ORIGINAL ARTICLE

Treatment outcomes after early initiation of antiretroviral therapy for human immunodeficiency virus–associated tuberculosis

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Objective To evaluate the optimal timing for initiating antiretroviral therapy in patients with human immunodeficiency virus (HIV)–associated tuberculosis in Hong Kong.

Design Historical cohort.

Setting Tuberculosis and Chest Service and Special Preventive Programme, Public Health Service Branch, Centre for Health Protection, Department of Health, Hong Kong.

Patients Consecutive patients with HIV-associated tuberculosis in a territory-wide TB-HIV registry encountered from 1996 to 2009.

Results Of the 260 antiretroviral therapy–naïve patients with HIV-associated tuberculosis, 32 (12%) had antiretroviral therapy initiated within 2 months after starting anti-tuberculosis treatment (early antiretroviral therapy). Early antiretroviral therapy was associated with a more favourable outcome (cure or treatment completion without relapse) at 24 months (91% vs 67%; P=0.007) than those with antiretroviral therapy started later or not initiated, and remained an independent predictor of a favourable outcome after adjustment for potential confounders. Adverse effects from anti-tuberculosis drugs tended to occur more frequently in patients with early antiretroviral therapy (13/32 or 41%) compared with the remainder (59/228 or 26%; P=0.08). A significantly higher proportion of patients in the former group experienced immune reconstitution inflammatory syndrome than in the latter group (7/32 or 22% vs 9/228 or 4%; P<0.001). There was no death attributable to immune reconstitution inflammatory syndrome.

Conclusions Early initiation of antiretroviral therapy is associated with more favourable tuberculosis treatment outcomes in patients with HIV-associated tuberculosis with a low CD4 count (<200/μL). Drug co-toxicity and immune reconstitution inflammatory syndrome that may be increased by earlier initiation of antiretroviral therapy does not undermine tuberculosis treatment outcomes to a significant extent.

Key words
Antiretroviral therapy, highly active; HIV; Treatment outcome; Tuberculosis

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New knowledge added by this study

- Most of the previous studies on timing of antiretroviral therapy (ART) on treatment outcomes of human immunodeficiency virus (HIV)–associated tuberculosis (TB) examined subjects from developing countries with high TB and HIV prevalence, especially from Africa. Data from intermediate-TB-burden countries with low HIV prevalence and good health infrastructure are scanty. Detailed descriptions on the manifestations of immune reconstitution inflammatory syndrome (IRIS) among patients suffering from this condition were also lacking in most of the previous studies. This study provides comprehensive data on IRIS among TB-HIV co-infected patients with early initiation of ART, and complements previous studies by providing evidence that early initiation of ART can improve treatment outcome of patients with HIV-associated TB with a low CD4 count in areas with an intermediate TB burden and low HIV prevalence.

Implications for clinical practice or policy

- Antiretroviral therapy should be initiated early in the course of anti-TB treatment in patients with HIV-associated TB and a low CD4 count of <200/μL. Programmes for provider-initiated HIV antibody testing and joint HIV/TB interventions to reduce delay in initiation of ART should continue and be enhanced.

Introduction

In relation to the Millennium Development Goals set by the World Health Organization (WHO), there have been worldwide achievements with respect to tuberculosis (TB) control in recent years. Incidence rates are falling in all six of the WHO's regions. Prevalence rates have also been falling, with an estimated 12.0 million cases of TB in 2011.[1] Nevertheless, in 2011, globally there were still an estimated 8.7 million incident cases of TB, one of the main drivers being the pandemic of human immunodeficiency virus (HIV) infection, for which the estimated incidence was 1.1 million (13% of all new cases of TB).[1-3]

The prognosis has dramatically improved for HIV-infected patients following the availability of highly active antiretroviral therapy (ART).[4] Yet, its concurrent use with anti-TB treatment is complicated by overlapping toxicities, immune reconstitution inflammatory syndrome (IRIS), and complex drug-drug interactions.[5,6] The optimal timing of ART in patients with HIV-associated TB remains controversial.[7,8] A 2005 WHO consultation paper concluded that "the optimal timing for initiating antiretroviral therapy" in co-infected patients is "the major research priority".[9] Some authors have reported improved survival in patients with early initiation of ART.[10-13] Data on the incidence of adverse drug effects and IRIS in relation to the timing of ART initiation, however, were less often reported.

