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CROI 2022: Tuberculosis and Infectious Complications in Persons With HIV

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Running Head: CROI 2022: Tuberculosis and Coinfections

Abstract: *Early treatment of anal high-grade squamous intraepithelial lesions compared with active monitoring reduced the risk of anal cancer by 57% in persons with HIV in a landmark randomized trial of 4446 participants. In a multicountry randomized trial, an entirely oral combination regimen consisting of bedaquiline, pretomanid, linezolid, and moxifloxacin for 24 weeks outperformed the World Health Organization recommended 36- to 96-week standard of care regimen for multidrug-resistant tuberculosis (TB), ushering in a new era of shorter multidrug-resistant TB treatment. These and other studies of TB and coinfections in persons with HIV presented at the 2022 Conference on Retroviruses and Opportunistic Infections provided new insights and are summarized herein.*

Keywords: HIV, CROI 2022, tuberculosis, coinfection, *Cryptococcus*, human papilloma virus

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Tuberculosis

Drug-Resistant Tuberculosis

Drug-resistant tuberculosis (DR-TB), including multidrug-resistant (MDR)-TB, is a major public health threat globally. Mortality remains high, treatment regimens are 18 to 24 months in duration, and drugs are extremely toxic and require injection (Symposium 5). Testing of shorter, entirely oral, better-tolerated DR-TB regimens was made possible by the recent introduction of new antimycobacterial agents. Nyang'wa and colleagues presented the preliminary results of TB-PRACTECAL (Pragmatic Clinical Trial for a More Effective Concise and Less Toxic MDR-TB Treatment Regimen[s]), a randomized, controlled, open label, phase II/III, noninferiority trial evaluating the comparative efficacy and safety of 3 different 24-week all-oral combination regimens for rifampicin (RIF)-resistant TB (RR-TB) (Abstract 79). Adolescents and adults (>15 years of age) with confirmed RR-TB were enrolled in Uzbekistan, Belarus, and South Africa, and were randomly assigned to 1 of 4 treatment arms: (1) bedaquiline (BDQ) 400 mg daily for 2 weeks transitioned to 200 mg thrice-weekly for 22 weeks, plus pretomanid (Pa) 200 mg daily for 24 weeks, plus linezolid 600 mg daily for 16 weeks decreased to 300 mg for 8 weeks (BPaL); (2) BPaL plus clofazimine (CFZ) 100 mg daily for 24 weeks (BPaLC); (3) BPaL plus moxifloxacin 400 mg daily for 24 weeks (BPaLM); or (4) the World Health Organization (WHO) standard of care (SoC) regimen for 36 to 96 weeks (control arm). The primary endpoint was any unfavorable outcome (eg, treatment failure, death, treatment discontinuation, recurrence, loss to follow-up) after 72 weeks, with a noninferiority margin of 12%. Overall, 152 (23% of whom were HIV-positive) participants were randomly assigned to BPaL,

126 (22% of whom were HIV-positive) to BPaLC, 126 (23% of whom were HIV-positive) to BPaLM, and 152 (23% of whom were HIV-positive) to the control regimen, before further randomization stopped after the Data Safety Monitoring Board recommended early termination. For the primary endpoint, BPaLM demonstrated superiority to the control arm in modified intention-to-treat analyses (absolute risk difference [ARD], -37.2%; 95% confidence interval [CI], [-∞]-[-21.6]), as did BPaLC (ARD, -29.7%; 95% CI, [-∞]-[-13.1]), and BPaL (ARD, -25.2%; 95% CI, [-∞]-[-7.7]). However, only BPaLM demonstrated noninferiority to the control arm in perprotocol analyses (ARD, -8.6%; 95% CI, [-∞]-[-4.5]). Grade 3 or greater serious adverse events were common among participants but less frequent in the BPaLM (19.4%), BPaLC (31.9%), and BPaL (21.7%) arms, than in the control arm (58.9%). These highly encouraging results showed that although all 24-week, oral, BPaL-based regimens were efficacious and safe for the treatment of RR-TB, BPaLM was superior to the current SoC with respect to efficacy and safety profile.

