*Invited Review*

# Virtual CROI 2020: Tuberculosis and Coinfections In HIV Infection

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*Due to COVID-19, this year marked the first virtual Conference on Retroviruses and Opportunistic Infections (CROI) in the conference's 27-year history. There were important studies presented that provided new insights into the prevention, diagnosis, and treatment of tuberculosis (TB) and other HIV coinfections. Highlights related to TB and HIV coinfections from this year's meeting are reviewed below.*

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## Tuberculosis

### Prevention and Treatment

Rifapentine and isoniazid once weekly for 3 months (3HP) is recommended as an alternative to 6 months of isoniazid (6H) for the treatment of latent tuberculosis (TB) infection in people with HIV (PWH) given the improved completion rates, decreased toxicity, and similar efficacy. Because TB rates in high transmission areas are still above targets for TB elimination with either of these interventions, Churchyard and colleagues undertook an individually randomized pragmatic trial to test whether periodic 3HP could provide additional protection against TB compared to a single 3HP cycle (Abstract 258). The study enrolled HIV-infected individuals from primary care clinics in South Africa, Ethiopia, and Mozambique who were 2 or more years of age, had no evidence of TB, and had been receiving 3 or more months of antiretroviral therapy (ART). Participants were randomized 9:9:2 to receive 3HP, p3HP, or 6H and were followed for either 24 months (3HP/p3HP) or 12 months (6H). Overall, treatment completion rates were substantially higher among those receiving 3HP than those receiving 6H (90.4% and 50.5%, respectively; risk difference, 39.9%; 95% confidence interval [CI], 35.0-44.9). However, TB incidence and mortality over 12 months did not differ. The incidence of TB over 24 months of follow-up did not differ between those receiving p3HP and those receiving 3HP (1.21 and 1.26 TB cases per 100 person-years, respectively; hazard ratio [HR], 0.96; 95% CI, 0.61-1.50; *P*=.85) and cumulative mortality over 24 months was similar (HR, 1.55; 95% CI, 0.86-2.76; *P*=.13). These data provide important evidence that annual 3HP is not more effective than a single course of 3HP for the prevention of TB disease among people with HIV in high TB burden settings.

Rifabutin may decrease tenofovir alafenamide (TAF) bioavailability because of reduced absorption due to P-glycoprotein induction. HIV outcomes in patients receiving concomitant TAF-containing antiretroviral therapy (ART) and rifabutin has not previously been reported. Balcombe and colleagues undertook a retrospective analysis among 23 individuals with HIV on TAF-containing regimens receiving rifabutin for the treatment of mycobacterial infections with a median duration of overlapping therapy of 33 weeks (interquartile range [IQR] 12-44 weeks) (Abstract 735). Four of 6 patients with initial viral suppression (≤200 copies/mL) maintained viral suppression, 14 of 17 patients with an initial viral load above 200 copies/mL achieved viral suppression, and the overall mean change from baseline CD4 count was +105 cells/μL (95% CI, -16-227). Due to the small size of this study, retrospective nature, and heterogeneity of patients, it is difficult to make any conclusions, although the data are encouraging. Current recommendations remain to avoid co-administration of TAF with rifabutin.

### Women and Children

Pregnant and postpartum women with latent TB infection, especially those with HIV, have a substantially increased risk of developing active TB disease. Previously, Gupta and colleagues in the IMPAACT (International Maternal Pediatric Adolescent AIDS Clinical Trials) Network published the results of the TB APPRISE (TB Ante vs Postpartum Prevention with INH in HIV Seropositive Mothers and Their Exposed Infants) study, which was a double-blind, placebo-controlled trial that showed worse maternal and infant outcomes when 28 weeks of isoniazid preventive therapy (IPT) was initiated antepartum compared with when it was deferred to 3 months postpartum.[1] Noting that there are many potential factors that could influence pregnancy outcomes, the authors undertook a multivariable analysis to determine the independent effect of IPT on pregnancy outcomes (Abstract 727). Among 925 HIV-infected pregnant women from 8 high burden TB countries, after adjusting for several risk-factors, the authors found that immediate IPT during pregnancy was independently associated with a 1.6- to 1.7-times increased odds of composite adverse pregnancy outcomes (preterm

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delivery, low birth weight, congenital anomalies, spontaneous abortion, stillbirth, or neonatal death). This updated analysis provides further confirmation of the potential dangers of starting IPT during pregnancy and the need to identify alternative TB preventative regimens that are safe and effective during pregnancy.

