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Invited Review

CROI 2025: Tuberculosis, Mpox, and Other Infectious Complications in People With HIV

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Abstract: *Updated strategies and new insights into tuberculosis and mpox treatment were a major focus at the 2025 Conference on Retroviruses and Opportunistic Infections, headlined by findings that high-dose rifampicin plus levofloxacin increased early mortality in hospitalized people with HIV with disseminated tuberculosis, whereas tecovirimat demonstrated no efficacy for clade II mpox. Herein, we summarize clinically relevant updates related to tuberculosis, mpox, Kaposi sarcoma, human papillomavirus, and other HIV-associated infectious complications presented at the conference.*

Keywords: coinfection, CROI, HIV, HPV, human papillomavirus Kaposi sarcoma, mpox, opportunistic infection, tuberculosis

Tuberculosis

Treatment

There remains an ongoing need to improve tuberculosis (TB) treatment outcomes, particularly for people with HIV (PWH) who have disseminated TB and high early mortality. Meintjes and colleagues (Abstract 114) presented the results of the NEW STRAT-TB (Testing New Strategies for Patients Hospitalised With HIV-Associated Disseminated Tuberculosis) trial, a 2×2 factorial randomized clinical trial at 3 hospitals in Cape Town, South Africa, evaluating intensified TB treatment (standard TB treatment with rifampicin [RIF] dose increased to 35 mg/kg/d plus levofloxacin) vs standard TB treatment, and prednisone (1.5 mg/kg/d) vs placebo in hospitalized adults with HIV-associated disseminated TB. Inclusion was limited to those aged 18 years and older, with confirmed TB and evidence of disseminated TB detected by urine lipoarabinomannan (LAM) antigen test or Xpert or blood Xpert assay (Cepheid, Inc). Among 563 participants in the modified intention-to-treat population (median CD4+ count, 42 cells/µL; 10% had an HIV RNA level <50 copies/mL), 14-day mortality was significantly higher in the intensified arm than in the standard arm (10.9% vs 5.0%; difference, 5.9%; 95% CI, 1.5–10.3; *P* = .008), prompting the data safety and monitoring board to stop the intervention arm early. By 12 weeks, this difference was no longer statistically significant (19.8% vs 15.4%; difference, 4.4%; 95% CI, -2.0 to 10.4; *P* = .18). Grade 3 or 4 adverse events (AEs), including hepatotoxicity, were similar between arms. The reasons for higher early mortality remain unclear, but the authors speculate that the increased bactericidal action of the intensified regimen may have triggered an overly robust inflammatory reaction, or greater induction of prednisone metabolism with high-dose RIF, and further work to investigate the drivers of this effect is ongoing. These findings suggest that intensified TB treatment should be avoided in critically ill patients with HIV and disseminated TB, contrasting with prior trials of higher-dose rifamycins that demonstrated safety and potential clinical benefit in ambulatory patients with pulmonary TB. Enrollment into the prednisone vs placebo arms is ongoing and will also provide key insights for clinical management in this population at high risk for death.

High-dose rifampicin with levofloxacin and standard TB treatment increased mortality in hospitalized PWH with disseminated TB

