MESA: Tuberculosis y virus de la inmunodeficiencia humana

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Lessons for Tuberculosis and HIV Control from the Netherlands

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The tuberculosis situation in The Netherlands will be reviewed with special emphasis on the characteristics of country moving towards TB elimination.

Main features that will be highlighted from this perspective are:

- TB becomes a rare disease of mostly elderly and immigrants with (at times unexpected) clustering in high risk groups.
- The need to strengthen the control strategy with "TB outbreak management" and "TB risk group management" (interventions characterized by selective use of systematic TB screening).
- The importance of maintaining classic procedures (such as Ziehl-Neelson microscopy and Directly Observed Treatment) and intelligently introducing new technologies (most importantly: DNA-fingerprinting).

Main challenges are:

- How to promote a unified and coordinated TB public health response?
- Experience in The Netherlands with a well-functioning National Tuberculosis Policy Committee responsible for (1) regularly updating and adjusting the TB control strategy and (2) maintaining the legal and regulatory framework will be discussed.
- How to maintain the TB public health network?
- Advantages and challenges of a specific TB public health network are discussed.
- How to maintain specialized and designated TB expertise within the TB public health network?

Strategies to maintain sufficient and adequate TB expertise in an environment where TB disease is rare will be highlighted.

The experience in The Netherlands will be discussed against the background of the new WHO Action Framework for TB Elimination in Low Incidence Countries. The presentation will also contrast the Dutch TB experience with the experiences in the HIV/AIDS response in the Netherlands.

TITL en coinfectados VIH-TB

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Después de la detección y tratamiento de casos de TB activa, la segunda medida más urgente en el control de la tuberculosis es el diagnóstico y tratamiento de las personas con un alto riesgo de desarrollar la enfermedad. Principios generales para el tratamiento de la infección tuberculosa latente El objetivo terapéutico es evitar la progresión de la latente para la TB activa. Sólo el 10% de los pacientes LTB están en riesgo de desarrollar la enfermedad de la tuberculosis. Por esta razón, y también porque el tratamiento que puede provocar efectos secundarios adversos graves y potencialmente mortales, el tratamiento LTB sólo se recomienda en aquellas personas que están en mayor riesgo de desarrollar tuberculosis. Por otra parte hay que recordar que la tuberculosis también puede desarrollarse debido a la rápida progresión de una infección reciente, especialmente en pacientes inmunocomprometidos (ICP). Esta posibilidad debe tenerse en cuenta al considerar iniciar el tratamiento profiláctico en IPC que han estado en contacto con TB activa. Algunos ICP puede tener una capacidad limitada para responder al antígeno tuberculosis y mostrar negativa a la prueba de la tuberculina, a pesar de estar infectados con *M. tuberculosis;* Por esta razón, la profilaxis de partida debe ser considerado en ICP después de la exposición obvio, a pesar de la prueba de la tuberculina negativa. Por último, la población bacilar en pacientes LTB es considerablemente más baja que la encontrada en pacientes con TB, por lo que el uso de la terapia de combinación de fármacos no es necesario para evitar el desarrollo de mutaciones resistentes.

Idealmente, el tratamiento LTB se debe recomendar exclusivamente para los que tienen un riesgo significativo de desarrollar TB y un bajo riesgo de toxicidad. Se recomienda el tratamiento LTB para aquellos que han tenido una conversión de prueba de la tuberculina reciente, para las personas con una reacción positiva a la tuberculina que pueden haber tenido un contacto significativo con portadores de tuberculosis, y para los pacientes con un alto riesgo de desarrollar tuberculosis. En este artículo revisamos las bases para el tratamiento de infecciones LTB, incluidas las producidas por cepas resistentes a los fármacos antituberculosos

Avances en el diagnóstico y tratamiento de la TB-VIH

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Más allá de los aspectos epidemiológicos, el diagnóstico y tratamiento de la tuberculosis (TB) en personas infectadas por el VIH presenta aspectos diferenciadores que se deben conocer para el correcto manejo de ambas entidades. Estas peculiaridades se derivan fundamentalmente del deterioro de la respuesta inmunológica en pacientes con sida, y de la interacción de los

tratamientos antituberculoso y antirretroviral (TAR). Por estos motivos, se considera conveniente que el tratamiento de estos pacientes se realice por profesionales con experiencia en el manejo de ambas infecciones.