The 3HP approach is an option for preventative therapy for TB, but it has not previously been tested in pregnant women. Mathad and colleagues sought to evaluate the impact of pregnancy and HIV-status on rifapentine pharmacokinetics (Abstract 259). They enrolled 50 women in the second and third trimesters of their pregnancies and undertook intensive followed by sparse pharmacokinetic sampling among women receiving 3HP. Rifapentine clearance during pregnancy was similar to historical non-pregnant controls suggesting no need to change dosing in pregnancy. Notably, HIV-infected pregnant women receiving efavirenz-based ART had a 29% lower drug exposure than HIV-negative women; although this was higher than expected, rifapentine concentrations remained within the therapeutic range. The study was not powered to assess safety, but all participants completed 12 weeks of the study regimen, none developed active TB disease, and there were no serious adverse events. No infants had serious adverse events attributable to the study regimen. Given serious concerns about the safety of IPT in pregnancy, these early pharmacokinetic and safety data among individuals with and without HIV are welcome and encouraging. Larger studies, including among women receiving integrase strand transfer inhibitor (InSTI)–based ART are needed to better define the safety and efficacy of 3HP during pregnancy.

***A single course of 3HP is as effective at preventing TB and mortality as annual 3HP***

HIV-exposed uninfected (HEU) infants who are born to HIV-infected mothers with HIV are at high risk of TB infection and subsequent progression to TB disease, especially in the first year of life. It is unknown if isoniazid (INH) can prevent primary *Mycobacterium tuberculosis* (MTb) infection in HEU infants. To address this gap, Lacourse and colleagues undertook a non-blinded, randomized controlled trial among HEU infants in Kenya to evaluate the efficacy of daily INH for preventing primary MTb infection (Abstract 253). Three hundred infants at 6 weeks of age were randomly assigned to receive 12 months of daily INH versus no INH therapy; 265 (89%) were successfully followed up until 12 months post-randomization and were assessed for MTb infection using tuberculin skin testing (TST) or QuantiFERON-TB gold testing. There was a trend toward reduced MTb infection at 12 months among infants receiving daily INH compared with those who did not receive daily INH (7.0 infections per 100 person-years versus 13.4 infections per 100 person-years, respectively; HR, 0.53; 95% CI, 0.24-1.14), but this did not reach statistical significance ($P$=.11). An even stronger trend for the efficacy of daily INH was observed when MTb infection was only assessed using TST-positivity (RR, 0.48; 95% CI, 0.22-1.05; $P$=.07). There were no serious adverse events associated with receipt of INH. This study provides important data on the safety and potential efficacy of daily INH in HEU infants; however, they are insufficient to change guidelines to include daily INH as an intervention to prevent MTb infection in this population.

### Multi-Drug Resistant Tuberculosis

High-dose linezolid (1200 mg daily) in conjunction with pretomanid and bedaquiline has recently been approved by the US Food and Drug Administration (FDA) for the treatment of extensively drug resistant (XDR) TB; however, the safety and pharmacokinetics of long-term, high-dose linezolid has not been well characterized. Savic and colleagues undertook population pharmacokinetic and toxicodynamic modeling to simulate and compare pharmacokinetic and safety outcomes among patients in the Nix-TB trial who received 6 months of high-dose linezolid (Abstract 734). Included in the analysis were 104 patients with verified and complete dosing history. Anemia was present in 40% of patients, with a median onset after 9 weeks. Simulations suggested that for patients with more than a 10% decrease in hemoglobin level from week 0 to week 4 of treatment, a linezolid dose reduction from 1200 mg to 600 mg could prevent 63% of severe anemia cases. Thrombocytopenia was only present in 6% of patients. Severe peripheral neuropathy was present in 16% of patients, and peaked at 6 months; however, nearly all patients had substantial improvement or complete resolution within 2 years of linezolid discontinuation. These data support early dose reduction of linezolid to prevent severe anemia among patients at risk.