Hong Kong is classified as a place in the Western Pacific region with an intermediate TB burden and good health infrastructure. The local TB notification rate decreased from a peak of 697.2 per 100 000 in 1952 to 69.7 per 100 000 in 2011,[14] and HIV-associated TB cases constituted around 1% of all TB notifications.[15] To enhance surveillance of HIV-associated TB locally, since 1996 a TB-HIV Registry has been jointly set up by the Tuberculosis and Chest Service (TB&CS) and the Special Preventive Programme (SPP) of Department of Health (DH).[16] The epidemiology and clinical manifestations of a cohort of 190 patients reported to the TB-HIV Registry as of 31 December 2006 have been reported previously.[16] To assess their treatment outcomes and address the issue of optimal timing for the initiation of ART in such patients, we set out to retrospectively review corresponding patient data reported to the TB-HIV Registry of the DH between 1 January 1996 and 31 December 2009.

早期使用抗反轉錄病毒治療對人類免疫缺乏病毒合併結核病治療效果的影響

目的 評估香港人類免疫缺乏病毒（HIV）合併結核病（TB）患者最適合開展抗反轉錄病毒治療（ART）的時間。

設計 回顧性隊列研究。

安排 香港衞生署轄下衞生防護中心公共衞生服務處內的胸肺科服務及特別預防計劃。

患者 1996至2009年期間全港性TB-HIV資料庫內HIV合併TB的所有患者。

結果 260名從未接受ART的HIV合併TB患者中，共有32人（12%）在治療TB首兩個月內開展ART（早期開展ART）。第24個月時，早期開展ART較後期開展或沒開展ART的患者有較佳治療效果（痊癒及完成治療而沒有復發）〔91%比67%；P=0.007〕，並且在調整潛在混雜因素後能預測良好的治療成效。32人中有13名（41%）早期開展ART的病人於服用TB藥物後有不良反應，稍多於其餘的病人（59/228或26%；P=0.08）。前者比後者有較多的免疫重建發炎症候群（7/32或22%比9/228或4%；P<0.001），當中沒有患者因免疫重建發炎症候群死亡。

結論 早期開展ART有利於HIV合併TB並具低CD4數目（<200/μL）的患者的治療效果。因早期開展ART而可能出現的藥物增效毒性及免疫重建發炎症候群沒有明顯地損害TB治療成效。

Methods

Programme record forms, which systematically collected TB and HIV data of cases reported to the TB-HIV Registry, were retrospectively reviewed.[16] For patients with significant adverse effects from drugs and IRIS during anti-TB treatment, the relevant clinical records were traced and reviewed. There were 296 patients reported to the TB-HIV Registry from 1 January 1996 to 31 December 2009 and managed by the DH in the analysis, including patients already discharged from hospital.

Patients in the early treatment arm were ART-naïve, and had their therapy initiated within 2 months from the date of starting anti-TB treatment (TBDOS). The comparator arm comprised patients who had ART initiated more than 2 months after TBDOS or who did not receive ART during the course of their anti-TB treatment. Treatment outcomes of TB were defined according to the WHO recommendations.[17] Patients with a cure or treatment completion without relapse within 24 months were considered to have favourable outcomes. All other outcomes, including those who failed treatment, were transferred out, defaulted treatment, or died within 24 months were considered to have unfavourable outcomes. A significant adverse effect from treatment was defined as one entailing the withholding or modification of their drugs, or one entailing premature cessation of treatment.

Regarding IRIS, it was defined as the

TABLE 1. Demographics and clinical presentation of patients reported from chest clinics and Special Preventive Programme (1996-2009)

Demographics/clinical presentation*	Group A (n=32)	Group B (n=228)	All patients (n=260)
Median (range) age (years)	44 (35-55)	39 (34-51)	40 (34-51)
Sex (male/female)	26/6	202/26	228/32
Ethnicity			
Chinese	27 (84.4%)	168 (73.7%)	195 (75.0%)
Non-Chinese Asians	4 (12.5%)	54 (23.7%)	58 (22.3%)
Caucasians	1 (3.1%)	4 (1.8%)	5 (1.9%)
Africans	0	2 (0.9%)	2 (0.8%)
Drug addiction	1 (3.1%)	17 (7.5%)	18 (6.9%)
Year of TB			
1996-2002	11 (34.4%)	74 (32.5%)	85 (32.7%)
2003-2009	21 (65.6%)	154 (67.5%)	175 (67.3%)
Case category			
New case	29 (90.6%)	214 (93.9%)	243 (93.5%)
Relapse case	2 (6.3%)	8 (3.5%)	10 (3.8%)
Re-treatment after default	1 (3.1%)	5 (2.2%)	6 (2.3%)
Other	0	1 (0.4%)	1 (0.4%)
Extra-pulmonary involvement	25 (78.1%)	141 (61.8%)	166 (63.8%)
Chest X-ray findings†			
Extensive disease‡	10 (38.5%)	43 (24.6%)	53 (26.4%)
Presence of cavity‡	2 (7.7%)	14 (8.0%)	16 (8.0%)
Hilar/mediastinal lymph node enlargement	8 (27.6%)	31 (15.8%)	39 (17.3%)
Pleural effusion (± lung parenchymal lesion)	7 (24.1%)	40 (20.4%)	47 (20.9%)
Miliary shadows	7 (24.1%)	26 (13.3%)	33 (14.7%)
Bacteriological data			
Positive sputum smear§	10 (32.3%)	97 (44.7%)	107 (43.1%)
Positive sputum and/or other cultures¶	28 (87.5%)	172 (75.4%)	200 (76.9%)
No resistance	25 (89.3%)	135 (79.4%)	160 (80.8%)
Any resistance (excluding MDR/XDR)	3 (10.7%)	32 (18.8%)	35 (17.7%)
MDR	0	3 (1.8%)	3 (1.5%)
XDR	0	0	0
Other ADI at TB diagnosis	5 (15.6%)	35 (15.4%)	40 (15.4%)
Median (IQR) CD4 count at TB diagnosis (cells/μL)‖	43.5 (17.0-96.5)	83.5 (33.8-199.5)	74.0 (29.0-181.0)
Median (IQR) viral load at TB diagnosis (copies/mL)	250 000 (115 000-660 000)	150 000 (59 000-430 000)	160 000 (62 750-440 000)