La complejidad en el diagnóstico se incrementa por el hecho de que los pacientes con infección por VIH presentan habitualmente la TB en situación de inmunodeficiencia intensa, lo que no ha variado sustancialmente en la época actual. Así, por ejemplo, en la cohorte multicéntrica española (CoRIS), la mediana de linfocitos CD4+ al diagnóstico de la TB fue de 120/µL[1]. En este contexto, las manifestaciones clínicas son superponibles a las de otras muchas enfermedades oportunistas, dificultando la sospecha diagnóstica.

El tratamiento antituberculoso sigue las mismas pautas que en la población general, pero se debe administrar a diario, al menos durante la fase de inducción. No se recomiendan en ningún caso las pautas administradas 2 veces por semana, que están absolutamente contraindicadas en pacientes con recuento de linfocitos CD4+ <100/µL, ya que se han asociado a mayor riesgo de selección de resistencia a rifamicinas. Por otra parte, en pacientes con bajo recuento de linfocitos CD4+ en los que no se prevea una respuesta inmunológica adecuada, y en los pacientes en los que no se pueda asegurar una toma adecuada de todas las dosis prescritas, es conveniente prolongar el tratamiento hasta los 9 meses[2].

La decisión sobre el momento óptimo para iniciar el TAR, ha sido también tema de controversia, ya que un inicio precoz puede asociarse con mayor toxicidad, mayor riesgo de reacciones inflamatorias por reconstitución inmune y complicar el manejo debido a las interacciones farmacológicas. Por otra parte, su demora se puede asociar a un incremento de la morbimortalidad. Diversos ensayos clínicos han permitido clarificar este tema, recomendándose en la actualidad el inicio precoz del TAR (en las 2 primeras semanas de iniciado el tratamiento antituberculoso) sólo en los pacientes con un recuento de linfocitos CD4+ inferior a 50/µL. En los pacientes con CD4+ superiores a 50/µL el inicio del TAR se puede demorar hasta las 8 semanas, una vez finalizada la fase de inducción del tratamiento[2]. Sin embargo, un ensayo clínico reciente, ha matizado esta recomendación, al demostrar que si el recuento de CD4+ es superior a 220/µL, es seguro demorar el TAR hasta finalizar los 6 meses de tratamiento antituberculoso[3].

En cuanto a los antirretrovirales a utilizar, la principal limitación se centra en el efecto inductor de la rifampicina, que impide el uso de los inhibidores de proteasa y algunos inhibidores de transcriptasa no análogos de nucleósidos (rilpivirina y etravirina). La máxima experiencia se tiene con efavirenz (junto a 2 nucleó[t]sidos), que es considerado el fármaco de elección en este escenario. Sin embargo, los problemas de tolerancia de efavirenz, así como la posible existencia de resistencias hacen necesario disponer de alterantivas. Dos inhibidores de integrasa (raltegravir y dolutegravir) son las principales opciones. Raltegravir ha demostrado su eficacia clínica en un pequeño ensayo fase 2[4], mientras que con dolutegravir solo disponemos de un estudio farmacocinético que muestra que mantiene niveles plasmáticos adecuados si se duplica su dosis (a 50 mg/12 horas) cuando se coadministra con rifampicina[5]. No son esperables otras interacciones entre los antirretrovirales y los antituberculosos distintos a las rifamicinas, con la única excepción de bedaquilina, que debería evitarse con los inhibidores de proteasa (por incrementar los niveles de bedaquilina y el riesgo de toxicidad) y los no-nucleósidos (por disminuir los niveles de bedaquilina, con riesgo de ineficacia).

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Diagnosis and Management of TB-IRS

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Abstract

Tuberculosis is the most common opportunistic infection in HIV-infected patients worldwide. A subgroup of patients with TB-HIV coinfection starting antiretroviral treatment may experience paradoxical worsening of their disease as a result of an exaggerated immune response towards an active (but also subclinical) infectious agent, despite an appropriate virological and immunological response to antiretrovirals. This clinical condition, known as immune reconstitution inflammatory syndrome, may cause significant morbidity and even mortality if it is not promptly recognized and treated.

