What do the clinical features of positive nontuberculous mycobacteria isolates from patients with HIV/AIDS in China reveal? A systematic review and meta-analysis

Jianwei Yuan, Yan Wang, Lin Wang, Hongxia Wang, Yuan Ren, Wenzhe Yang

Background China has a high burden of nontuberculous mycobacterial (NTM) infections. Immunocompromised populations, such as those with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), are at a higher risk of being infected with NTM than immunocompetent individuals. Yet, there is a paucity of information on the clinical features of positive NTM isolates from patients with HIV/AIDS in China. To address this gap, we conducted a systematic review and meta-analysis of existing studies, comparing them against current expert consensus to provide guidance for clinical practice.

Methods Two researchers independently searched eight databases (SinoMed, China National Knowledge Infrastructure, Wanfang, VIP, Cochrane Library, PubMed, Embase, and Web of Science) from inception to 26 December 2022 to retrieve published Chinese- and English-language studies reporting clinical features of NTM-positive isolates among patients with HIV/AIDS in China.

Results We included 28 studies with 1861 patients. The rate of positive NTM isolates detected from men among all patients was 87.3%. NTM species distribution was mainly Mycobacterium avium complex (64.3%), which was predominant in different regions. The five most common clinical symptoms were fever (68.5%), cough or expectoration (67.0%), appetite loss (49.4%), weight loss (45.5%), and superficial lymphadenectasis (41.1%). The prevalence of laboratory tests were as follows: albumin <35 g/L (55.6%), erythrocyte sedimentation rate >20 mm/h (91.4%), anaemia (59.0%), predominantly mild, CD4+ T cell count ≤50 pieces/μL (70.3%), and CD4+ T cell count 51-200 pieces/μL (22.1%). Lesion manifestations in thoracic imaging mainly included bilateral lung involvement (83.8%), showed stripe shadows (60.3%), patchy shadows (42.9%), nodules (40.6%), and bronchiectasis (38.6%). Accompanied signs included thoracic lymph node enlargement (49.5%). Seventy per cent of symptoms improved after treatment.

Conclusions Focusing on clinical symptoms, laboratory tests, and thoracic imaging helps with initial screening for NTM infections. Physicians should raise awareness of the diagnosis and treatment of Mycobacterium avium complex, providing guidance for experimental treatment, screening of priority populations for NTM infections, and prophylactic treatment of NTM disease.

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Human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) is a major contributor to the global burden of disease, accounting for the second highest number of disability-adjusted life years among 10-24, and 25–49-year-olds [1]. At least one million people are currently living with HIV/AIDS in China, with a growing number
of reported cases across all age groups [2]. Simultaneously, antiretroviral therapy (ART) has led to a reduction in morbidity and mortality, a gradual increase in average life expectancy, and a decrease in associated opportunistic infections (OIs) in patients with HIV/AIDS [3].

However, the rapid increase in CD6+ T-cell counts during the first three to four months of ART treatment may promote the development of OIs [4]. In high-income countries, including the USA and Canada, disseminated Mycobacterium avium complex or Mycobacterium kansasii infection of the species nontuberculous mycobacterial (NTM) is the third most common OI, after pneumocystis jirovecii pneumonia and oesophageal candidiasis [5]. Moreover, people living with HIV with NTM disease were associated with a long-term case-fatality rate (CFR), with overall CFR increasing from 15.7% at one year to 22.6% at five years [6].

In low- and middle-income countries (LMICs), NTM infections are largely overlooked due to limitations in medical resources and technology, with the first case of NTM lung disease in Ecuador being diagnosed in 2017 [7]. There is also a significant delay in the diagnosis of NTM diseases, especially in rural areas [8], and a high risk of misdiagnosis of Mycobacterium tuberculosis (MTB) infections, with a misdiagnosis rate of 92.81% and a maximum misdiagnosis time of 21 years [9]. NTM infections are not a notifiable infectious disease in most countries, and these factors combine to make NTM infections uncommon in studies of OIs in patients with HIV/AIDS in LMICs [10,11].

