Invited Review

CROI 2021: Tuberculosis, Opportunistic Infections, and COVID-19 Among People with HIV

Andrew D. Kerkhoff, MD, PhD, MSc; Diane V. Havlir, MD

Tuberculosis (TB) remains a main driver of morbidity and mortality among people with HIV along with other opportunistic infections. This review summarizes key highlights related to TB, and other opportunistic infections in HIV as well as studies from the virtual *2021 Conference on Retroviruses and Oppoprtunitstic Infections evaluating outcomes among HIV-COVID-19 coinfected patients.*

Keywords: HIV, CROI 2021, tuberculosis, coinfection, cryptococcosis, HPV, KSHV, COVID-19

Tuberculosis

Prevention and Treatment

Shorter tuberculosis (TB) treatment regimens represent a long-awaited advance in the field. Their global impact will be maximized if these regimens are effective and safe in people with HIV. At the *virtual* 2021 Conference on Retroviruses and Opportunistic Infections (CROI), Petit and colleagues reported the important subgroup comparison in people with HIV of the recently completed TB treatment shortening study (TB Trials Consortium Study 31/AIDS Clinical Trial Group [ACTG] A5349) that showed that a 4-month daily regimen of high-dose rifapentine, moxifloxacin, isoniazid (INH) and pyrazinamide (PZA) (rifapentine-moxifloxacin) but not a 4-month daily regimen of high-dose rifapentine, INH, PZA, and ethambutol (EMB)(rifapentine alone), was noninferior to the standard of care (SOC) 6-month TB regimen (2 months rifampicin/INH/PZA/EMB then 4 months of rifampicin/INH).[1] The primary endpoint was TB disease-free survival at 12 months from randomization with a noninferiority margin of 6.6%. Of the total 2516 persons enrolled in the study, 214 (8%) were people with HIV. People with HIV were required to have a CD4+ count above 100 cells/μL and be on an efavirenz-based antiretroviral treatment (ART) regimen. TB disease-free survival occurred in 53 of 58 (91%) in the rifapentine-moxifloxacin arm, 48 of 65 (74%) in the rifapentine-alone arm, and 50 of 59 (85%) in the SOC arm.

The standard 6-month, 4-drug TB treatment can be shortened to a 4-month regimen with high-dose rifapentine, moxifloxacin, isoniazid, and pyrazinamide

The rifapentine-moxifloxacin regimen was noninferior to the SOC regimen (absolute difference [AD] in TB disease-free survival, -6.6%; 95% confidence interval [CI], -18.3-5.0) and the rifapentine-alone regimen was not noninferior to the SOC regimen (AD, +10.9; 95% CI, -3.2-25.0). There was no difference in efficacy for each treatment regimen according to HIV status. Grade III or higher adverse events were less common in the rifapentine-moxifloxacin (14%) and the rifapentine-alone (17%) arms than in the SOC arm (21%); 0 deaths occurred in the rifapentine-moxifloxacin arm compared with 3 in the rifapentine-alone arm and 2 in the SOC arm. This practice-changing study provides strong evidence that a 4-month rifapentine-moxifloxacin regimen is non-inferior to the current standard 6-month regimen and is safe and well-tolerated, independent of HIV status. Notably, this study only enrolled people with HIV on an efavirenz-based ART regimen. As the global scale up of dolutegravir continues, further studies must demonstrate the safety and efficacy of rifapentine once daily with dolutegravir-based regimens before the rifapentine-moxifloxacin regimen can be utilized widely for the treatment of drug-susceptible TB in people with HIV.

The intersection between bictegravir, a highly potent integrase strand transfer inhibitor, and rifapentine, a key agent in the treatment of latent TB infection (LTBI), was explored in 2 studies at CROI this year; both suggest that bictegravir cannot be coadministered with rifapentine. In the first study among people with HIV with LTBI receiving concomitant bictegravir/emtricitabine (FTC)/tenofovir alafenamide (TAF) and daily INH plus rifapentine for 28 days (1HP), Sun and colleagues evaluated the proportion completing LTBI therapy, maintaining therapeutic bictegravir trough concentrations, and virologic suppression (Abstract 132). The study enrolled 50 people with HIV who had been on bictegravir/TAF/FTC for at least 2 weeks, were virologically suppressed (HIV RNA <200 copies/mL), and had evidence of LTBI confirmed by a positive interferon gamma release assay (IGRA). Investigators measured

Dr Kerkhoff is a senior research fellow at Zuckerberg San Francisco General Hospital and Trauma Center and the University of California San Francisco. Dr Havlir is Chief of the Division of HIV, Infectious Diseases, and Global Medicine at the Zuckerberg San Francisco General Hospital and Trauma Center and the University of California San Francisco. Send correspondence to Andrew D. Kerkhoff, MD, PhD, MSc, Division of HIV, Infectious Diseases and Global Medicine, Zuckerberg San Francisco General Hospital and Trauma Center, University of California San Francisco School of Medicine, 1001 Potrero Ave, 409, San Francisco, CA 94110 or email Andrew.Kerkhoff@ucsf.edu.

bictegravir trough concentrations, cytokine levels, and HIV viral load prior to initiation of and at days 14 and 28 of 1HP therapy. Overall, 49 of 50 (98%) participants completed 1HP therapy, with 1 participant discontinuing on day 15 due to fever and generalized rash. At days 14 and 28 of 1HP therapy, 56% and 35% of participants, respectively, had a bictegravir trough concentration above the 95% effective concentration (EC_{95}, 162 ng/mL) and 8% and 2%, respectively, had viral loads of 200 copies/mL or higher; all patients were virologically suppressed 3 months after completion of 1HP.