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Higher doses of RIF are increasingly being used for the treatment of pulmonary TB, although it is unknown whether increased RIF doses reduce dolutegravir (DTG) levels further due to greater induction of the UGT1A1 drug transporter. Singh and colleagues (Abstract 645) conducted the DoRIS (Drug Interactions Between Dolutegravir and Escalating Doses of Rifampicin) study, an open-label, fixed-sequence, 4-phase pharmacokinetic study to evaluate the effects of escalating RIF doses on DTG among people without HIV (PWoH) with TB from South Africa and Uganda nearing the end of the continuation phase of TB treatment. The study enrolled 36 participants and compared DTG (50 mg BID for 1 week) exposure when dosed with RIF at standard (10 mg/kg; day 14), medium (20 mg/kg; day 28), and high (35 mg/kg; day 42) doses, as well as 4 or more weeks post TB treatment (DTG daily). RIF exposure increased supraproportionally with dose, with geometric mean ratio (GMR) of the area under the curve $(AUC)_{0\text{-}12}$ increasing 3.7-fold at 20 mg/kg and 5.9-fold at 35 mg/kg compared with 10 mg/kg. Compared with daily DTG at 5 weeks after TB treatment, DTG (dosed BID) maximum concentration (C_{max}) and $AUC_{0\text{-}12}$ were significantly lower with standard-dose RIF on day 14: 0.55 (95% CI, 0.49-0.64) and 0.70 (95% CI, 0.63-0.78), medium-dose RIF on day 28: 0.59 (95% CI, 0.52-0.67) and 0.71 (95% CI, 0.64-0.80), and high-dose RIF on day 42: 0.57 (95% CI, 0.51-0.65) and 0.72 (95% CI, 0.64-0.80). Despite this, geometric mean DTG trough concentrations (C_{tau}) remained consistent across all RIF dose groups (665, 660, 657 ng/mL vs 687 ng/mL post treatment), with a high proportion of measurements (79%, 88%, 90% vs 83% post treatment) remaining above the DTG EC_{90} (the concentration to achieve 90% of the maximum effect) (342 ng/mL) regardless of RIF dose. These findings suggest that maximum enzyme induction occurs at the standard 10 mg/kg RIF dose and that further DTG dose adjustments beyond twice daily (BID) are not necessary when coadministered with higher RIF doses for TB treatment.

Tenofovir alafenamide (TAF), commonly used in modern antiretroviral therapy (ART) regimens, is a substrate of drug transporters that are induced by RIF, making it potentially more prone to drug–drug interactions than tenofovir disoproxil fumarate (TDF). Although studies in healthy volunteers suggest that TAF can still achieve adequate intracellular levels when coadministered with RIF, this has not been evaluated in PWH. Two studies presented at this year's CROI aimed to address this important evidence gap. Osuala and colleagues (Abstract 647) conducted a pharmacokinetic (PK) substudy of the INSIGHT (InSTIs For the Management of HIV-Associated TB) trial evaluating TAF with RIF in PWH and TB who received bictegravir (BIC)/emtricitabine (FTC)/TAF BID until 2 weeks post TB treatment and once daily (QD) thereafter. Tenofovir (TFV) and intracellular TFV-diphosphate (TFV-DF) levels were quantified from plasma and dried blood spots (DBSs) of intensive sampling at weeks 4 and 12 during TB treatment and week 32 post TB treatment. Among 43 participants, the geometric least square mean ratio (GLSMR) for $AUC_{0\text{-}24}$ was 1.28 (90% CI, 1.10-1.50) and 1.24 (90% CI, 1.06-1.45) at weeks 4 and 12 (TAF BID with RIF) relative to week 32 (QD TAF without RIF); similarly, GLSMR for TFV-DP at weeks 4 and 12 relative to week 32 was 1.33 (90% CI, 1.17-1.52) and 1.62 (90% CI, 1.42-1.86), respectively. Notably, 95% of participants were virally suppressed at week 24 (end of TB treatment) and no BIC/TAF/FTC adverse drug reactions were reported.