BDQ, CFZ, and Pa are each increasingly utilized for the treatment of DR-TB. Although each drug is associated with QT interval prolongation, there are limited data on the combined QT effects when these drugs are used in combination. Abdelwahab and colleagues reported the results of modeling the combined effects on QT interval (QTcF) among 105 patients with drug-susceptible TB enrolled in a 14-day early bactericidal activity study of CFZ, alone or in combination with BDQ or Pa (Abstract 655). QT profile was simulated in 3 scenarios: 1) standard dose BDQ and CFZ as part of a MDR-TB regimen; 2) loading dose of CFZ (300 mg) for 2 with standard BDQ dosing; and 3) standard BDQ dosing with Pa as part of BPaL. Patients receiving BDQ and CFZ as a loading dose had the largest QTcF increases, although the effects were less than additive, and those receiving BDQ with Pa had only

mild QT interval increases. Although these data add to the literature of the relative safety of these drugs as part of combination DR-TB regimens, it is important that cardiac monitoring is undertaken, especially during the early treatment period, to mitigate cardiac arrhythmias due to prolonged QT intervals.

Treatment

Rosuvastatin is a widely available, well-tolerated, and inexpensive cholesterol-lowering medication that has previously shown promise as a potential adjunctive therapy for TB. Cross and colleagues undertook a randomized, controlled, multicountry trial among persons with confirmed RIF-susceptible TB, to determine if rosuvastatin 10 mg daily when given in conjunction with standard anti-TB therapy (intervention) was safe and associated with faster times to sputum culture conversion compared with standard TB therapy alone (control) (Abstract 76). Among 135 participants (4% of whom had HIV coinfection), the primary endpoint, time to liquid culture conversion of sputum within 8 weeks of randomization, did not differ between the rosuvastatin and control groups (42 days [95% CI, 35-49] vs 42 days [95% CI, 36-53], respectively; hazard ratio [HR], 1.30 [95% CI, 0.88-1.91]; *P*=.188). Grade 3 or 4 adverse events did not differ between groups (5 in the intervention arm vs 4 in the control arm). This study did not show a clear benefit for adding rosuvastatin to standard TB therapy.

Dorman and colleagues previously published the exciting results of the ACTG (AIDS Clinical Trial Group) A5349 TB treatment shortening study, demonstrating that a 4-month daily regimen of high-dose rifapentine (RPT), moxifloxacin, isoniazid (INH), and pyrazinamide (PZA) (HPZM), but not a 4-month daily

regimen of high-dose RPT, INH, PZA, and ethambutol (HPZE), was noninferior to the SoC 6-month TB regimen (2 months RIF/INH/PZA/EMB then 4 months of RIF/INH).[1] Chang and colleagues undertook a patient-level pooled analysis of the A5349 study to identify different patient risk groups that might be successfully treated with the HPZE regimen (Abstract 661). Among 2343 patients with drug-susceptible TB, the strongest predictors for poor outcomes and that defined the “high-risk” group included high disease burden (e.g., Xpert *Mycobacterium* tuberculosis [Mtb]/RIF cycle threshold <18, or >50% involvement of chest X-ray) and the presence of HIV or diabetes. In low- and moderate-risk groups (74% of all participants), HPZE was noninferior to both HPZM and SoC regimens. This post-hoc analysis suggests that individuals with TB and lower disease burden and without HIV or diabetes can potentially be successfully cured with the 4-month HPZE regimen as well as with the 4-month HPZM regimen.

There remains an unmet need to identify nonculture-based biomarkers that can reliably predict TB treatment outcomes. Imperial and colleagues analyzed 55 biomarkers from 628 patients with drug-susceptible TB, collected at several time points before, during, and after TB treatment, to determine which ones had the highest predictive value for TB treatment outcomes (Abstract 649). Biomarker signatures that incorporated week 8 serum amyloid A1 (SAA1) and regulated on activation, normal T cell expressed and secreted (RANTES) predicted week 8 sputum culture conversion (area under the curve [AUC], 0.77-0.79) but not TB recurrence after treatment completion (AUC <0.5). Week 0 and 2 serum neopterin levels, and to a lesser extent lipoarabinomannan levels, were the strongest predictors of TB recurrence following treatment completion. These results suggest

that differential host and pathogen signatures are likely needed to predict discrete TB clinical outcomes.

