Invited Review

CROI 2023: Tuberculosis and Infectious Complications in Persons With HIV

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Abstract. Novel implementation strategies to increase uptake and adherence to tuberculosis (TB) preventive therapy hold promise for reducing TB incidence in persons with HIV in high-burden settings. In persons who develop drug-susceptible TB, progress to shorten TB treatment continues to be made with the introduction of new drugs and novel treatment strategies that could allow for treatment shortening to 2 months for most people. A global case series provided powerful evidence that mpox should be considered an HIV-related opportunistic infection given its severe manifestations and poor outcomes. Studies of TB and infectious complications in people with HIV presented at the 2023 Conference on Retroviruses and Opportunistic Infections (CROI) are summarized herein.

Keywords: coinfection, CROI 2023, tuberculosis, TB, HIV, opportunistic infection, mpox, Kaposi sarcoma, anal cancer

Tuberculosis

Treatment in Adults
The development of anti-tuberculosis (TB) treatment regimens that are shorter and less toxic, but that remain highly effective, continues to be a priority for the field. For adults with or without HIV who have drug-susceptible TB (DS-TB), the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) recommend a 4-month regimen of rifapentine (RPT), moxifloxacin (MOX), isoniazid (INH), and pyrazinamide (PZA) for 2 months followed by 2 months of RPT, MOX, and INH (RPT-MOX). At this year’s Conference on Retroviruses and Opportunistic Infections (CROI), Paton and colleagues presented the results of the open-label, noninferiority, multicountry, randomized TRUNCATE-TB (Two-Month Regimens Using Novel Combinations to Augment Treatment Effectiveness for Drug-Sensitive Tuberculosis) trial that evaluated whether a novel, adaptive treatment strategy leveraging newer antimycobacterial agents could be used to go even further and reduce the treatment duration to as short as 8 weeks for many individuals (Abstract 113). Adults with confirmed rifampicin (RIF)-susceptible pulmonary TB were randomly assigned 1:1:1:1:1 to receive either the standard 6-month INH, RIF, PZA, and ethambutol (EMB) treatment regimen (2HRZE/4HR), or 1 of 4 different 5-drug regimens initially for 8 weeks, then extended to 12 weeks if there was evidence of ongoing symptoms and a positive sputum smear (at 8 weeks), then switched to complete the standard 6-month treatment if there were ongoing symptoms and a positive sputum smear again (at 12 weeks). The 4 different 5-drug investigational regimens were (1) high-dose (h)RIF + linezolid (LZD), (2) bedaquiline (BDQ) + LZD, (3) RPT + LZD, and (4) hRIF + clofazimine (CFZ), each in combination with INH/PZA/EMB (except RPT + LZD, which used levofloxacin instead of EMB). For pragmatic reasons (eg, challenges importing the drugs into trial countries), the trial stopped enrollment early for the RPT + LZD and hRIF + CFZ arms. The primary outcome was any unfavorable outcome (death, ongoing treatment, or active disease) up to 96 weeks, with a noninferiority margin of 12%. Notably, the trial initially excluded, but later allowed the inclusion of, persons with HIV and those with a very high mycobacterial burden (sputum smear 3+ positive or chest radiographic evidence of large, >4 cm cavitation). Among 674 participants (54% had chest cavitation present on chest X-ray [CXR], 0% persons with HIV), 92% of hRIF + LZD participants (n =...
Current TB treatment regimens for DS-TB and drug-resistant TB (DR-TB) differ in the drugs used and the total duration of therapy. Newer TB drugs now make it possible to evaluate regimens that could be used for patients with DS-TB and DR-TB. In the SimpliciTB trial, Cevik and colleagues evaluated the BPaMZ regimen, consisting of BDQ, pretomanid (Pa), MOX, and PZA, for DS-TB (4 months) and DR-TB (6 months) (Abstract 109). DS-TB patients were randomly assigned 1:1 (open label) to receive the BPaMZ regimen for 4 months (4BPaMZ) or the standard 6-month regimen (2HRZE/4HR), and DR-TB patients received the BPaMZ regimen for 6 months (6BPaMZ). The primary study endpoint across the 3 arms was culture-negative disease at 8 weeks; however, a key secondary endpoint was relapse-free cure at 52 weeks (noninferiority margin, 12% for DS-TB participants). Over all, 455 participants were enrolled (19% were persons with HIV and 78% had lung cavitation present on CXR) including 150 and 153 DS-TB patients in the 4BPaMZ and 2HRZE/4HR arms, respectively, and 152 DR-TB patients in the 6BPaMZ arm; there was no DR-TB control arm. DS-TB and DR-TB participants receiving BPaMZ had a substantially higher likelihood of having culture-negative disease by week 8 (84.1% and 85.7%, respectively) than DS-TB participants receiving 2HRZE/4HR (47.3%); for DS-TB, this met the threshold of superiority. However, at 52 weeks, 16.7% (24/144) and 16.5% (22/133) of participants receiving 4BPaMZ and 6BPaMZ, respectively, had an unfavorable outcome compared with 6.9% (10/144) of participants receiving 2HRZE/4HR. Compared with DS-TB participants receiving 2HRZE/4HR, 4BPaMZ did not meet the threshold for noninferiority in the modified intention to treat analysis (mITT) (unadjusted risk difference, 9.7%; 95% CI, −2.4 to 20.8). Notably, study withdrawals due to adverse events accounted for 60.8% (28/46) of unfavorable outcomes in the BPaMZ arms and were predominantly due to elevated liver enzyme levels greater than 3 times the upper limit of normal (ULN); 7.5% (21/281) of all participants receiving a BPaMZ regimen had liver enzyme elevations greater than 8 times ULN. Thus, a novel 4-month regimen for DS-TB with BPaMZ had high mycobactericidal activity, but it was not noninferior to the standard 6-month TB treatment regimen.
TB receiving DTG twice-daily ART during RIF-based TB treatment in public health programs in 6 resource-limited countries (Abstract 755). The 91 participants had a median CD4+ count of 120 cells/µL, and 87% had an initial HIV viral load above 1000 copies/mL. Of 73 participants with an HIV-1 RNA test result at the end of TB treatment, 68 of 69 (95%) had viral suppression, and 88% had below 50 copies/mL. None of the 4 nonsuppressed participants had emergent DTG resistance identified. The combined ART and TB regimens were well tolerated. Although numbers are limited, these data demonstrate the potential feasibility and effectiveness of DTG twice daily in people with HIV-associated TB in resource-limited settings.