In the second study, Arora and colleagues undertook a phase I, open-label, 3-period, fixed-sequence, multiple-dose study among healthy HIV-negative volunteers to determine bictegravir/FTC/TAF pharmacokinetic parameters when given with weekly rifapentine (Abstract 369). Participants received bictegravir/FTC/TAF daily on days 1 to 8, underwent a washout period from days 9 to 14, then received bictegravir/FTC/TAF daily on days 15 to 30 with weekly rifapentine given on days 15, 22 (both codosed), and 29 (given 12 hours before bictegravir/FTC/TAF). Bictegravir trough concentrations declined by 40% (codosed) and 57% (12 hours before) following administration with weekly rifapentine, were reduced by up to 83% at 4 days post rifapentine dosing, and did not return to steady-state concentrations between rifapentine doses. These studies collectively show substantially reduced bictegravir concentrations when given with daily or weekly rifapentine; therefore, 1HP and 3HP should not be coadministered with bictegravir/FTC/TAF.

Another critical question in the TB/HIV field is the compatibility of drug interactions between high-dose rifampicin, a potent liver enzyme inducer, with dolutegravir- or efavirenz-based ART regimens. Sekaggya-Wiltshire and colleagues performed a randomized open-label phase IIb trial among people with HIV with newly diagnosed TB in Uganda to determine the safety and effect of high-dose rifampicin on dolutegravir and efavirenz pharmacokinetic parameters (Abstract 90). A total of 120 people with HIV on dolutegravir- or efavirenz-based ART continued their current regimen (dolutegravir adjusted to 50 mg twice daily) and were randomly assigned to receive high-dose

Bictegravir levels are subtherapeutic in patients receiving rifapentine either daily or weekly for TB prevention

rifampicin (35 mg/kg/day) or standard-dose rifampicin (10 mg/kg/day) during the 8-week intensive TB treatment phase. Among those receiving dolutegravir-based ART, mean dolutegravir trough concentrations were 48% lower in those receiving high-dose rifampicin than in those receiving standard-dose rifampicin (geometric mean ratio [GMR], 0.52; 95% CI, 0.23-1.16). However, 16% (n=4) versus 5% (n=1) of participants in the high-dose and standard-dose rifampicin arms, respectively, had trough concentrations below the protein-adjusted 90% inhibitory concentration (IC_{90}) of dolutegravir (≥0.064 mg/L) (P=.36); none had virologic failure after 6 months of TB treatment. Efavirenz mid-dose concentrations were 42% lower among those receiving high-dose rifampicin than in those receiving standard-dose rifampicin (GMR, 0.58; 95% CI, 0.31-1.10), and only 1 participant in each arm had an efavirenz mid-dose concentration below the minimum target threshold (1 mg/L). Grade III or IV adverse events did not differ between the treatment arms. Participants receiving high-dose rifampicin were more likely than those receiving standard-dose rifampicin to achieve 8-week sputum culture conversion (84% vs. 63%, respectively; P=.06). This study shows that high-dose rifampicin appears safe when given with twice-daily dolutegravir and may improve TB treatment efficacy. However, given moderate reductions in dolutegravir serum concentration, at times below the IC_{90}, further studies are needed before high-dose rifampicin coadministered with dolutegravir can be recommended.

Coadministration of dolutegravir with rifampicin substantially reduces plasma dolutegravir levels, and therefore twice-daily dolutegravir is recommended when given with rifampicin. Prior studies had found that dolutegravir levels are increased when given with food. Therefore, Ueaphongsukkit and colleagues conducted an open-label, randomized study among 28 ART-naive, TB-coinfected adults in Thailand to evaluate dolutegravir pharmacokinetic parameters among those receiving dolutegravir 50 mg daily with food (intervention group; n=12) compared with dolutegravir 50 mg twice daily (control group; n=16) (Abstract 370). All participants received SOC treatment for drug-susceptible TB disease (rifampicin 10 mg/kg/day), and dolutegravir was given with 2 nucleoside reverse transcriptase inhibitors (nRTIs). Dolutegravir minimum concentrations (C_{min}) and dolutegravir trough concentrations were 70% (GMR, 0.30; 95% CI, 0.26-0.36]) and 80% (GMR, 0.20; 95% CI, 0.11-0.35) lower, respectively, with daily dolutegravir given with food than with twice-daily dolutegravir. Dolutegravir C_{min} was below the IC_{90} (≥0.064 mg/L) in 17% versus 6% in the daily dolutegravir with food arm and twice-daily dolutegravir arms, respectively (P=.16). After 12 weeks, 75% of participants receiving daily dolutegravir with food were virologically suppressed compared with 82% in the twice-daily dolutegravir arm. These data show that among people with HIV receiving rifampicin, daily dolutegravir with food may result in subtherapeutic dolutegravir levels and increased likelihood of virologic failure, and therefore reinforce current recommendations for twice-daily dolutegravir dosing in this context.