Prevention

Isoniazid preventive therapy (IPT) is an effective tool for the prevention of TB disease among people with HIV, but uptake remains low in many high TB settings. Kakande and colleagues reported the results of a cluster randomized trial in Uganda evaluating the efficacy of a unique approach to increase IPT uptake among people with HIV (Abstract 75). The trial randomly assigned midlevel health managers, who oversee health service delivery at the district level to large populations, to a control arm (39 districts) or a novel strategy (43 districts) consisting of the following: (1) mini-collaboratives facilitated by Ugandan TB/HIV experts, (2) business leadership/management training for managers, (3) SMS platform access to improve communication, and (4) data feedback via dashboards. Overall, the IPT initiation rate was 0.74 starts per person-year and 0.65 starts per person-year in the intervention and control arms, respectively (incidence rate ratio [IRR], 1.14; 95% CI, 0.88-1.46; *P*=.16). However, after accounting for secular trends, the IPT initiation rate was 0.32 starts per person-year and 0.25 starts per person-year in the intervention and control arms, respectively (IRR, 1.27; 95% CI, 1.00-1.61; *P*=.03). Mixed methods research found greater IPT-specific knowledge among district managers and improved interdistrict collaboration and communication in the intervention clusters. Despite not finding higher IPT rates in the primary endpoint analysis, this study demonstrates that targeted leadership and management training for midlevel health managers represents a promising approach for

facilitating the scale-up of recommended evidence-based practices in resource-limited settings.

Four weeks of daily INH and RPT (1HP) is a highly efficacious and patient-centered option for the treatment of latent TB infection (LTBI); however, its safety in persons with HIV taking dolutegravir (DTG)-containing antiretroviral therapy (ART) is unknown. Podany and colleagues presented an interim analysis of the A5372 study (Abstract 78), a multisite pharmacokinetic (PK) study that enrolled virally suppressed adults on a DTG-based regimen to measure DTG trough concentrations during coadministration with 1HP. Twenty-five participants underwent PK sampling, and DTG dosing was increased to 50 mg twice daily during 1HP coadministration. The median DTG trough concentration on day 0 (reflecting daily DTG dosing prior to 1HP) was 1745 ng/mL compared with 4454 ng/mL, 2127 ng/mL, 2594 ng/mL, and 2146 ng/mL at days 3, 14, 21, and 28 of 1HP, respectively. No DTG concentrations were observed below the target trough concentration (>158 ng/mL), and no hypersensitivity or serious adverse events were observed. All participants maintained virologic suppression at day 42. Further data will be needed to inform clinical recommendations, including the potential safety of daily DTG dosing, but this small interim study preliminarily supports the efficacy and safety of 1HP with twice daily DTG dosing in persons with HIV.

The safety of weekly INH and RPT for 3 months (3HP) for LTBI in persons with HIV receiving a cobicistat-boosted darunavir (DRV/c)-containing ART regimen has not been evaluated. Brooks and colleagues reported the results of an open label, fixed sequence, 2-period crossover study in healthy adults without HIV to evaluate DRV PK parameters when DRV/c is coadministered with 3HP (Abstract 431). Participants received DRV/c 800 mg/150 mg daily for 19 days, and 3HP was coadministered on days 5, 12, and

19. Among 13 participants, DRV trough concentrations (predose plasma concentration [C_{0h}] geometric mean ratio [GMR], 0.04:0.19), 24 hours postdose concentration ([C_{24h}] GMR, 0.04:0.11), and concentration over 24 hours ([AUC_{0-24h}] GMR, 0.29:0.64) were substantially lower when 3HP was given 48 to 72 hours before and concurrent with DRV/c, respectively. Given significantly lower DRV concentrations, 3HP should not be given as LTBI therapy in patients with HIV on DRV/c-based ART regimens.

