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MESA: VIH y TB

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Modern antiretroviral therapy and tuberculosis

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Tuberculosis (TB) remains the leading cause of death among-people with Human Immunodeficiency Virus (HIV), representing up to 30% of AIDS related deaths worldwide. In people with HIV (PWH) with TB, management of treatment-related adverse events is more complex because antiretroviral therapy (ART) and drugs used for TB treatment share common side effects and because it is not always easy to identify the causative drug in case of rash or hepatotoxicity. Also, drug-drug interactions between antiretrovirals and the combination of drugs used to treat TB, especially rifampicin, leave only few options for ART.

Based on the results of the Phase 2 INSPIRING trial, the latest World Health Organization (WHO) guidelines for lowand middle-income countries (LMICs), recommend to use the-second-generation integrase strand transfer inhibitor (INSTI) dolutegravir for all PWH since 2018 and to double the dose in case of tuberculosis[1,2]. Until then, the non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz was the drug of choice, in association with two nucleoside reverse transcriptase inh bitors (NRTIs) for ART in PWH treated for tuberculosis[3]. European and US guidelines recommend to use dolutegravir, raltegravir or efavirenz-based ART.

INSTI-based regimens, despite high anti-viral efficacy in patients without tuberculosis, have lower rates of virological uppression at week 48 than efavirenz-based regimens inpatients with tuberculosis[2,4]. The INSPIRING non-comparative, open-label, randomised trial evaluated dolutegravir 50 mg twice daily and efavirenz 600 mg once daily in adult PWH with TB. Of note, participants with CD4 counts <50/mm^3 were not eligible and almost all participants had pulmonary, pleural or mediastinal tuberculosis. The rates of viral suppression were similar between the two groups, 75% (52/69) and 82% (36/44) in the dolutegravir and efavirenz arms, respectively[2]. The ANRS 12300 Reflate TB 2 trial is one of the few phase III non-inferiority trials evaluating virologic efficacy of ART in PWH with TB and the only non-inferiority trial to evaluate an INSTI-based regimen in this context. The trial failed to show the non-inferiority of a raltegravir based-regimen compared with an efavirenz-based regimen in terms of virological suppression at week 48. Participants with baseline HIV-1 RNA <100,000 copies/mL at baseline had 75% rates of virologic success in the raltegravir arm and 71% in the efavirenz arm compared to 45% and 61% for those with baseline HIV-1 RNA ≥500,000 copies/mL[4].

Mortality in patients with CD4 T-cell counts <50/mm^3, is reduced in those initiating ART 2 weeks after starting TB treatment as compared to those who initiated ART 4 to 8 weeks after TB treatment initiation in several studies[5]. These results were key to shape the recommendation to start ART 2 weeks after antituberculosis treatment initiation in patients with CD 4 counts <50/mm^3[1,3]. The benefits in patients with CD4 counts ≥200/mm^3 were not demonstrated in these trials, consequently, ART could be delayed in such patients but no later than 8 weeks after the beginning of TB treatment1. More recently, this recommendation was changed in the era of universal treatment and it is now recommended to initiate ART within 2 weeks of antituberculosis

therapy in all PWH with tuberculosis regardless of CD4 counts, except for TB meningitis.

In the context of HIV/TB co-infection, to date, efavirenz-based ART remains the best treatment if we look at virologic outcomes and no other option has been validated in a non-inferiority trial. However, Dolutegravir-based regimens have several advantages as it has a better tolerance profile and is more robust with higher barrier to resistance and forgiveness. In LMICs where resistance monitoring is difficult, these are important advantages, and this explains why dolutegravir replaced efavirenz. We need to continue to evaluate new ART combinations for PWH with TB in phase III trials, especially with the advent of new ART formulations as long-acting injectables and new TB treatments. In the meanwhile, data from large cohorts in LMICs should provide insights on the efficacy of dolutegravir-based ART, the now standard of care as per WHO guidelines in LMICs.

