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Introduction

The World Health Organization (WHO) estimates that 9.6 million cases of tuberculosis (TB) occurred in 2014 (corresponding to 133 cases per 100,000 population) with 1,5 million deaths [1]. Furthermore, 3.3% of new and 20% of previously treated cases harbour multidrug-resistant (MDR-) TB strains. Eastern European and central Asian countries still have the highest prevalence of MDR-TB. In low TB incidence countries (largely covering North America and Western Europe, Figure 1) 155,000 TB cases occur every year with over 10,000 deaths [2].

Rapid diagnosis and effective treatment of newly diagnosed TB cases, the majority of whom are susceptible to first-line anti-TB drugs, constitutes the essence of TB control by curing the patient of TB and rapidly halting further transmission of in the community [3]. It is widely recognised that MDR- and XDR- (extensively drug resistant) TB emergence and spread is largely driven by mismanagement of misadventures in diagnosis, treatment and control of TB, which is compounded by inadequacy of necessary human and financial resources at different levels [3,4

In the last 24 months the WHO published two core documents focusing on the importance of the correct case- management of TB: the 'End Tuberculosis Strategy' and the 'Framework towards TB Elimination in low incidence countries' [3,6]. Both documents emphasise the importance of prompt diagnosis and effective treatment of newly diagnosed TB cases.

Although there are recently published International Standards for TB Care and their European adaptation [7-9], and the WHO is presently updating its Treatment Guidelines [10], major international scientific societies have a critical role to play in the development and implementation of case management guidelines for TB due to their wide membership and access to considerable clinical experience of utilising recommendations. Consequently, the American Thoracic Society (ATS) and the European Respiratory Society (ERS) have developed TB guidelines [11,12] focused predominantly on TB care in settings without significant resource limitations, which have now been updated. Using GRADE (Grading of Recommendations, Assessment, Development and Evaluation) methodology, the American Thoracic Society (ATS), Centers for Disease Control and Prevention (CDC), and Infectious Diseases Society of America (IDSA) jointly sponsored the development of a new Treatment of Drug-Susceptible Tuberculosis clinical practice guidelines, which has been subsequently endorsed by both the European Respiratory Society (ERS) and the U.S. National Tuberculosis Controllers Association, and published in July 2016 in Clinical Infectious Diseases [13].

As before these guidelines are aimed at providing recommendations on the clinical and public health management of TB in adults and children in settings where diagnostic tests and drugs are available on a routine basis and without restrictions.

Process and methods

A selected panel of experts, managed for pertinent conflicts of interest according to strict criteria set by the participating Societies, with the necessary competencies, skills and perspectives (pulmonary medicine, infectious diseases, pharmacokinetics, pediatrics, primary care, public health and systematic review methodology) participated as part of the writing committee.
Nine PICO questions (Population, Intervention, Comparators, Outcomes) viewed by the writing committee as key clinical questions in the management of active TB, and their associated recommendations were developed based on the evidence that was appraised using GRADE [14,15], and are summarized in Table 1. This editorial provides a brief summary of the panel's recommendations; additional important information providing context and references for each recommendation, as well as detailed guidance on the management of TB in special populations, treatment of tuberculosis in the presence of HIV infection, TB in children, TB during pregnancy and breastfeeding, extrapulmonary TB among other clinical situations is available online in the full text version of the guidelines [13]. Additional detailed guidance on the practical aspects of anti-TB treatment, drug-drug interactions, therapeutic drug monitoring (TDM) and management of adverse events is also available online in the full text version of the guideline.

What are the principles of anti-TB chemotherapy?

Anti-TB treatment aims to cure the patient, prevent complications and death, avoid relapses, reduce the transmission potential to susceptible individuals and limit the emergence and spread of drug-resistant strains. For all these reasons, the therapeutic approach to TB requires the use of multiple drugs [12].