In fact, the number of NTM infections in LMICs is grossly underestimated. A national survey of tuberculosis (TB) prevalence among participants aged ≥15 years in Gambia showed an NTM separation rate of 39.8% [12] and 29.0% in India [13]. The National TB Epidemiological Sample Survey in China showed that the prevalence rate of NTM isolation increased from 11.1% in 2001 to 22.9% in 2010 [14,15]. The rate of NTM isolation of patients with HIV/AIDS in Shanghai was much higher than suggested by the National TB Epidemiological Sample Survey [16]. Some MTB infections have co-infection with NTM, particularly among patients with HIV [17-19]. NTM infections are also one of the common opportunistic infections in Chinese patients with HIV/AIDS [20-22].

NTM refers to mycobacterial species other than MTB complex and Mycobacterium leprae [23], which are commonly found in the natural environment (eg, water and soil) [24,25] and cause infection in susceptible individuals with underlying diseases, including chronic obstructive pulmonary disease, immunodeficiency, and HIV infection [26]. Various NTM infections, which do not have a specific clinical presentation [27], are less susceptible to standard anti-tuberculous drug regimens and require longer treatment durations than MTB infections [28,29].

Currently, there is little information on the clinical features of NTM isolates from patients with HIV/AIDS, which can easily lead to misdiagnosis, underdiagnosis, and even delay in clinical treatment. An expert consensus on diagnosis and treatment of patients with HIV/AIDS combined with NTM infections was published in China only in 2019 [30] and has not been updated since. Moreover, it was based on small sample studies and was unsupported by a systematic review and meta-analysis, the highest level of evidence in evidence-based medicine. Therefore, studying NTM isolates from patients with HIV/AIDS is of great significance not only for China, but for LMICs at large. Accordingly, we conducted a systematic review and meta-analysis of positive NTM isolates from patients with HIV/AIDS in China in terms of gender distribution, species distribution, clinical symptoms, laboratory tests, thoracic imaging manifestations, and treatment outcome.

METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines in conducting this study [31-33].

Search strategy

We systematically searched Chinese (SinoMed, China National Knowledge Infrastructure (CNKI), Wanfang, and VIP) and English databases (Cochrane Library, PubMed, Embase, and Web of Science). To capture all relevant literature, we used a combination of subject terms and free terms such as “HIV”, “AIDS”, and “NTM”, adjusted for each database (Table S2 in the Online Supplementary Document). We set no restrictions on the type of published literature and limited the time span from inception to 26 December 2022. We searched the included studies’ references for potentially relevant information.
Inclusion and exclusion criteria

We included cross-sectional, case-control, cohort, or case series studies on Chinese patients with HIV/AIDS associated with positive NTM isolates. The observed indicators were clinical symptoms, laboratory tests, thoracic imaging manifestations, species distribution and treatment outcome. If multiple articles examined a clinical indicator, but were based on the same sample data (e.g., data from the same institution or from the same study period), we only included the article with the most descriptive statistics of the data in question. All articles had to meet the diagnostic criteria for NTM isolated from culture [23].

The exclusion criteria were as follows: non-Chinese and -English literature; duplicate publications; unavailability of the required data; case studies, reviews, book chapters, expert opinions, comments, and so on; and basic studies, such as cellular and animal studies.

Study selection

Two researchers (L Wang and HX Wang) independently searched the literature, conducted deduplication, and performed the initial title/abstract screening, followed by a full-text screening of the retrieved studies. Subsequently, they collected the relevant data and cross-checked for the appropriateness of inclusion. Disagreements were resolved through discussion or negotiation with a third researcher (Y Ren).

Quality assessment

As we included studies with varying designs, we used a different risk of bias tools to assess possible sources of bias, depending on the design in question. We used the scales recommended by the Agency for Healthcare Research and Quality (AHRQ) [34] to assess the quality of cross-sectional studies, the Newcastle-Ottawa Scale (NOS) for case-control and cohort studies [35], and the Joanna Briggs Institute (JBI) Critical Appraisal Checklist [36] for case-series studies (Table S3-S6 in the Online Supplementary Document). Two investigators (L Wang and HX Wang) independently evaluated the risk of bias in the included studies and cross-checked the results with a third investigator (Y Ren), resolving disagreements through discussion. We tabulated data from the included studies to identify bias in the quality evaluation phase.