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Tuberculosis and HIV: Focus on Eastern Europe

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Introduction

Tuberculosis (TB) and Human Immunodeficiency Virus (HIV) co-infection remain a critical public health concern worldwide. However, Eastern Europe faces a unique set of challenges in managing this dual epidemic. This presentation aims to provide an overview of the epidemiology, standards of health care and opportunities for improvement, and the impact of the war in Ukraine. We also discuss the implications for necessary actions on a policy and health care level locally, nationally and supranationally.

Global and regional epidemiology

Tuberculosis (TB) continuous to be the preeminent infectious cause of global mortality, eclipsed only momentarily by COVID-19. In 2021, a staggering 10.6 million novel TB cases and 1.6 million TB-related fatalities were documented, with 187,000 of those occurring in People with HIV[1]. The global TB burden remains markedly disproportionate, with eight high-incidence nations within Southeast Asia, Africa, and the Western Pacific collectively representing two-thirds of the overall caseload. Notably, the World Health Organization (WHO) European Region

has demonstrated a consistent downtrend in TB cases since 2000, culminating in a cumulative 25% reduction during the 2015–2020 timeframe, surpassing the goals of their 2020 End TB strategy. Nevertheless, the persistent challenges in this region primarily reside in Eastern Europe and the former Soviet Union nations, typified by a high prevalence of multi-drug-resistant (MDR)-TB and elevated rates of TB/HIV coinfection. These countries register the world's highest per capita disability-adjusted life years (DALYs) loss due to MDR-TB at 290.7 DALYs/100,000 population[2]. Concurrently, the prevalence of HIV among new and recurrent TB cases ranges between 20-50%[1]. Within Eastern Europe, people with HIV afflicted by TB face a one-year mortality rate of up to 30%, while 10-year mortality rates can reach 60% in certain populations[3]. Key contributory factors encompass HIV-related stigma and discrimination, rampant injecting drug use, fragmented healthcare infrastructures beset by diagnostic and therapeutic access constraints, insufficient support for antiretroviral and anti-TB adherence, and a dearth of legalized or accessible opioid substitution therapy (OST). Furthermore, the confluence of poverty and the penitentiary environment in former Soviet Union countries has served as a crucible for the TB, HIV, and hepatitis C syndemic[4].

Standard of care and opportunities across different countries

Within Eastern Europe, the landscape of TB/HIV healthcare standards, legal frameworks, and policies exhibits significant heterogeneity. Certain nations, particularly within Central Eastern Europe, have achieved substantial reductions in both TB incidence and mortality rates among People with HIV. Conversely, within the former Soviet Union, and notably in Russia—where 70% of the region's People with HIV are situated—progress in this regard has lagged. Consequently, addressing these multifaceted challenges necessitates a country-specific political commitment towards the prioritization of integrated, person-centered TB, HIV, and HCV services co-located within a single facility. Equally imperative is the unrestricted provision of OST for all individuals engaged in injecting drug use, coupled with antiretroviral treatment adherence support, the widespread availability of TB drug-susceptibility testing, including rapid molecular tests. Further, isoniazid preventive therapy, affordable pharmaceuticals (ideally free of charge) for (MDR-)TB and HIV, and the establishment of a well-resourced and proficient healthcare workforce are important[4]. Simultaneously, the advent of novel diagnostic test, exemplified by the Urine-LAM test, and notably, shorter all-oral regimens for (MDR-)TB treatment, holds the potential to catalyze a transformative shift in TB/HIV outcomes, provided they are comprehensively integrated and implemented on a broad scale[5].