A key responsibility of clinicians is making the decision to initiate appropriate treatment for TB. Clinicians decide to start anti-TB chemotherapy based on a variety of data, including clinical, radiographic, laboratory, patient and public health criteria. Commonly, empirical treatment is initiated prior to having definitive confirmation of *M. tuberculosis*, so as to minimize morbidity and

to halt further transmission in the community. Today, fortunately, molecular tests offer rapid diagnosis before culture results are available [16].

Once initiated, treatment success depends upon many factors, and increased risk of relapse has been described among patients with extensive disease (i.e., cavitations or extensive infiltrates on chest radiograph) [17-21], and/or slow response to treatment (i.e., culture conversion at 2 or 3 months) [18,22-24].

We summarise below the rationale and recommendations of the different PICO Questions.

Case management interventions (PICO question 1)

The evidence supports the use of case management strategies in the treatment of TB. In order to ensure patient's adherence and maximize the potentialities for treatment success it is recommended to assign a public health nurse and/or a treatment supporter [13], with whom an individualized "case management plan" is designed, according to a patient-centred approach, as recommended by the ISTC document [7-9], based on the following elements: 1) educating the patient on the different aspects of treatment and potential adverse events; 2) discussing treatment monitoring procedures and 3) fostering infection control measures, using simple terms and cultural mediators if necessary (Table 1).

Directly Observed Therapy (DOT; PICO question 2)

The evidence supports the use of DOT in the treatment of TB. Numerous systematic reviews have been conducted to compare outcomes between self-administered therapy (SAT) and DOT (the practice of observing the patient swallow their anti-TB drugs). However, DOT is a part of a multifaceted public health intervention and as such is not amenable to conventional clinical trials approaches assessing benefits/risks. The systematic review conducted to obtain evidence in support of the ERS-endorsed ATS/CDC/IDSA practice guideline did not find any differences between SAT and DOT when assessing mortality, treatment completion, and relapse, however, DOT was significantly associated with improved treatment success (the sum of patients cured and patients completing treatment) and with increased sputum smear conversion during treatment, as compared to SAT. As such, these and other international guidelines support the use of DOT, provided in a patient-centred approach, as one component, of TB case management [7-10].

The administration schedule of preferred treatment regimens for drug-susceptible TB (PICO questions 3-4)

The preferred regimen for treating adults with TB caused by strains known or suspected to be drug-susceptible consists of an *intensive phase* of 2 months (isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA) and ethambutol (EMB) followed by a *continuation phase* of 4 months (INH and RIF) [25-27]. Four drugs during the *intensive phase* of treatment ensure its effectiveness in case of INH mono-resistance [13].

If drug susceptibility test (DST) results are known and the patient's isolate is susceptible to both INH and RIF, EMB is not essential and can be discontinued, in this case the intensive phase is composed of INH, RIF and PZA. Pyridoxine (vitamin B6) is given with INH to patients at risk of neuropathy (e.g., pregnant women; breastfeeding infants; HIV-coinfected individuals; elderly, patients with diabetes, alcoholism, malnutrition or chronic renal failure).

The recommended frequency of treatment administration is once daily for both the intensive and continuation phases (see PICO Questions 3 and 4). However, some experts believe that 5 day-a-week drug administration by DOT is an acceptable alternative to 7 days-a-week. Other alternative regimens that are variations of the preferred regimen, which may be acceptable in certain clinical and/or public health situations are available in the full text version of the guideline [13].

During treatment, a sputum specimen for direct smear and culture examination are recommended at monthly intervals until two consecutive specimens are negative on culture. As culture status at the completion of the *intensive phase* of treatment (2 months) has been shown to correlate with the likelihood of relapse after completion of treatment for pulmonary TB, culture conversion needs to be assessed at the end of the two months of treatment in new cases [21,28-30]. Cavitation on the initial chest radiograph has also been shown to be a risk factor for relapse [21,31]. In patients with cavitation at baseline failing to convert culture after the *intensive phase* of treatment, rates of relapse have been shown to be higher than among patients with neither factor (20% vs. 2% [21,29]), and based on expert opinion, the extension of the continuation phase with INH and RIF for an additional 3 months (i.e., a continuation phase of 7 months, corresponding to a total of 9 months of therapy) is an option left to the physician in discussion with the patient. Additional factors to be considered in deciding to prolong treatment in patients with either cavitation or a positive culture at 2 months (but not both) might include being underweight (>10%), or active smoker, having

diabetes, HIV infection, or other immunosuppressing condition; or having extensive disease on chest radiograph [30, 32-36].