Although unhealthy alcohol use is associated TB disease progression and reduced ART adherence, its effects on IPT adherence have not been well documented. Muyindike and colleagues undertook an observational study among persons with HIV in Uganda receiving daily IPT for 9 months to evaluate the association between alcohol use and IPT adherence (Abstract 653). Of 279 participants receiving IPT for 3 or more months, 21.9% and 50.5% were classified as having moderate and unhealthy alcohol use, respectively. Suboptimal IPT adherence at 3 months (31.3%) and 6 months (43.9%) was common and was independently associated with moderate alcohol use (adjusted odds ratio [aOR], 1.59; 95% CI, 0.94-2.71) and unhealthy alcohol use (aOR, 2.78; 95% CI, 1.62-4.76) compared with abstaining from alcohol. These data suggest that alcohol reduction strategies may be an important facet of larger strategies to improve adherence to TB-preventative therapies among persons with HIV in sub-Saharan Africa.

Women and Children

To mitigate pregnancy-related health risks for women being treated for TB disease, it is crucial that emergency contraception is accessible and safe. Single-dose levonorgestrel

(LNG) 1.5 mg, an emergency contraceptive, is metabolized via cytochrome P450 (CYP) 3A4, and the optimal dose when given with RIF, a potent CYP3A4 inducer, is unknown. Mngqibisa and colleagues reported the results of a multicountry, parallel group, PK trial of premenopausal women comparing LNG concentrations in women with TB (but without HIV) who received a 1-time double dose of LNG (3 mg from the standard 1.5 mg dose) (n=34; RIF group) and women with HIV on DTG-based therapy who also received a single dose of LNG 1.5 mg (n=32; control group) (Abstract 77). Overall, the LNG maximal concentration (C_{max}) was higher in women in the RIF group (GMR, 1.27; 90% CI, 1.09-1.49), whereas AUC over 8 hours (GMR, 1.16; 90% CI, 1.09-1.49) and 24 hours (GMR, 0.96; 90% CI, 0.79-1.17) was similar between groups. Only 3 participants (2 in the RIF group vs 1 in the control group) had grade 2 or 3 LNG-related adverse events. These results show that a double dose of LNG (3 mg x 1) in women receiving RIF for TB treatment was safe and support current recommendations to increase LNG from 1.5 mg to 3 mg in women receiving RIF for whom LNG is indicated.

Even though CFZ is recommended as part of a combination regimen for the treatment of DR-TB among children, limited safety and PK data are available for CFZ in this population. Ali and colleagues reported the results of an observation study among children with HIV and DR-TB being treated with a weight-based CFZ-containing regimen to characterize CFZ PK parameters and assess its potential QT interval prolonging effects (Abstract 656). Among 54 children (65% <5 years old, 9% of whom were HIV-positive), the median predose QTcF was 389 ms (2.5th-97.5th percentile, 331-463); there were 6 QTcF prolonged events greater than 450 ms (all mild-to-moderate), and CFZ concentrations were directly associated with QTcF prolongation. The addition of moxifloxacin to CFZ had modest effects

(approximately 7%) on QTcF when given with CFZ. CFZ C_{max} concentrations in children were frequently higher than simulated concentration in adults; the CFZ clearance rate was nearly 2-times higher among children with HIV (CL/F [%], 1.9; 95% CI, 0.3-5.0), but there were only 5 children with HIV included. The authors concluded that their findings did not support allometric scaling (weight-banded dosing) of CFZ among children, and further studies are needed to determine appropriate weight-based dosing ranges.

Diagnosis of pediatric TB remains challenging, in large part because of the limitations of current diagnostic tools and approaches. LaCourse and colleagues evaluated the performance of a novel TB assay: a clustered regularly interspaced short palindromic repeats (CRISPR)-based assay that detects Mtb-specific multicopy insertion element (IS6110) in cell-free DNA (CRISPR-TB), for diagnosing pediatric TB and monitoring treatment response (Abstract 673). The CRISPR-TB assay was run on cryopreserved sera collected at weeks 0, 2, 4, 12, and 24, from hospitalized, ART-naive children (<12 years of age) with HIV in Kenya who had been intensively investigated for the presence of TB disease. Among 153 children with HIV (median age, 2 years; 68% with severe immunosuppression), CRISPR-TB had a sensitivity of 100% (95% CI, 75-100) and 84.8% (95% CI, 71.1-93.7) for confirmed and clinical TB, respectively. CRISPR-TB detected that Mtb cell-free DNA concentrations declined during therapy and were almost completely cleared after 6 months of anti-TB therapy. CRISPR-TB shows promise for pediatric TB diagnosis and treatment monitoring; however, larger prospective evaluations among diverse populations, including those less ill, are required.