Data extraction

We extracted the following information: first author, publication date, region of study subjects, sample size, study type, and gender distribution, observation indicators (clinical symptoms, laboratory tests, thoracic imaging manifestations, species distribution, and treatment outcome), and key elements of risk of bias evaluation.

Statistical analysis

Based on clinical considerations, we pooled similar and appropriate characteristics. We performed meta-analyses using Stata, version 17.0 (StataCorp, College Station, Texas, USA) for observations with three or more included studies. We conducted Freeman-Tukey double inverse sine transformation for dichotomous variables with extreme rates (r) of 0 or 1 [37]. We converted continuous variables from medians and quartiles to means and standard deviations according to Luo et al. (online calculator: https://www.math.hkbu.edu.hk/~tongt/papers/median2mean.html) [38], with effect scale mean deviation values/event rates (R values) and 95% confidence intervals (CIs) as effect size indicators. We performed meta-analyses using a fixed-effects model when $I^2$ was <50% and $P$ was ≥0.10 (indicating no statistical heterogeneity in the literature); if $I^2$ was ≥50% or $P$ was ≤0.10 (indicating statistical heterogeneity), we used a random-effects model. Additionally, we performed subgroup analyses of regions and sample sizes to explore the sources of heterogeneity. We considered differences statistically significant at $P<0.05$.

RESULTS

Search results

We retrieved 709 studies from the preliminary search, including 140 studies in English and 569 in Chinese. After the screening process, we included 28 studies (Figure 1).

Characteristics and quality assessment of included studies

Twenty-eight studies involved 1861 patients with HIV/AIDS-positive NTM isolates, including 23 cross-sectional studies, three case-control studies, one cohort study, and one case series. They were published between
2008 and 2022, with 15 (53.6%) being published between 2018 and 2022. The studies were conducted in 13 regions (provinces, municipalities directly under the central government, and autonomous regions), mostly in the southern region, chiefly Guangxi (Figure 2, Table 1, and Table S7 in the Online Supplementary Document). Most of the patients were men (87.3%; 95% CI = 83.2-91.0) (Figure 3).

Figure 1. Flowchart of positive NTM in patients with HIV/AIDS systematic review study selection.

Figure 2. China maps for distribution of included studies.
Table 1. Essential information and quality assessment of included literature in systematic review of positive NTM from patients with HIV/AIDS in China