Twice-daily DTG may be feasible during TB treatment, but it is more complex for programs to administer and for patients to take. Furthermore, based on prior data, it is not clear that the second DTG dose is needed. Griesel and colleagues undertook a phase IIb, randomized, double-blind, controlled trial to evaluate HIV virologic outcomes among persons with HIV with TB who received placebo (daily DTG, intervention) or supplemental twice-daily DTG (control) in addition to their normal ART regimen of tenofovir (TDF)/lamivudine (3TC)/DTG until 2 weeks after finishing RIF-based TB treatment (Abstract 110). Participants were followed up for 48 weeks to determine HIV virologic outcomes (RNA <50 copies/mL) and treatment-emergent DTG resistance. Among 108 enrolled participants, 81% were ART naive, the median CD4+ count was 184 cells/µL, and median HIV viral load was 5.2 \( \log_{10} \) copies/mL. Characteristics were well matched between arms. HIV virologic suppression in both arms was similar during the follow-up period. At 24 weeks (the completion of TB treatment), 83% (95% CI, 70-92) were suppressed in both the intervention and control arms; however, at week 48 virologic suppression declined to 67% (95% CI, 53-90) and 69% (95% CI, 55-82) in the intervention and control arms, respectively. TDF concentrations in dried blood spots suggested that this decline largely reflected poorer adherence at week 48 than at week 24. None of the 19 participants with study-defined virologic failure had evidence of emergent DTG resistance. The most striking finding of this study was the low rates of viral suppression at 48 weeks in both arms due to poor ART adherence. Regarding the need for twice-daily DTG dosing in the presence of RIF, this small study provides some evidence that it may not be needed. Confirmation in a larger study would be required before once-daily DTG in the setting of TB can be widely recommended.