TB Epidemiology

TB notification data and prevalence surveys around the world have demonstrated higher rates of TB among men than among women; however, there are limited data on sex-specific differences for TB in persons with HIV. Chaisson and colleagues conducted a retrospective cohort study of people with HIV in Rio de Janeiro between 2010 and 2016 to evaluate differences in TB incidence rates between men and women (Abstract 657). Of the 54,957 persons with HIV included (65% male; median age, 35 years), TB incidence was higher among men than among women (IRR, 1.24; 95% CI, 1.15-1.34). Sex differences in TB incidence were even more pronounced among those not on ART (IRR, 1.51; 95% CI, 1.33-1.72) and among those with newly diagnosed HIV and CD4+ count less than 350 cells/μL (IRR, 1.68; 95% CI, 1.37-2.04). These data are consistent with prior studies demonstrating a higher TB risk among men and suggest that tailored strategies to improve TB diagnosis and care engagement in men are likely important for TB control efforts.

South Africa has the world's largest HIV-associated TB epidemic. Kubjane and colleagues undertook a modeling study to evaluate the impact of scaling up several TB control interventions in South Africa between 1990 and 2019, including ART, directly observed therapy, IPT, increased TB screening, and Xpert Mtb/RIF (Abstract 659). During the 20-year analysis period, 8.0 million persons developed TB and 2.1 million died from TB, of whom 67.4% and 76.4%, respectively, were persons with HIV. Between 2009 and 2019, TB incidence declined by 35.3%. It was estimated that 25.2% of reductions in adult TB incidence was attributable to ART, 25.0% to TB screening, 1.7% to IPT, 1.4% to directly observed therapy, and 0.2% to Xpert Mtb/RIF. This study demonstrates the public health impact of several interventions on reducing South Africa's TB burden and points to

the need to further increase the availability of and access to these important interventions to further decrease TB incidence, especially ART and TB screening.

Opportunistic Infections

Cryptococcosis

Central nervous system (CNS) infections, especially cryptococcal meningitis (CM), remain an important cause of death in persons with HIV in low- and middle-income counties. Kanyama and colleagues presented an implementation research project that sought to define the epidemiology of HIV-related CNS infections and reduce associated mortality in Tanzania, Malawi, and Cameroon (Abstract 663). The primary intervention was implementation of a diagnostic and treatment algorithm for HIV-related CNS infections. Scale-up was facilitated by a strategy (DREAMM [Epidemiological Findings and Cryptococcal Meningitis Outcomes]) consisting of empowering of local leadership, strengthening health systems, and creating communities of practice. In the preimplementation period, only 10% (n=14/139) of adults with HIV presenting with a suspected CNS infection had a CNS infection microbiologic confirmation. Following implementation of DREAMM, 75% (n=269/356) of such patients had a probable or confirmed CNS infection. CM (55%) and TB meningitis (17%) were the most frequent CNS infections. Overall, all-cause mortality at 2 and 10 weeks was 25% (n=67/264) and 42% (n=110/163), respectively. This study showed that a novel strategy to implement a multifaceted diagnostic intervention was associated with a substantial increase in the microbiologic confirmation of specific HIV-CNS infectious etiologies, of which

CM was highly prevalent. Nonetheless, short-term mortality was extremely high, indicating an urgent need to identify and scale-up effective interventions to reduce mortality due to CNS infections among persons with HIV in low-resource settings.