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Location (W/E/N/S/C)</th>
<th>Survey date</th>
<th>Total sample size</th>
<th>Men, n (%)</th>
<th>Observed indicators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Song et al., 2011 [39]</td>
<td>Case-series study</td>
<td>Beijing (N)</td>
<td>2009-2010</td>
<td>5</td>
<td>4 (80)</td>
<td>No</td>
</tr>
<tr>
<td>Ding et al., 2022 [40]</td>
<td>Cross-sectional study</td>
<td>Beijing (N)</td>
<td>2016-2021</td>
<td>71</td>
<td>62 (87.3)</td>
<td>Yes</td>
</tr>
<tr>
<td>Wang et al., 2017 [41]</td>
<td>Cross-sectional study</td>
<td>Beijing (N)</td>
<td>2009-2015</td>
<td>33</td>
<td>28 (84.8)</td>
<td>No</td>
</tr>
<tr>
<td>Wu et al., 2017 [42]</td>
<td>Cross-sectional study</td>
<td>Guangdong (S)</td>
<td>2008-2013</td>
<td>31</td>
<td>28 (90.3)</td>
<td>Yes</td>
</tr>
<tr>
<td>Cao et al., 2021 [43]</td>
<td>Cross-sectional study</td>
<td>Guangdong (S)</td>
<td>2014-2019</td>
<td>43</td>
<td>38 (88.4)</td>
<td>Yes</td>
</tr>
<tr>
<td>Jiang et al., 2014 [44]</td>
<td>Cross-sectional study</td>
<td>Guangdong (S)</td>
<td>2006-2010</td>
<td>13</td>
<td>13 (100)</td>
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</tr>
<tr>
<td>Meng et al., 2018 [45]</td>
<td>Cross-sectional study</td>
<td>Guangxi (S)</td>
<td>2012-2015</td>
<td>29</td>
<td>19 (65.5)</td>
<td>Yes</td>
</tr>
<tr>
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<td>Guangxi (S)</td>
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<tr>
<td>Zhang et al., 2011 [47]</td>
<td>Cross-control study</td>
<td>Guangxi (S)</td>
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<tr>
<td>R. Lan et al., 2011 [48]</td>
<td>Cross-control study</td>
<td>Guangxi (S)</td>
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<td>Yes</td>
</tr>
<tr>
<td>Yin et al., 2015 [49]</td>
<td>Cross-sectional study</td>
<td>Guangxi (S)</td>
<td>2009-2012</td>
<td>97</td>
<td>77 (79.4)</td>
<td>Yes</td>
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<tr>
<td>Huang et al., 2022 [50]</td>
<td>Cross-sectional study</td>
<td>Guangxi (S)</td>
<td>2018-2019</td>
<td>11</td>
<td>NA</td>
<td>No</td>
</tr>
<tr>
<td>Zhou et al., 2012 [51]</td>
<td>Cross-sectional study</td>
<td>Guangxi (S)</td>
<td>2006-2010</td>
<td>135</td>
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<td>Wang et al., 2022 [52]</td>
<td>Cross-sectional study</td>
<td>Hubei (C)</td>
<td>2019-2021</td>
<td>9</td>
<td>8 (88.9)</td>
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<td>Li et al., 2016 [53]</td>
<td>Cross-sectional study</td>
<td>Hubei (C)</td>
<td>2012-2015</td>
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<td>24 (88.9)</td>
<td>Yes</td>
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<td>Deng et al., 2013 [54]</td>
<td>Cross-sectional study</td>
<td>Hubei (C)</td>
<td>2008-2011</td>
<td>63</td>
<td>NA</td>
<td>Yes</td>
</tr>
<tr>
<td>Wang et al., 2021 [55]</td>
<td>Cross-sectional study</td>
<td>Jiangsu (E)</td>
<td>2017-2020</td>
<td>97</td>
<td>NA</td>
<td>No</td>
</tr>
<tr>
<td>Huang et al., 2021 [56]</td>
<td>Cross-sectional study</td>
<td>Jiangxi (E)</td>
<td>2017-2020</td>
<td>22</td>
<td>16 (72.7)</td>
<td>No</td>
</tr>
<tr>
<td>Li, 2018 [57]</td>
<td>Cross-sectional study</td>
<td>Shaanxi (W)</td>
<td>2016-2017</td>
<td>50</td>
<td>50 (100)</td>
<td>Yes</td>
</tr>
<tr>
<td>Zhu et al., 2013 [58]</td>
<td>Cross-sectional study</td>
<td>Shanghai (E)</td>
<td>2007-2012</td>
<td>27</td>
<td>27 (100)</td>
<td>Yes</td>
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<td>Sun et al., 2019 [59]</td>
<td>Cross-sectional study</td>
<td>Shanghai (E)</td>
<td>2006-2013</td>
<td>377</td>
<td>329 (87.3)</td>
<td>No</td>
</tr>
<tr>
<td>Tian et al., 2022 [60]</td>
<td>Case-control study</td>
<td>Shanghai (E)</td>
<td>2015-2021</td>
<td>169</td>
<td>161 (95.3)</td>
<td>No</td>
</tr>
<tr>
<td>Wang et al., 2021 [61]</td>
<td>Cross-sectional study</td>
<td>Sichuan (W)</td>
<td>2014-2018</td>
<td>59</td>
<td>50 (84.7)</td>
<td>Yes</td>
</tr>
<tr>
<td>Zhang et al., 2021 [62]</td>
<td>Cross-sectional study</td>
<td>Yunnan (W)</td>
<td>2012-2019</td>
<td>90</td>
<td>69 (76.7)</td>
<td>No</td>
</tr>
<tr>
<td>Li et al., 2018 [63]</td>
<td>Cross-sectional study</td>
<td>Chongqing (W)</td>
<td>2013-2015</td>
<td>23</td>
<td>16 (69.6)</td>
<td>Yes</td>
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<td>Liu et al., 2021 [64]</td>
<td>Cross-sectional study</td>
<td>Chongqing (W)</td>
<td>2019-2020</td>
<td>44</td>
<td>34 (77.3)</td>
<td>Yes</td>
</tr>
<tr>
<td>Chou et al., 2011 [65]</td>
<td>Cross-sectional study</td>
<td>Taiwan (E)</td>
<td>2004-2008</td>
<td>22</td>
<td>21 (95.5)</td>
<td>Yes</td>
</tr>
<tr>
<td>Chuang et al., 2020 [66]</td>
<td>Retrospective cohort study</td>
<td>Taiwan (E)</td>
<td>1996-2016</td>
<td>94</td>
<td>86 (91.5)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Species distribution