* TB denotes tuberculosis, MDR multidrug resistance, XDR extensively drug resistance, ADI AIDS-defining illness, and IQR interquartile range

† Among 225 (86.5%) patients with abnormal chest X-ray (29 patients in group A and 196 patients in group B); excluding 3 patients who had a positive sputum bacteriology but X-ray results were unknown and 1 patient who had a positive sputum smear but apparent normal chest radiograph

‡ Among 26 (81.3%), 175 (76.8%), and 201 (77.3%) patients with lung parenchymal lesion in group A, group B, and all patients, respectively; extensive disease defined as lung lesion occupying more than the equivalent of right lung

§ Among 31 (96.9%), 217 (95.2%), and 248 (95.4%) patients with sputum smear examination performed at the time of tuberculosis diagnosis in group A, group B, and all patients, respectively

¶ Sensitivity results among 28 (87.5%), 170 (74.6%), and 198 (76.2%) patients with positive cultures of sputum and/or other specimens and drug susceptibility tests performed in group A, group B, and all patients, respectively. Two patients with positive cultures from group B did not have sensitivity test performed

‖ All P>0.05 except P=0.007 for CD4 count at TB diagnosis between patients from the two groups

development of recurrent, new, or worsening symptoms or signs of TB, or radiological deterioration of TB after initiation of treatment, and after exclusion of alternative diagnoses.[18]

All the data collected were imported into Epi-Info software, and exported into a statistical package (Statistical Package for the Social Sciences Windows version 16.0; SPSS Inc, Chicago [IL], US) for analysis. For the identification of variables that might affect treatment outcomes, comparison of favourable versus unfavourable outcomes was made using the Mann-Whitney test for continuous variables, and

Chi squared or Fisher's exact tests for categorical variables. A logistic regression analysis using a forward conditional approach was then performed to identify variables that were independently associated with adverse anti-TB treatment outcomes.

This study was an evaluation of the public health programme for HIV-associated TB in Hong Kong and did not constitute human subject research. Throughout the reviewing process, we nevertheless exercised due care to protect the privacy of patients by excluding personal identifying information from the electronic database.

Results

Of the 296 patients reported to the TB-HIV Registry during the study period and managed by the DH, six (2%) had incomplete clinical records, whilst 30 (10%) were already on ART when TB was diagnosed. The demographics and clinical presentations of the remaining 260 (all ART-naïve) patients are shown in Table 1. As a whole, the patients had relatively advanced HIV disease at the time TB was diagnosed, as evidenced by a low median (interquartile range [IQR]) CD4 count of 74/μL (29-181/μL) and a high median (IQR) viral load of 160 000 (62 750-440 000) copies/mL.

Regarding the 260 ART-naïve patients, 32 (12%) had ART initiated within 2 months (median, 40; IQR, 14-51 days) from TBDOS (group A). The ART regimens used mostly comprised two nucleoside reverse-transcriptase inhibitors, and one non-nucleoside reverse-transcriptase inhibitor or a protease inhibitor. In the remaining 228 patients (group B), ART was initiated more than 2 months after TBDOS (n=131; or 50%) or not initiated during the course of anti-TB treatment (n=97 or 37%; Fig). There were no significant differences in the demographic and clinical characteristics of the two groups, except that patients from group A had a lower median CD4 count than those in group B (43.5/μL vs 83.5/μL; P=0.007) [Table 1].