Lawrence and colleagues recently presented the results of the AMBITION (Ambisome Therapy Induction Optimisation) trial, which demonstrated that for the induction portion of CM treatment in individuals with HIV, a single high dose of liposomal amphotericin B (L-AmB)(10 mg/kg) given with 14 days of flucytosine 100 mg/kg per day and fluconazole 1200 mg per day (L-AmB regimen) was noninferior to and had fewer adverse events than the current WHO-recommended SoC regimen consisting of amphotericin B deoxycholate 1 mg per kg daily for 7 days plus flucytosine 100 mg per kg per day for 7 days followed by fluconazole 1200 mg per day for 7 days.[2] Click or tap here to enter text.However, due to the high cost of L-AmB compared with amphotericin B deoxycholate, Muthoga and colleagues evaluated the cost-effectiveness of scaling up the L-AmB treatment approach in Malawi and 4 additional high–HIV-incidence countries (Abstract 664). Overall, the authors found that the L-AmB regimen had a mean cost of US $1369 (95% CI, 1314-1424) compared with US $1237 (95% CI, 1181-1293) for the SOC regimen. The L-AmB regimen was associated with a mean incremental cost-effectiveness ratio of US $128 (95% CI, 53-257) per life-year saved, which was estimated to be even lower under real-world implementation settings ($80 [95% CI, 15-275] per life-year saved); this was similar across all 5 countries. These results demonstrate that the L-AmB regimen is an effective and cost-effective therapeutic option for CM in patients with HIV in sub-Saharan Africa compared with the current SoC regimen.

Talaromycosis

Talaromycosis remains an important opportunistic infection among persons with HIV in Southeast Asia, for which L-AmB is recommended for the initial induction phase of therapy. However, because L-AmB is poorly tolerated by many patients and is often unavailable in resource-limited settings, Chen and colleagues evaluated the comparative efficacy and safety of voriconazole versus amphotericin B deoxycholate (AmB) for induction therapy for talaromycosis among adults with HIV in China (Abstract 74). This open-label, nonrandomized, controlled trial enrolled 359 hospitalized patients with HIV and confirmed talaromycosis; 255 (median CD4+ count, 13 cells/μL) received induction therapy with AmB 0.5 mg per kg to 0.7 mg per kg for 14 days, and 104 (median CD4+ count, 12 cells/μL) received induction therapy with voriconazole 6 mg per kg twice daily for 1 day, then 4 mg per kg twice daily for 3 days, then 200 mg twice daily for 10 days. Mortality at 14 days (adjusted hazard ratio [aHR], 1.90; 95% CI, 0.46-7.78) and 48 weeks (aHR, 1.01; 95% CI, 0.41-2.49) was similar between the voriconazole and AmB arms. Patients in the voriconazole induction arm had lower odds of clinical resolution (aOR, 0.54; 95% CI, 0.34-0.87) and fungal clearance at 14 days (aOR, 0.61; 95% CI, 0.38-0.97) than the AmB arm. Although participants in the AmB arm were more likely to experience severe anemia (hemoglobin<7.4 g/dL) (aOR, 0.51; 95% CI, 0.31-0.83) and severe hypokalemia (potassium level <2.4 mmol/L) (aOR, 0.14; 95% CI, 0.012-1.05), there were no further differences in clinical and laboratory adverse events. This study showed that AmB induction therapy results in more rapid clinical and microbiologic improvement of talaromycosis in patients with advanced HIV/AIDS; however, voriconazole induction therapy was associated with similar mortality rates and should be considered when L-AmB is unavailable or cannot be feasibility given.

Kaposi Sarcoma Herpesvirus and Human Papilloma Virus

Kaposi Sarcoma Herpesvirus

Little is known about the characteristics, treatment, and outcomes of persons who require admission to the intensive care unit (ICU) with Kaposi sarcoma herpesvirus (KSHV)-associated disorders (KAD, which include Kaposi sarcoma, KSHV inflammatory cytokine syndrome [KICS], primary effusion lymphoma [PEL], and multicentric Castleman disease). Hansen and colleagues presented the results of a retrospective observational study of these patients at a single US center between 2010 and 2021 (Abstract 571). There were 47 patients identified with KAD who required ICU admission during the defined study period of whom 46 had HIV. Among the patients with HIV, 94% were on ART, the median CD4+ count was 88 cells/μL (interquartile range [IQR], 39-223), and the median HIV RNA level was 23 copies/mL (IQR, 20-95); 38 patients had 2 or more KADs (n=19 had Kaposi sarcoma and KICS) and 21 (45%) received KAD-directed chemotherapy in the ICU. Sixty-day survival was 83%, and the median overall survival duration was 9 months. Patients with PEL or KICS had a substantially higher risk of death (HR, 5.0; 95% CI, 1.5-17.2), and those who received chemotherapy during their admission did not (HR, 1.5; 95% CI, 0.7-3.3). Severe KAD largely occurred among persons with advanced HIV who were suppressed on ART, adding to existing literature showing that KICS and PEL each have a poor prognosis.

