

Understanding and intervening in HIV-associated tuberculosis

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ABSTRACT

HIV-associated tuberculosis can present as extremes, ranging from acute life-threatening disseminated disease to occult asymptomatic infection. Both ends of this spectrum have distinct pathological correlates and require specific diagnostic and treatment approaches. Novel therapeutics, targeting both pathogen and host, are needed to augment pathogen clearance. In latent tuberculosis infection, enhancement of immune activation could be desirable. Antiretroviral therapy augments the beneficial effects of antitubercular therapy. However, in the context of high bacillary burden, antiretroviral therapy can also result in pathology (tuberculosis immune reconstitution inflammatory syndrome). In the immune reconstituting patient, modulation of immune activation controls tissue destruction. Interventions should also be appropriate and sustainable within the programmatic setting.

KEYWORDS: HIV, tuberculosis, latent tuberculosis infection, paucibacillary, multibacillary, diagnostics, immune reconstitution inflammatory syndrome, immune modulation, host-directed therapies

Introduction

An estimated 35 million people were living with HIV worldwide at the end of 2013, 24.7 million of whom were in sub-Saharan Africa.¹ Around 1.1 million (12%) of the 9 million people who developed tuberculosis in 2013 were coinfecting with HIV.² Up to a third of the world's population is latently infected with tuberculosis. In a study done in a South African setting with a high burden of HIV and tuberculosis, the rate of latent tuberculosis infection was estimated to be much higher – 69%.³ The lifetime risk of progression from latent infection to post-primary active tuberculosis is estimated to be 5–10%.

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People living with HIV have a 26–31-fold increased risk of developing active tuberculosis compared with HIV uninfected people, and the frequency of tuberculosis rises with advancing immunosuppression.² People with fewer than 100 CD4 lymphocytes per mm³ have a more than tenfold-increased risk of tuberculosis per 100 person-years compared with those with more than 500 CD4 cells per mm³.⁴

Commencement of antiretroviral therapy (ART) is associated with a substantial sustained reduction in the incidence of tuberculosis at all CD4 strata on both the individual and the community level. However, evidence⁵ suggests that, compared with HIV-uninfected people, people living with HIV have a higher risk of developing tuberculosis, even when their CD4 counts are higher than 500 cells per mm³. There is also evidence that person time accrued at lower CD4 strata is associated with an increased risk of tuberculosis after commencement of ART.^{4,6} Implementation of integrated HIV and tuberculosis care programmes is essential to reduce the dual burden of disease.

Tuberculosis accounts for around 25% of HIV-associated deaths each year. 80% of HIV–tuberculosis coinfections and associated deaths occur in sub-Saharan Africa. In patients in lower CD4 strata, the diagnostic challenges are substantial because of a high proportion of smear-negative, extra-pulmonary and disseminated tuberculosis.⁷ In four randomised controlled studies, commencing ART earlier for patients with low CD4 T-cell counts (2 weeks for patients with fewer than 50 CD4 cells per mm³, otherwise within 4–12 weeks of treatment for tuberculosis) was associated with a survival benefit.⁸

During advanced immunosuppression, initiation of ART in patients coinfecting with HIV and tuberculosis can lead to both unmasking of tuberculosis in those with previously undiagnosed disease or a paradoxical immune reconstitution inflammatory syndrome (IRIS). A meta-analysis of 20 studies showed that paradoxical tuberculosis IRIS occurs in 18% of patients living with HIV commencing ART; 25% of these patients are admitted to hospital as a result, and IRIS-attributed death is reported in 2%.⁹ Mortality attributable to IRIS of the central nervous system has been reported at 13–23%.^{10,11}

This article focuses on interventions at opposite ends of the spectrum in adults coinfecting with HIV and tuberculosis. The first is the state encountered during latent tuberculosis infection when, despite a moderate-to-low bacillary load, sub-optimal host inflammatory response prevents eradication of infection. The second is the diagnostically challenging disseminated

disease in advanced immunosuppression when immune reconstitution after ART can lead to a hyper-inflammatory response.

Hypoinflammatory moderate bacillary load disease (latent tuberculosis infection)

Pathogenesis

Latent tuberculosis infection is now thought of as a spectrum ranging from immune sensitisation as the only evidence of otherwise cleared infection to a quiescent paucibacillary state in which the immune system controls bacterial replication without eradicating infection, to asymptomatic (subclinical) but microbiologically diagnosable infection (Fig 1).