**Treatment in Children**

In the multicountry SHINE (Shorter Treatment for Minimal TB in Children) trial, for children with nonsevere DS-TB, a 4-month regimen (2 months RIF/INH/PZA with or without EMB, then 2 months RIF/INH) was noninferior to the standard 6-month regimen (2HRZE/4HR regimen for children with and without HIV). The composite endpoint was treatment failure, lost to follow-up, or death by 72 weeks.\(^3\) This 4-month TB regimen is now recommended by the WHO as an option for treatment of nonsevere childhood and adolescent TB.\(^4\) However, children with HIV may have poorer clinical TB treatment outcomes than HIV-negative children; therefore, Chabala and colleagues undertook a secondary analysis of the SHINE trial results to determine whether these outcomes differed according to HIV status (Abstract 824). Of 1204 enrolled participants, 11% (n = 127) were children with HIV, of which 54% (n = 68) were ART naive and the median CD4+ count was 719 cells/µL. Similar to previous studies, children with HIV were less likely to have microbiologically confirmed TB (6.3% vs 14.6%, respectively; \(P < .001\)) and more likely to have lymph node disease and to be underweight and anemic than children without HIV. Deaths were overall infrequent (2.6%; n = 31), but they were substantially higher among children with HIV (10.2%; n = 13) than among children without HIV (1.7%; n = 18; adjusted hazard ratio [aHR], 2.6; 95% CI, 1.2-5.8). The risks of hospitalization (adjusted odds ratio [aOR], 2.4; 95% CI, 1.3-4.6) and grades 3 or 4 adverse events (aOR, 4.4; 95% CI, 2.3-8.5) were also much higher among children with HIV. Among children with HIV with available virologic data, the proportion with a viral load below 1000 copies/mL was 45% and 61% at weeks 24 and 48, respectively. This study points to the need for new interventions beyond shortening TB treatment to reduce the unacceptably high morbidity and mortality in this population.

Although the indication for DTG-based ART therapy has recently been expanded to include children weighing 20 kg to 35 kg, there are limited data on the safety and potential efficacy of twice-daily DTG in the setting of TB treatment in children with HIV-associated TB. Therefore, Naidoo and colleagues undertook an open-label, nonrandomized, prospective pharmacokinetic (PK) study among 13 children with HIV receiving RIF-based TB therapy and DTG twice daily for HIV (Abstract 827). The median CD4+ count and HIV viral load among participants was 109 cells/µL and 2.5 \( \log_{10} \) copies/mL, respectively. DTG PK parameters at steady state showed similar median trough concentrations (\(C_{\text{trough}}\)) of 1.6 mg/L vs 1.5 mg/L and 24-hour area under the curve concentrations (\(AUC_{0-24}\)) of 33.6 h•mg/L vs 36.7 h•mg/L while receiving DTG twice-daily ART with RIF-based...
TB therapy compared with once-daily DTG-based ART after stopping RIF-based TB therapy. All children had undetectable viral loads at weeks 12 and 24. Two participants had grade 3 adverse events (serum amylase level elevation), but no serious adverse events occurred. These preliminary data suggest that ART with twice-daily DTG during RIF-based TB therapy may be safe and well tolerated, but further data are needed to confirm these findings.

**Multidrug-Resistant TB (MDR-TB)**

Linezolid is an important therapeutic option in the treatment of MDR-TB, but common and predictable toxic effects, namely, hematologic effects and peripheral neuropathy, often limit its longer-term use. Sutezolid is a novel agent closely related to linezolid that is proposed to have an improved safety profile. Heinrich and colleagues undertook a phase Ib, open-label, randomized, dose-ranging trial in which 75 participants (2 persons with HIV) with smear-positive DS-TB were randomly assigned to receive BDQ + delamanid + MOX and 1 of 5 sutezolid doses (range, 0 mg to 800 mg twice daily) for 12 weeks to evaluate safety and impact on decline in weekly sputum culture time to positivity (TTP) (Abstract 114). Sputum TTP increased over 12 weeks, suggesting declining mycobacterial burden across all 5 arms, but it did not significantly differ by arm. No episodes of neuropathy occurred, and 1 participant developed myelosuppression that was more likely attributable to nondrug-related causes. Although not directly compared, sutezolid appears to have an improved safety profile compared with linezolid, but it did not clearly improve antimycobacterial activity when given with a potent 3-drug regimen. Further study of the effectiveness and safety of sutezolid as part of a combination treatment for TB disease is warranted.

