reported AIDS cases with TB as a primary AIDS-defining illness during the study period. The Cochran–Armitage trend test was also used to examine changes in demographic features and clinical manifestations during the same period. Where relevant, we compared the demographic features of patients reported to the TB-HIV Registry during the study period with the

features of a historical cohort from the period 1996 to 2006[13] using the Chi squared test. P values <0.05 were considered statistically significant.

This study was an extension of a previous study designed to evaluate the public health programme for HIV-associated TB in Hong Kong[15]; it did not constitute research on human participants. Throughout the review process, we implemented all reasonable precautions to protect the confidentiality of personal data and excluded personally identifiable information from the electronic database.

Results

Tuberculosis as a primary acquired immunodeficiency syndrome–defining illness

All 390 cases reported to the TB-HIV Registry from 1 January 2007 to 31 December 2020 were included in this retrospective analysis. Information about whether TB constituted a primary AIDS-defining illness was available for 363 of 390 (93.1%) patients, where TB was listed as a primary AIDS-defining illness in 251 of those cases (69.1%). Overall, TB as a primary AIDS-defining illness represented a decreasing trend of 18.3% of 1375 reported AIDS cases during the period 2007 to 2020[12] (Cochran–Armitage trend test, P<0.001) [Fig], compared with 28.2% (192/680; Chi squared test, P<0.001) among the historical cohort of patients reported during the period 1996 to 2006.[13]

Demographic features

Trends in demographic features, including age, sex, case category, ethnicity, residence, primary source of care (first presentation), and smoking status, for the 390 HIV-associated TB cases reported to the TB-HIV Registry during the study period are shown in Table 1. The proportion of female patients significantly increased whereas that of ever-smokers significantly decreased (Cochran–Armitage trend test, P=0.035 and P=0.029, respectively). No significant trends were detected in other variables examined. Additionally, the proportions of Chinese individuals and permanent residents were lower in the present cohort than in the historical cohort of 1996 to 2006[13] (260/390, 66.7% vs 152/190, 80.0%; Chi squared test, P=0.001 and 258/390, 66.2% vs 144/190, 75.8%; Chi squared test, P=0.018, respectively). The proportion of female patients was significantly higher in the present cohort than in the historical cohort[13] (82/390, 21.0% vs 21/190, 11.1%; Chi squared test, P=0.003).

Clinical manifestations

Trends in clinical manifestations, including symptoms, presence of pulmonary TB, radiographic features (for cases with abnormalities on chest radiographs), presence of extrapulmonary TB (EPTB), most common EPTB sites, sputum smear positivity status, drug susceptibility patterns, presence of TB risk factors, CD4 cell count at TB

