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 focuses on the selection of presentations and the synopsis included in this report. This report is not an endorsed activity of CROI itself.

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 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
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].

AS274 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/mm². 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 95%. 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/mm³. MDR TB treatment success rates increased from 67% to 86% as CD4 counts increased from < 100 to > 350 cells/mm³ 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
that we may be able to do better with our current drugs if we use them in new ways in light of this evidence and fewer patients will ask “Why do I have to take so many pills?” the title of his talk [11].

The potential of beta lactam drugs which have been generally believed to be ineffective against M. tuberculosis, as antituberculosis agents was presented by Andreas Diacon of Stellenbosch University. Groups of 15 patients with newly diagnosed smear positive pansusceptible pulmonary tuberculosis were treated with meropenem and amoxicillin/clavulanic acid (A/CA), or faropenem (an oral carbapenem) and A/CA or standard antituberculosis treatment for two weeks. The mycobacterial spu tum load was significantly decreased with the meropenem, A/CA treatment and with standard treatment but not with faropenem, A/CA. The carbapenem/beta-lactam treatments were well tolerated, however intermittent diarrhea was noted by > 50% of patients in both carbapenem groups. The combination of intravenous meropenem and oral A/CA in this study had similar mycobacterial activity as the regimen of rifampin (10 mg/kg), pyrazinamide and bedaquiline over the first 2 weeks of treatment. Where IV treatment is feasible and treatment options are limited, IV meropenem combined with oral A/CA should be considered. An oral bioavailable carbapenem combined with a beta lactamase inhibitor should be further explored as a tuberculosis treatment [12].

**TB and antiretroviral therapy**

Patients with TB and HIV are usually chronically ill and the impact of each illness on the other is often profound. Additional understanding of the impact each illness has on the other would be clinically helpful.

Investigators from Switzerland examined the CD4 cell and HIV-RNA viral load changes in 113,000 HIV infected ART naïve European patients with and without a history of TB after starting ART. They found CD4 recovery to be slower in patients with active or recent tuberculosis and HIV viral load decline slower for patients with active tuberculosis during the first 6 months of ART. They did not comment on the possibility of drug–drug interactions contributing to this finding. They found these unfavorable effects to be more pronounced among immigrants from high-incidence TB countries. The reasons for slower CD4 recovery and viral load decline with ART in HIV individuals with active or recent TB requires further investigation [13].

**Pharmacokinetics in HIV and drug–drug interactions**

Interactions between HIV medications and antituberculosis medications are common and often complicate treatment. The following studies evaluated a variety of pharmacokinetic issues and drug-drug interactions between ARTs and antituberculosis medications.

A particularly problematic drug–drug interaction occurs with rifampin and protease inhibitors. Cobicistat and ritonavir are both used to boost levels of protease inhibitors through inhibition of cytochrome P450 3A4 and 2D6. They are not however completely interchangeable and a team of investigators from the University of Liverpool found that although ritonavir and cobicistat both attenuated the intrinsic clearance of darunavir induced by rifampin, ritonavir reversed rifampin induction more strongly than cobicistat. Cobicistat is likely to be used increasingly frequently in patients with HIV. Clinicians need to remember that despite cobicistat’s mechanism of action being similar to ritonavir’s; dosage adjustment for impacted medications is likely to be different than the adjustment for ritonavir [14].

An Indian study compared pharmacokinetics of antituberculosis drugs in children coinfected with HIV and TB, to children infected only with TB. HIV infected children were treated with efavirenz and lamivudine, and either stavudine, zidovudine, tenofovir or abacavir. They found a lower Cmax of INH and Rifampin in HIV/TB coinfected children and lower AUC of rifampin. Unfavorable outcomes were associated with a lower body mass index, smaller head circumference; lower Cmax and AUC of rifampin and pyrazinamide. HIV/TB coinfected children were significantly more likely to be underweight, have a lower albumin and smaller head circumferences that children infected with only TB. It is unclear from this study if the lower drug levels in HIV infected children is related to poorer nutritional status, drug-drug interactions or a combination [15].