The species distribution of NTM isolates positive was mainly *Mycobacterium avium* complex (MAC) (64.3%; 95% CI = 51.8-76.7), *Mycobacterium kansasii* (9.4%; 95% CI = 5.4-14.2), *Mycobacterium gordonae* (8.7%; 95% CI = 4.4-13.0), *Mycobacterium abscessus* complex (4.0%), and other mycobacterial species (16.0%) (Table 2).

Clinical symptoms

The more common clinical symptoms included fever (68.5%; 95% CI = 61.8-75.1), cough or expectoration (67.0%; 95% CI = 54.5-79.5), appetite loss (49.4%; 95% CI = 1.7-97.1), weight loss (45.5%; 95% CI = 28.9-62.2), superficial lymphadenectomy (41.1%; 95% CI = 30.5-51.6), fatigue (38.2%; 95% CI = 18.1-58.3), dyspnoea (34.9%; 95% CI = 17.0-52.8), erythra (30.6%), abdominal pain or diarrhoea (27.4%), chest pain (24.3%), night sweats (17.4%), and haemoptysis (4.3%) (Table 3).

Laboratory tests

In the laboratory tests, the haemoglobin count was 93.907 g/L (95% CI = 82.988-104.827 g/L) and CD4+ T cell count was 33.772 pieces/μL (95% CI = 15.289-52.253). Albumin (ALB) levels <35 g/L were observed.
Thoracic imaging manifestations

Thoracic imaging manifestations (Table 6) show that the distribution of lesions was mainly bilateral lung involvement (83.8%; 95% CI = 70.7-93.9), followed by single lung involvement (12.8%; 95% CI = 5.1-22.8) and with no rare abnormalities (8.7%; 95% CI = 0.0-26.0). Furthermore, changes in lesion morphology and density mostly manifested as stripe shadow (60.3%; 95% CI = 41.9-77.4), patchy shadows (42.9%; 95% CI = 26.8-58.9), nodules (40.6%; 95% CI = 27.7-53.5), bronchiectasis (38.6%; 95% CI = 27.7-49.5), ground glass opacity (33.4%; 95% CI = 15.8-51.0), and some as cavitary lesions (13.0%), while millet shadows (4.6%) were rare. The accompanying signs were thoracic lymph node enlargement (49.5%; 95% CI = 25.8-73.3), abdominal lymph node enlargement (26.4%; 95% CI = 19.1-43.7), pleural thickening (14.9%; 95% CI = 8.1-21.7), hydrothorax (12.2%), and hydropericardium (11.2%).
Treatment outcome

Analysis of treatment outcome showed that symptoms improved (70.0%; 95% CI = 56.9-83.0) in most patients after treatment, with death and other outcomes accounting for 6.2% (95% CI = 3.2-9.9) and 22.6% of total outcomes (Table 7).

Table 7. Results of meta-analysis of treatment outcome with positive NTM isolates from patients with HIV/AIDS

<table>
<thead>
<tr>
<th>Treatment outcome</th>
<th>Pooled estimate (95% CI)</th>
<th>Number of studies</th>
<th>Heterogeneity</th>
<th>Event/total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>P-value</td>
<td>I², %</td>
</tr>
<tr>
<td>Symptoms improve*</td>
<td>70.0 (56.9-83.0)</td>
<td>6</td>
<td>&lt;0.001</td>
<td>83.2</td>
</tr>
<tr>
<td>Death</td>
<td>6.2 (3.2-9.9)</td>
<td>6</td>
<td>&lt;0.001</td>
<td>83.2</td>
</tr>
<tr>
<td>Others†</td>
<td>22.6 (9.9-35.3)</td>
<td>6</td>
<td>&lt;0.001</td>
<td>86.8</td>
</tr>
</tbody>
</table>

CI – confidence interval

*Symptom improvement is defined as getting better after treatment during hospitalisation.
†Others include automatic discharge, transfer to another hospital, and no apparent improvement.