In an open-label, 3-period sequential PK study, Ngara and colleagues (Abstract 646) evaluated standard-dose TAF (25 mg) in PWH with viral suppression who were in the maintenance phase of treatment (RIF/isoniazid [INH]) with drug-susceptible TB. Participants had TFV-DP and plasma TFV concentrations measured during 3 treatment periods: (1) TDF 300 mg daily with RIF; (2) TAF 25 mg daily with RIF; and (3) TDF alone, 1 month after TB treatment completion. Among 18 participants, TAF+RIF was associated with significantly higher intracellular TFV-DP concentrations than TDF+RIF (GMR, 5.58; 95% CI, 4.34-7.17) and TDF alone (GMR, 5.43; 95% CI, 3.90-7.55). Plasma TFV concentrations were significantly lower with TAF+RIF than with TDF with or without RIF (GMR, 0.07; 95% CI, 0.06-0.09). There were no serious AEs or study discontinuations. These complementary findings suggest that TAF-containing regimens can achieve adequate drug exposure despite RIF coadministration and support current Department of Health and Human Services guidance to use such regimens with caution when alternatives are not available. BIC/TAF/FTC BID dosing data were encouraging in this PK study,

> ***TAF-containing regimens can achieve adequate drug exposure despite RIF coadministration and support current guidance to use such regimens with caution when alternatives are not available***

but it cannot yet be recommended in this setting due to limited safety and efficacy data.

Rifapentine (RPT) is being studied for use in shorter TB treatment regimens, and in Study 31/A5349 (Rifapentine-Containing Treatment-Shortening Regimens for Pulmonary Tuberculosis), which compared two 4-month RPT-containing regimens (with and without moxifloxacin [MXF]) with standard 6-month therapy (RIF, INH, ethambutol, and ethionamide), RPT exposure was a key determinant of treatment outcomes. Hypothesizing that host genetics strongly contributed to the large interindividual variability in RPT and its metabolite (des-RPT) clearance, Liu and colleagues (Abstract 958) conducted a pharmacogenomic analysis of participants from Study 31/A5349. Using low-coverage whole-genome sequence data from 1094 participants (6.5% PWH) receiving daily RPT 1200 mg, they found the AADAC rs1803155 G allele was significantly associated with increased RPT clearance ($P = 1.1^{-11}$), with stronger associations in participants receiving concomitant MFX ($P = 1.1^{-9}$ with vs $P = 4.3^{-4}$ without MFX). PK modeling showed that RPT clearance increased by 0.266 L/h in GG and by 0.059 L/h in AG genotypes compared with AA. Additionally, UGT1A1 rs887829 was associated with RPT and with des-RPT clearance at genome-wide significance ($P = 6.3^{-19}$ and $P = 3.7^{-26}$), but in PK modeling it only impacted des-RPT clearance. These findings help explain interindividual variability in RPT PK and point to a potential role for host genetics in informing future evaluation of RPT-containing regimens, especially when combined with other metabolically active agents like MFX.

DTG and BIC, although highly effective for HIV treatment, are rarely associated with neuropsychiatric symptoms, and it is unknown whether the BID (from daily) dose required with concomitant RIF among patients receiving TB treatment increases the likelihood of such adverse effects. Naidoo and colleagues (Abstract 187) conducted a secondary analysis of the INSIGHT study to evaluate neuropsychiatric outcomes in PWH with TB receiving either BID BIC/FTC/TAF (BIC arm; n = 80) or DTG/lamivudine (3TC)/TFV (DTG arm; n=42) during TB treatment. Participants (60% with, <200 cells/µL) underwent regular neuropsychiatric assessments using standardized screening tools for anxiety, depression, and sleep disorders. Anxiety was observed in 2% in the BIC arm vs 7% in the DTG arm, depression occurred in 12% vs 17%, respectively, and sleep disruption occurred in 59% vs 74%, respectively; these did not differ meaningfully from baseline assessments with daily DTG and BIC dosing. Only 1 event of severe depression and anxiety occurred during with DTG BID, with rapid resolution and no events required treatment discontinuation or neuropsychiatry interventions. These data provide reassurance regarding the neuropsychiatric safety profile of double-dosed BIC or DTG when coadministered with RIF-based TB treatment.