Treatment in special situations

Detailed recommendations on the management of TB in special situations are available online in the full text version of this guideline [13]. Five PICO questions with summary recommendations pertinent to the management of tuberculosis in HIV patients, steroid use in pericardial or meningeal tuberculosis, and culture-negative TB are summarized below and in Table 1.

HIV infection

Detailed guidance on the management of TB in HIV-infected patients is provided in the new guidelines, including recommendations on the optimal initiation of antiretroviral therapy (ART), the management of potential drug-drug interactions, especially between rifamycins and ART, paradoxical reactions among others complexities involved in management of HIV/TB. Several key features are summarized here.

Based on data that show significant reductions in mortality and AIDS-defining illnesses, patients with HIV infection and TB should receive ART in conjunction with daily anti-TB drugs**.** For HIV-infected patients receiving ART, the standard 6-month daily anti-TB regimen is recommended.
In the uncommon situation in which an HIV-infected patient does not receive ART during anti-TB treatment, the new ATS/CDC/IDSA guidelines suggest extending the continuation phase (INH and RIF) for an additional 3 months (i.e., a continuation phase of 7 months in duration, corresponding to a total of 9 months) for treatment of drug-susceptible pulmonary TB (PICO Question 5, Table 1). As high rates of relapse and the emergence of drug resistance has been associated with the use of intermittent regimens, resulting in low serum concentrations of key component drugs in the setting of low CD4 lymphocyte count (<100/mm^3), based on systematic reviews treatment of HIV-related TB should be administered daily in both the intensive and continuation phases.

On the basis of systematic review and meta-analysis, high quality evidence exists showing that benefits outweigh harms; the guidelines recommend that patients with tuberculosis and HIV co-infection receive ART during anti-TB treatment. ART should ideally be started within 2 weeks for those patients with a CD4 count <50/mm^3 and by 8 to 12 weeks for those with a CD4 count

≥50/mm^3 (see PICO Question 6). However, in HIV-infected patients with TB meningitis, ART is not initiated in the first 8 weeks of anti-TB therapy due to an associated with increased rates of adverse events and higher mortality [37]. The concurrent administration of ART and rifamycins is a major treatment challenge, and details on the co-administration of these medications, including the use of rifabutin (RFB), are available online in the full-text version of the guidelines [13].

Patients with TB and HIV co-infection are at increased risk of developing paradoxical worsening of symptoms, signs, or clinical manifestations of tuberculosis after beginning anti-TB and antiretroviral treatments, known as immune reconstitution inflammatory syndrome (IRIS). More common in patients with earlier ART initiation and CD4+ cell counts < 50 cells/mm3 [38], IRIS may include high fever, worsening respiratory symptoms, inflammation and increased size of involved lymph nodes, new lymphadenopathy, expanding central nervous system lesions, worsening of pulmonary parenchymal infiltrations, new or increasing pleural effusions, and development of intra-abdominal or retroperitoneal abscesses [39].

Management of IRIS is symptomatic. Based on expert opinion, for most patients with mild IRIS, anti-TB and antiretroviral therapies can be continued adding anti-inflammatory drugs such as ibuprofen. For patients with worsening pleural effusions or abscesses, drainage is indicated. For more severe cases of IRIS, corticosteroid treatment is effective. In a trial of prednisone for patients with moderate IRIS, prednisone 1.25 mg/kg/day significantly reduced the need for hospitalization or surgical procedures [40]. For patients developing IRIS, prednisone may be administered at a dose of 1.25 mg/kg/day (50-80 mg/day) for 2-4 weeks, with tapering over a period of 6-12 weeks or longer.