Subgroup analyses

We found differences between regions and some disease characteristics in the subgroup analyses (Table S8 and S9 in the Online Supplementary Document). For example, cough or expectoration was more frequent in the western (88.4%; 95% CI = 79.4-97.4) than the northern region (33.8%; 95% CI = 23.9-45.4, P < 0.001). We found no significant association between sample size (per study) and disease characteristics; however, fever (74.6%; 95% CI = 68.3-80.8 vs 61.6%; 95% CI = 50.6-72.7 (P = 0.045)), night sweats (33.2%; 95% CI = 17.1-49.3 vs 14.8%; 95% CI = 9.2-20.4 (P = 0.034)), and manifestations of stripe shadows on thoracic imaging (78.3%; 95% CI = 49.9-97.5 vs 44.0%; 95% CI = 27.6-61.1 (P = 0.042)) were more common in sample sizes of with <50 than those with ≥50 patients, while anaemia was less frequent in sample sizes with <50 than in ones with ≥50 patients (53.9%; 95% CI = 32.8-75.0 vs 86.4%; 95% CI = 75.5-93.0 (P = 0.005)).

Both subgroup analyses showed a high degree of heterogeneity and an I²≥50%. We hypothesise that the above-mentioned differences were caused by confounding factors outside the selected subgroup criteria, including data collection era, clinical typing (pulmonary NTM disease, extrapulmonary NTM disease, or disseminated NTM disease) and infection strain species.
DISCUSSION

Clinical significance of positive NTM isolates

Positive NTM isolation from clinical specimens at different sites has different implications: NTM isolated from non-sterile sites, such as sputum and bronchial lavage fluid, should exclude the possibility of specimen contamination or respiratory colonisation, while that from sterile sites, such as blood, cerebrospinal fluid, and puncture fluid, is more likely to be infectious or pathogenic [67,68]. When contamination of the specimen is excluded, positive NTM isolates include NTM colonisation, NTM infections, and NTM disease. As the immune status of the body changes, NTM colonisation or infections may progress to NTM disease, resulting in systemic tissue and organ damage.

Initial screening strategies for NTM infections from patients with HIV/AIDS in China

Both TB infections and NTM infections can cause the same clinical symptoms, with the four clinical symptoms recommended by the World Health Organization for screening for TB infections including cough, fever, night sweats, and weight loss [69]. Moreover, a recent systematic review of patients co-infected with HIV and TB shows that C-reactive protein testing and chest imaging can be useful for screening TB infections [70]. There is no recommended screening strategy for NTM infections from patients with HIV/AIDS in China. We found that fever, cough or expectoration, appetite loss, weight loss, and superficial lymphadenecasis were the five most common clinical symptoms, while the incidence of haemoptysis was 4.3%, unlike TB, which is the leading cause of haemoptysis worldwide [71]. Therefore, these clinical symptoms can be used for the initial screening of NTM infections.

In our study, 55.6% of patients had an ALB<35 g/L, 91.4% had an ESR>20 mm/h, and 59% had anaemia, which was predominantly mild. Moreover, most patients had thoracic imaging involvement, and only 8.7% of patients had no thoracic imaging changes, mainly showing stripe shadows, patchy shadows, nodules, bronchiectasis, and signs of thoracic lymph node enlargement. However, some studies have found that acute infections of HIV/AIDS combined with MTB, with the thoracic imaging manifestations being mainly pneumonia-like exudates or solid shadow and nodules are rare [72]. Thus, thoracic imaging (x-ray or computed tomography) should be used as a routine and necessary means to diagnose NTM infections, regardless of whether they present with clinical symptoms, which is important for the early detection of the disease.

In summary, we consider that clinical symptoms, including fever, cough or expectoration, appetite loss, weight loss, and superficial lymphadenecasis without haemoptysis, laboratory tests, including ALB, erythrocyte sedimentation rate, and haemoglobin, and thoracic imaging are helpful in the initial screening for NTM infections.