In latent tuberculosis infection in individuals living with HIV, there is a complex interplay between key pro-inflammatory and anti-inflammatory molecules and their effect on disease progression versus disease containment. An illustration of this interplay comes from the zebrafish model, in which either overexpression or underexpression of the enzyme leukotriene A4 hydrolase (LTA4H), compared with wild-type expression, leads to increased *Mycobacterium marinum* infection. LTA4H catalyses the final step in pro-inflammatory eicosanoid leukotriene B4 (LTB4) synthesis and mediates the balance of LTB4 and anti-inflammatory lipoxin A₄. Overexpression of LTA4H results in increased LTB4 and increased production of tumour necrosis factor α (TNF α) production. Underexpression of LTA4H results in increased lipoxin A₄ and impaired TNF α production.¹³

Just as pro and anti-inflammatory balance of the eicosanoid pathway can affect disease pathogenicity, intra-host heterogeneity in evolution of lesions can affect the response to host directed therapy. It is also important to appreciate heterogeneity between lesions and the potential for host-directed therapy to do harm.

Diagnosis and prognostic indicators

The tests for latent tuberculosis infection – tuberculin skin tests and interferon- γ release assays – cannot differentiate

between immune sensitisation, quiescent and active disease.¹⁴ Subclinical tuberculosis is associated with abnormal chest radiographs in only a proportion of cases. In high-burden settings, subclinical tuberculosis rates can be as high as 8.5%.¹⁵

In view of the burden of latent tuberculosis in people living with HIV, there is an urgent need for a more sensitive and specific biomarker to predict which individuals with latent infection will progress to active tuberculosis. Research focusing on host–pathogen transcriptomics, proteomics and metabolomics; multi-cytokine expression profiling; and tuberculosis-associated circulating micro RNAs show potential in the differentiation of active and latent disease and monitoring of response to treatment.¹⁶ Imaging modalities such as combined computed tomography and positron emission tomography provide a valuable tool for longitudinal analysis of the change in individual lung lesions over the course of novel or existing preventive or therapeutic regimens in both people and animal models.¹⁷

Management

ART is the most efficacious host-directed therapy to prevent progression of latent tuberculosis to active infection. In resource-constrained settings with a high burden of disease, the World Health Organization recommends 6–36 months of isoniazid preventive therapy (IPT) for adults and adolescents living with HIV who have been screened for tuberculosis, irrespective of ART status and results of tuberculin skin tests. In low-burden settings, IPT should be prescribed on an individualised level on the basis of duration of ART and CD4 cell count. In a randomised controlled trial by Rangaka and colleagues in patients living with HIV taking ART, IPT plus ART was associated with a 37% reduction (hazard ratio (HR) 0.63, 95% CI 0.41-0.94) in the incidence of tuberculosis comparable with ART alone, and had acceptable tolerability. Contrary to previous findings, IPT was most protective in participants with baseline negative tuberculin skin tests or interferon- γ release assays, suggesting that the regimen could be useful in reducing incidence of tuberculosis in moderate-to-high-burden settings, regardless of TST/IGRA status.¹⁸