High-dose isoniazid (INH) may be beneficial as part of a multidrug treatment for MDR-TB, but it is not well known if it is effective against *Mycobacterium tuberculosis* (Mtb) strains containing mutations in the katG gene, which is a common cause of INH resistance. Gausi and colleagues undertook a phase IIA, open-label trial among patients with MDR-TB and katG-mediated INH resistance to evaluate early bactericidal activity (EBA) of 2 high INH monotherapy doses (Abstract 750). Twenty-one participants (4 persons with HIV) were randomly assigned 1:1 to receive either 15 mg/kg or 20 mg/kg INH daily for 7 days. Daily sputum was collected to determine TTP, and TTP was averaged over 7 days as a correlate of EBA. The initial average TTP was 143 hours, and the average TTP over the 7-day treatment period did not significantly change in either the 15 mg/kg group (1.8 hours/day; 95% CI, −1.7 to 7.3) or the 20 mg/kg group (2.4 hours/day; 95% CI, −1.3 to 5.5). These data suggest that high-dose INH likely has no benefit in the treatment of Mtb strains with katG mutations.

**Prevention**

Improving uptake of and adherence to TB preventive therapy (TPT) among persons with HIV is a key public health priority for reducing HIV-associated TB and related mortality. TPT is recommended by the WHO for all persons with HIV living in high TB burden settings following exclusion of active TB disease. Shapiro and colleagues evaluated the effect of integrating isoniazid preventive therapy (IPT) initiation and continuation for persons with HIV into community-based ART-differentiated service delivery (DSD) models in KwaZulu-Natal, South Africa (Abstract 111). This represented a substudy of the DO ART (Delivery Optimization for Antiretroviral Therapy) study that previously showed that community-based ART improved virologic suppression compared with facility-based care. Participants were randomly assigned 1:1 to receive ART and IPT via a facility-based care model (all services at health facility), a hybrid-care model (ART and IPT initiation at facility, monitoring and refills in the community via mobile van), or a community-care model (ART and IPT initiation, monitoring, and refills in the community via mobile van). All IPT refills were synchronized with quarterly ART refills. The relative risks (RRs) of initiating and continuing IPT (defined by IPT dispensed or by self report) in the hybrid-care and community-care model, relative to the facility-based care model, were determined. Of 1212 persons with HIV randomly assigned to start ART, 1039 started ART, of which 573 (55.1%) initiated IPT in the first year of study follow-up. Among initiators of ART (n = 1039), 19.7% of people in the facility-based care model, 48.0% in the hybrid-care model (RR, 2.4; 95% CI, 1.9-3.1), and 90.5% in the community-care model (RR, 4.6; 95% CI, 3.7-5.7) started IPT. Among those who initiated IPT (n = 573), IPT was “continued” by 48.5% of...
persons in the facility-based care model, 83.7% in the hybrid-care model (RR, 1.7; 95% CI, 1.3-2.4), and 89.4% in the community-care model (RR, 1.8; 95% CI, 1.4-2.4), respectively. These data suggest that a person-centered TPT delivery strategy integrated within community-based ART DSD models has the potential to improve TPT uptake and continuation among persons with HIV in high TB burden settings.