Human Papilloma Virus

One of the most highly anticipated presentations at this year's Conference on Retroviruses and Opportunistic Infections (CROI) was the ANCHOR (Anal Cancer/HSIL Outcomes Research) study, which was presented by Palefsky and colleagues in a special session and followed by a panel discussion (Abstract 106). Persons with HIV, especially men who have sex with men, are at substantially increased risk for the development of anal cancer, a complication of human papilloma virus infection. Anal and cervical cancers are similar diseases, and both are preceded by high-grade squamous intraepithelial lesions (HSILs). Although regular screening for and early treatment of cervical HSIL is widely known to prevent cervical cancer, there is, to date, a lack of evidence to suggest that a similar approach for anal cancer is effective. To address this important gap in clinical understanding, the ANCHOR study, a randomized, controlled trial, was undertaken to determine the efficacy of HSIL treatment in reducing the incidence of anal cancer compared with active monitoring. Persons with HIV aged 35 years and older were recruited from sites throughout the United States and screened for the presence of HSIL. Those with biopsy-proven HSIL were enrolled and randomly assigned (stratified according to study site, CD4+ cell count nadir, and perianal/anal canal lesion size) to treatment or to active monitoring. Persons in the treatment arm received immediate treatment of HSIL with one of several modalities according to clinician recommendation (eg, electrocautery ablation, infrared coagulation, topical fluorouracil, topical imiquimod), followed and rescreened for HSIL at least every 6 months (anal cytology, high-resolution anoscopy [HRA]), and retreated if persistent HSIL was identified on biopsy. Persons in the active monitoring arm were also seen every 6 months for anal cytology, swabs, and HRA, and had an annual biopsy to confirm the continued presence of HSIL. The

primary study endpoint was time to incident anal cancer. There were 10,723 persons with HIV screened for HSIL before the study was stopped early for efficacy, of which 52% had biopsy-proven HSIL (53% in men, 46% in women, 63% in transgender persons) and 17 had prevalent anal cancer (prevalence, 160/100,000 person-years). Investigators randomly assigned 4446 people with HIV 1:1 to the treatment arm (n=2227) or to active monitoring (n=2219). Baseline demographics and characteristics (median age, 51 years, 81% male, 51% with CD4+ count <200 cells/μL, approximately 90% with HIV-RNA <200 copies/mL) and median follow-up time were similar between arms. The proportion with a large anal/perianal lesion at baseline (13%) was also similar between arms. Ultimately, 30 cases of anal cancer were diagnosed during the follow-up period, 9 in the treatment arm (173/100,000 person-years) versus 21 (402/100,000 persons-years) in the active monitoring arm (57% reduction; 95% CI, 6%-80%; *P*=.029). Adverse events were uncommon; there were 43 study-related adverse events in the treatment arm, including 7 serious adverse events, and 4 and 1, respectively, in the active monitoring arm. No study-related deaths occurred. This practice-changing study clearly demonstrates anal HSIL is highly prevalent in men, women, and transgender persons with HIV, and that early treatment of anal HSIL is effective in preventing anal cancer among persons with HIV. It should therefore be considered SoC. The next step will be to optimize implementation strategies in clinical settings.

Abstracts cited in the text appear in the virtual CROI 2022 Abstract eBook, available online at www.CROIconference.org.

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Additional References Cited in Text

1. Dorman SE, Nahid P, Kurbatova EV, et al. Four-month rifapentine regimens with or without moxifloxacin for tuberculosis. *N Engl J Med.* 2021;384(18):1705-1718.
Ref ID: 17055

2. Lawrence DS, et al. Single high-dose liposomal amphotericin based regimen for treament of HIV-associated cryptococcal menigitis: results of the phase-3 ambition-cm randomised trial. Poster presented at: 11th IAS Conference on HIV Science; July 18-21, 2021.
Ref ID: 17056