Women and Children

The World Health Organization (WHO) recommends INH for 6 or 9 months as a preventative therapy for TB (IPT) in pregnant people with HIV; however, there is mixed evidence on the safety of INH in pregnancy and limited data on the safety of INH taken during the first trimester. Gupta and colleagues undertook a prespecified secondary analysis

of the BRIEF-TB (Brief Rifapentine-Isoniazid Evaluation for TB Prevention) trial[2] to compare pregnancy outcomes (non-live births, preterm birth, low birth weight, and APGAR scores) among women living with HIV, who became pregnant while they were receiving INH with those who became pregnant after completing IPT (Abstract 178). The present analysis included women 13 years or older, those randomly assigned to the IPT arm (due to a contraceptive requirement in the 1HP arm), and those who became pregnant during the 36 months of study follow up (pregnancy at entry was an exclusion criterion).

INH use in the first trimester of pregnancy is associated with a higher likelihood of non-live births

Overall, 128 of 812 (16%) women in the IPT arm became pregnant and had known pregnancy outcomes, of which 39 (36 definite, 3 possible) were exposed to INH during conception, and 89 became pregnant after completion of IPT. The proportion of women with non-live births was substantially higher in the INH-exposed arm (n=16/39; 41%) than in the INH-unexposed arm (n=19/89; 21%) (relative risk [RR], 1.92; 95% CI, 1.11-3.33). Most non-live births were due to spontaneous abortion (n=25/35; 71%). In an adjusted analysis that excluded induced abortions, composite adverse pregnancy outcomes were higher in the INH-exposed arm (n=13/35; 36%) than in the INH-unexposed arm (n=16/89; 19%) (adjusted RR [aRR], 1.98; 95% CI, 1.08-3.65). Gestational age at birth, birth weight, and APGAR scores did not differ according to INH exposure. These data raise important concerns about the safety of INH during the first trimester of pregnancy in women with HIV and suggest the need for contraception among women of reproductive age to avoid INH exposure during the first trimester.

Multidrug-Resistant TB

The Nix-TB study showed an all-oral regimen for the treatment of highly drug-resistant (DR) TB consisting of bedaquilline 200 mg thrice-weekly, pretomanid 200 mg daily, and linezolid 1200 mg daily for 6 months (BPaL regimen) was highly efficacious through 6 months.[3] An important question centers on this regimen's long-term efficacy and safety, including the effects of linezolid on peripheral neuropathy. Howell and colleagues presented an updated analysis of the efficacy and safety of the BpaL regimen through 2 years of follow up after treatment completion (Abstract 562). Of 109 individuals (65% with extensively drug-resistant tuberculosis (XDR-TB), 35% multi-drug resistant (MDR)-TB, and 51% with HIV), all but 1 individual who survived completed the entire therapy course. Only 2 participants had additional unfavorable outcomes between 6 and 24 months (1 with treatment relapse after 15 months and 1 lost to follow up); therefore, 88% did not have treatment failure or disease relapse through 24 months of follow up. This did not differ by sex or HIV status. Among 103 individuals completing the BPaL regimen, 37 (36%) were able to complete 26 weeks of linezolid at any dose, and only 16 (16%) were able to complete 26 weeks at the 1200 mg daily dose (1200 mg once daily or 600 mg twice daily). Of the 84 participants without peripheral neuropathy at baseline, 57 (68%) developed peripheral neuropathy (23 cases were severe), but this fully resolved by 24 months in 42 of 57 (74%) and lessened in severity among 7 of 57 (13%). These data demonstrate that the BPaL regimen maintains long-term efficacy. Although peripheral neuropathy is common, it improves or resolves entirely in the large majority of individuals.

A 'one-size-fits-all' approach underpins current MDR-TB treatment strategies, but it is unknown whether the optimal treatment duration may differ according to TB disease severity. Garcia-Cremades and colleagues analyzed individual-level patient data from published observational and investigational MDR-TB treatment studies in order to develop a risk stratification algorithm that could predict individuals at higher risk for unfavorable outcomes (treatment failure or death) possibly requiring longer treatment regimens from those at lower risk for poor outcomes who may successfully be cured with shorter treatment regimens (Abstract 561). Of 7750 individuals with known outcomes, 76% (n=5869) were successfully treated, 8% (n=628) had treatment failure, and 16% (n=1253) died. Several variables were associated with unfavorable outcomes, but notably, HIV-positivity was the strongest predictor in 3 separate multivariable models (adjusted odds ratio [aOR], 2.3; 95% CI, 1.7-3.0). Individual risk scores were determined using the multivariable models, and patients were categorized into high-, medium-, and low-risk phenotypes. The proportion of patients with an unfavorable outcome differed substantially according to risk phenotype. Approximately 75% of individuals with MDR-TB classified as at high risk experienced an unfavorable outcome through 36 weeks of follow up. This study suggests that it may be possible to predict treatment success in individuals with MDR-TB and therefore tailor the duration of therapy accordingly. This represents an interesting area for further research.