Universal access to drug susceptibility testing is an important TB control strategy. Egger and colleagues (Abstract 736) used whole-genome sequencing to identify mutations conferring TB drug resistance that were missed in routine practice and examined the potential impact on mortality. There were 582 adult patients (247 with HIV) from 7 high burden countries who underwent drug resistance testing using Xpert, line-probe assays, or culture, in accordance with local procedures. Whole-genome sequencing of all isolates revealed that 2.5% of rifampicin resistance and 25% of isoniazid resistance was missed, and that 48% to 100% of resistance to other first- and second-line TB drugs was missed. Mutations conferring resistance to first- and second-line TB drugs were independently associated with increased mortality during TB treatment (odds ratio [OR], 4.2-12.2), many of which were not detected by locally available tests. These data highlight the importance of expanding access to rapid drug-susceptibility testing for first- and second-line agents in line with currently recommended treatment regimens.

Pretomanid is an important new drug for the treatment of drug resistant TB; however, it is not known if it can be safely coadministered with rifamycins. Abdelwahab and colleagues undertook

an interim pharmacokinetics study of a phase IIB randomized controlled trial to assess the safety and efficacy of pretomanid when added to first-line TB drugs over the first 12 weeks of therapy (Abstract 733). Due to substantially faster clearance, patients receiving rifampicin had a 44% reduction in pretomanid concentrations (area under the curve) compared with those receiving rifabutin. They also found important food effects on pretomanid, such that pretomanid drug exposure with rifampacin was similar to exposure with pretomanid alone, without food. Overall, pretomanid coadministered with rifabutin is more likely than rifampicin to maintain adequate pretomanid drug exposure levels. However, when rifampicin and pretomanid are dosed with food, pretomanid levels can likely be maintained in a therapeutic range.

### Tuberculosis Transmission and Contact Tracing

Systematic investigation of household contacts of people with MDR-TB (household contact tracing) is implemented inconsistently in many high TB burden settings. Kim and colleagues conducted a repeated cross-sectional study to determine the prevalence of and factors associated with prevalent latent TB infection among adult household contacts of people with MDR-TB as well as the incidence of TB infection 1 year later (Abstract 254). There were 278 adult index cases with pulmonary MDR-TB enrolled from 8 countries. Among adult household contacts, 686 of 712 (96.3%) had determinate interferon-gamma release assay (IGRA) results, and 471 were positive (prevalence, 68.7%). The strongest independent predictors of a positive IGRA result were a history of incarceration (adjusted odds ratio [aOR], 7.3; 95% CI, 1.5-34.0), substance or alcohol use (aOR, 2.6; 95% CI, 1.3-5.2), and sleeping proximity to the index case (aOR, 2.4; 95% CI, 1.4-4.2). There were 219 household contacts with an initially negative or indeterminate IGRA who underwent repeat IGRA testing 1 year later of which 45 of 177 (25.4%) converted to positive. Notably, only 5% of eligible household contacts received TB preventative therapy. These results build on previous evidence that suggests that household contact tracing among individuals with MDR-TB is a feasible and pragmatic approach to reach a population at high risk for TB disease.

Although the association between indoor air pollution and lower respiratory tract infections is well described, little is known about the potential risk of TB associated with indoor air pollution among people with HIV. Katoto and colleagues undertook a case-control study in the Democratic Republic of Congo among adults with HIV who had current or recent pulmonary TB patients (cases) who were age- and sex-matched to adults with HIV without evidence of TB (controls) (Abstract 721). There were 435 cases and 842 controls enrolled. In adjusted analyses there was an independent, concentration-dependent association between carbon monoxide (CO) exposure and pulmonary TB, such that those in the highest CO exposure quintile had an aOR of 4.6 (95% CI, 1.0-20.7) for pulmonary TB. Among women there was also an independent dose-dependent relationship between hours spent cooking over a wood fire and pulmonary TB. These data suggest indoor air pollution may be an important risk factor for pulmonary TB. Prospective studies in adults both with HIV and without HIV are needed to confirm this very plausible observation.

## Opportunistic Infections

### Bacterial Infections

The value of trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis in the contemporary ART era among populations that have achieved viral suppression and CD4+ cell count restoration in Sub-saharan Africa has not been evaluated. Mungwira and colleagues conducted a randomized, controlled, open-label trial in a malaria-endemic region of Malawi comparing 3 strategies: 1) continued daily TMP-SMX prophylaxis, 2) TMP-SMX discontinuation and new weekly chloroquine prophylaxis, and 3) TMP-SMX prophylaxis discontinuation (Abstract 252). A total of 1,499 adults with HIV on ART longer than 6 months with a CD4+ cell count at or above 250µL and an undetectable HIV viral load were randomized 1:1:1 to each study arm. The primary end point was death or World Health Organization (WHO) Stage 3/4 events.