Investigators in Zambia sought to determine an appropriate efavirenz (EFV) dose for HIV infected infants and children between 3 and 36 months being treated for tuberculosis. Additionally wide variations in EFV plasma concentrations have been described in children with a single nucleotide polymorphism in the CYP 2B6 gene. The CYP 2B6 516 TT (mutant) genotype is associated with decreased clearance and greater EFV plasma exposure. Amplified dosing (<65 mg/kg) in co-infected HIV+/TB+ children with nonmutant CYP2B6 GG/GT genotype produced therapeutic EFV concentrations in 6/8 children <2 years. A lower dose is predicted to be needed for children in this age group with slow CYP2B6 metabolism (mutant CYP2B6 genotype) who are being treated for tuberculosis. The investigators conclude that pre-treatment genotyping will allow for appropriate EFV dosing with optimal exposure of EFV in HIV+/TB+ children <2 years of age [16].

An Indian study retrospectively compared those treated with an atazanavir/ritonavir (ATV/r) ART regimen plus a 150 mg daily or thrice weekly rifabutin-containing TB regimen with those treated with a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based ART regimen in conjunction with a daily rifampicin containing TB regimen. Over 4000 HIV/TB infected patients were evaluated with 3740 having been treated with an NNRTI-based ART regimen and a rifampicin TB regimen and 292 an ATV/r-based ART regimen with a rifabutin TB regimen. Those in the ATV/r-Rifabutin group were less likely to develop relapse/recurrent TB and had lower all-cause mortality compared to those in the NNRTI-Rifampicin group. In addition, those in the Rifabutin group that received intermittent rifabutin had lower clinical cure rates compared to those who received daily rifabutin, although there was no statistically significant difference in rate of relapse/recurrent TB and all-cause mortality between these two subgroups. A limitation of this study is its retrospective nature and the inclusion of patients diagnosed over a wide time period (between 1996 and 2014) when other changes in health care likely occurred, that may have influenced the results. This large, retrospective study observed that antituberculosis treatment with rifabutin was overall effective, and daily rifabutin dosing may be more effective than intermittently-dosed rifabutin for the treatment of uncomplicated TB in HIV/TB co-infected individuals on a boosted PI-based ART regimen [17].

Doravirine a novel NNRTI developed by Merck is primarily metabolized by oxidation via Cytochrome P450 3A4 (CYP3A4) and rifamycins are inducers of this cytochrome. Rifampin has been shown to significantly decrease doavirine levels and should not be coadministered with doravirine. Investigators associated with Merck studied how rifabutin which is a more moderate inducer of CYP3A4 affected doravirine pharmacokinetics. Rifabutin decreased doravirine AUC by 50%. The investigators speculate that increasing the dose of doravirine may allow for use of doravirine with rifabutin but further study is required [18].

**Immune reconstitution inflammatory syndrome (IRIS)**

Paradoxical inflammatory syndromes have been recognized in patients being treated for TB long before the HIV epidemic. Individuals coinfected with TB and HIV are at high risk of developing
this syndrome called IRIS. IRIS can occur in HIV-infected individuals not only during active treatment of TB but with treatment of other infections and with ART alone. Two studies attempted to better understand the immunology behind this syndrome.

Investigators at an HIV clinic in Cape Town South Africa investigated the hypothesis that matrix metalloproteinases (MMPs), previously implicated in TB tissue destruction, were associated with TB-IRIS. They recruited 49 HIV antiretroviral naïve patients with CD4 counts < 200 cells/mm³, presenting with pulmonary tuberculosis. Twenty-nine developed TB-IRIS after a median of 14 days of ART. Plasma MMPs, most significantly MMP-8, were elevated in TB-IRIS patients with the greatest difference observed at the time TB treatment was initiated, followed by 2 weeks of antiretroviral therapy. These findings implicate systemic MMP dysregulation in TB-IRIS pathophysiology. Neutrophil-derived MMP-8 may be a predictive and diagnostic marker for TB-IRIS and potentially a therapeutic target [19].