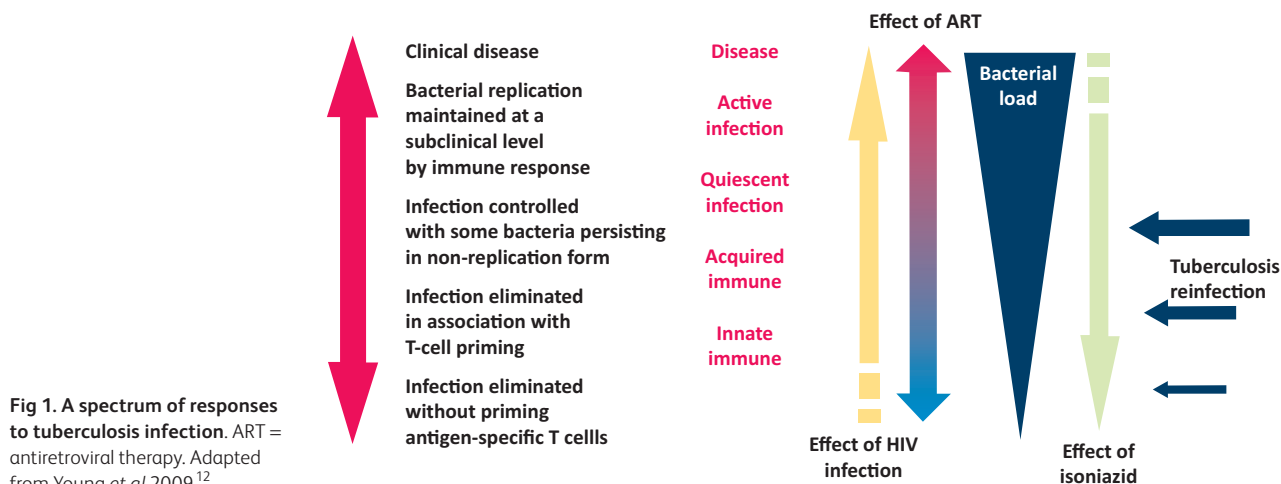


Fig 1. A spectrum of responses to tuberculosis infection. ART = antiretroviral therapy. Adapted from Young *et al* 2009.¹²

The BOTUSA study showed that 36 months of IPT was more efficacious than 6 months of IPT in people living with HIV, of whom 45% were on ART.¹⁹ Martinson and colleagues did a randomised controlled trial in patients not taking ART, in which they compared novel prophylactic combinations of rifapentine–isoniazid (900 mg once weekly for 12 weeks), rifampicin–isoniazid (600 mg/900 mg twice weekly for 12 weeks) and isoniazid (300 mg daily for up to 6 years) with

standard of care (300 mg daily isoniazid for 6 months). The rate of tuberculosis infection did not differ significantly between the regimens.²⁰ Outstanding questions about the management of latent tuberculosis infection include determination of the optimum regimen and duration of treatment.

Several classes of compounds are under investigation as adjunctive therapies, and target different aspects of the host immune response (Table 1).^{21–23} Many of these compounds

Table 1. Potential novel therapies for latent tuberculosis infection and IRIS, by class.^{17,21–23,27,28}

Drug and class	Possible indication	Mechanism of action
Fluoroquinolones: ofloxacin, moxifloxacin, gatafloxacin	Latent tuberculosis infection	DNA gyrase inhibitor
Diarylquinolines: bedaquiline	Latent tuberculosis infection	Mycobacterial ATP synthase inhibitor
Nitro-dihydro-imidazo-oxazole: delamanid	Latent tuberculosis infection	Inhibition of mycolic acid synthesis (cell wall)
Nitro-imidazo-oxazine: PA-824	Latent tuberculosis infection	Inhibition of ketomycolate synthesis (cell wall) and production of toxic reactive nitrogen species release following bioreduction
Oxalizidinone: sutezolid	Latent tuberculosis infection	Inhibition of protein synthesis in non-replicating bacteria
Quinone oxidoreductase: nitazoxanide	Latent tuberculosis infection	Activity against replicating and non-replicating bacilli; induces autophagy
Thiazolidinediones: rosiglitazone	Latent tuberculosis infection	Peroxisome proliferator-activated receptor gamma antagonist (lipid-sensing nuclear receptor antagonists); regulation of cytokine production, lipid body biogenesis, and <i>Mycobacterium tuberculosis</i> replication in macrophages
Interleukin 1 α/β antagonist: anakinra	IRIS	Reduced pro-inflammatory cytokine production and apoptosis
Lipoxygenase-5 inhibitor: zileuton	IRIS	Reduction of pro-inflammatory eicosanoids LTB4 and impaired TNF α function
TNFα inhibitor: adalimumab	IRIS	Granuloma disruption and reactivation of quiescent lesions Potent inhibition of TNF α -mediated inflammation
Secosteroid: cholecalciferol (vitamin D3)	Latent tuberculosis infection, IRIS	Transcription of antimicrobial peptide LL37 (cathelicidin) – induced killing of <i>M tuberculosis</i> and induction of autophagy in infected macrophages
Cytochrome P450 blockers: clotrimazole, econazole	Latent tuberculosis infection, IRIS	Reduced calcium-induced potassium efflux from cells leading to activation of NALP3 inflammasome. Proautophagic, anti-inflammatory and anti-apoptotic
IL-6 blocker: tocilizumab	IRIS	Blockade of IL-6-mediated inflammation
Cyclooxygenase inhibitors: aspirin	IRIS	Reduced synthesis of pro-inflammatory eicosanoids and TNF α
MMP inhibitor: Ro32-3555, doxycycline	IRIS	Blockade of MMP1, MMP8 and MMP13 (Ro32-3555) or MMP1 and MMP9 (doxycycline)
Corticosteroids: dexamethasone, prednisolone, methylprednisolone	IRIS	Blockage of glucocorticoid receptor leading to downregulation of transcriptional regulators NF- κ B and AP1, resulting in decreased inflammatory cytokines and MMPs
COX-2 inhibitor: meloxicam	IRIS	Inhibition of TNF α -induced prostaglandin E ₂ production, and vice versa
CCR5 inhibitor: maraviroc	IRIS	Blockage of interaction of CCR5 with endogenous ligands, leading to decreasing influx of CCR5-expressing immune cells to site of inflammation