Diabetes mellitus (DM) is an important risk factor for TB and is associated with more severe disease and higher mortality. To investigate an unexpectedly lower risk of TB treatment-related adverse drug reactions (ADRs) previously found in persons with uncontrolled DM, Ridolfi and colleagues (Abstract 957) correlated INH plasma concentrations and hemoglobin (Hb) $_{A1}$c levels among an adult cohort of microbiologically confirmed patients in Brazil with pulmonary TB to see whether this was due to lower INH levels. Plasma samples were collected from participants within 8 hours of the previous TB treatment dose at 1 and 2 months. Among 379 participants (median HbA_{1c}, 5.9%), 131 (34%) had normal HbA_{1c} (<5.7%), 154 (41%) had pre-DM (HbA_{1c}, 5.7%-6.49%), and 94 (25%) had DM. Despite participants with DM having higher INH exposure (AUC, 10.0 µg/*h/mL) than those with pre-DM (AUC, 7.6 µg/*h/mL) or normal HbA_{1c} (AUC, 7.0 µg/*h/mL), there was a significant inverse correlation between log-INH concentration and HbA_{1c} category (coefficient, –0.118; $P < .001$), indicating a lower maximal concentration of INH among those with pre-DM and DM. This study suggests that lower INH maximal concentration as HbA_{1c} increases, possibly due to altered drug dynamics, may explain a lower risk of TB treatment ADRs among persons with DM than among those with normoglycemia.

Prevention

For women with HIV, the Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO) recommend daily INH as TB preventive therapy (TPT) to address their high risk of TB; however, the TB APPRISE (Evaluating the Safety of Immediate Versus Deferred Isoniazid Preventive Therapy Among HIV-Infected Pregnant Women) study demonstrated greater adverse pregnancy events with 6 months of daily INH in pregnant vs postpartum women with HIV.[1] The 3HP (12 weeks of once-weekly INH and RPT) and 1HP (1 month of daily INH and RPT regimens are increasingly preferred TB-preventive therapy (TPT) options among nonpregnant patients, but pregnant women were excluded from earlier trials, and thus, the optimal dosing of DTG to maintain HIV viral suppression in pregnant women taking TPT has not been established. Mathad and colleagues (Abstract 116) presented results from

DOLPHIN-Moms (Pharmacokinetics of Dolutegravir and HIV Viral Suppression With 1HP or 3HP in Pregnancy) (NCT95122026), an ongoing open-label phase II trial in South Africa investigating the safety and PKs of DTG in pregnant PWH initiated on either 1HP or 3HP. Pregnant PWH at 20 to 34 weeks' gestation with HIV viral suppression on DTG-based ART were randomly assigned 1:1 to receive 1HP or 3HP, with all participants initiating DTG BID before starting TPT. Among 50 pregnant PWH (median age, 33 years; mean gestational age, 26.8 weeks; mean CD4+ count, 696 cells/µL), there were no significant differences in median DTG trough levels between 1HP and 3HP (2730 ng/mL vs 2890 ng/mL; $P = .91$) on day 1. However, by day 17 of TPT, median DTG troughs were significantly lower in the 1HP arm than in the 3HP arm (871 ng/mL vs 1890 ng/mL; $P < .01$). One participant per arm had DTG trough levels below 64 ng/mL (protein-adjusted 90% inhibition concentration), both with documented nonadherence. Simulations of QD DTG (excluding the 2 nonadherent participants) predicted median DTG trough levels of 88 ng/mL (5^{th}–95^{th} percentiles, 28–212) with 1HP, which was below the acceptable level (ie, 5^{th} percentile DTG troughs >158 ng/mL) and 436 ng/mL (5^{th}–95^{th} percentiles, 209–781) with 3HP, which was above acceptable targets. These findings suggest that in pregnant PWH, 1HP or 3HP administered with BID DTG yield therapeutic DTG troughs among adherent participants. Although these data suggest that QD DTG dosing will not achieve target DTG concentrations when administered with 1HP and should be avoided, the next phase of the trial (ongoing) will confirm PK and virologic outcomes of QD DTG with 3HP in pregnant PWH.