TB Screening and Detection

In high TB burden settings, systematically testing all individuals presenting to health facilities regardless of symptoms may detect a large burden of TB; however, such a strategy is resource intensive and therefore may not be feasible to implement. Lebina and colleagues undertook a cluster-randomized trial at 60 clinics in South Africa to determine whether a pragmatic strategy of targeted systematic TB testing among individuals at very high risk for TB resulted in a greater number of TB cases detected than the SOC (Abstract 134). At clinics randomizedly assigned to the intervention arm (n=30), systematic TB testing (sputum Xpert Ultra and culture) of individuals belonging to a high-risk group (people with HIV, close contacts of a person with TB in the last year, and those treated for TB in the prior 2 years) was undertaken regardless of symptoms. SOC clinics (n=30) continued use of symptoms-based TB

screening followed by testing for individuals screening positive. Among 30,513 high-risk individuals tested in the intervention arm, the diagnostic yield of microbiologically confirmed TB was high (6.0%) and differed according to risk factor: people with HIV (5.0%), close contact (7.5%), and prior TB (12.2%). The primary specified outcome analysis showed that intervention clinics diagnosed 14% (95% CI, -6%-38%) more TB cases per month, but the difference did not reach statistical significance. In an adjusted difference-in-difference analysis, intervention clinics diagnosed 17% (95% CI, 14%-19%) more TB cases than the prior year, and SOC clinics diagnosed 8% (95% CI, 7%-9%) fewer TB cases than in the preceding year. This study demonstrates that a strategy of systematic, facility-based TB testing of all individuals at very high risk detected many TB cases that may have otherwise been missed and substantially more cases than a symptoms-based screening approach that mirrors current recommendations.

Biomarkers that accurately predict TB disease progression in individuals with LTBI are lacking but could greatly improve prevention and treatment approaches. Kroidl and colleagues evaluated *Mycobacterium tuberculosis* (Mtb)-specific T-cell activation, which has previously shown a strong correlation with active TB disease, among people with HIV with LTBI (remained asymptomatic and Mtb never detected), prevalent active TB disease (Mtb detected at base line visit) and incipient TB (asymptomatic at baseline, Mtb detected during subsequent follow up) (Abstract 557). Patients were drawn from the AFRICOS (African Cohort Study) in which people with HIV from 4 African countries were evaluated annually from 2013 to 2017 for the presence of TB disease using sputum Xpert testing and followed up from between 3 years before and 4 years after TB disease diagnosis. The study included 46 patients matched on age, sex, and ART regimen with longitudinal peripheral blood mononuclear cell (PBMC) samples (11 active TB, 19 incipient TB, and 16 LTBI). Among people with HIV who had active TB disease, CD38 expression on Mtb-specific T cells ($P<.001$), but not bulk CD4+ T cells ($P=.4$), was substantially higher than those with LTBI; CD38 expression on Mtb-specific T cells declined following initiation of TB treatment ($P<.001$). CD38+ Mtb-specific CD4+ T cells were present in 23% and 67% of people with HIV with incipient TB at 12 and 6 months, respectively, prior to TB detection. The majority of individuals with LTBI demonstrated transient Mtb-specific T-cell activation that largely normalized without receipt of IPT. Further, there was persistent Mtb-specific T-cell activation in those with recurrent TB disease following treatment completion. These data support CD38+ Mtb-specific CD4+ T cells as an important surrogate biomarker of TB disease activity in individuals with HIV.

Screening for LTBI, either with tuberculin skin testing (TST) or IGRA, remains a key barrier to improving TB preventative therapy (TPT) coverage among people with HIV in some high TB burden settings. In the pilot period of a larger study aimed at increasing TPT, Chaisson and colleagues evaluated whether integrating IGRA testing with routine blood draws for CD4+ cell counts and viral load monitoring would improve LTBI screening compared with SOC. Among 972 people with HIV, 967 (99%) had an IGRA ordered, 672 (93%) of IGRA orders were paired with CD4+ cell count or viral load monitoring, and 672 (69%) had an IGRA completed, of whom 132 (20%) were positive. These data suggest that routinization of IGRA testing could help overcome barriers to LTBI screening.

The diagnosis of TB in children remains challenging, in large part because existing diagnostic tools are insufficiently sensitive and may require difficult-to-obtain, nonsputum clinical specimens. Exosomes are small extracellular vesicles (EVs) secreted by cells originating from endosomal cell compartments and Mtb-specific EVs (either released from Mtb or Mtb-infected macrophages) that are thought to play in important role in TB pathogenesis. LaCourse and colleagues retrospectively evaluated an internally developed nanoplasmon-enhancing scattering (nPES) assay that detects and quantifies 2 Mtb-specific markers (LprG and LAM) in EVs of cryopreserved plasma from hospitalized children with HIV in Kenya (Abstract 558). All children were intensively tested for TB at entry using Xpert testing and culture of sputa or gastric aspirate samples and Xpert testing of stool samples and were classified as having confirmed, unconfirmed, or unlikely TB. Plasma was collected frequently during the 24 weeks of follow-up. Among 72 hospitalized children with HIV included (81% with severe immunosuppression), the sensitivity of the Mtb-EV nPES assay was 86% (6/7) and 72% (26/36) in those with confirmed and unconfirmed TB, respectively; the specificity was 48% (14/29) in those with unlikely TB. Mtb-EV concentrations were higher in those with confirmed or unconfirmed TB versus those with unlikely TB ($P=.048$) and declined over 24 weeks following TB treatment initiation. This study shows that the nPES assay that detects Mtb-EVs may be a promising non-sputum-based target for improving TB diagnosis and treatment monitoring among children with HIV; however, additional studies are needed, including among less severely ill children with HIV.