Many of these agents are postulated to also have potential to shorten treatment and enhance disease resolution or prevent reactivation. AP1 = activator protein 1; CCR5 = C-C chemokine receptor type 5; COX-2 = cyclooxygenase 2; IL = interleukin; IRIS = immune reconstitution inflammatory syndrome; MMP = matrix metalloproteinase protein; NF- κ B nuclear factor kappa-light-chain-enhancer of activated B cells; TNF- α = tumour necrosis factor α .

have dual antimicrobial action to hasten clearance of the pathogen. Vitamin D is one such potential therapeutic agent. Vitamin D deficiency is associated with progression of latent tuberculosis infection to active infection.²⁴ Martineau *et al* showed an inverse relationship between seasonal vitamin D concentrations and tuberculosis notification rates in a South African setting with a high burden of HIV and tuberculosis.²⁵ Studies of prophylactic therapies should be stringently designed and adequately powered to detect an attributable risk reduction in tuberculosis rates greater than that associated with the currently endorsed standard of care. Use of appropriate modes of administration and balancing side-effect profiles and potential drug interactions is challenging.

Tuberculosis vaccines are categorised as therapeutic, pre-exposure prophylactic and post-exposure prophylactic and can be given either instead of the Bacillus Calmette–Guérin vaccine or as a heterologous prime boost strategy. They range from killed mycobacteria and viable recombinant mycobacteria to adjuvant subunit and viral vector vaccines.²¹ The MVA85A candidate vaccine is an adjuvant subunit and viral vector vaccine. Although it was administered safely with demonstrable immunogenicity in people living with HIV,²⁶ so far no vaccine candidate has efficaciously prevented the transition of latent infection to active tuberculosis. Six prime-booster vaccines are undergoing phase II or III clinical trials in paediatric and adult populations, and a further five pre- and post-exposure vaccine candidates are in phase I studies. There is also ongoing work looking at novel routes of vaccine administration and combination vaccination strategies.²¹

High bacillary load, hypoinflammatory disease

Pathogenesis

Advancing immunosuppression in people living with HIV leads to functional disruption and decreased responsiveness within the microenvironment of the granuloma that can be accompanied by increased bacterial replication.²⁹ Mediators of tissue extracellular matrix destruction, fibrosis and remodelling, such as matrix metalloproteinases, are also downregulated, leading to less tissue necrosis and cavitory disease.³⁰ In advanced immunosuppression, the bacteriological and histological diagnostic yield from both pulmonary and extra-pulmonary samples is paradoxically poor. The failure to diagnose such occult disseminated tuberculosis might be associated with unmasking of tuberculosis after commencement of ART in such patients.

The pathophysiology of mycobacterial sepsis and multiorgan failure syndrome in HIV–tuberculosis is incompletely understood and further studies are needed to characterise pathways of pro-inflammatory and anti-inflammatory immune dysregulation leading to death.

Diagnosis

An algorithm issued by the World Health Organization in 2007 aims to expedite diagnosis and treatment of tuberculosis in people living with HIV with smear-negative and extra-pulmonary disease in low-resource settings via expanded case definitions in conjunction with timely initiation of

broad-spectrum antibiotic treatment for suspected bacterial pneumonia and co-trimoxazole prophylaxis.³¹

The diagnostic yield of *Mycobacterium tuberculosis* can be enhanced via methods such as sputum induction, bronchoalveolar lavage, computed tomography, ultrasonography or endobronchial ultrasonography-guided biopsy and the use of multiple specimen sampling. In patients living with HIV with advanced immunosuppression (CD4 <250 cells/mm³), diagnostic yield of *M tuberculosis* is up to 20% positivity in blood cultures.³² Although, there is a greater probability of normal chest radiographs in advanced HIV, mediastinal or parasternal adenopathy, lower and mid-zone interstitial involvement, pleural effusions and miliary tuberculosis are well recognised. Radiological modalities have useful diagnostic value for extra-pulmonary and disseminated tuberculosis in the central nervous system, bone and joints, visceral adenopathy and serositis (pleural and pericardium), but must be interpreted within a broader differential diagnosis.