INH-induced hepatotoxicity remains a substantial concern in TB prevention and treatment, particularly among those with a slow acetylator phenotype. Hiranpuram and colleagues (Abstract 956) conducted a prospective cohort study to explore the relationship between N-acetyltransferase 2 (NAT2) genotypes and hepatotoxicity risk among Thai PWH receiving INH-containing treatment or TBT regimens. Participants had genotyping performed for 6 NAT2 single-nucleotide polymorphisms and hepatotoxicity (≥ grade 2: aspartate transaminase and alanine transaminase levels >2.5-times the upper limit of normal) assessed by NAT2 phenotype (slow, intermediate, or rapid acetylator) and genotype. The study enrolled 500 PWH (median CD4+ count, 335 cells/µL) receiving either INH with RPT (1HP/3HP) for TB preventive therapy (88%) or INH, RIF, pyrazinamide, and ethambutol (HRZE) for active TB treatment (12%). Hepatotoxicity occurred in 53 participants (10.6%) overall and was strongly associated with acetylator phenotype: 16.6% of slow, 11.0% of intermediate, and 5.4% of rapid acetylators ($P < .001$). Compared with participants with the rapid acetylator phenotype, those with slow (adjusted odds ratio [aOR], 3.7; 95% CI, 1.6-8.7) and intermediate phenotypes (aOR, 2.5; 95% CI, 1.1-6.2) had an independently higher hepatotoxicity risk after adjusting for relevant confounders. The NAT2 **6A/*6A* genotype (n = 88; 18%) was strongly associated with greater hepatotoxicity risk (aOR, 2.6; 95% CI, 1.3-5.5), whereas the wild-type, fast acetylator genotype NAT2 **4/*4* (n = 120; 24%) was associated with lower hepatotoxicity risk (aOR, 0.14; 95% CI, 0.03-0.6). These findings provide further evidence that NAT2 genotype is an important predictor of INH-related hepatotoxicity in PWH.

High-risk alcohol use is associated with increased risk for active TB, but the incidence of TB after TPT and how this differs by degree of alcohol use is unclear. To address this question, Hahn and colleagues (Abstract 968) reviewed clinic records of PWH in Uganda with prior positive TST result who had received 6 months of TPT. High-risk alcohol use was defined as Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) score of 6 or higher or phosphatidylethanol (PEth) level of 200 ng/mL or higher. Among 968 participants (median CD4+ count, 627 cells/µL) with 3229 person-years of follow-up, there were 21 confirmed TB cases (0.65%/person-year). After adjusting for confounders, high-risk alcohol use was associated with a 3.74 (95% CI, 1.29-10.79) increased hazard of TB, and cigarette smoking (adjusted hazard ratio [aHR], 2.42; 95% CI, 0.99-5.92) and HIV nonsuppression (aHR, 5.58; 95% CI, 1.64-18.98) were also independently associated. These findings suggest ongoing TB acquisition or reactivation after TPT among PWH with high-risk alcohol use, highlighting the need for comprehensive strategies that integrate TB prevention with alcohol use reduction in this population.

Four months of RIF is a recommended short-course TPT regimen; however, drug-drug interactions (DDIs) may limit uptake and use in patients taking concomitant essential medications. Fraegonese and colleagues (Abstract 969) conducted a posthoc analysis of the 2R2 (Higher Dose Rifampin for 2 Months vs Standard Dose Rifampin for Latent TB) trial in which participants in Canada, Vietnam, and Indonesia were randomly assigned to receive 1 of 3 RIF-based TPT regimens (RIF 10 mg/kg daily for 4 months, 20 mg/kg daily for 2 months, or 30 mg/kg daily for 2 months) to assess the safety and completion of rifampin-based TPT among persons taking medications with potential DDIs. Among 1368 participants, 282 (20.6%) were classified as taking at least 1 "essential" concomitant medication (commonly amlodipine, statins, and TFV or efavirenz) with a possible RIF interaction. TPT completion did not differ significantly between the DDI and non-DDI groups (70% vs 73%; risk difference [RD], 0.04; 95% CI, –0.02 to 0.09). Protocol-defined AEs leading to permanent discontinuation occurred in 9.9% of the DDI group vs 5.6% of the non-DDI group (RD, 0.02; 95% CI, –0.01 to 0.06), and participants in the DDI group were more likely to have 2 or more additional unscheduled visits (12% vs 5%; *P* < .001). These findings suggest that, with close clinical monitoring, RIF-based TPT can be safely completed by most individuals taking essential medications with potential DDIs; however, despite a longer duration, INH-based TPT may still be preferable for many due to fewer DDI risks and greater ease of management.