Rapid ART Start in Patients with TB Symptoms

Rapid ART start is now the global standard; however, in high TB burden settings, ART initiation is often delayed among people with HIV who have TB symptoms while undertaking TB investigations. This may result in high rates of pre-ART losses to follow up. It is unknown how same-day TB testing and treatment and ART initiation among people with HIV with suspected TB may affect HIV and TB outcomes in resource-limited settings. Dorvil and colleagues randomly assigned 500 newly diagnosed adults with HIV and TB symptoms systematically tested for TB using Xpert Ulta to a same-day TB

test result notification and TB or ART treatment strategy or to Haiti's SOC TB testing and treatment approach (Abstract 184). In the SOC arm, patients initiated TB treatment on day 2 if TB was detected or ART on day 7 if TB was not detected. The proportion of people with HIV with prevalent TB disease (18.0% vs. 16.4%, respectively), started on TB treatment (100% vs. 97.6%, respectively) and initiated on ART (99.6% vs. 97.6%, respectively) did not differ between the same-day and SOC arms. Similarly, the proportion of people with HIV retained in care at 48 weeks (90.8% vs. 93.6%, respectively) and virologically suppressed (72.0% vs. 76.7%, respectively) was similar between the 2 treatment arms. The authors noted that the low 48-week virologic suppression rates might reflect a high prevalence of transmitted efavirenz resistance in this setting (as high as 20%), severe political instability during the study period, and service disruptions caused by the COVID-19 pandemic. This study shows comparable outcomes between same-day or day-7 ART start among people with HIV under evaluation for TB and supports the 2021 updated WHO recommendations for rapid ART in this population.

TB Contact Tracing

Contact tracing and systematic screening for TB among TB patients' household members are recommended but inconsistently implemented in many high-burden settings due to the resources required and its unclear impact on population control. Martinson and colleagues randomly assigned households of index TB patients in South Africa to determine whether intensive household contact TB and HIV screening with supported linkage to care (intensive screening arm) could improve outcomes among household contacts compared with a passive referral strategy (referral arm) (Abstract 133). In the intensive screening arm, all household members were systematically tested for TB (sputum Xpert testing and culture, TST) and HIV, offered home-based IPT initiation (if eligible), and provided immediate linkage support for TB treatment and ART (as necessary). In the referral arm, patients with TB were asked to provide all household members with a referral letter that could be presented at local health facilities for TB and HIV testing. All household contacts were followed up for 15 months to determine the composite endpoint of either incident TB or death. Overall, 1032 households (4129 contacts) and 1030 (4459 contacts) were randomly assigned to the intensive screening and referral arms, respectively. A large burden of previously undiagnosed TB (69/2166; 3.2%) and HIV (104/2972; 3.5%) was detected among household contacts in the intensive screening arm at baseline; however, after 3 months, only 54% of household contacts with TB disease started treatment, 53% of people with HIV and children 5 years or younger initiated IPT, and 80% of newly diagnosed people with HIV started ART. There was no difference in the primary outcome (TB disease-free survival through 15 months) between the study's intensive screening arm (2.9%) and its referral arm, (3.1%) (hazard ratio, 0.90; 95% CI, 0.66-1.24). There was also no difference in the prevalence of undiagnosed/untreated HIV among household members between arms through 15 months (1.3% vs. 1.3%; OR, 1.02; 95% CI, 0.64-1.64). Unexpectedly, the prevalence of TST positivity (≥10 mm) was higher among children in the intensive screening arm than those in the referral arm (4.5% vs. 1.9%; OR, 2.25; 95% CI, 1.07-4.72). This study demonstrated that an intensive testing and treatment strategy among household TB contacts identified many individuals with untreated TB and HIV. It did not substantially improve TB disease-free survival at 15 months compared with a simple contact referral letter strategy. Reasons for the lack of difference in TB disease-free survival between study arms may include limited uptake of TB and HIV treatment in the intensive screening arm, a relatively short follow-up period of 15 months, and widespread access to clinic-based TB and HIV testing and treatment in this setting.