Priority population for screening for NTM infections from patients with HIV/AIDS in China

We found the CD4+ T cell count to be 33.772 pieces/μL (95% CI = 15.289-52.255 pieces/μL) in the included studies, with 70.3% of patients having a CD4+ T cell count ≤50 pieces/μL (95% CI = 57.5-81.7). Men comprised 87.3% of the total population. Water and soil are important transmission routes for NTM infections [24,25], and some species such as Mycobacterium abscessus can be transmitted interpersonally [73]. Therefore, we propose that patients with HIV/AIDS who are severely immunosuppressed (CD4+ T cell count <50 pieces/μL), especially men and patients with HIV/AIDS who are chronically exposed to unclean water sources in occupations related to exposure to soil (eg, farmers, gardeners) and have been or are being exposed to repeated NTM infections or NTM disease may be a priority population for screening for NTM infections.

Principles of treatment for NTM disease from patients with HIV/AIDS in China

There is a lack of studies on the distribution of the NTM species over large areas of China. We found that the distribution of NTM species in China was dominated by Mycobacterium avium complex, which accounted for 64.3% of the species, while being predominant in different regions. Mycobacterium avium complex is a slow-growing mycobacterium. Therefore, when the results of the NTM species identification are unclear, experimental treatment for Mycobacterium avium complex infections may be feasible for critically ill patients or in cases when the disease is progressing rapidly. Physicians should also raise awareness of the diagnosis and treatment of Mycobacterium avium complex.
Prophylactic treatment of NTM disease for patients with HIV/AIDS in China

Current Chinese expert consensus recommends prophylactic treatment for patients with HIV/AIDS with a CD4+ T cell count <50 pieces/μL [30], mainly based on guidelines and literature from high-income countries in Europe and North America that do not correspond to the circumstances in LMICs with scarce medical resources and weak economies. We found that approximately 30.0% of hospitalised patients failed to improve after treatment, making prophylactic treatment particularly important. Patients with HIV/AIDS should receive prophylactic anti-tuberculosis treatment with isoniazid, rifampicin, and rifapentine after active TB has been ruled out, regardless of the degree of immunosuppression or being tested for MTB infections [69]. Prophylactic treatment for NTM disease includes azithromycin, clarithromycin, and rifabutin [67,68]. We found that 22.1% of patients had a CD4+ T cell count of 51-200 pieces/μL, and the Food and Drug Administration showed weak drug interactions between clarithromycin, rifabutin, and the three prophylactic anti-tuberculosis drugs [74]. Therefore, it may be more appropriate to up-regulate CD4+ T cell count to ≤200 pieces/μL for the prophylactic treatment of NTM disease in patients with HIV/AIDS in China.

Strengths and weakness

This is the first systematic review of positive NTM isolates from patients with HIV/AIDS in China. We followed PRISMA guidelines [31-33] in reporting and conducting the review, ensuring that all relevant studies are included. Consequently, it not only provides theoretical support for existing expert consensus in China, but also fills a relevant gap and provides information for future clinical research directions.

This study had certain limitations. Most of the included studies did not specify the type of clinical infection, and the selected control groups varied (eg, HIV/AIDS co-infection with NTM vs MTB and HIV/AIDS vs non-HIV/AIDS co-infection with NTM). Therefore, we were unable to make a definitive analysis of HIV/AIDS co-infection with NTM/MTB and HIV/AIDS co-infection with pulmonary NTM disease/extrapulmonary NTM disease/disseminated NTM disease. Additionally, the sample size of the included studies was too small, and the findings cannot be applied to all regions. Moreover, some of our recommendations are based on hypothetical reasoning inferred from our findings, and their specific clinical value and feasibility require further confirmation through cohort studies, clinical trials, and cost-benefit analyses.

CONCLUSIONS

Focusing on clinical symptoms, laboratory tests, and thoracic imaging helps with initial screening for NTM infections. Physicians should raise awareness of the diagnosis and treatment of Mycobacterium avium complex, providing guidance for experimental treatment, screening of priority populations for NTM infections, and prophylactic treatment of NTM disease.
Positive nontuberculous mycobacteria in HIV/AIDS patients


38 Luo DH, Wan X, Liu JM, Tong TJ. [How to estimate the sample mean and standard deviation from the sample size, median, extremes or quartiles?]. Chinese Journal of Evidence-Based Medicine. 2017;17:1350-6. Chinese.


Positive nontuberculous mycobacteria in HIV/AIDS patients