A standard anti-TB regimen based on isoniazid, rifampicin or rifabutin, pyrazinamide in the initial phase, and isoniazid and rifampicin or rifabutin in the continuation phase was used for 165 (64%) of the patients; 72 (28%) experienced one or more significant adverse effects from anti-TB drugs. The details of these adverse effects are shown in Table 2, which revealed a greater proportion in group A than B patients (13/32 or 40.6% vs 59/228 or 25.9%), but this difference did not reach statistical significance (P=0.08).

Of the 260 patients, 16 (6%) who were ART-

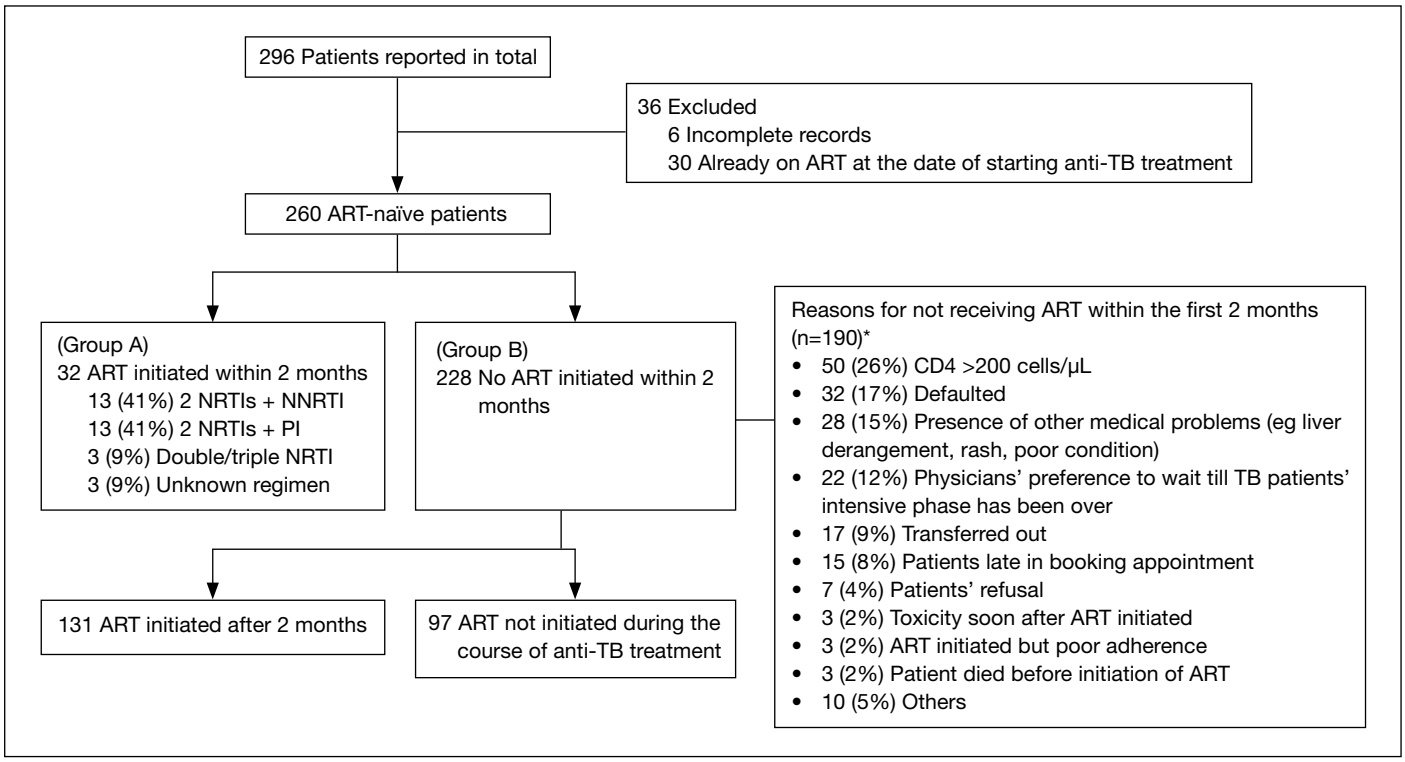

FIG. A flowchart showing antiretroviral therapy among 296 patients managed at Tuberculosis and Chest Service and Special Preventive Programme from January 1996 to December 2009

ART denotes antiretroviral therapy, NRTI nucleoside reverse-transcriptase inhibitor, NNRTI non-nucleoside reverse-transcriptase inhibitor, PI protease inhibitor, and TB tuberculosis

* Information on reasons for not receiving ART in the first 2 months were available in 190 patients only

TABLE 2. Significant adverse effects due to anti-tuberculosis drugs experienced by group A and group B patients during the course of anti-tuberculosis treatment*