Another group of investigators from Cape Town investigated the immunologic basis of Bacillus Calmette–Guérin vaccine (BCG) associated IRIS in HIV infected infants and children < 6 years old initiating ART. 41% of infants (<6 months old) developed IRIS following initiation of ART with 21 experiencing BCG IRIS related events 2-8 weeks after ART initiation. Cases were compared with 21 non-IRIS controls matched by age, nadir CD4, frequency and duration of ART at time of IRIS diagnosis. The investigators compared a number of immune cells between cases and controls. At entry, compared to controls, cases exhibited reduced absolute CD3 and CD4 T cell counts, higher frequencies of CD14+CD16+ inflammatory monocytes and NK cells; lower frequencies of BCG-specific IL22+CD4+ T cell and gagg-specific CD4 T cells expressing IFN-g. Tumor necrosis factor alpha, interleukin 10, and CD154. Significant increase in CD4 absolute counts were evident in cases but not controls. A dynamic immune reconstitution of BCG-specific Th1 cells was observed at IRIS diagnosis, compared to control samples. By contrast, reconstitution of gagg-specific CD4 T cells was not different across groups. At time of IRIS diagnosis frequencies of NK cells remained higher in cases compared to controls. The investigators conclude that these findings imply that underlying immune deficiency and lack of BCG-specific Th22 cells coupled with inflammation involving monocytes contributes to the pathophysiology of BCG IRIS [20].

Transmission

Understanding TB transmission is an important public health concern and key to controlling and preventing TB outbreaks. The final two studies in this report address this important topic.

Investigators in Switzerland compared estimations of transmission among immigrants with TB, HIV infected individuals and Swiss born individuals with tuberculosis using traditional and whole gene sequencing (WGS). Using traditional genotyping they identified 35 clusters of patients suggesting active transmission. Only 17/35 (49%) traditionally-defined transmission clusters were confirmed “true” clusters by WGS; the other 18 clusters contained pairs separated by > 12 single nucleotide polymorphisms. Traditional genotyping methods led to an overestimation of recent transmission among foreign-born TB patients in this study [21].

A South African study used social networking analysis to characterize patterns of transmission of extensively drug resistant TB (XDR TB) in a high HIV prevalence area in KwaZulu-Natal province. They reported having previously demonstrated that up to 83% of XDR TB cases are genotypically-clustered, suggesting person-to-person transmission is driving the XDR TB epidemic in this high-HIV prevalence setting rather than poor TB treatment with development of resistance. In the current study, they employed social network analysis to further characterize patterns of transmission. Patients with XDR TB were interviewed at the time of diagnosis about their social networks at home, work, and other community locations, as well as about hospitalizations in the five years preceding their XDR TB diagnosis. Epidemiologic links were identified for 287 (71%) patients. 83 (21%) patients were linked as social network contacts; of these, 92% lived in the same home, and 267 (66%) patients overlapped with other XDR TB patients in the hospital. There were 63 (16%) patients with both hospital and social network links to other XDR TB patients. The authors conclude that the XDR TB epidemic in this high HIV prevalence setting is being driven by direct transmission of drug-resistant TB strains in both households and communities [22].

Summary

The TB presentations at CROI struck both hopeful and cautionary notes. Progress has been made in controlling HIV-TB epidemics when resources that engage the affected population are put in place. Recurrent epidemics are likely to occur in disenfranchised populations with barriers to receiving health care. The high percentage of XDR cases that appear to be due to person-person transmission emphasizes the importance of early identification of cases and appropriate isolation. Public health officials need to continually evaluate the challenges and strengths in their respective communities, and formulate strategies that will not only be able to address epidemics but are proactive and will prevent their occurrence. New drugs, new studies of old drugs and new diagnostics remain important areas of study if we hope to avoid epidemics of MDR and XDR TB in the future.

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