Hazardous alcohol use (HAU), which is common in people with HIV, is an important risk factor for TB disease and nonadherence to IPT. Chami and colleagues undertook a 2x2 factorial, randomized, controlled trial among adult persons with HIV on stable ART in Uganda, who had evidence of latent TB infection (tuberculin skin test [TST] ≥5 mm) and HAU, to determine whether a novel strategy using conditional financial incentives could reduce alcohol use and improve IPT adherence during the 6-month daily course (Abstract 112). Participants were randomly assigned 1:1:1:1 to 1 of 4 arms: arm 1, no incentives, control; arm 2, incentives contingent on no recent alcohol use (determined using urine-based point-of-care [POC] ethyl glucuronide test, a biomarker of recent alcohol use); arm 3, incentives contingent on IPT adherence (determined using urine-based POC IsoScreen assay, a biomarker of recent INH use); or arm 4, incentives for satisfying either no recent alcohol use or IPT adherence, or both. The intervention arms (arms 2, 3, and 4) used an escalating financial incentive structure, such that for each consecutive month of negative POC urine test results, participants would be awarded more scratch cards with differing values (range $5 to $50 USD); the number awarded would reset if POC tests revealed recent alcohol use or lack of recent IPT. Of 680 persons with HIV, 69.1% were male and 90.2% were virologically suppressed (HIV RNA <40 copies/mL). Baseline characteristics were well balanced across arms. Overall, participants receiving financial incentives were more likely to have no hazardous alcohol use (measured by self-report and blood biomarker) than those who did not receive financial incentives (17.6% vs 9.9%, respectively; \( P = .003 \)). However, there was no difference in IPT adherence (measured by electronic bottle cap openings) between incentivized and nonincentivized arms (72.8% vs 72.9%, respectively; \( P = .944 \)). This study shows that contingent, escalating financial incentives reduced heavy alcohol use among persons with HIV receiving IPT, but it did not improve adherence to a 6-month, daily IPT regimen.

HAU may serve as a key barrier to starting IPT in persons with HIV, as it is recommended that persons with HAU do not receive IPT, given concerns of hepatotoxicity. Hahn and colleagues undertook a single-arm trial in Uganda among persons with HIV on stable ART with a positive TST (≥5 mm) and normal liver transaminase levels (aspartate aminotransferase [AST] and alanine transaminase [ALT] levels ≤2x ULN), and who either reported recent alcohol use (last 3 months, \( n = 200 \)) or no recent alcohol use (last 1 year, \( n = 101 \)) to evaluate the frequency of severe hepatotoxicity during IPT (Abstract 743). Monthly visits until 1 month following IPT completion were conducted to assess INH refills, to measure transaminase levels, and to monitor symptoms. Of 301 participants enrolled, 92.1% were virologically suppressed. Twenty-five participants (8.3%) experienced a grade 3 or higher INH-related toxicity (defined as AST or ALT ≥5x ULN); 12 of 200 (6.0%; 95% CI, 3.1-10.2) occurred in those reporting recent alcohol use and 13 of 101 (12.9%; 95% CI, 7.0-21.0) were in those reporting no recent alcohol use. There was a trend toward grade 2 toxicities (AST or ALT, 2-5x the ULN) being more common among those reporting recent alcohol use (25.0%; 95% CI, 19.0-31.8) than those reporting no alcohol use in the past year (14.8%; 95% CI, 8.1-23.9). Multivariable analyses demonstrated that biomarker-confirmed degree of recent alcohol use (using phosphatidylethanol) was not associated with grade 3 or higher hepatotoxicity. However, high and very high recent alcohol use was independently associated with grade 2 hepatotoxicity (aOR, 3.6; 95% CI, 1.4-8.9). These data suggest that unless baseline transaminase levels are greater than 2x the ULN, IPT in persons with HIV reporting alcohol use is unlikely to be associated with severe hepatotoxicity, and thus among such patients this important preventive tool should not be deferred.

It is not well known whether IPT can effectively reduce TB incidence among persons with HIV in settings where there is a high prevalence of MDR-TB, which by definition includes resistance to INH. Sodeke and colleagues undertook a retrospective study based in Ukraine, a country with a high MDR-TB burden (31% of national notifications), from 2018 to 2022 using national electronic medical records, to evaluate TB incidence among persons with HIV who had received IPT (Abstract 758). Overall, 128,314 persons with HIV with complete data on IPT and TB diagnosis were included; 66.2% (\( n = 84,901 \)) had received no IPT (defined as <28 days of IPT), 8.4% (\( n = 10,787 \)) had received partial IPT (defined as 28-146 days of IPT), and 25.4% (\( n = 32,626 \)) completed IPT (defined as ≥146 days of IPT). The adjusted rates of TB incidence among persons with HIV who had received IPT were 2.1, 3.9, and 9.8 cases per 100 person-years for those with complete IPT, partial IPT (incidence rate ratio [IRR] compared with complete IPT, 1.9), and no IPT (IRR = 4.7), respectively. These rates were similar across the 4 study observation years. The proportion of participants with
incident MDR-TB diagnosed did not significantly differ across IPT groups (33.9% no IPT, 29.8% partial IPT, and 33.1% complete IPT). These population-level data offer compelling evidence that IPT can effectively reduce TB incidence among persons with HIV in high MDR-TB burden settings.