Adverse effect	Group A (n=32)	Group B (n=228)	P value
Any adverse effects	13 (40.6%)	59 (25.9%)	0.08
Skin rash	6 (18.8%)	23 (10.1%)	0.15
Liver derangement	5 (15.6%)	14 (6.1%)	0.06
Severe gastro-intestinal upset	2 (6.3%)	8 (3.5%)	0.50
Leukopenia	1 (3.1%)	5 (2.2%)	0.87
Visual disturbance	0	6 (2.6%)	0.64
Fever	0	7 (3.1%)	0.58
Arthropathy	0	4 (1.8%)	0.74
Dizziness	0	2 (0.9%)	0.86
Thrombocytopenia	0	8 (3.5%)	0.55
Neuropathy	1 (3.1%)	3 (1.3%)	0.41
Others	2 (6.3%)	2 (0.9%)	0.08

* Some patients experienced more than one significant adverse effect from anti-tuberculosis drugs

naïve at TB diagnosis experienced IRIS during anti-TB treatment. Female patients were more likely than male patients to experience IRIS (6/32 or 19% vs 10/228 or 4%; P=0.002). A significantly higher proportion of group A than B patients experienced IRIS (7/32 or 22% vs 9/228 or 4%; P<0.001). The details of ART therapy and manifestations of the IRIS in these patients are shown in Table 3. Among the seven patients with IRIS from group A, their median CD4 count at the time of initiation of ART was 98/μL (IQR, 30-121/μL). Four (57%) of the patients were treated with corticosteroid. Five (71%) were hospitalised. Antiretroviral therapy was terminated in two (29%) patients who had pericardial involvement without significant cardiac tamponade. No death occurred as a result of IRIS episodes.

The median duration of effective treatment was 12 (IQR, 9-13) months. The TB treatment outcomes at 24 months from TBDOS are shown in Table 4. Cure/treatment completion without relapse within 24 months was effected in 182 (70.0%) patients. Whereas 32 (12.3%) patients died within 24 months (30 before and 2 after completion of anti-TB treatment). The median interval from TBDOS to death was 6 (IQR, 4-10) months; two died within 2 months (both from group B). Among the 30 deaths in group B, the cause was TB in eight, non-TB in 11, and could not be traced in 11. The two patients from group A died from non-TB causes. A significantly higher proportion of group A patients had favourable TB treatment outcomes than in group B (29/32 or 91% vs 153/228 or 67%; P=0.007).

Follow-up data were available in 161 of the 182 patients who had a cure/treatment completion; 21 patients were lost to follow-up immediately after completion of anti-TB treatment, eight (5%) had a relapse (4 bacteriological, 1 histological, and 3 radiological-clinical) at a median of 39 (IQR, 20-75) months from TBDOS. Three of these relapses were early (within 24 months and from group B). Overall, the relapse rate among the patients available for follow-up was 1 in 27 person-years. There was no statistically significant difference in relapse rates for patients in groups A (2/25 or 8%) and B (6/136 or 4%) [P>0.05].

Of the variables that might be associated with treatment outcomes, older age, being non-Chinese, and no initiation of ART within 2 months were independent predictors for unfavourable outcomes based on multiple logistic regression analysis (Table 5). Subjects with no initiation of ART within 2 months had a 3.82 odds (95% confidence interval [CI], 1.10-13.3; P=0.035) of having a poor treatment outcome compared with those having ART initiated during that period. Similar findings were observed after excluding patients who were transferred out, had defaulted, or died within 2 months of anti-TB treatment (Table 5).

Among the 32 patients with ART initiated within 2 months, the improvement in CD4 count and the suppression of viral load was maintained at 12 and 24 months from TBDOS. The median CD4 count was 44/μL (IQR, 17-97/μL), 179/μL (IQR, 107-292/μL), and 251/μL (IQR, 141-404/μL) at baseline and at 12 and 24 months from TBDOS, respectively. The corresponding median viral loads were 250 000 (IQR, 115 000-660 000), 400 (IQR, 105-625), and 400 (IQR 86-400) copies/mL, respectively.

Discussion

Our study showed that HIV-associated TB carried a relatively high case fatality rate. Patients with ART initiated within 2 months from TBDOS had better treatment outcomes compared with their counterparts, notwithstanding an increased frequency of adverse effects from anti-TB drugs and IRIS. All in all, older age, being non-Chinese, and ART not being initiated within 2 months were independent predictors of an unfavourable outcome at 24 months.