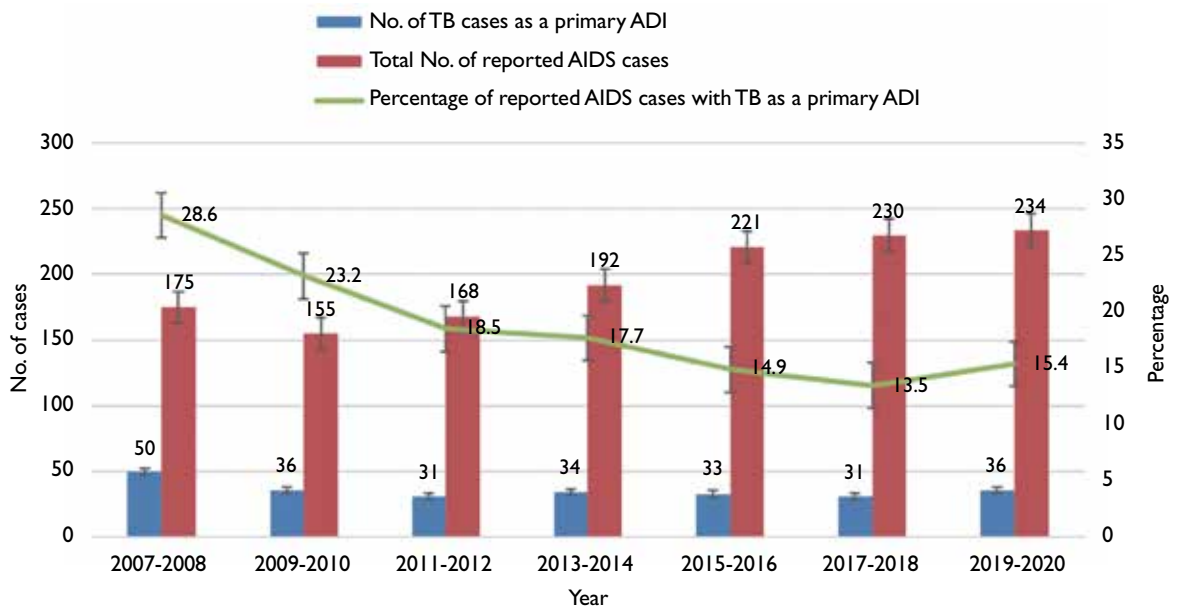

FIG. Tuberculosis as a primary acquired immunodeficiency syndrome–defining illness in Hong Kong among 390 cases reported to the Tuberculosis–Human Immunodeficiency Virus Registry from 2007 to 2020

Abbreviations: ADI = acquired immunodeficiency syndrome–defining illness; AIDS = acquired immunodeficiency syndrome; TB = tuberculosis

TABLE 1. Demographics and modes of presentation of patients reported to the Tuberculosis–Human Immunodeficiency Virus Registry from 2007 to 2020 (n=390)

	2007-2008	2009-2010	2011-2012	2013-2014	2015-2016	2017-2018	2019-2020	Total	All years P value for trend in proportion of patients with reference characteristic*
Age, y									
<60 (reference)	65 (83.3%)	54 (90.0%)	35 (76.1%)	41 (89.1%)	52 (89.7%)	46 (90.2%)	45 (88.2%)	338 (86.7%)	0.241
≥60	13 (16.7%)	6 (10.0%)	11 (23.9%)	5 (10.9%)	6 (10.3%)	5 (9.8%)	6 (11.8%)	52 (13.3%)	
Sex									
Female (reference)	8 (10.3%)	12 (20.0%)	11 (23.9%)	13 (28.3%)	11 (19.0%)	16 (31.4%)	11 (21.6%)	82 (21.0%)	0.035
Male	70 (89.7%)	48 (80.0%)	35 (76.1%)	33 (71.7%)	47 (81.0%)	35 (68.6%)	40 (78.4%)	308 (79.0%)	
Case category (n=386)									
New cases (reference)	72 (92.3%)	52 (89.7%)	41 (91.1%)	38 (82.6%)	51 (89.5%)	45 (88.2%)	46 (90.2%)	345 (89.4%)	0.536
Retreatment and other cases	6 (7.7%)	6 (10.3%)	4 (8.9%)	8 (17.4%)	6 (10.5%)	6 (11.8%)	5 (9.8%)	41 (10.6%)	
Ethnicity									
Chinese (reference)	56 (71.8%)	40 (66.7%)	32 (69.6%)	27 (58.7%)	36 (62.1%)	32 (62.7%)	37 (72.5%)	260 (66.7%)	0.570
Non-Chinese	22 (28.2%)	20 (33.3%)	14 (30.4%)	19 (41.3%)	22 (37.9%)	19 (37.3%)	14 (27.5%)	130 (33.3%)	
Residence status									
Permanent (reference)	57 (73.1%)	39 (65.0%)	32 (69.6%)	25 (54.3%)	33 (56.9%)	35 (68.6%)	37 (72.5%)	258 (66.2%)	0.627
Non-permanent	21 (26.9%)	21 (35.0%)	14 (30.4%)	21 (45.7%)	25 (43.1%)	16 (31.4%)	14 (27.5%)	132 (33.8%)	
Primary source of care (n=388)									
Tertiary centre (reference)	61 (79.2%)	43 (71.7%)	36 (80.0%)	38 (82.6%)	45 (77.6%)	39 (76.5%)	44 (86.3%)	306 (78.9%)	0.356
Other centres	16 (20.8%)	17 (28.3%)	9 (20.0%)	8 (17.4%)	13 (22.4%)	12 (23.5%)	7 (13.7%)	82 (21.1%)	
Smoking status (n=372)									
Ever smoker (reference)	52 (68.4%)	35 (64.8%)	25 (54.3%)	22 (52.4%)	34 (61.8%)	27 (52.9%)	24 (50.0%)	219 (58.9%)	0.029
Never smoker	24 (31.6%)	19 (35.2%)	21 (45.7%)	20 (47.6%)	21 (38.2%)	24 (47.1%)	24 (50.0%)	153 (41.1%)	