Co-trimoxazole (trimethoprim-sulfamethoxazole) prophylaxis has been shown to reduce morbidity and mortality in HIV-coinfected patients with newly diagnosed TB [41-43]. WHO recommends co-trimoxazole for all HIV-infected individuals with active TB regardless of their CD4 cell count [44], while in high-income countries co-trimoxazole is primarily used in HIV-infected patients with CD4 counts <200 cells/mm3 [45]. The use of ART during anti-TB treatment in HIV co-infected patients also reduces mortality rates significantly while decreasing the risk of developing AIDS-related conditions.

TB pericarditis

Based on systematic reviews conducted in support of the guidelines, informed greatly by a recent placebo-controlled randomized clinical trial with 1400 participants [46], adjunctive corticosteroids should not be used routinely in the treatment of patients with pericardial TB (PICO Question 7) [46-50]. However, selective use of corticosteroids in patients who are at the highest risk for inflammatory complications might be appropriate.

TB *meningitis*

Treatment for TB meningitis includes INH, RIF, PZA, and EMB in the initial 2-month phase. In the continuation phase of treatment, for meningitis due to strains known or presumed to be drug-susceptible, INH and RIF should be continued for an additional 7-10 months, although the optimal duration of chemotherapy is not defined (12 months in the UK). Expert opinion suggest that repeated lumbar punctures may be used to monitor changes in CSF cell count, glucose, and protein, especially in the early phases of treatment. In children with TB meningitis, the regimen recommended consists of INH, RIF, PZA and ethionamide, if possible, or an aminoglycoside, for 2 months followed by 7 to 10 months of INH and RIF [51]. For adults, based on expert opinion, the guidelines recommend using EMB as the fourth drug composing the regimen.

The role of adjunctive corticosteroid therapy in the treatment of TB meningitis has been investigated by numerous studies [52-64], and the updated systematic review conducted in support of the guidelines showed a mortality benefit from the use of adjuvant corticosteroids. Therefore, the guidelines recommend adjunctive corticosteroid therapy with dexamethasone or prednisolone tapered over 6-8 weeks for patients with TB meningitis (PICO Question 8).

Culture-negative pulmonary TB in adults

Based on a systematic review conducted in support of the guideline, a 4-month treatment regimen was shown to be adequate for sputum smear-negative, culture-negative pulmonary TB (PICO Question 9). The intensive phase of treatment includes INH, RIF, PZA, and EMB daily and continued even when the initial bacteriologic studies are negative. If all cultures on adequate samples are negative (culture-negative TB) and there is clinical or radiographic response after 2 months of intensive phase therapy, the continuation phase with INH and RIF may be shortened to 2 months in HIV-negative adults (but the quality of evidence for this recommendation is very low). Alternatively, if there is concern about the adequacy of work-up or the accuracy of the microbiologic evaluations, a standard six-month regimen remains preferred [7,8]. Importantly, the

guidelines note that causes of failure to isolate organisms should be considered and these include the recent use of antibiotics with bactericidal activity against *M. tuberculosis* (e.g., fluoroquinolones), low bacillary populations, inadequate sputum specimens, temporal variations in the number of expelled bacilli, overgrowth of cultures with other microorganisms, and errors in specimen processing [65]. At a minimum, patients suspected of having pulmonary TB have two sputum specimens (using sputum induction with hypertonic saline if necessary) for Alcohol Acid Fast Bacilli smears and cultures for mycobacteria or for rapid molecular testing for *M. tuberculosis* as part of the diagnostic evaluation. Bronchoscopy with bronchoalveolar lavage and/or biopsy, have also to be considered before making a presumptive diagnosis of culture-negative TB.