Untreated latent TB is the main driver of new TB cases in the US, making appropriate testing of high-risk individuals essential for TB elimination

Untreated TB infection (LTBI) is the main driver of new TB cases in the US, making appropriate testing of high-risk individuals essential for TB elimination. Kluesner and colleagues (Abstract 967) conducted a serial cross-sectional study using electronic health record data from 2008 to 2023 to evaluate LTBI testing practices (either a tuberculin skin test [TST] or interferon-gamma release assay) and alignment with current policy among 6.6 million adults enrolled in Kaiser Permanente Northern California. Overall, 1.4 million (21%) of all members were tested, and there was little change in testing rates over time. Strikingly, 79% of testing occurred among individuals with no TB risk factors. Persons born in TB-endemic countries, who account for 82% of TB cases in California, had a 25.2% lower prevalence of LTBI testing (adjusted prevalence ratio [aPR], 0.75; 95% CI, 0.74–0.75) than US-born individuals. In contrast, those with risk factors such as HIV (aPR, 3.58; 95% CI, 3.53–3.63) or a TB contact (aPR, 2.67; 95% CI, 2.63–2.71), and those who were unhoused (aPR, 1.30; 95% CI, 1.27–1.32) were more likely to be tested. These findings highlight persistent gaps in guideline-concordant LTBI testing in California, particularly among the population at the highest risk for TB.

As summarized in an excellent symposium by Nueremberger (Abstract 36), long-acting (LA), injectable TPT formulations are in early phase development and may offer a compelling alternative to current oral therapies by improving treatment completion and outcomes. To assess the potential acceptability of LA-TPT, Vermeulen and colleagues (Abstract 971) conducted a cross-sectional survey of patient and practitioner preferences and concerns. The researchers surveyed 409 patients from India and South Africa (26% with prior TPT) and 94 health care practitioners from 25 low- and middle-income countries. Injectable TPT was the most preferred modality among patients (68% vs 19% for pills), and 75% expressed strong willingness to try it; this was driven by perceived ease of administration and perceived efficacy compared with pills. Practitioner preferences aligned with those of patients, with 43% favoring injectables vs 26% for pills, and 75% indicating a willingness to prescribe. However, concerns around potential cost, AEs, and implementation feasibility were also reported. These findings suggest that LA-TPT would be highly acceptable to patients and practitioners if concerns of cost and safety barriers can be addressed.