Opportunistic Infections

Cryptococcus

Although the incidence of cryptococcal meningitis has substantially declined since the global expansion of ART coverage, cryptococcal meningitis remains an important cause of death among people with HIV, especially those with advanced HIV (Abstract 565). It is unknown whether using a clinic-based, rapid point-of-care cryptococcal antigen (CrAg) testing strategy among patients with advanced HIV may reduce cryptococcal meningitis and mortality by expediting the initiation of fluconazole prophylaxis. Drain and colleagues undertook a pre-post study in South Africa among individuals presenting for HIV testing to compare outcomes associated with 3 different CrAg testing strategies rolled out over 3 periods: period 1, CrAg testing ordered by a clinician at their discretion (2013-2015); period 2, routine laboratory-based CrAg reflex testing for anyone with a blood sample with a CD4+ count below 100 cells/μL (2015-2017); and period 3, clinic-based point-of-care CrAg testing among persons with a CD4+ count at or below 200 cells/μL (2017-2019) (Abstract 564). Among 908 people with HIV with a CD4+ count at or below 200 cells/μL, clinic-based point-of-care CrAg testing (period 3) increased the proportion screened for CrAg ($P<.001$), had CrAg detected in blood ($P=.020$), started on fluconazole preventative therapy ($P=.010$), and started on ART ($P=.012$), compared with clinician-directed CrAg testing (period 1). The proportion of patients diagnosed with cryptococcal meningitis (4.5% vs. 1.5%; $P=.06$), all-cause hospitalization (9.5 vs. 8.7; $P=.76$), and all-cause mortality (8.1% vs. 9.6%; $P=.65$) was not different between the clinic-based point-of-care testing strategy and the clinician-directed testing strategy, respectively. No outcomes differed between the clinic-based point-of-care testing and laboratory reflex testing strategies. In this quasi-experimental study, a systematic, clinic-based point-of-care CrAg testing strategy for people with advanced HIV did not appear to improve

outcomes meaningfully, but other interventions occurring during the study period may have biased the results.

Human Papillomavirus and Kaposi Sarcoma Herpesvirus

Human Papillomavirus

Cervical cancer is a leading cause of cancer-related mortality in sub-Saharan Africa, especially among women with HIV; however, the prevalence of different high-risk human papillomavirus (HPV) genotypes in sub-Saharan Africa is poorly defined. Uldrick and colleagues prospectively enrolled a cohort of women with and without HIV in Uganda who had abnormalities detected during cervical cancer screening (visual inspection with acetic acid [VIA]) in order to determine the prevalence of and risk factors for high-risk HPV and cervical high-grade squamous intraepithelial lesions (HSILs) (Abstract 474). Among 16,380 women (60% with HIV) screened, 815 (5.0%) had a positive VIA of whom 328 (200 with HIV [median CD4+ cell count, 667/µL], and 128 HIV-negative) had lesions suitably sized for biopsy and were included. High-risk HPV was detected in 67% of women with HIV compared with 45% of HIV-negative women (adjusted prevalence ratio [aPR]: 1.5; 95% CI, 1.2-1.9). Compared with HIV-negative women, those with HIV were also more likely to have multiple high-risk HPVs (aPR, 3.2; 95% CI, 1.2-8.4), and have a high-risk HPV only covered by the nonavalent vaccine (aPR, 1.9; 95% CI, 1.1-3.1) or no vaccine (aPR, 1.7; 95% CI, 1.0-3.0). Among women with HIV, a lower CD4+/CD8+ cell ratio was associated with having any high-risk HPV, multiple high-risk HPVs, and a high-risk HPV only covered by the nonavalent vaccine. Additionally, HSIL was more common in women with HIV than in HIV-negative women (29% vs. 9%, respectively). These data show that high-risk HPV is common among young women in Uganda and more prevalent in women with HIV, and provide support for prioritizing the nonavalent HPV vaccine for adolescents in this setting.

Women with HIV are at increased risk for high-risk HPV associated precancer and cancer of the lower anogenital tract; however, the dynamics of cervical and anal HPV infection and their relationship to anal precancers (HSILs) is poorly understood. Weiss and colleagues enrolled 144 women with HIV in New York City from 2013 to 2019 to determine the prevalence of cervical and anal high-risk HPV infection (HPV 16, 18, and others), the persistence of anal HPV over time, and the association between cervical and anal high-risk HPV infection and anal HSILs (Abstract 473). Overall, 45% had anal high-risk HPV infection only, 28% had both cervical and anal high-risk HPV infection, and 3% had cervical high-risk HPV infection only. Among 41 participants with dual-site high-risk HPV infection, HPV type concordance between the anus and cervix was observed in 56%, and anal high-risk HPV infection persistence was observed in 54% after a median of 534 days. Biopsy-proven anal HSIL was detected in 31%. Anal HSIL was much more likely among those with anal high-risk HPV persistence versus those with clearance (incidence rate ratio [IRR], 6.84; 95% CI, 1.66-28.16), those with anal HPV type 16 or 18 versus not (IRR, 6.22; 95% CI, 3.20-12.09), but not those with cervical HPV type 16 or 18 versus not (IRR = 1.44; 95% CI, 0.57-3.62). These data showed that anal HPV was more common than cervical HPV among women with HIV and that the presence and persistence of anal high-risk HPV but not cervical high-risk HPV predicted anal HSIL. This study suggests that greater consideration should be given to anal cancer screening among women with HIV, independent of cervical HPV status, but further study is required.