* Temporal trends in proportions assessed using Cochran–Armitage trend test

diagnosis, presence of other AIDS-defining illnesses at the time of co-infection, and antiretroviral therapy (ART) status (among patients with a diagnosis of HIV infection before TB), among the 390 TB cases are presented in Tables 2 and 3. The proportions of patients presenting with site-specific symptoms (other than chest-related symptoms) and with EPTB both significantly increased during the period 2007 to 2020 (Cochran–Armitage trend test, P=0.029 and P=0.008, respectively) [Table 2]. The most common EPTB sites were lymph nodes (42.8%), pleura (21.5%), and abdomen (13.8%). Among patients who underwent sputum smear tests, the proportion of patients with sputum smear positivity significantly decreased (Cochran–Armitage trend test, P=0.006) [Table 2]. Among patients with lung parenchymal lesions on chest radiographs, a decreasing trend was observed in the proportion of patients in which the lower zone was the predominant lesion site (Cochran–Armitage trend test, P=0.045) [Table 3]. Among patients with a diagnosis of HIV infection before TB, the proportion of patients receiving ART at TB diagnosis significantly increased (Cochran–Armitage trend test, P=0.003) [Table 2].

TABLE 2. Clinical manifestations of patients reported to the Tuberculosis–Human Immunodeficiency Virus Registry from 2007 to 2020 (n=390)