War in Ukraine and displaced populations

The enduring conflict in Ukraine has exacted a profound toll on the healthcare infrastructure and services within the region. Prior to the onset of hostilities, Ukraine had been making significant strides in enhancing its HIV and TB healthcare systems. Nevertheless, the displacement of populations, the disruption of vital supply chains, and the weakening or outright destruction of healthcare infrastructures have, almost certainly, catalyzed a surge in the prevalence of HIV and TB infections. Concurrently, the migration of individuals from Ukraine has mandated European nations, especially those in close geographic proximity, to assume the responsibility of ensuring the provision of adequate healthcare services for these displaced populations, with a specific focus on addressing the challenges posed by TB and HIV.

Conclusions

TB and HIV in Eastern Europe remain major public health challenges. While progress has been made in Central Eastern Europe, significant gaps persist in particular in countries of the former Soviet Union, requiring concerted efforts at local, national, and supranational levels. Locally, strengthen healthcare infrastructure and workforce, improve access to diagnostics and treatment, and reduce stigma associated with TB and HIV. On the national level allocate sufficient resources to TB and HIV programs, implement integrated care models and enhance collaboration between healthcare sector and legalize and/or enable universal access to OST. On the supranational level foster regional cooperation, share best practices, and support countries affected by external factors, such as the Ukrainian war.

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Evaluation of the Effect on Quantiferon kinetics of 3HP vs Periodic 3HP vs 6H in HIV-Positive Individuals: WHIP3TB study

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Tuberculosis (TB) is the most important cause of death from an infectious disease, and has enormous social and economic impact. There were estimated 10.6 million new cases of TB in 2021, and 1.6 million people died, including 187,000 HIV-positive individuals[1]. A quarter of the global population is infected with *Mycobacterium tuberculosis* (MTB), which is a precursor to TB disease and an important threat to TB control[2].

TB infection (TBI) is a state with few bacilli in a dormant stage[3]. Although TBI testing is not a requirement for initiating preventive treatment (PT) in people living with HIV (PLHIV), those who have a positive test for TBI are at higher risk of developing active TB and will have a greater benefit from the therapy than those who have a negative TBI test[4,5].

However, TBI management is a complex process and several issues hamper the successful completion of the entire cascade of care. In particular, testing for TBI has been associated with larger losses in follow up during case management[6]. More evidence is necessary on the benefits of TBI testing, not only for case detection, but also for determining risk of progression and, potentially, monitoring PT outcomes.

The Interferon- γ release as- says (IGRAs), appeared as a more reliable tool to substitute TST. This is an *in-vitro* diagnostic test which uses a peptide cocktail simulating ESAT-6 and CFP-10 proteins from *Mycobacterium tuberculosis* complex (MTBC). These antigens stimulate cells that release IFN-γ that is quantified as measure of response against MTBC[7]. Apart from detecting TBI cases, new studies are focusing on the use of IFN-γ as a biomarker of preventive therapy success[8,9]. Recent prevention of infection vaccine trials, postulate that an IGRA reversion following an initial conversion might mean that the infection was transient and that several consecutive IGRA positive results would be compatible with a persistent TB infection[10].

However, reports on the utility and meaning of conversions (infection) and reversions (treatment success) are heterogeneous in study design, population, and in accounting for confounding factors. Changes in IFN-γ levels after TBI treatment remain controversial[11] and data on the long-term IFN-γ responses after PT are limited, mainly among HIV-positive patients[12].

Furthermore, the novel QuantiFERON-TB Gold Plus (QFT-Plus), unlike the previous QFT contains two different tubes that stimulate both, CD4 and CD8 response, increasing sensitivity of this test, especially among those with impaired immune response.

Using data of the WHIP3TB drug preventive trial, we evaluated whether different regimens of PT influence the kinetics of the T-cell IFN-γ responses to Mtb specific antigens in a high burden TB and HIV area.

Preliminary results will be presented at the XXVII UITB's international conference on TB.