**Diagnosis and Case Finding**

The Xpert MTB/RIF Ultra assay using sputum is recommended by the WHO as a first-line assay for the diagnosis of pulmonary TB, but its performance on urine for extrapulmonary/disseminated disease is poorly characterized. Stead and colleagues undertook a cross-sectional study in South Africa to evaluate the diagnostic yield for TB of the bedside urine lipoarabinomannan (LF-LAM) POC test and Xpert on centrifuged urine (urine Ultra), alone and in combination, in consecutively enrolled persons with HIV requiring hospitalization with presumptive TB (Abstract 761). Among 238 participants (median CD4+ count, 76 cells/µL), 62 (26.1%) had confirmed TB diagnoses and 92 (38.7%) had definite or probable TB diagnoses. Overall, urine LF-LAM had a sensitivity and specificity of 55% and 90%, respectively, and for urine Ultra it was 70% and 100%, respectively. For definite TB, the yield of sputum Ultra was 34% (n = 21), urine LF-LAM was 45% (n = 28), urine Ultra was 68% (n = 42), and urine LF-LAM + Ultra was 73% (n = 45). For definite or probable TB, the yield of sputum Ultra was 23% (n = 21), urine LF-LAM 39% (n = 36), urine Ultra was 57% (n = 52), and urine LF-LAM + Ultra was 64% (n = 59). Urine Ultra also detected 5 cases of RIF-resistant TB. These data showed that urine Ultra had improved accuracy for TB compared with urine LF-LAM, and that both urine-based tests had improved yield compared with sputum Ultra, given the ease of urine collection. When available in high TB burden settings, urine Ultra testing should be used to improve TB detection among hospitalized persons with HIV.

HIV testing among close household contacts of persons with newly diagnosed TB represents an important opportunity for knowing one’s status and linking to care, but in some settings up to 50% of household contacts identified through household contact tracing decline HIV testing. Armstrong-Hough and colleagues undertook a cluster (household-level) randomized trial to evaluate the efficacy of a brief social behavioral “norming” strategy to increase acceptance and uptake of HIV testing among contacts (≥15 years old) without known HIV, during TB household contact tracing in Kampala, Uganda (Abstract 1050). The brief norming intervention had several components including the following: (1) guided selection of the first tester in the household most likely to accept testing; (2) use of a standardized, encouraging script by community health care workers (CHWs); (3) HIV test offered using opt-out framing; (4) optional invitation for the first tester to share the decision to test (but not results) with other household members; and (5) masking of household members’ decision not to test. Overall, in the intervention arm there were 99 index TB patient households with 328 total contacts, and in the standard of care arm there were 86 index TB patient households with 224 total contacts. Uptake of HIV testing was higher in the intervention arm (98%) than the control arm (92%) (difference, +6%; 95% CI, 2-10; P = .004). CHWs reported that the norming strategy required similar time to the standard HIV testing strategy. This study demonstrated that a brief intervention to normalize HIV testing was feasible and could provide a small increase in HIV testing uptake among TB household contacts.

**Opportunistic Infections**

For cryptococcal meningitis, flucytosine (5FC) acts as an important component of the induction phase for some regimens by reducing the time to cerebrospinal fluid sterilization. However, the requirement for dosing 4 times a day is challenging, especially in resource-limited settings. Krantz and colleagues undertook a phase I, open-label, randomized, single-dose, 4-period, crossover study among 37 health participants to evaluate the safety and PKs of 3 different prototypes (B, C, and D) of sustained-release (SR) 5FC prototype pellets given once (1 x 3000 mg at 0 hours) compared with 5FC immediate release (IR) (A) (3 x 500 mg given twice at 0 and 6 hours) (Abstract 503). No serious or adverse events were identified during any of the 4 treatment phases. The AUC$_{0-24}$ (µg•h/mL) of the 3 prototypes was 179 for prototype B, 228 for prototype C, and 258 for prototype D, compared with 472 for prototype A, the reference IR formulation. Physiologically based pharmacokinetic (PBPK) modeling suggested a double dose of prototype D could achieve similar 5FC concentrations to 5FC IR under fasting conditions. These preliminary data suggest 5FC SR pellets could be available in the future to simplify CM treatment, and the double dose of prototype D will be evaluated in further phase I and II studies.