	2007-2008	2009-2010	2011-2012	2013-2014	2015-2016	2017-2018	2019-2020	Total	All years P value for trend in proportion of patients with reference characteristic*
Presence of symptoms									
Yes (reference)	72 (92.3%)	52 (86.7%)	43 (93.5%)	42 (91.3%)	53 (91.4%)	50 (98.0%)	50 (98.0%)	362 (92.8%)	0.050
No	6 (7.7%)	8 (13.3%)	3 (6.5%)	4 (8.7%)	5 (8.6%)	1 (2.0%)	1 (2.0%)	28 (7.2%)	
Chest symptoms									
Yes (reference)	38 (48.7%)	28 (46.7%)	26 (56.5%)	30 (65.2%)	33 (56.9%)	30 (58.8%)	25 (49.0%)	210 (53.8%)	0.358
No	40 (51.3%)	32 (53.3%)	20 (43.5%)	16 (34.8%)	25 (43.1%)	21 (41.2%)	26 (51.0%)	180 (46.2%)	
Systemic symptoms									
Yes (reference)	60 (76.9%)	40 (66.7%)	34 (73.9%)	33 (71.7%)	34 (58.6%)	37 (72.5%)	33 (64.7%)	271 (69.5%)	0.161
No	18 (23.1%)	20 (33.3%)	12 (26.1%)	13 (28.3%)	24 (41.4%)	14 (27.5%)	18 (35.3%)	119 (30.5%)	
Site-specific symptoms									
Yes (reference)	21 (26.9%)	25 (41.7%)	14 (30.4%)	20 (43.5%)	26 (44.8%)	24 (47.1%)	21 (41.2%)	151 (38.7%)	0.029
No	57 (73.1%)	35 (58.3%)	32 (69.6%)	26 (56.5%)	32 (55.2%)	27 (52.9%)	30 (58.8%)	239 (61.3%)	
Pulmonary involvement									
Yes (reference)	62 (79.5%)	46 (76.7%)	35 (76.1%)	34 (73.9%)	43 (74.1%)	35 (68.6%)	36 (70.6%)	291 (74.6%)	0.130
No	16 (20.5%)	14 (23.3%)	11 (23.9%)	12 (26.1%)	15 (25.9%)	16 (31.4%)	15 (29.4%)	99 (25.4%)	
Extrapulmonary TB involvement									
Yes (reference)	53 (67.9%)	35 (58.3%)	30 (65.2%)	35 (76.1%)	43 (74.1%)	39 (76.5%)	42 (82.4%)	277 (71.0%)	0.008
No	25 (32.1%)	25 (41.7%)	16 (34.8%)	11 (23.9%)	15 (25.9%)	12 (23.5%)	9 (17.6%)	113 (29.0%)	
Sputum smear status (n=336)									
Positive (reference)	35 (50.0%)	20 (37.7%)	14 (41.2%)	12 (31.6%)	17 (33.3%)	11 (25.0%)	14 (30.4%)	123 (36.6%)	0.006
Negative	35 (50.0%)	33 (62.3%)	20 (58.8%)	26 (68.4%)	34 (66.7%)	33 (75.0%)	32 (69.6%)	213 (63.4%)	
Drug susceptibility pattern (n=279)									
Favourable (reference)	53 (85.5%)	32 (80.0%)	19 (79.2%)	23 (67.6%)	35 (83.3%)	33 (82.5%)	36 (97.3%)	231 (82.8%)	0.290
Unfavourable	9 (14.5%)	8 (20.0%)	5 (20.8%)	11 (32.4%)	7 (16.7%)	7 (17.5%)	1 (2.7%)	48 (17.2%)	
Isoniazid resistance (n=278)†									
Present (reference)	5 (8.1%)	4 (10.0%)	2 (8.3%)	5 (14.7%)	5 (11.9%)	2 (5.1%)	0	23 (8.3%)	0.256
Absent	57 (91.9%)	36 (90.0%)	22 (91.7%)	29 (85.3%)	37 (88.1%)	37 (94.9%)	37 (100.0%)	255 (91.7%)	
Rifampicin resistance (n=280)†									
Present (reference)	2 (3.2%)	0	1 (4.2%)	1 (2.9%)	3 (7.0%)	2 (5.0%)	0	9 (3.2%)	0.774
Absent	60 (96.8%)	40 (100.0%)	23 (95.8%)	33 (97.1%)	40 (93.0%)	38 (95.0%)	37 (100.0%)	271 (96.8%)	
Risk factors for TB									
Yes (reference)	14 (17.9%)	11 (18.3%)	11 (23.9%)	10 (21.7%)	12 (20.7%)	12 (23.5%)	14 (27.5%)	84 (21.5%)	0.198
No	64 (82.1%)	49 (81.7%)	35 (76.1%)	36 (78.3%)	46 (79.3%)	39 (76.5%)	37 (72.5%)	306 (78.5%)	
CD4 cell count at TB diagnosis (n=341)									
<200/μL (reference)	47 (75.8%)	34 (73.9%)	24 (60.0%)	31 (73.8%)	36 (69.2%)	34 (70.8%)	37 (72.5%)	243 (71.3%)	0.736
≥200/μL	15 (24.2%)	12 (26.1%)	16 (40.0%)	11 (26.2%)	16 (30.8%)	14 (29.2%)	14 (27.5%)	98 (28.7%)	
Other ADI at TB diagnosis (n=270)									
Yes (reference)	7 (12.7%)	8 (28.6%)	5 (17.9%)	7 (28.0%)	7 (15.2%)	9 (20.9%)	12 (26.7%)	55 (20.4%)	0.283
No	48 (87.3%)	20 (71.4%)	23 (82.1%)	18 (72.0%)	39 (84.8%)	34 (79.1%)	33 (73.3%)	215 (79.6%)	
Receiving ART at TB diagnosis (n=139)‡									
Yes (reference)	11 (36.7%)	10 (52.6%)	5 (38.5%)	5 (35.7%)	15 (71.4%)	14 (66.7%)	15 (71.4%)	75 (54.0%)	0.003
No	19 (63.3%)	9 (47.4%)	8 (61.5%)	9 (64.3%)	6 (28.6%)	7 (33.3%)	6 (28.6%)	64 (46.0%)	

Abbreviations: ADI = acquired immunodeficiency syndrome–defining illness; ART = antiretroviral therapy; TB = tuberculosis

* Temporal trends in proportions assessed using Cochran–Armitage trend test

† Patients with either a positive bacteriological (sputum and/or other specimen) result and phenotypic drug susceptibility test performed or molecular test performed

‡ Patients with a diagnosis of human immunodeficiency virus infection before TB and available information regarding ART at TB diagnosis; patients were assumed to be receiving ART at TB diagnosis if they had been receiving ART for at least 1 month prior to TB diagnosis

TABLE 3. Radiographic features of patients with abnormalities on chest radiographs reported to the Tuberculosis–Human Immunodeficiency Virus Registry from 2007 to 2020*