Kaposi Sarcoma Herpesvirus

The treatment of Kaposi sarcoma herpesvirus (KSHV) inflammatory cytokine syndrome (KICS) and KSHV-associated and multicentric Castleman disease (MCD) cooccurring with Kaposi sarcoma (KS) may include rituximab with liposomal doxorubicin. However, rituximab can worsen KS in a majority of patients. Therefore, rituximab-sparing treatment options are needed for such patients. Pomalidomide and doxorubicin are 2 systemic treatment options approved for extensive cutaneous KS or visceral KS, but the safety and activity of their combined use in KS alone or with KSHV-associated diseases is not known. To address this question, Ramaswami and colleagues undertook a phase I/II study among 2 groups of patients with KS requiring systemic therapy: those with KS alone (G1) and those with KS plus concurrent MCD or KICS (G2) to assess the safety and tolerability of combination pomalidomide/doxorubicin (Abstract 167). All participants received liposomal doxorubicin 20 mg IV once on day 1 of a 28-day cycle and pomalidomide once daily orally on days 1 to 21 at increasing doses (2 mg, 3 mg, 4 mg) until a plateau in response was observed, disease progressed, or dose-limiting toxic effects occurred. In total, 34 men (94% people with HIV, all on ART [median CD4+ count, 217 cells/µL; median HIV viral load 46 copies/mL]) with severe KS were enrolled of which, 22 (65%) had prior chemotherapy for KS. There were 21 participants in G1 and 13 in G2; those in G2 were more likely to have visceral KS (92% vs. 38%, respectively) and had lower CD4+ counts (92 vs. 286 cells/µL, respectively). No dose-limiting toxic effects were observed in G1, and all were treated with the maximum tolerated pomalidomide dose (4 mg daily). By comparison, 2 participants in G2 had dose-limiting toxic effects at pomalidomide 3 mg daily. After a median of 6 cycles, the response rate (partial or complete) was 81% (17/21) in G1 and 50% (5/10) in G2; among those in G2 with KICS and MCD, 57% (4/7) and 50% (3/6), respectively, showed at least partial response to treatment. The most common adverse event observed was neutropenia in 65% (22/34). This small study demonstrated that the rituximab-sparing pomalidomide/doxorubicin regimen had activity and tolerability among heavily pretreated patients with KS alone or with concurrent KSHV-associated diseases. Larger studies are

needed before this regimen can be recommended in this setting.

HIV and COVID-19

COVID-19 Outcomes Among People with HIV

To date, there is mixed evidence as to whether people with HIV are at increased risk for acquiring COVID-19 or for experiencing more severe COVID-19 compared with HIV-negative individuals. Several studies at this year's CROI added to this literature.

Using patient-level data from 34 US sites in the National COVID Cohort Collaborative (N3C) between January 2020 and February 2021, Sun and colleagues evaluated whether people with HIV and individuals with solid organ transplants with COVID-19 were more likely to be hospitalized or require intubation than those without an immunocompromising condition (Abstract 103). Among 575,445 COVID-19-positive adult patients, there were 2932 people with HIV, 4633 transplant recipients, and 111 people with HIV and a solid organ transplant. Overall, 157,765 (31%) patients required hospitalization (49% of people with HIV, 64% of transplant recipients), and 10,300 (2%) required intubation (6% of people with HIV, 10% of transplant recipients). In unadjusted analyses, people with HIV had a 2.14-times (95% CI, 1.99-2.30) higher odds of hospitalization, and individuals with solid organ transplants had a 4.00-times (95% CI, 3.77-4.25) higher odds of hospitalization. However, multivariable analyses adjusted for comorbidities showed that the odds of hospitalization were strongly attenuated but remained significantly elevated among people with HIV (aOR, 1.32; 95% CI, 1.22-1.43; $P<.01$) and solid organ transplant recipient patients (OR, 1.69; 95% CI, 1.58-1.81). Additional analyses among people with HIV demonstrated that a history of cardiopulmonary or renal disease independently predicted hospitalization. Multivariable analyses also demonstrated that the odds of mechanical ventilation were higher among people with HIV (aOR, 1.86; 95% CI, 1.56-2.22) and solid organ transplant patients (aOR, 1.96; 95% CI, 1.74-2.12) than among individuals without these immunocompromising conditions.

Tang and colleagues undertook a retrospective cohort analysis among 235,609 patients (1.5% people with HIV) at a single center in southern California from March to November 2020 to compare COVID-19–related diagnostic and clinical outcomes between people with and without HIV (Abstract 542). People with HIV were much more likely to be tested for COVID-19 during the study period than HIV-negative individuals (34% vs. 10%, respectively), and among those tested, people with HIV were more likely to be COVID-19 positive (8% vs. 3%, respectively; aOR, 3.41; 95% CI, 2.65-4.39). Among those with confirmed COVID-19, and after adjusting for potential confounders including comorbidities, the likelihood of hospitalization (aOR, 0.61; 95% CI, 0.27-1.38), intensive care unit (ICU) admission (aOR, 1.33; 95% CI, 0.44-3.96), mechanical ventilation (aOR, 2.35; 95% CI, 0.62-8.96), and death (aOR, 3.04; 95% CI, 0.46-19.94) did not differ according to HIV status; however, there was a small number of clinical outcome events as indicated by the wide confidence intervals that may have limited statistical power to detect a true difference if one were present.