An association between early initiation of ART and a favourable TB treatment outcome has been reported in previous studies, mostly in African subjects.[19-21] More recently, randomised controlled trials have been conducted that addressed the issue of when to start ART in patients with HIV-associated TB, which were mostly in developing countries with high prevalence rates of TB and HIV.[22-25] In the STRIDE trial on patients with CD4 counts of <50/μL, 16% who received ART within 2 weeks from TBDOS had a new AIDS-defining illness or died, in contrast

TABLE 3. Manifestations of IRIS experienced by seven patients with ART initiated within 2 months from TBDOS (group A) and nine patients with ART initiated after 2 months or ART not initiated during the course of anti-TB treatment (group B)*

Patient No.	Sex	Age (years)	CD4 count at IRIS (/μL)	ART regimen	Interval between TBDOS and ART (months)	Clinical feature	Remark
Group A (32 patients with ART initiated ≤2 months)							
1	M	34	98	CBV, IDV	2	Increased cervical lymph node, fever, night sweat	Steroid therapy, TB Px prolonged to 12 months
2	M	38	13	IDV, 3TC, AZT	2	Increased pleural effusion	Hospitalisation, TB Px prolonged to 12 months
3	F	39	147	AZT, ddI-EC, EFV	0	Development of new cervical lymph node	Steroid therapy, TB Px prolonged to 14 months
4	M	31	30	TDF, FTC, Kaletra	1	Increased bilateral lung shadows, pleural and pericardial effusion	Hospitalisation, ART discontinued
5	M	41	62	3TC, ABC, d4T, LPVr	0	Development of pericardial effusion without cardiac tamponade	Hospitalisation, steroid therapy, ART discontinued, Px prolonged to 12 months
6	F	48	100	3TC, d4T, LPVr	2	Increased cervical and mediastinal lymph node, development of pelvic abscess	Hospitalisation, incision and drainage, TB Px prolonged to 15 months
7	M	45	121	3TC, d4T, EFV	2	Increased axillary mass	Hospitalisation, steroid therapy, incision and drainage
Group B (228 patients with ART initiated >2 months or no ART initiated)							
1	M	37	52	CBV, IDV	3	Increased left lower lobe shadow and development of left pleural effusion	Hospitalisation
2	M	52	24	3TC, d4T, IDV	2.5	Development of miliary shadows on CXR	Hospitalisation, TB Px prolonged to 12 months
3	F	20	13	3TC, d4T, IDV	3	Increased right upper lobe shadow	Hospitalisation
4	F	37	15	Nil	NA	Systemic fever	Hospitalisation, NSAID therapy
5	M	38	152	Nil	NA	Systemic fever	Hospitalisation, steroid therapy
6	F	35	981	Nil	NA	Increased upper lobe shadows	Hospitalisation
7	M	54	116	Nil	NA	Increased sub-mandibular lymph node	Steroid therapy
8	M	73	44	Nil	NA	Developed bilateral pleural effusion	-
9	F	34	14	Nil	NA	Increased supra-clavicular lymph node	-

* ABC denotes abacavir, ART antiretroviral therapy, AZT zidovudine, CBV combivir, CXR chest X-ray, d4T stavudine, ddI-EC Videx EC, EFV efavirenz, FTC emtricitabine, IDV indinavir, IRIS immune reconstitution inflammatory syndrome, LPVr lopinavir co-formulated with ritonavir, NA not applicable, NSAID non-steroidal anti-inflammatory drug, Px treatment, TB tuberculosis, TBDOS date of starting anti-TB treatment, 3TC lamivudine, and TDF tenofovir

TABLE 4. Tuberculosis treatment outcomes at 24 months from date of starting anti-TB treatment (TBDOS) among 260 patients reported from chest clinics and Special Preventive Programme*

Treatment outcome	Group A (n=32)	Group B (n=228)	All patients (n=260)
Cure/treatment completion without relapse within 24 months	29 (90.6%)	153 (67.1%)	182 (70.0%)
Died	2 (6.3%)	30 (13.2%)†	32 (12.3%)
Defaulted	1 (3.1%)	28 (12.3%)‡	29 (11.2%)
Transferred out	0	13 (5.7%)§	13 (5.0%)
Failure	0	1 (0.4%)	1 (0.4%)
Relapse at 24 months¶	0	3 (1.3%)	3 (1.2%)

* P=0.007

† Median interval from TBDOS to death, 6.0 (interquartile range [IQR], 3.8-9.8) months; two patients died within 2 months

‡ Median interval from TBDOS to default, 6.3 (IQR, 3.0-9.0) months; three patients defaulted within 2 months

§ Median interval from TBDOS to transferred out, 2 (IQR 1.0-7.5) months; four patients were transferred out within 2 months

¶ Seven out of 29 patients (24.1%) in group A and 37 out of 153 patients (24.2%) in group B who had cure/treatment completion were lost to follow-up within 24 months from TBDOS. Relapse rates were compiled by cross-reference to the Hong Kong Tuberculosis notification registry