The Xpert MTB/Rif test, which is endorsed by the World Health Organization, has been rolled out at concessional prices to speed up microbiological diagnosis and drug sensitivity testing in 108 countries. It has a sensitivity of over 95% in smear-positive patients. The overall sensitivity of the Xpert MTB/RIF assay for HIV-associated tuberculosis is 58.3–91.7% and highest in patients who had a cough for 2 weeks or longer.³³ The use of the assay in active case finding (irrespective of symptoms) is limited by both its reduced sensitivity (131 colony forming units per mL versus 10–50 colony forming units per mL for liquid culture) and the presence of false positive results in retreatment patients secondary to persistence of pathogen DNA even several months after treatment.³² Pooled data from 20 studies of Xpert MTB/RIF testing in patients with extrapulmonary tuberculosis (both with and without HIV) showed the following sensitivity and specificity, respectively: lymph node aspirate 84.9 and 92.5%, gastric fluid 83.8 and 98.1%, tissue biopsy 81.2 and 98.1%, and cerebrospinal fluid 79.5 and 98.6%.³³ In patients with advanced HIV-TB (CD4 strata less than 50 cells/mm³ or patients requiring inpatient management),^{34,35} the sensitivity of Xpert MTB/RIF in concentrated urine was 44–47.8%, compared to a culture gold standard. Diagnostic yield reduced as CD4 strata increased above 150 cells/mm³.³⁴

Unstimulated interferon- γ in pleural fluid has shown value as a rule-in test for pleural tuberculosis in both patients living with HIV and uninfected individuals, and has improved sensitivity and specificity compared with adenosine deaminase and Xpert MTB/RIF.³⁶ An *M tuberculosis* antigen-specific enzyme-linked immunospot (EliSpot) was used to test both mononuclear cells from cerebrospinal fluid and peripheral blood lymphocytes and had sensitivity of 94%.³⁷ A study by Feng and coworkers showed sensitivity of 82.9% and specificity of 85.0% for a modified Ziehl-Neelsen stain and sensitivity of 75.1% and specificity of 69.4% for ESAT-6 immunostain for intracellular *M tuberculosis* in cerebrospinal fluid when compared with a clinical gold standard. The former has potential to be widely adopted in low-resource settings to hasten diagnosis of tuberculous meningitis.³⁸ A point-of-care immunochromatographic test that detects mycobacterial lipoarabinomannan in urine can identify up to 59% of cases of culture-positive tuberculosis in people living with HIV whose CD4 count is lower than 100 cells per mm.^{3,39}

Management

The REMEMBER study (ClinicalTrials.gov identifier: NCT01380080) is an ongoing multinational study of safety and reduction in early mortality and morbidity associated with empirical treatment for tuberculosis concurrently with ART in patients with fewer than 50 CD4 cells per mm³.