	2007-2008	2009-2010	2011-2012	2013-2014	2015-2016	2017-2018	2019-2020	Total	All years P value for trend in proportion of patients with reference characteristic†
Extensive lung lesions (n=276)‡									
Yes (reference)	17 (30.4%)	9 (20.5%)	8 (25.0%)	12 (36.4%)	11 (26.2%)	14 (40.0%)	15 (44.1%)	86 (31.2%)	0.059
No	39 (69.6%)	35 (79.5%)	24 (75.0%)	21 (63.6%)	31 (73.8%)	21 (60.0%)	19 (55.9%)	190 (68.8%)	
Presence of cavity (n=285)§									
Yes (reference)	5 (8.8%)	4 (8.9%)	3 (8.6%)	3 (8.8%)	4 (9.3%)	2 (5.7%)	7 (19.4%)	28 (9.8%)	0.318
No	52 (91.2%)	41 (91.1%)	32 (91.4%)	31 (91.2%)	39 (90.7%)	33 (94.3%)	29 (80.6%)	257 (90.2%)	
Predominant lesion in LZ (n=276)‖									
Yes (reference)	12 (21.4%)	9 (20.5%)	6 (18.8%)	10 (30.3%)	1 (2.4%)	3 (8.6%)	5 (14.7%)	46 (16.7%)	0.045
No	44 (78.6%)	35 (79.5%)	26 (81.3%)	23 (69.7%)	41 (97.6%)	32 (91.4%)	29 (85.3%)	230 (83.3%)	
Miliary shadows on CXR (n=390)									
Present (reference)	12 (15.4%)	7 (11.7%)	4 (8.7%)	6 (13.0%)	7 (12.1%)	8 (15.7%)	8 (15.7%)	52 (13.3%)	0.742
Absent	66 (84.6%)	53 (88.3%)	42 (91.3%)	40 (87.0%)	51 (87.9%)	43 (84.3%)	43 (84.3%)	338 (86.7%)	
LN enlargement on CXR (n=384)¶									
Present (reference)	12 (16.4%)	6 (10.2%)	1 (2.2%)	4 (8.7%)	5 (8.6%)	9 (17.6%)	2 (3.9%)	39 (10.2%)	0.293
Absent	61 (83.6%)	53 (89.8%)	45 (97.8%)	42 (91.3%)	53 (91.4%)	42 (82.4%)	49 (96.1%)	345 (89.8%)	
Pleural effusion (n=384)¶									
Present (reference)	14 (19.2%)	7 (11.9%)	11 (23.9%)	7 (15.2%)	11 (19.0%)	11 (21.6%)	14 (27.5%)	75 (19.5%)	0.178
Absent	59 (80.8%)	52 (88.1%)	35 (76.1%)	39 (84.8%)	47 (81.0%)	40 (78.4%)	37 (72.5%)	309 (80.5%)	

Abbreviations: CXR = chest radiograph; LN = lymph node; LZ = lower zone

* Six patients with bacteriological evidence of pulmonary TB had clear CXR on presentation

† Temporal trends in proportions assessed using Cochran–Armitage trend test

‡ Patients with lung parenchymal lesions on CXR and available information regarding extent; extensive shadows were defined as lung parenchymal lesions occupying more than the equivalent of one lung

§ Patients with lung parenchymal lesions on CXR and available information regarding cavity presence or absence

‖ Patients with lung parenchymal lesions on CXR and available information regarding lesion site

¶ Patients with abnormal CXR and information on LN enlargement and available information regarding pleural effusion presence or absence (either side)

Discussion

This study revealed a decreasing trend in the proportion of reported AIDS cases with TB as a primary AIDS-defining illness during the period 2007 to 2020. The overall proportion (18.3%) was also lower than the proportion (28.2%) in the historical cohort of cases reported during the period 1996 to 2006.[13] The proportions of Chinese individuals and permanent residents were lower, whereas the proportion of female patients was higher, in our cohort compared with the historical cohort.[13] The proportions of female patients and patients with extrapulmonary involvement significantly increased, whereas the proportions of ever-smokers and the proportion with sputum smear positivity among pulmonary TB cases significantly decreased during the period 2007 to 2020. A decreasing trend was observed in the proportion of patients with pulmonary TB in which the lower zone was the predominant site of lung parenchymal lesions. Among patients with a diagnosis of HIV infection before TB, an increasing trend was observed in the proportion of patients receiving ART.