***Among adults with HIV who are virally suppressed, continued TMP-SMX prophylaxis prevents bacterial and malarial infections in malaria endemic areas***

Overall there were only 24 deaths reported over 4,958 person-years of follow-up. The primary endpoint did not differ by study arm, nor did rates of viral suppression or adverse events. However, continued daily TMP-SMX prophylaxis was associated with a reduced rate of common bacterial infections as well as malarial infections. This study shows that TMP-SMX prophylaxis among virally-suppressed individuals prevents malarial and non-serious bacterial infections in endemic regions.

### Cryptococcus

Boulware and colleagues investigated the association between early fungicidal activity (EFA) and all-cause mortality in a cohort of patients with cryptococcal meningitis enrolled from the COAT (Cryptococcal Optimal ART Timing) trial, the ASTRO-CM (Adjunctive Sertraline for the Treatment of HIV-Associated Cryptococcal Meningitis) pilot, and the ASTRO-CM trial (Abstract 744). All patients received amphotericin B and fluconazole induction therapy and at a minimum had cerebrospinal fluid (CSF) quantitative cultures performed on days 1, 7, and 14. EFA was calculated using the $\log_{10}$ transformed colony forming units (CFUs) per mL CSF over the first 10 days of therapy. Among 738 patients without a sterile baseline CSF culture, those with an EFA below 0.2 $\log_{10}$ CFU/mL/day had a cumulative mortality of 50%

through 18 weeks compared with 37%, 39%, and 36% in those with EFAs of 0.2 to 0.29, 0.3 to 0.39, and at or above 0.4 $\log_{10}$ CFU/mL/day, respectively. In adjusted analyses an EFA below 0.2 $\log_{10}$ CFU/mL/day independently predicted 18-week mortality (adjusted HR, 1.8; 95% CI, 1.4-2.4; $P < .0001$). This study builds substantially on prior work that suggests that EFA may be an appropriate surrogate endpoint for phase II trials that could help accelerate the evaluation and approval of new and improved therapies for cryptococcal meningitis.

Cryptococcal antigen (CrAg) titer may predict the risk of meningitis and death. Two studies evaluated the diagnostic performance of a new CrAg semi-quantitative (SQ) lateral flow assay (LFA) on serum and CSF in people with advanced HIV using the currently available immunochromatographic assay (IMMY) CrAg LFA as a reference standard (Abstract 743 and 745). Both studies found that the CrAg SQ assay had excellent sensitivity and specificity (more than 95%) and that the SQ band grade-positivity was strongly associated with CSF culture positivity and 10-week mortality. Further studies are required to determine whether use of the CrAg SQ assay could improve clinical outcomes through rapid diagnosis and risk stratification.

### Talaromycosis

Talaromycosis is one of the leading causes of death among people with HIV in Southeast Asia with approximately 17,000 new cases and 4,900 deaths annually (Abstract 749). *Talaromyces marneffei* was previously known as *Penicillium marneffei*. Presently, the diagnosis of talaromycosis relies on microscopy of skin lesions (a late clinical manifestation) and blood cultures, which have a sensitivity of approximately 70% and take up to 2 weeks to yield a result; diagnostic delays and missed diagnoses are a key factor contributing to the high mortality observed among persons with talaromycosis. Ly and colleagues undertook a prospective study to assess the diagnostic accuracy of an Mp1p (an immunogenic surface protein) enzyme immunoassay (EIA) assay for talaromycosis (Abstract 750). Among 533 people with HIV with CD4+ counts below 100 cells/μL followed up for 6 months, 81 (15%) developed talaromycosis. Against a composite culture-based reference standard (all positive cultures over a 6-month period), the sensitivity of the of the Mp1p assay on sera, plasma, and urine was 89%, 90%, 94%, respectively, with a specificity of 97% or higher for all sample types. Mp1p tests were positive up to 16 weeks in advance of culture results. If confirmed in subsequent evaluations, these data demonstrate that the Mp1p assay could substantially improve the diagnosis of talaromycosis.

**All cited abstracts appear in the CROI 2020 Abstracts eBook, available online at www.CROIconference.org**

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