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Tuberculosis: A Report from CROI 2016

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ABSTRACT

The Conference on Retroviruses and Opportunistic Infections (CROI) is a major annual scientific meeting on HIV/AIDS and associated conditions. Tuberculosis (TB) is the number one cause of death among people living with HIV in developing countries and is the subject of numerous CROI presentations. This report will focus on the presentations at CROI that the author believes are most relevant to clinicians, the public health community and investigators interested in tuberculosis.

Introduction

The Conference on Retroviruses and Opportunistic Infections (CROI) is a major annual scientific meeting on HIV/AIDS and associated conditions. Tuberculosis (TB) is the number one cause of death among people living with HIV in developing countries and is the subject of numerous CROI presentations. This report focuses on a select group of presentations at CROI 2016 on Tuberculosis. The author is solely responsible for the selection of presentations and the synopsis included in this report. This report is not an endorsed activity of CROI itself.

Poverty, HIV and TB

The linkage between Poverty, HIV, and TB has been recognized since the early HIV epidemic. Several of the following presentations and abstracts highlight the fact that health disparities among the poor with HIV continue to exist, including an increased risk of tuberculosis.

The opening session of CROI included a session by Gerald Friedland from Yale, entitled *Confronting HIV and TB from the Bronx, NY to Tugela Ferry, South Africa*. Dr. Friedland noted that in the 1980's in the poorest area of New York City, (the Bronx), Intravenous drug use (IVDU) led to an epidemic of HIV in an area where systematic neglect had led to overcrowding, lack of basic services, and barriers to health care. This was fertile ground for an epidemic of multidrug resistant tuberculosis (MDR TB). Twenty years later an explosive HIV epidemic occurred among the poorest of the poor in Durban, South Africa and an epidemic of extremely drug resistant tuberculosis (XDRTB) followed. Apartheid and policies based on discrimination and stigma, along with a mining industry that crowded workers into small living spaces fueled the epidemic. Poverty in both epidemics led to delays in diagnosis, challenges with appropriate isolation and treatment, with resultant high morbidity and mortality. Interventions in both epidemics that used the communities' strengths and were based on the rights of residents to public health services were ultimately effective. Dr. Friedland noted that future public health disasters can be averted if principles of social justice and human rights are recognized and put into practice [1].

Dr. Gosawami and colleagues from Emory presented research showing that poverty, HIV and TB remain linked in areas of the US. They identified newly diagnosed patients with HIV infection in 2012, and using spatial tools looked for an overlap with TB diagnosis and homelessness. Newly diagnosed HIV individuals who were "poorly linked to care" were defined by absence of CD4 or HIV viral load testing over three months. They identified statistically significant spatial clustering of new diagnoses in multiple metro Atlanta counties, smaller clusters of poorly linked individuals in two counties, and a poor HIV viral suppression cluster in a single county. In the single virally unsuppressed cluster, there were 5 cases of virally unsuppressed persons per square mile (vs 0 in other areas). Within this cluster, there was a high density of homeless persons (60–200 homeless persons per census block). There was overlap of TB clusters with the HIV clusters of patients poorly linked to care including the poor viral suppression cluster. The authors note that the spatial overlap of HIV patients poorly

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linked to care, with TB disease and with a high density of homeless suggests continued opportunities to partner with TB and homeless service providers to improve local HIV outcomes [2].

Investigators in Botswana showed that with antiretroviral coverage exceeding 90%, mortality due to TB in HIV-infected individuals substantially decreased with cancer mortality now likely exceeding mortality due to TB. [3] Botswana's results help prove that when resources are put in place, the linkage of HIV and TB can be broken with a subsequent decrease in the morbidity and mortality from TB. The decline in TB related mortality is a great success and brings new challenges to the care of HIV-infected persons in Botswana.

TB in resource limited countries

Tuberculosis continues to be a significant problem in resource limited countries, and requires unique approaches to diagnosis and treatment. The following studies in countries as diverse as South Africa, Zambia and Haiti evaluated unique approaches to treatment and diagnosis.

HPTN 071 (PopART) aims to determine the impact of a combination prevention intervention on HIV incidence. Community HIV healthcare workers in Zambia are responsible for the delivery of the intervention and linkage to care. The investigators decided to evaluate if these workers could also use a simple questionnaire to screen individuals for TB, and obtain sputum on TB suspects. 1.2% of screened individuals (212,819 persons) had symptoms of TB and 9% of these were identified as having TB. Community health care workers appeared with little training to be able to contribute to active case finding and linkage to care[4].

A5274 REMEMBER study is a multi-country randomized clinical trial comparing antiretroviral therapy (ART) + four-drug empiric TB therapy vs. ART + isoniazid preventive therapy (IPT) in HIV-infected individuals with CD4 counts < 50 cells/mm^3. At week 48, there was no statistical difference in mortality or AIDS progression between the empiric group and the IPT group. The empiric treatment group had more TB at week 48 compared to the IPT group. The investigators concluded that in a population with a high burden of TB and advanced HIV, there was no demonstrable benefit of empiric TB therapy on mortality or prevention of TB at 48 weeks [5].