Introduction

Despite the fact that combined antiretroviral therapy (cART) leads to good control of HIV infection in individuals starting treatment with a CD4+ T-cell count above 200 cells/ml, delayed diagnosis of HIV infection can mean that some patients initiate cART with severe impairment of their immune system. Despite efforts to diagnose HIV infection earlier, a considerable proportion of patients still present late, with a CD4+ T-cell count less than 200/mm^3, an AIDS-defining condition, or both.

A low CD4+ T-cell count exposes the patient to a higher risk of opportunistic infections (OIs) and to a less sustained virological response when cART is started. The presence of a concomitant OI can complicate management, and pharmacokinetic and pharmacodynamic interactions between cART and drugs used to treat OI can occur (e.g. between rifampin and protease inhibitors)[1]. Moreover, a worsening of clinical condition can be observed in a subgroup of patients starting cART as a result of an immune response to an active (but also subclinical) opportunistic agent, despite a correct virological response to cART. This syndrome, which is known as immune reconstitution disease (IRD) or immune reconstitution inflammatory syndrome (IRIS), may result from a reconstitution of the adaptative immune system's ability to recognize pathogens/antigens in patients with an already diagnosed or latent OI[2], although more recent data have implicated the innate immunity in the pathogenesis of this clinical picture. Although the vast majority of IRIS cases have been described in the context of advanced HIV infection after the commencement of effective cART, clinical deterioration has also been observed in other clinical contexts, such as after stem cell transplant and in some HIV-negative patients with tuberculosis after starting anti-tuberculous treatment.

Case definition and Clinical Manifestations

A case definition for use in resource-limited settings and partially applicable to resource-rich settings has been published for TB-associated IRIS[3]. The definitions distinguish between 'paradoxical' TB-associated IRIS (diagnosis of TB is made before the initiation of cART and immune reconstitution enhances the inflammatory response against viable mycobacteria), and 'unmasking' TB-associated IRIS (TB is diagnosed after the initiation of cART as a prominent inflammatory reaction that may be the consequence of the immune system attempting to recognize latent viable or nonviable mycobacteria). The inflammatory characteristics of unmasking IRIS differentiate this clinical syndrome from antiretroviral-associated TB, in which active TB is diagnosed after the initiation of cART but which does not have the inflammatory component of IRIS [15]. However, all these definitions are provisional and need to be validated in clinical practice. In a study published by Haddow *et al.* in 2010 a clinical validation of this case definition was applied in 333 clinical events, in which a diagnosis of TB-IRIS or ART-associated TB was possible. Based on expert opinion, there were 18 paradoxical TB-IRIS events, of which 13 (72.2%) were also IRIS under the INSHI case definition. Among the 19 unmasking TB-IRIS events based on expert opinion, 12 (63.2%) were considered TB-IRIS under the INSHI definition. Of 240 non-IRIS and possible IRIS events in the potential unmasking

TB-IRIS group, there was 100% agreement by the INSHI definition. Overall, this study showed a good agreement between expert opinion and the INSHI case definition for both paradoxical and unmasking events. These data support the adoption of this definition in clinical practice also outside resource-limited settings. From a clinical perspective, TB-associated IRIS is characterized by fever, enlarged lymph nodes (mainly cervical, intra-thoracic, and intra-abdominal nodes, but also axillary, supraclavicular, and inguinal nodes), worsening of lung infiltrates, CNS manifestations such as meningitis or abscesses, serositis (pleural effusion, ascites, pericardial effusion), gastrointestinal perforation, and skin or intra-abdominal abscesses. The more uncommon manifestations are ocular, suprarenal, and genitourinary. Risk factors for TB-associated IRIS are the same as those stated above for all causes of IRIS. Early initiation of cART, low CD4+ T-cell count, higher viral load, black race, and extrapulmonary TB are the most common risk factors for TB-associated IRIS[3]. Below, we address the clinical management of TB-associated IRIS and optimal timing for initiating cART after diagnosis of TB in an antiretroviral-naïve HIV-infected patient.