Decreasing trend of tuberculosis as an acquired immunodeficiency syndrome–defining illness

In Hong Kong, TB is considered an AIDS-defining illness when the disease is extrapulmonary. Pulmonary TB and cervical lymph node TB are considered AIDS-defining illnesses only when the CD4 cell count at the time of TB diagnosis is <200/μL, as recommended by the Scientific Committee of the Advisory Council on AIDS in 1994.[16] Since then, there have been no changes in the criteria for TB as an AIDS-defining illness among individuals infected with HIV. The decreasing trend in Hong Kong regarding the proportion of reported AIDS cases with TB as a primary AIDS-defining illness might be due to decreased community transmission of TB through better TB control, the expansion of HAART since its introduction in 1997, and (perhaps to a lesser extent) increased acceptance of testing for latent TB infection and preventive treatment for TB among HIV-infected individuals since the early 2000s. Similar decreasing trends related to HAART-induced improvements in immune status among HIV-infected individuals have also been identified during studies conducted in some other countries.[7,9,17] In an observational, retrospective study of AIDS cases included in the Barcelona AIDS register between 1994 and 2005, decreases were observed regarding the incidence of TB as an AIDS-defining illness among both native and immigrant populations.[7] Another study examining trends in the incidence of AIDS-defining opportunistic illnesses over a 25-year period in Brazil showed a reduction in TB incidence from 1991-1993 to 2009-2012.[9] A prospective cohort study of participants in the HIV Outpatient Study at 12 HIV clinics within the US indicated that TB incidence decreased after HAART introduction.[17] Conversely, among participants in the HOMER cohort study (HAART Observational Medical Evaluation and Research) conducted during the period 1996 to 2007 in Canada, no statistically significant trends were observed in the proportion of cases with TB as the AIDS-defining illness, probably because the small number of TB cases reported in each time period limited the ability to detect significant changes in the reported cases.[18] Another study examining AIDS notification data in Australia during the period 1993 to 2000 revealed that the proportion of AIDS cases with TB as the AIDS-defining illness was higher during 1996 to 2000 (post-HAART era) than during 1993 to 1995 (pre-HAART era); the authors attributed this difference to the increasing proportion of Australian patients with AIDS who had been born in sub-Saharan Africa and Asia during the 1990s, among whom the risk of TB was considerably higher.[19] Further studies examining trends in TB as an AIDS-defining illness, as well as location-specific factors that may influence such trends in the post-HAART era, are warranted to facilitate control strategies for HIV-associated TB.

Changes in demographic features and their implications

Further attention is needed regarding the observation of higher proportions of non-Chinese individuals (mostly Asians and Africans, who have much higher TB incidence than the rate among Hong Kong Chinese individuals) and non-permanent residents of Hong Kong in the 2007-2020 cohort compared with the historical 1996-2006 cohort. Similar findings of higher incidences of AIDS-associated TB in foreign-born populations from countries with much higher TB incidence compared with the native population have been reported on the basis of some studies conducted in developed countries.[7,20,21] These observations highlight the need for TB screening and prophylaxis for people living with HIV who were born in countries with a high background prevalence of TB.

Intriguingly, we observed an increasing trend in the proportion of women during the period 2007 to 2020. The reason for this increase is unclear; it may be related to changes in the societal roles of men and women that influence exposure risk. The role of an increased proportion of EPTB (reportedly associated with female sex and observed throughout our cohort, as discussed below) requires further investigation.

The proportion of ever-smokers significantly decreased during the period 2007 to 2020, consistent with the findings of some studies conducted in the US.[22,23] In an analysis of patients from a HIV surveillance system in the US, the prevalence of current smoking declined from 37.6% in 2009 to 33.6% in 2014.[22] In another prospective cohort study that examined smoking trends among HIV-positive patients in the US, a decline in the annual prevalence of current smoking from 1984 to 2012 was also reported; however, disparities were noted according to race, ethnicity, and education.[23] Nonetheless, because smoking increases HIV-related and non–HIV-related morbidity and mortality among people living with HIV, smoking cessation interventions remain an essential component of routine care for such individuals.

Changes in clinical manifestations

The predominance of the lower zone as the site of lung parenchymal lesions on chest radiographs is a relatively common feature among patients with HIV-associated pulmonary TB, according to our previous report on the 1996 to 2006 cohort[13] and some other reports.[24,25] The present study showed that the lower zone was less frequently the predominant site of lung parenchymal lesions during the period 2007 to 2020. The proportion of

patients in the 2007 to 2020 cohort with the lower zone as the predominant site (16.7%) was also lower compared with the proportion of patients in the historical 1996 to 2006 cohort (32.4%).[13] This difference may be related to the higher CD4 cell count at TB diagnosis among patients in the current cohort compared with patients in the historical cohort (median CD4 cell counts at TB diagnosis: 100/μL and 78/μL, respectively). Nonetheless, lower zone involvement was present in approximately one-sixth of pulmonary TB cases reported during 2007 and 2020. A high index of suspicion is required for the accurate and timely diagnosis of pulmonary TB in people living with HIV.