TABLE 5. Demographic, clinical, and treatment characteristics in 260 ART-naïve patients with HIV-associated TB and their comparison by univariate and multiple logistic regression analyses*

Variable	Treatment outcome at 24 months		P value (univariate analysis)	Multiple logistic regression analysis		
	Favourable (n=182)	Non-favourable (n=78)		P value	OR	95% CI
Age >60 years	23 (12.6%)	13 (16.7%)	0.389	0.029	2.46	1.10-5.52
Female sex	19 (10.4%)	13 (16.7%)	0.161	0.634	-	-
Non-Chinese	32 (17.6%)	33 (42.3%)	<0.001	0.001	3.09	1.55-6.17
Year of TB			0.885	0.361	-	-
1996-2002	60 (33.0%)	25 (32.1%)				
2003-2009	122 (67.0%)	53 (67.9%)				
Extra-pulmonary TB	120 (65.9%)	46 (59.0%)	0.284	0.942	-	-
CD4 count (/μL)†			0.857	0.803	-	-
<100	96 (56.8%)	36 (57.1%)				
100-199	37 (21.9%)	12 (19.0%)				
≥200	36 (21.3%)	15 (23.8%)				
Presence of other ADI at TB diagnosis	28 (15.4%)	12 (15.4%)	0.079	0.811	-	-
Presence of resistance to anti-TB drugs‡	25 (17.0%)	13 (25.5%)	0.033	0.185	-	-
ART not initiated within 2 months	153 (84.1%)	75 (96.2%)	0.007	0.035	3.82	1.10-13.33§

* ADI denotes AIDS-defining illness, ART antiretroviral therapy, CI confidence interval, HIV human immunodeficiency virus, OR odds ratio, and TB tuberculosis

† Information on CD4 count available in 169 patients with favourable outcome and 63 patients with non-favourable outcome, respectively

‡ Information on drug sensitivity pattern available in 147 patients with favourable outcome and 51 patients with non-favourable outcome with positive cultures (any specimens), respectively

§ P=0.048, OR=3.53 (95% CI, 1.01-12.35) if nine cases that were either transferred out, defaulted or died within 2 months from group B were excluded from the analysis

to 27% who received it between 8 and 12 weeks from TBDOS (the 95% CI for the difference in rates was 1.5-20.5%; P=0.02).[22] However, although the studied subjects were recruited from four continents, most were Africans and South Americans; only 7% were Asians. In the SAPIT trial,[23] the studied subjects were also Africans, with an observed 68% lower rate of AIDS or death among patients with CD4 counts of <50/μL, who received ART within 4 weeks from TBDOS compared with that of other patients; though the difference was substantial it was not statistically significant (P=0.06). The CAMELIA trial[24] studied Asian subjects and showed a significant survival benefit when ART was initiated 2 weeks after the start of TB treatment in HIV-infected patients with CD4 counts of <200/μL. However, details on the manifestations of IRIS (numbers required to withhold ART, receiving steroid treatment, and hospitalised) were lacking. The present study provides comprehensive data on the manifestations of IRIS among patients with early initiation of ART, and complements previous studies by providing evidence that early ART can improve TB treatment outcomes in patients with low CD4 counts. Moreover, this ensued in areas with an intermediate TB burden and low HIV prevalence, despite a higher rate of adverse effects from drugs and IRIS. Thus, the findings from our study lend further support to the WHO recommendation in patients with HIV-associated TB that ART should be started as early as possible after the onset of anti-TB treatment.[26]

The less-favourable treatment outcomes seen in non-Chinese subjects may have been due to genetic differences in pharmacokinetics of the anti-TB and anti-retroviral drugs administered, or to differences in health-seeking behaviour. Differences in access to medical service cannot be excluded as the SPP service was not free of charge, unlike that provided by TB&CS. It is also possible that some non-Chinese patients who were not eligible or less well-off had less easy access to the SPP service. Advanced age was another independent predictor of treatment outcomes inferred from the multiple logistic regression analysis. Being elderly was associated with unfavourable TB treatment outcomes, especially in those who were underweight and had co-existing medical diseases.[27] In our series, of the 32 patients who died before completion of anti-TB treatment, more than one third were aged >60 years.

Adverse effect from drugs during concomitant anti-TB and anti-retroviral therapy is a competing factor in deciding when to start ART in patients with HIV-associated TB. Our study shows that patients with ART initiated early tended to experience more significant adverse effects compared with the remainder, though the difference did not reach statistical significance. Better treatment outcomes in this group of patients suggested that negative effect due to drug co-toxicity brought about by early initiation of ART was offset by the restoration of immune function.