Best timing for starting cART in the context of TB-HIV coinfection

TB is the second most common OI in some resource-rich settings and the most common worldwide. Almost all randomized clinical trials on timing of cART in the context of HIV/TB co-infection have been conducted in resource-limited settings, whereas in resource-rich countries only observational data are available. The SAPiT study found that antiretroviral treatment should be started during anti-TB treatment in patients with pulmonary TB and should not be delayed after finalization of the latter, at least for patients with pulmonary TB and CD4+ T-cell counts equal to or lower than 500 cells/µL. A subanalysis of this trial concluded that, in patients with pulmonary TB and a CD4+ T-cell count under 50 cells/µL, initiation of cART within 4 weeks was associated with better AIDS-free survival, even when the patient was at higher risk of IRIS. Furthermore, a CD4+ T-cell count greater than 50 cells/µL reduced the risk of IRIS without compromising AIDS-free survival. Data from the ACTG 5221 STRIDE and CAMELIA trials also confirmed that, for very immunosuppressed individuals (CD4+ T-cell count under 50 cells/µL, mainly from resource-limited countries), early cART (within 2 weeks) significantly reduced the risk for disease progression and death despite a higher incidence of IRIS in early treatment arms. However, it is unlikely that these findings can be generalized to patients with TB meningitis, since data from another strategy trial comparing early initiation with deferred initiation of cART in HIV-infected patients with TB meningitis revealed that delayed cART was not significantly associated with higher mortality during a 9-month follow-up or with a higher incidence of severe adverse events and intracranial inflammatory response (probably IRIS) in the early treatment arm. However, the high proportion of patients with advanced TB meningitis severity grades was a key factor in the overall mortality in this study and may have been related to the prolonged symptom duration (median duration of symptoms, 21 days; interquartile range, 10–30 days) prior to study entry.

Marais *et al.* found a proportion of TB-IRIS of 44% in patients with tuberculous meningitis starting HAART within 14 days from TB diagnosis, with a mortality of 25% during the first 9 months of follow-up. The risk for IRIS was significantly associated to high CSF neutrophil counts and *Mycobacterium tuberculosis* CSF positive culture at baseline. This study also determined that high levels of TNF- alfa and low levels of IFN-gamma in the CSF might predict IRIS.

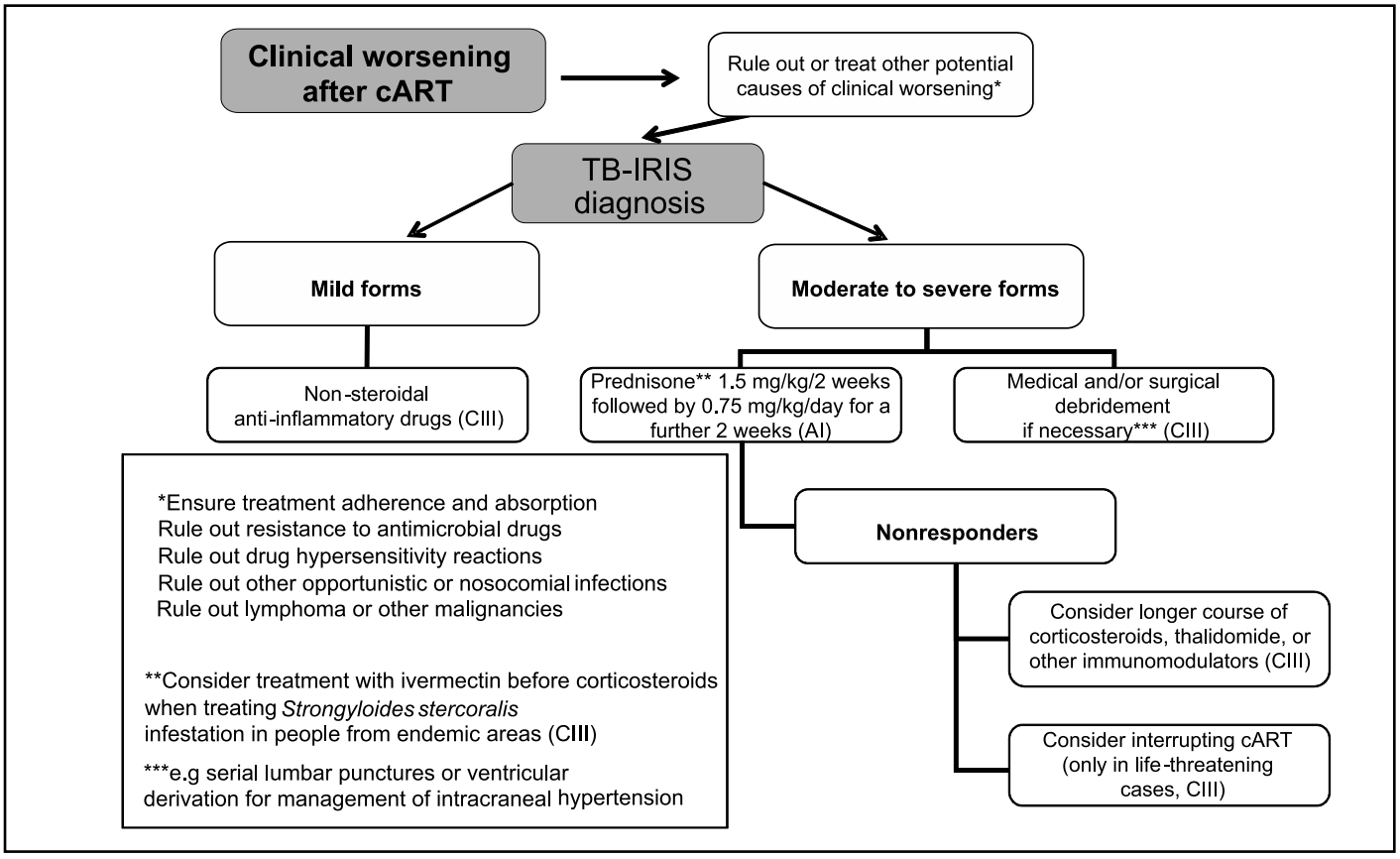
Based on data from clinical trials, we can offer some advice on the best timing for starting cART in the context of HIV-TB co-infection:

- For active TB other than tubercular meningitis:
  - In patients with a CD4+T-cell count of less than 50 cells/mm^3, cART should be started during the first two weeks after starting TB treatment.
  - In patients with a CD4 T cell count equal to or above 50 cells/mm^3, cART should be started between 2 and 8 weeks after starting TB treatment.
- For tubercular meningitis, and independent of the CD4+ T-cell count, cART should be started between 4 and 8 weeks after starting specific anti-TB treatment.

Clinical Management

IRIS is a potentially life-threatening condition (mortality, 3%-20%), and optimal clinical management is crucial for good prognosis. However, heterogeneous pathogenesis and clinical manifestations and the lack of controlled data for treatment of IRIS make it difficult to provide clear guidelines. The most important aspect of management is probably physicians' ability to suspect and recognize this clinical picture in order to rule out other possible causes of clinical worsening. Although no controlled data are available, some authors and the US national institute of health guidelines for treatment of opportunistic infections in adults suggest that mild cases may be treated with non-steroidal anti-inflammatory drugs, even if particular attention must be paid to avoiding interactions with cART, especially if a regimen based on protease inhibitors is administered. For more severe forms of IRIS, the drugs of choice are high-dose corticosteroids.

Figure 1. Shows a proposed clinical management algorithm for TB-IRIS.



The only controlled data on corticosteroid use in the context of moderately severe TB-IRIS were published in 2010 by Meintjes *et al*[4] who showed that a 2-week course of prednisone at 1.5 mg/kg/day followed by 2 weeks of 0.75 mg/kg/day significantly reduced symptom severity, improved quality of life, and reduced hospital stay without severe corticosteroid-related side effects. In more severe cases, larger periods of corticosteroids and/or other immunomodulators (e.g., thalidomide, pentoxifylline, chloroquine, TNF-α inhibitors, and leukotriene antagonists) may prove useful, although clinical experience is very limited. In order to prevent hyperinfestation by *Strongyloides stercoralis* in patients who reside or have lived in endemic areas, empirical eradication with ivermectin before high-dose corticosteroid regimens should be strongly considered. Surgery may be necessary in cases of bowel perforation, splenic rupture, or enlarged lymph nodes responsible for airway or deep vein compression.

The CCR5 inhibitor maraviroc could have a potential role in the down-regulation of HIV-associated chronic inflammation by blocking the recirculation and trafficking of infected cells in inflamed tissue. However, as stated above, in the CADIRIS trial[5] maraviroc failed to demonstrated advantages in preventing IRIS.

Death is rarely observed in patients with IRIS and is more often associated with expansive mass lesions in the brain. IRIS involving the CNS is usually the most life-threatening condition. Interruption of cART should not be a standard approach in the management of IRIS, since other AIDS-defining conditions can develop, and should only be considered in life-threatening cases or following poor response to corticoids.

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