Investigators in South Africa examined if early TB treatment of HIV infected individuals with low CD4 counts could impact mortality and hospitalization. They randomized primary care clinics to either an intervention arm where nurses categorized ART naïve HIV infected individuals with CD4 counts < 150 as being high risk, moderate risk or low risk for TB based on clinical criteria. High risk individuals were immediately started on antituberculous treatment (ATT), medium risk individuals had additional TB investigations and reevaluation in one week and low risk individuals were started on ART. Mortality was approximately 20% in both arms and this strategy did not reduce mortality or the risk of hospitalization over 6 months. Additional work is needed to identify strategies to reduce early mortality among persons with advanced HIV at high risk for TB [6].

Investigators in Haiti evaluated the diagnostic yield of an integrated TB/HIV symptom screen and the added value of the GeneXpert MTB/Rif (Xpert) testing for patients at the time of HIV testing. The Xpert test is an automated diagnostic cartridge based nucleic acid amplification test (NAAT) that can identify *Mycobacterium tuberculosis* DNA and resistance to rifampicin. Patients were screened for cough at the time of HIV testing, and those with cough received evaluation for active TB by chest x-ray (CXR), acid fast bacilli smear, and Xpert testing. 30,316 patients were tested for HIV and screened for cough and 11% tested HIV-positive. 33% of the HIV-infected patients reported cough, and 23% were diagnosed with TB. 20% HIV-negative patients also reported cough, and 22% were diagnosed with TB. 1469 patients were diagnosed with TB at the time of HIV testing, and 228 patients (16%) were smear-negative but Xpert positive. The Xpert sputum testing allowed for early identification of 16% of patients with TB that would otherwise not have been diagnosed until cultures returned positive. The cost effectiveness of sputum Xpert should be further studied in additional settings [7].

A small study conducted in Kenya looked at the sensitivity of stool Xpert and Urine lateral flow lipoarabinomannan (LAM) when compared to the combined gold standard of sputum or gastric culture and sputum or gastric Xpert for tuberculosis. 9 children were found to have microbiologically confirmed TB, 6 of the 9 children were positive by stool Xpert for a sensitivity of 67%, and 130 were classified as negative for a specificity of 99%. Among 114 children with a urine sample, LAM identified 3 of 6 confirmed TB cases for sensitivity of 50% and classified 96 of 108 children without confirmed TB as negative. Stool Xpert may be useful addition to testing for tuberculosis in children when sputum or gastrics samples are challenging to obtain [8].

Investigators from India noted that TB is more likely to occur postpartum than at any other time in a woman's life and examined if immune changes in pregnancy and postpartum affect the interferon-gamma (IFN-g) response to *M. tuberculosis* antigens in HIV infected and uninfected women. They screened women for latent TB with an IFN-g release assay (QuantiFERON Gold in tube, (QGIT)) during 2nd/3rd trimester of pregnancy, at delivery and 3 months postpartum. IFN-g reached a nadir for both HIV-infected and uninfected women at delivery; and HIV-infected women had a larger decrease in IFN-g. HIV uninfected women had a significant increase in IFN-g production postpartum while HIV infected women did not. The authors speculate that lower IFN-g production during pregnancy, may facilitate progression to active TB, despite symptoms not appearing until postpartum, when IFN-g production increases again. Clinicians using QGIT for diagnosing latent TB during pregnancy need to be aware of the lower sensitivity of this test during pregnancy [9].

A study from Botswana, a country that has been remarkably successful in rolling out ART, found an overall MDR TB treatment success rate of 74% for HIV infected individuals compared to 57% treatment success rates in the pre-ART era. Risk of dying decreased from 33% to 13% as CD4 at the time of diagnosis increased from < 100 to > 350 cells/mm^3. MDR TB treatment success rates increased from 67% to 86% as CD4 counts increased from < 100 to > 350 cells/mm^3 at the time of diagnosis. The importance of early diagnosis and treatment of HIV is once again highlighted [10].

New treatments for TB

New drugs, better tolerated drugs, and shorter effective treatment programs are needed not only for MDR and XDR TB but would be beneficial for pansusceptible TB. Patients often don't complete recommended treatment courses for both active and latent TB. Significant resources are required to ensure completion of current treatment programs. Two presentations discussed the possibility of using available drugs in new ways.

Eric Rubin from the Harvard School of Public Health discussed in his plenary session theories on the pathophysiology of latent tuberculosis; including the long held belief that in latent infection the tuberculosis bacteria are dormant and they must "wake up" to cause active symptomatic infection. He presented an alternative hypothesis of latent tuberculosis and active tuberculosis as a spectrum of disease related to bacterial burden. The higher the bacterial load the more likely one is to become symptomatic. Dr. Rubin noted that not only is there work in primate models supporting this hypothesis, but latent tuberculosis can be treated with isoniazid (INH) alone and INH kills replicating bacteria. He proposed