Late initiation of ART may avoid IRIS. Our study showed patients with early initiation of ART experienced IRIS more often than their counterparts. However, ART was stopped only in two cases, and no death was attributed to IRIS. Our findings therefore suggest that with careful attention for IRIS, the benefits from early initiation of ART outweigh its negative effects. It should be noted, however, that in our study the incidence of IRIS was low compared with other series with figures of 8% to 43%.[28-30] This may be due to the retrospective nature of our study, genetic or nutritional factors, or to difference in doctors' practices for the timing of ART initiation. The absence of TB meningitis among our reported cases with IRIS may also explain the better outcomes in our series. Nevertheless, the fact that most of the cases were manageable and none resulted in death was reassuring.

There is a theoretical risk of impaired antivirological effect of ART because of a potential drug-drug interaction, when initiated early in the course of anti-TB treatment. Modifications of both anti-TB and anti-retroviral drug regimens are often needed. For the majority of patients, rifampicin-based regimens can be successfully combined with the non-nucleoside reverse-transcriptase inhibitors nevirapine and efavirenz, though their plasma concentrations may be reduced.[31] There are reassuring data on the effectiveness of standard doses of efavirenz with concomitant rifampicin, but a higher risk of virological failure with nevirapine has been reported.[32] Notably, the improvement in CD4 count and suppression of viral load were maintained at 12 and 24 months among patients in whom ART was initiated early. The findings from our study suggest that with careful tailoring of regimens for TB and HIV, the outcomes for both diseases are not compromised.

The high case fatality rate at 24 months from TBDOS in our cohort was in line with that reported among HIV-associated TB patients in some other studies.[33-35] Given that HIV-associated TB carries a relatively high risk of death, often from other opportunistic infections, and early initiation of ART improves treatment outcome, it is imperative that HIV antibody testing be provided for all patients with TB attending chest clinics. Assessment of the patient's immune and virological status to determine the need for ART can then be carried out, and appropriate prophylactic treatment against other opportunistic infections can also be provided.

The strength of our study is that we retrieved relatively complete sets of data on adverse effects from drugs and IRIS in relation to the timing of ART initiation; such data being less frequently reported in previous studies. As discussed, most of the previous studies examined subjects from developing countries with a high HIV prevalence, especially in Africa. Data in intermediate TB burden countries with a low HIV prevalence and good health infrastructure are meagre. Thus, our findings shed light on the optimal timing of initiation of ART in patients with HIV-associated TB in Hong Kong and other Asian areas with similar TB and HIV epidemiology.

One limitation of the present study was that HIV infection is not statutorily notifiable in Hong Kong. So co-infected patients not treated in the government HIV clinics may not be identifiable and therefore not included in the registry. It is unclear if this could have led to a systematic bias. Second, as with other retrospective studies, it may not be possible to examine all factors that may affect patient outcomes. Third, adverse effects from drugs and IRIS may have been underreported because of the retrospective nature of the study. Nevertheless, we reviewed the clinic records of the patients intensively whenever necessary, and believe the reporting on adverse effects from drugs and IRIS was reasonably complete, except for the mildest cases. Fourth, there was a possible selection bias in the analysis of predictors of treatment outcome, as some group B cases were transferred out, defaulted, or died within 2 months of anti-TB treatment before ART could be initiated. Their inclusion could have biased towards non-initiation of ART within 2 months as a predictor of unfavourable treatment outcome. Nevertheless, after the exclusion of these cases, non-initiation of ART within 2 months remained an independent predictor of unfavourable treatment outcomes. Fifth, some cases labelled as a cure/treatment completion were lost to follow-up within 24 months from TBDOS. However, relapse rates were compiled by cross-referencing with the Hong Kong TB notification registry. Moreover, of the seven group A cure/treatment-completion patients lost to follow-up within 24 months, five were Chinese residing in Hong Kong, and only two were non-Chinese. As TB is a notifiable disease in Hong Kong, it is unlikely that the five Chinese had a relapse within 24 months. Even assuming that the two non-Chinese patients from group A had had a relapse within 24 months, the difference in the proportion of patients with favourable treatment outcomes at 24 months still remained statistically significant (27/32 or 84% vs 153/228 or 67%; P=0.048). Bias due to misclassification of outcomes was therefore unlikely.

Conclusions

Early initiation of ART is associated with favourable TB treatment outcomes in patients with HIV-associated TB and a low CD4 count of <200/μL. Our findings suggest that the burden of polypharmacy, drug co-toxicity, and IRIS due to earlier initiation of ART does not undermine TB treatment outcomes to a significant extent. Further prospective randomised

controlled trials that address the timing of ART initiation among such subjects in the Asia-Pacific region will better inform interventions for improving treatment outcomes in HIV patients with TB in this region.

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