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Mycobacterium avium y VIH. Actualización en personas con VIH

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La infección diseminada por el complejo *Mycobacterium avium* (MAC) en personas con VIH ha disminuido notablemente desde la introducción de la terapia antirretroviral (TAR) eficaz. Sin embargo, las enfermedades por micobacterias no tuberculosas todavía ocurren en personas que viven con VIH, aunque la incidencia ha caído a ≤2 casos por 1.000 personas-año entre las personas en tratamiento, partiendo de unas cifras en los años 90 de más de 40% afectados entre aquellos con recuentos de CD4+< 50 células/µl. Es bien conocido que el riesgo de infección por MAC en personas con VIH aumenta a medida que el recuento de CD4 desciende por debajo de 50 células/microL, aunque existen otros factores de riesgo como la replicación viral persistente, algunas comorbilidades o la manipulación respiratoria previa como la realización de broncoscopia entre otros. En un estudio observacional realizado después del año 2.000 en pacientes con MAC, se observó que la mayoría de los casos se concentraban en grupos subrepresentados, en pacientes con inicio tardío del tratamiento antirretroviral o con mala vinculación al cuidado sanitario. Por otro lado, el riesgo de MAC no parece variar según el sexo, el origen étnico o la vía de transmisión. Sin embargo, el riesgo sí puede variar según la ubicación geográfica, siendo más frecuente el diagnóstico en los Estados Unidos que en Europa. En este sentido, se han comunicado tasas más altas de MAC diseminado en países con más recursos en comparación con países con recursos limitados (10 a 22% versus 2 a 3%). Por último, los pacientes con MAC diseminado también pueden tener una predisposición genética a la infección; en concreto se ha encontrado asociación de la enfermedad con mayor frecuencia de HLA de clase II (DRB1, DQB, DM).

Todavía se siguen comunicando casos aislados de infección por MAC en personas con VIH, sobre todo en relación con reconstitución inmune o presentaciones atípicas o graves como infartos esplénicos. También se han analizado las características clínicas y microbiológicas de la infección por las micobacterias no tuberculosas (MNT), incluida MAC, en personas con VIH en países asiáticos. Una cohorte retrospectiva en Corea del Sur de más de 10 años (inclusión de diagnosticados entre enero de 2000 y marzo de 2021) incluyó un total de 34 casos, siendo el MAC el más frecuente. Fue más habitual presentación pulmonar de las MNT que la extrapulmonar (58,8% versus 41,2%) y la localización extrapulmonar más frecuente fue la ganglionar (64,3%). La afectación extrapulmonar se asoció con pacientes más jóvenes (37,0 frente a 49,0 años). El recuento medio de células CD4+ en el momento del diagnóstico de la enfermedad NTM fue de 186,6 células/µl (rango: 1-1394) y el 26,5% de pacientes tenían cargas virales completamente suprimidas en el momento del diagnóstico de la enfermedad NTM, evidenciando que la infección puede aparecer también entre los pacientes bien suprimidos. Todos los aislados de MAC en esta cohorte fueron sensibles a la claritromicina, pero las tasas de resistencia a moxifloxacino, linezolid, etambutol y rifampicina fueron del 75%, 37,5%, 12,5% y 12,5%, respectivamente. La duración media del tratamiento

fue de 17 meses y la tasa de mortalidad alcanzó la cifra nada desdeñable del 8,8%.

Por último, la recomendación de profilaxis ha cambiado desde hace unos años. Un estudio de cohortes realizado en 2014 con pacientes que habían tenido al menos una determinación de CD4+<50 células/µl evidenció que la incidencia de MAC no difirió significativamente entre los grupos que tomaban o no profilaxis si estaban recibiendo TAR (3,4/100 personas-año versus 0,8/100 personas-año). En base a este estudio, se modificaron los criterios para la profilaxis primaria de MAC, y actualmente sólo está indicada en pacientes sin TAR inmediato y recuentos de células CD4 <50 células/µl, utilizando azitromicina semanal (la claritromicina o macrólidos son una alternativa a azitromicina). El tratamiento se interrumpe cuando los pacientes inician TAR eficaz.

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