A decreasing trend was observed in the proportion of patients with sputum smear positivity during the period 2007 to 2020. The overall proportion of patients with sputum smear positivity in the 2007 to 2020 cohort (36.6%) was also lower than the proportion in the historical cohort of 1996 to 2006 (42.2%)[13]; it was similar to the proportion identified during a population database study in South Korea (36.4%).[26] These results suggest that TB cases have been diagnosed at increasingly earlier stages due to enhanced active TB screening efforts among people living with HIV, as well as the increased use of molecular testing that enhanced the diagnosis of smear-negative cases in Hong Kong. These results highlight the need for continued TB screening efforts and early detection of TB among people living with HIV.

Our findings indicate that EPTB became more common among HIV-associated TB patients during the period 2007 to 2020. The overall proportion of patients with EPTB was also higher in the present cohort compared to that reported in a local study that examined risk factors for mortality in an earlier cohort (2006 to 2015) and that in the historical 1996 to 2006 cohort (71.0%, 64.9%,[15] and 62.6%,[13] respectively). These differences may have arisen through enhanced diagnosis of EPTB with the increased use of molecular testing in Hong Kong. An increasing trend of extrapulmonary involvement among TB patients has also been reported in some other studies, although such studies are mostly population-based.[27-29] Few reports have been published regarding temporal trends in EPTB specifically among HIV-associated TB patients.[30] Further studies are needed to examine these trends and associated factors.

Strengths and limitations

Strengths of this study included its use of cohort data from the TB-HIV Registry covering a relatively long period (14 years) to study temporal changes in the epidemiology and clinical manifestations of HIV-associated TB. However, some limitations should be considered when interpreting the results of this study. First, the TB-HIV Registry may not capture all HIV-associated TB cases—some patients encountered in the SPP were not referred to a chest clinic but underwent anti-TB treatment in private clinics or other countries. The total number of HIV-associated TB cases in the HIV Surveillance Report of SPP was approximately 10% higher than the number in the TB-HIV Registry; the difference mostly comprised non-permanent residents temporarily staying in Hong Kong. Nonetheless, data from the HIV Surveillance Report showed a similar decreasing trend in TB as a primary AIDS-defining illness during the study period (data not shown). Second, this study utilised a retrospective design, and data present in the database of the TB-HIV Registry may be incomplete. Information regarding some parameters such as case category, co-morbidities, and CD4 cell count was unavailable for some patients. To overcome this limitation, we traced and reviewed relevant clinical records from chest clinics and hospitals when necessary. Therefore, we expect minimal bias due to missing data. Finally, the sample size may have led to insufficient statistical power for detecting temporal changes in some less common parameters.

Conclusion

This study showed that TB has become less important as a primary AIDS-defining illness in Hong Kong over the 14 years of the study period. Nonetheless, it remains the second most common primary AIDS-defining illness after *P jirovecii* pneumonia. Important temporal changes were also observed in the patterns of demographic features and clinical manifestations. Continued surveillance regarding the patterns of demographic features and clinical manifestations is needed to inform policymakers during the formulation of TB control strategies to improve patient care and treatment outcomes among people living with HIV. This surveillance is especially important in situations such as the coronavirus disease 2019 era, during which resources from TB programmes may be diverted to management of the global pandemic.

Author contributions

Concept or design: ACK Chan, SS Huang.
Acquisition of data: ACK Chan, SS Huang.
Analysis or interpretation of data: ACK Chan, SS Huang.
Drafting of the manuscript: ACK Chan, SS Huang.
Critical revision of the manuscript for important intellectual content: KH Wong, CC Leung, MP Lee, TY Tsang, WS Law, LB Tai.

Conflicts of interest

All authors have disclosed no conflicts of interest.

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Ethics approval

This research was a retrospective analysis of observational data routinely collected in a local Registry as part of the ongoing evaluation of the public health programme for human immunodeficiency virus–associated tuberculosis in Hong Kong. Approval for the evaluation and exemption from obtaining informed patient consent has been granted by the Ethics Committee of the Department of Health of the Hong Kong SAR Government (Ref No.: L/M 416/2017).

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