Comorbidities are the biggest predictor of poor COVID-19 outcomes in persons living with HIV

Shapiro and colleagues assessed predictors of increased COVID-19 disease severity among all people with HIV with PCR-confirmed COVID-19 disease between March and December 2020 from 7 sites in the Center for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) cohort using Poisson regression models (Abstract 543). Of 15,969 people with HIV in the CNICS cohort, 582 (3.6%) were diagnosed with COVID-19. Female sex (aRR, 1.41; 95% CI, 1.19-1.68), diabetes (aRR, 1.25; 95% CI, 1.04-1.51) and a body mass index of 30 and above (aRR, 1.50; 95% CI, 1.27-1.76) were independent predictors for being diagnosed with COVID-19. Among 582 people with HIV with COVID-19, 104 (17.9%) were hospitalized, 28 (4.8%) required ICU admission and 17 (2.9%) required mechanical ventilation. Independent predictors of hospitalization were age 60 years or older (aRR, 1.78; 95% CI, 1.25-2.54), CD4+ count below 350 cells/μL (aRR, 2.29; 95% CI, 1.63-3.22), hepatitis C (aRR, 1.53; 95% CI, 1.04-2.25), elevated atherosclerotic cardiovascular disease risk score ([per 10% increase] aRR, 1.41; 95% CI, 1.25-1.60), diabetes (aRR, 1.45; 95% CI, 1.02-2.42), use of antihypertensive drugs (aRR, 1.69; 95% CI, 1.17-2.42), and impaired renal function (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73m^2]; aRR, 2.28; 95% CI, 1.61-3.24), although chronic obstructive pulmonary disease had borderline significance (aRR, 1.61; 95% CI, 0.98-2.65). Notably black race and HIV virologic control were not independent predictors of hospitalization among people with HIV.

Yendewa and colleagues undertook a retrospective cohort analysis using the TriNetx database (a large global health research network) to evaluate differences in outcomes according to HIV status among adults with COVID-19 presenting to any of 44 US healthcare facilities from January to December 2020 (Abstract 548). In total, 297,194 adults with confirmed COVID-19 were enrolled, of which 1,638 (0.6%) had HIV (48% had an HIV-1 RNA <20 copies/μL). Compared with HIV-negative COVID-19 patients, people with HIV who had COVID-19 were more likely to be younger, male, African American or Hispanic, have cardiovascular disease, and be obese; people with HIV also tended to have higher procalcitonin and interleukin-6 levels. In a propensity score analysis matched on demographics and medical comorbidities, people with HIV had a higher odds of hospitalization (OR, 1.26; 95% CI, 1.04-1.53; $P=.023$) and ICU admission for mechanical ventilation (OR, 1.32; 95% CI, 1.10-1.58; $P=.003$) than HIV-negative patients. Thirty-day mortality was comparable between people with HIV and without HIV (2.9% and 2.3%, respectively; $P=.123$).

Moran and colleagues determined factors associated with hospitalization among all people with HIV with COVID-19 at 2 hospitals in Atlanta, Georgia, from March to November 2020 (Abstract 547). Overall, 180 people with HIV were enrolled (78% male, 78% black, 14% Latinx), of whom 97% were on ART and 91% had a suppressed HIV viral load. 72% of people with HIV had at least 1 medical comorbidity. The most common comorbidities were hypertension (46%), dyslipidemia (34%), obesity (31%), and diabetes (22%); 22% had 4 or more medical comorbidities. Hospitalization occurred in 33% (n=60) of people with HIV. In a multivariable analysis, only age (aOR, 1.07; 95% CI, 1.04-1.11) and diabetes (aOR, 2.65; 95% CI, 1.03-6.85) were associated with hospitalization. However, in a second analysis adjusted only for age, there was a dose-response relationship observed between the number of comorbidities and the odds of hospitalization, such that people with HIV with 4 or more comorbidities had nearly a 3-times higher odds of hospitalization than people with HIV with none or 1 comorbidity (aOR, 2.85; 95% CI, 1.17-6.91). Notably, CD4+ cell count and HIV viral load were not associated with hospitalization.

To assess the impact of COVID-19 in pregnant women with HIV, De Waard and colleagues conducted an observational cohort study among COVID-19–positive pregnant women attending hospital in Cape Town, South Africa, between May and July 2020 and followed them up through October 2020 to determine pregnancy and birth outcomes (Abstract 171). Overall, 103 of 275 (38%) symptomatic women tested positive for COVID-19, and 100 were included in the analysis; this included 28 (28%) women with HIV who had a median CD4+ count of 441 cells/μL. Demographic characteristics and medical comorbidities did not differ according to HIV status. Half of the women (50%) delivered within 2 weeks of their COVID-19 diagnosis, 40% required supplemental oxygen, 15% required mechanical ventilation, and 8% died. Regarding neonatal outcomes among women with COVID-19 (n=91 live births), 30% were delivered before 37 weeks, and 28% had low birth weight. Notably, no maternal or infant outcomes differed according to HIV status. Maternal deaths among pregnant women with COVID-19 were substantially higher than pregnant women without COVID-19 during the study period (8.8% vs. 0.2%, respectively; $P<.001$).

Collectively, studies from this year's CROI suggest that people with HIV may have an increased risk for severe COVID-19 related outcomes. However, the risk appears to be predominantly driven by comorbid medical conditions, which may be more prevalent among people with HIV than in the general population.

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