HIV-associated tuberculous meningitis has a mortality of more than 60%.⁴⁰ Torok and colleagues showed no mortality benefit for early ART versus delayed ART in HIV-associated tuberculous meningitis with higher grade 4 adverse events in the early ART group.⁴⁰ This is reflected in some national guidelines regarding delay of commencement of ART in HIV-TB meningitis to 8 weeks post start of anti-TB therapy, regardless of CD4 strata. Ruslami *et al* showed significantly reduced mortality in TB meningitis with treatment intensification for the first 14 days with use of higher dose (13 mg/kg) intravenous rifampicin compared with standard dose (10 mg/kg) oral rifampicin.⁴¹ Thwaites *et al* showed, in the absence of coma at baseline, there was a significant reduction in mortality with addition of oral fluoroquinolone to the standard regimens for the first 60 days. There was a 'U' shaped relationship between exposure in the plasma and cerebrospinal fluid (CSF) and the outcome of death or disability, with intermediate exposures being optimal. CSF penetration was greater with levofloxacin than gatifloxacin or ciprofloxacin.⁴² Studies have shown improved outcomes in tuberculous meningitis when high-dose intravenous rifampicin⁴¹ is given with a fluoroquinolone, with levofloxacin showing optimal penetration of the central nervous system.⁴² An ongoing randomised controlled trial in Vietnam is assessing the efficacy of high-dose oral rifampicin and fluoroquinolones to improve tissue-specific penetration and bactericidal activity in tuberculous meningitis (ISRCTN 61649292). A meta-analysis by Critchley and colleagues⁴³ suggested non-organ-specific reduction in tuberculosis mortality when adjunctive corticosteroid therapy is given, but this hypothesis has not been supported by a randomised controlled trial assessing the use of corticosteroids (prednisolone) in tuberculosis-associated pericarditis⁴⁴ or by five-year follow-up data from a trial assessing the effect of corticosteroids (dexamethasone) on survival benefit and reduction of severe neurological disability in tuberculous meningitis.⁴⁵ Unmasking and progression of HIV-associated cancers and impaired glycaemic control are also potentially serious complications of corticosteroids.

High bacillary load, hyperinflammatory disease

Pathogenesis

Paradoxical tuberculosis IRIS is characterised by organ-specific or systemic inflammatory response in response to a persistent antigen load during immune recovery after ART. Risk factors include a low CD4 count, short duration between commencing tuberculosis treatment and ART, and disseminated tuberculosis. Onset is usually within 2–4 weeks of commencing ART. Lungs and lymph nodes are frequent sites of involvement.

Diagnostic predictors

A positive urinary lipoaribomannan could be of use in identifying individuals with a high systemic bacterial burden

and hence increased risk of IRIS.⁴⁶ C-reactive protein, an acute-phase reactant, is upregulated in response to interleukin 6 and is a sensitive but non-specific biomarker of IRIS.⁴⁷ Culture positivity, high neutrophil count, high TNF α and low interferon γ in the cerebrospinal fluid at baseline are predictive of tuberculous meningitis IRIS.¹⁰

Management

Prednisolone and non-steroidal anti-inflammatory drugs are the most widely used treatment for paradoxical IRIS, with the former used for more severe cases. In a double-blinded placebo-controlled study by Meintjes *et al*, daily administration of 1.5 mg/kg prednisolone for 2 weeks, followed by 0.75 mg/kg for 2 weeks resulted in significantly less time in hospital and fewer outpatient therapeutic procedures.⁴⁷ Tobin and colleagues showed that the efficacy of response to dexamethasone in tuberculous meningitis was related to high-expression of the LTA4H genotype.⁴⁸ Marais and colleagues showed that corticosteroids had little effect on cytokines and cytokine concentrations in cerebrospinal fluid, and postulated that inflammation in the central nervous system in tuberculous meningitis IRIS is chiefly mediated via interleukin 17 and S100A8/A9-dependent neutrophil aggregation.⁴⁹ Two studies have shown an increased incidence of HIV-associated lymphoma and Kaposi's sarcoma in patients living with HIV given corticosteroids while severely immunosuppressed.^{43,50} In both studies, early ART was not prescribed to all patients. Hence, in the context of current standard of care, rates of corticosteroid-induced HIV-associated cancers might be lower. The ongoing PredART study (ClinicalTrials.gov identifier NCT01924286) is examining the safety and efficacy of prophylactic 40 mg prednisolone daily for 2 weeks, followed by 20 mg daily for 2 weeks for the prevention of IRIS. The proposed tuberculosis–IRIS non-steroidal anti-inflammatory drug cyclooxygenase-2 inhibitor prevention trial (ClinicalTrials.gov identifier NCT02060006) suggests the prophylactic use of meloxicam daily for 8 weeks to prevent tuberculosis IRIS. In the CADIRIS study, maraviroc, a C-C chemokine receptor type 5 antagonist, did not significantly reduce the to an IRIS event by 24 weeks of ART in patients with baseline CD4 cell counts of fewer than 100 cells per mm³.⁵¹

In conclusion, to intervene in the dual spectrum of HIV–tuberculosis disease, widespread rollout of ART in conjunction with both established and targeted novel therapies is needed to reduce bacterial burden more effectively and appropriately modulate the host immune response. This must be in the context of improved diagnostics and prognostic biomarkers and via streamlined programmatic algorithms and strengthening of health systems. ■

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