*Pneumocystis jirovecii* pneumonia (PJP) still occurs in the modern ART era. Epling and colleagues undertook a retrospective, US-based cohort study of 81 persons with HIV with a history of PJP and compared characteristics and outcomes up to 96 weeks in persons with HIV without prior PJP, but with a CD4+ count nadir below 100.
cells/µL (Abstract 747). Of 81 participants with a history of PJP, 64 (79.0%) had their PJP diagnosed within 100 days of ART initiation. The median baseline CD4+ count in the PJP group was 14 cells/µL, compared with 24 cells/µL in the non-PJP group (P < .001). Compared with persons with HIV with no history of PJP, persons with HIV and a history of PJP had similar 96-week CD4+ cell counts and plasma HIV viral loads. Cytomegalovirus end-organ disease was associated with receipt of steroids for PJP (OR, 2.3; 95% CI, 1.0-5.0). Persistent chest computed tomography (CT) changes more than 1 year later were more common among persons with HIV with prior PJP but were relatively rare overall; 11% had bronchiectasis and 11% had subpleural cysts. Although no deaths were directly attributable to PJP, persons with a history of severe PJP had a substantially higher risk of mortality through 96 weeks (hazard ratio [HR], 6.2; P = .046) and notably most deaths occurred more than 24 weeks after ART initiation. PJP remains an important HIV-related opportunistic infection, and these data show that in the era of modern ART, persons with HIV presenting with severe disease remain at increased risk for poor outcomes and should be closely monitored after recovery from their acute illness.

Kaposi sarcoma (KS) also still occurs in the modern ART era. Martin and colleagues undertook a cohort study of adult persons with HIV with newly diagnosed, pathologically confirmed KS in Kenya and Uganda between October 2021 and August 2022, to determine their extent of disease at baseline and vital status over time (Abstract 150). Among 180 persons with HIV, the median CD4+ count was 197 cells/µL (26% had a CD4+ count of 50 cells/µL or below), and 46% had an HIV viral load of 40 copies/mL or below. Overall, 86% had evidence of advanced KS at the time of diagnosis, with a median of 7 anatomic sites of involvement with KS lesions per participant. There were 56 participants who died during the follow-up period, and the cumulative incidence of death at 2, 6, and 8 months following KS diagnosis was 24%, 33%, and 38%, respectively. These concerning contemporary data from East Africa demonstrate that KS is still being diagnosed at late stages with advanced disease and that short-term survival is poor. Innovations are needed for earlier detection and treatment of HIV and KS in sub-Saharan Africa.

Talaromycosis, which is caused by the dimorphic fungus Talaromyces marneffei (Tm), is a leading cause of death in persons with HIV in Southeast Asia, in part due to challenges with timely diagnosis that include a reliance on blood cultures, which may take up to 4 weeks to grow. Nguyen and colleagues undertook a prospective diagnostic accuracy study of a novel enzyme immunoassay (EIA), which detects a Tm-specific cell-wall antigen (Mp1p) in urine or blood, among hospitalized adults with advanced HIV disease (CD4+ count <100 cells/µL or WHO stage III/IV disease) in Vietnam (Abstract 765). All participants had blood cultures performed, as well as microscopic evaluation and culture of other specimens as clinically indicated. They were followed up for 6 months for the development of culture-confirmed talaromycosis to inform a composite reference standard. Among 662 participants, the overall prevalence of talaromycosis was 16.8% (95% CI, 14.0-19.9; n = 111 diagnoses). The sensitivity and specificity of the Mp1p assay on serum and urine samples were 82.0% and 96.0%, and 81.1% and 98.0%, respectively; both had greater sensitivity than conventional blood culture for the diagnosis of talaromycosis (66.7%). In this study, in which a high prevalence of talaromycosis was identified, the Mp1p assay demonstrated favorable diagnostic accuracy, especially compared with current culture-based approaches, and if further developed may be a useful first-line test among hospitalized persons with HIV in settings endemic for talaromycosis.