Conclusions

The main goals of anti-TB treatment are to cure individual patients and minimise transmission of *M. tuberculosis* within the community. The standard 4-drug regimen (INH, RIF, PZA and EMB) remains the preferred initial treatment for drug-susceptible pulmonary TB. Treatment needs to start even before direct smear microscopy, molecular tests, and mycobacterial culture results are known in patients with a high likelihood of having TB and/or who are seriously ill.

Variations of the preferred regimen that are appropriate in certain public health situations or in special clinical situations and additional detailed information on TB treatment are available in the full-text version of the guidelines available online at (weblink) [13].

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Table 1

	PICO Question	Recommendation (R)	Comments
1	Does adding case management* interventions to curative therapy improve outcomes compared to curative therapy alone among patients with tuberculosis? *Case management: patient education/counseling, field/home visits, integration/coordination of care with specialists and medical home, patient reminders, incentives/enablers.	R1. We suggest using case management interventions during treatment of patients with tuberculosis	Conditional recommendation/ Very low quality of evidence
2	Does self-administered therapy (SAT) have similar outcomes compared to directly observed therapy (DOT) in patients with various forms of tuberculosis?	R2. We suggest using DOT rather than SAT for routine treatment of patients with all forms of tuberculosis).	Conditional recommendation/low quality of evidence
3	Does intermittent dosing in the intensive phase have similar outcomes compared to daily dosing in the intensive phase for treatment of drug-susceptible pulmonary tuberculosis?	R3a: We recommend the use of daily rather than intermittent dosing in the intensive phase of therapy for drug-susceptible pulmonary tuberculosis R3b: Use of three times weekly therapy in the intensive phase (with or without an initial two weeks of daily therapy) may be considered in patients who are not HIV-infected and are also at low risk of relapse (pulmonary tuberculosis caused by drug-susceptible organisms, that at the start of treatment is non-cavitary and/or smear negative) R3c: In situations where daily or three times weekly DOT therapy is difficult to achieve, use of twice weekly therapy after an initial two weeks of daily therapy may be considered for patients who are not HIV-infected and are also at low risk of relapse (pulmonary tuberculosis caused by drug-susceptible organisms, that at the start of treatment is non-cavitary and/or smear negative)	Strong recommendation / Moderate quality of evidence Conditional recommendation / Low quality of evidence Conditional recommendation / Very low quality of evidence) Note: if doses are missed in a regimen using twice weekly dosing then therapy is equivalent to once weekly, which is inferior (see PICO Question 4).

4	Does intermittent dosing in the continuation phase have similar outcomes compared to daily dosing in the continuation phase in patients with drug-susceptible pulmonary tuberculosis patients?	R4a: We recommend the use of daily or three times weekly dosing in the continuation phase of therapy for drug-susceptible pulmonary tuberculosis R4b: If intermittent therapy is to be administered in the continuation phase, then we suggest use of three times weekly instead of twice weekly therapy. R4c: We recommend against use of once weekly therapy with INH 900 mg and RPT (rifapentin) 600 mg in the continuation phase	Strong recommendation / Moderate quality of evidence Conditional recommendation / Low quality of evidence). This recommendation allows for the possibility of some doses being missed; with twice weekly therapy, if doses are missed then therapy is equivalent to once weekly, which is inferior Strong recommendation / High quality of evidence In uncommon situations where more than once-weekly DOT is difficult to achieve, once weekly continuation phase therapy with INH 900 mg plus RPT 600 mg may be considered for use only in HIV-negative persons without cavitation on chest radiography.
5	Does extending treatment beyond 6 months improve outcomes compared to the standard 6-month treatment regimen among pulmonary tuberculosis patients co-infected with HIV?	R5a: For HIV-infected patients receiving antiretroviral therapy, we suggest using the standard 6-month daily regimen consisting of an intensive phase of 2 months of INH, RIF, PZA and EMB followed by a continuation phase of 4 months of INH and RIF for the treatment of drug-susceptible pulmonary tuberculosis R5b: In uncommon situations in which HIV-infected patients do NOT receive antiretroviral therapy during tuberculosis treatment, we suggest extending the continuation phase with INH and RIF for an additional 3	Conditional recommendation / Very low quality of evidence Conditional recommendation / Very