Human papillomavirus and anal cancer rates are higher in persons with HIV. At last year’s CROI, Palefsky and colleagues shared the practice-changing results of the ANCHOR (Treatment in Preventing Anal Cancer in Patients With HIV and Anal High-Grade Lesions) study, which showed that early treatment of anal high-grade squamous intraepithelial lesions (HSILs) reduced the risk of anal cancer in persons with HIV by 57%. One crucial gap in knowledge following these results is how to optimize screening for identifying HSIL, especially as the current standard screening approach. Anal cytology has poor specificity (46%-65%), which results in many patients requiring high-resolution anoscopy (HRA). Serrano-Villar and colleagues recruited 213 persons with HIV undergoing HSIL screening with HRA, who had anal biopsies performed to confirm HSIL, in order to identify anal microbiota predictive of HSIL (Abstract 148). The median CD4+ count of participants was 704 cells/µL, and 94%...
were men who have sex with men. There were several proteins overexpressed by bacteria in the anal microbiome of participants with HSIL, and they frequently converged in the production (and increased levels) of succinyl-CoA and cobalamin. Compared with anal cytology screening, the combination of succinyl-CoA and cobalamin had improved accuracy for HSIL, where the sensitivity was 96.6% versus 91.2%, respectively, and specificity was 81.8% versus 34.1%, respectively. Further, succinyl-CoA and cobalamin screening would have reclassified 49 of 61 (82%) false-positive cytology-based HSILs diagnosed to true negative diagnoses. Succinyl-CoA and cobalamin are promising biomarkers for improving HSIL screening in persons with HIV and should undergo further development and validation.

Mpqx is an opportunistic infection in persons with advanced HIV defined by numerous severe complications and high mortality risk

Mpqx—A New Opportunistic Infection

During the outbreak of mpox across 110 countries in 2022 and 2023, up to 50% of the approximately 85,000 cases were among persons with HIV. Most people had CD4+ counts above 500 cells/µL, were virologically suppressed on ART, and had similar clinical features and outcomes to persons without HIV. To address limitations in knowledge regarding mpox outcomes in persons with advanced HIV disease, Orkin and colleagues undertook a global case series (19 countries) of persons with HIV with CD4+ counts below 350 cells/µL and polymerase chain reaction (PCR)-confirmed mpox to characterize the natural history of disease (Abstract 173). Of 382 persons, 96% were cisgender men, 8.6% had a new HIV diagnosis, the median CD4+ count was 211 cells/µL (22.3% had a CD4+ counts below 100 cells/µL), 50.5% had an HIV viral load below 50 copies/mL, and 8.4% had a concurrent opportunistic infection. People with CD4+ counts below 100 cells/µL were substantially more likely than those with a CD4+ count above 300 cells/µL to have severe complications with new mpox. These clinical manifestations, some of which have not been previously reported, included large, painful, coalescing necrotizing skin conditions (54.1% vs 6.7% for lower vs higher CD4+ counts, respectively); lung involvement (29.4% vs 0%, respectively); ocular complications (15.3% vs 1.3%, respectively); anorectal complications (52.9% vs 28.0%, respectively); genitourinary complications (34.1% vs 9.3%, respectively); and secondary bacterial infections (43.5% vs 9.3%, respectively). In the overall cohort, 28.0% of patients were hospitalized and 7.1% died (all 27 deaths occurred in persons with CD4+ counts below 200 cells/µL); among those with CD4+ counts below 100 cells/µL, 62.4% were hospitalized and 27.1% died, compared with 16.0% and 0%, respectively, among those with CD4+ counts above 300 cells/µL. Immune reconstitution inflammatory syndrome was suspected in up 24.7% of patients (n = 21/85) started or restarted on ART, but due to the observational nature of the data, it is not possible to infer recommendations on ART start time. These data demonstrate that mpox behaves as an opportunistic infection in persons with advanced HIV, and it is a distinct clinical syndrome marked by various severe complications and a high risk of mortality.

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Additional References Cited in Text


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