		months (i.e., a continuation phase of 7 months in duration, corresponding to a total of 9 months of therapy) for treatment of drug-susceptible pulmonary tuberculosis	low quality of evidence)
6	Does initiation of anti-retroviral therapy during tuberculosis treatment compared to at the end of tuberculosis treatment improve outcomes among tuberculosis patients co-infected with HIV?	R6. We recommend initiating anti-retroviral therapy during tuberculosis treatment. Anti-retroviral therapy should ideally be initiated within the first 2 weeks of tuberculosis treatment for patients with CD4 cell counts $<50/mm^3$ and by 8-12 weeks of tuberculosis treatment initiation for patients with CD4 cell counts $\geq 50/mm^3$	Strong recommendation / High quality of evidence) Note: an exception is patients with HIV infection and tuberculous meningitis
7	Does the use of adjuvant corticosteroids in tuberculous pericarditis provide mortality and morbidity benefits?	R7. We suggest initial adjunctive corticosteroid therapy not be routinely used in patients with tuberculous pericarditis	Conditional recommendation / Very low quality of evidence
8	Does the use of adjuvant corticosteroids in tuberculous meningitis provide mortality and morbidity benefits	R8. We recommend initial adjunctive corticosteroid therapy with dexamethasone given for six weeks for patients with tuberculous meningitis	Strong recommendation / Moderate quality of evidence
9	Does a shorter duration of treatment have similar outcomes compared to the standard 6-month treatment duration among HIV-negative patients with paucibacillary tuberculosis (i.e., smear negative, culture negative)?	R9. We suggest that a 4-month treatment regimen is adequate for treatment of HIV-negative adult patients with AFB smear- and culture-negative pulmonary tuberculosis	Conditional recommendation / Very low quality of evidence

Figure 1. TB low-incidence countries <10 cases per 100,00 population (in blue, 2013 data)

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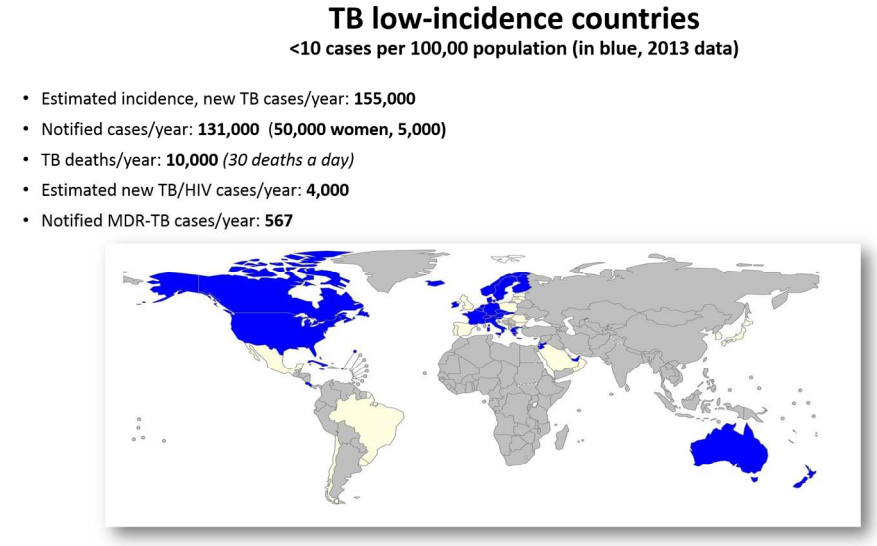

TB low-incidence countries
<10 cases per 100,00 population (in blue, 2013 data)
Figure 1
530x305mm (96 x 96 DPI)