Transmission

Understanding where and by whom transmission occurs is crucial for developing effective TB control strategies. Gandhi and colleagues (Abstract 115) conducted a prospective study combining genomic, social network, and geospatial analyses to evaluate the role of casual contact in drug-resistant TB transmission in South Africa and identify locations where transmission occurs. The study enrolled 305 (80%) of the 383 total patients diagnosed with extensively or preextensively drug-resistant TB between 2019 and 2022, with median age of 36 years (IQR, 30-44 years), 45% female, and 73% PWH (median CD4+ count, 405 cells/µL). Of the 253 (83%) participants with sequenced TB isolates, 141 (56%) were genomically clustered (≤12 SNP difference). Participants were interviewed about locations visited regularly (>2 hours most weeks) in the 2 years before TB diagnosis, including homes, hospitals, clinics, and community locations, with global positioning system coordinates collected at all sites. Notably, only 13 (9%) genomically clustered participants were linked by a close contact (person-to-person link or overlapping hospitalization), and an additional 81 (57%) were linked through casual contact (co-named clinics, community locations, or proximate home or community locations ≤500 meters of each other), and 47 (33%) had no identifiable epidemiologic link. Of casual contacts, 56 (40%) were the same-named clinics, 39 (28%) were proximate locations, and 10 (7%) were the same-named community location. In this study, close contact explained only 1 in 10 links between TB cases, and casual contact in community locations, explained most of the potential transmissions; these findings provide additional evidence that challenge the historic paradigm that TB transmission primarily occurs through close, prolonged contact. They suggest that TB control strategies need to expand beyond household contact tracing to address transmission in community settings such as clinics and other public spaces.

In high TB burden settings, casual, not close contact accounts for most TB transmissions

Diagnosis

LTBI testing is an important step toward initiation of TPT, but current interferon gamma release assay (IGRA) tests require advanced laboratory capabilities, highlighting a need for simplified LTBI tests in resource-limited settings. Nguyen and colleagues (Abstract 964) conducted a cross-sectional diagnostic accuracy study comparing the standard F TB-Feron fluorescent immunoassay (TB-Feron), a simplified IGRA requiring less specialized processing, with QuantiFERON-TB Gold Plus (QFT-Plus). Blood samples were tested with both assays, with QFT-Plus serving as the reference standard. The study enrolled 345 participants across 3 groups: microbiologically confirmed patients with TB (n = 95), household contacts of patients with TB (n = 200), and individuals with recent negative IGRA tests and no known TB exposure (n = 50). Overall, TB-Feron had high sensitivity (90.2%; 95% CI, 84.5-94.3) but moderate specificity (73.9%; 95% CI, 66.7-80.2). Among confirmed TB patients, sensitivity was 88.4% (95% CI, 80.2-94.1), among household contacts, sensitivity and specificity were 89.2% (95% CI, 79.8-95.2) and 75.4% (95% CI, 66.9-82.6), respectively, and in persons without known TB exposure specificity was 70.0% (95% CI, 55.4-82.1). The concordance between TB-Feron and QFT-Plus was 81% (Cohen's κ, 0.62; $P < .001$). TB-Feron shows promise as a near-point-of-care LTBI test, but the performance of the current version in this clinical study would be insufficient to recommend for implementation.

Point-of-care diagnostics for TB are urgently needed to facilitate rapid diagnosis for people with advanced HIV disease (AHD), particularly those unable to produce sputum. Adzemovic and colleagues (Abstract 965) conducted a prospective diagnostic accuracy study of the FujiLAM II assay, which detects LAM antigen in urine, among outpatients with AHD (CD4+ count <200 cells/µL) in Uganda. Among 617 participants, FujiLAM II demonstrated moderate sensitivity (54%; 95% CI, 40-69) and high specificity (95%; 95% CI, 93-98) for microbiologically confirmed TB (positive sputum Xpert or culture). Sensitivity was substantially higher among those with CD4+ counts below 100 cells/µL (69%) than those with CD4+ counts of 100 cells/µL or higher (21%), and specificity remained above 94% across subgroups. Despite incomplete sensitivity, FujiLAM II may improve TB yield among persons with AHD; head-to-head comparisons with the currently available, widely implemented point-of-care urine LAM test are needed.

Tongue swabs are a highly promising emerging sample type for TB diagnosis, especially for those unable to produce sputum; however, the performance of and preferences for health care workers (HCWs) vs self-collection are largely unexplored. David and colleagues (Abstract 963) conducted a cross-sectional study in South Africa to assess HCW-collected (HCWC) and self-collected (SC) tongue swabs from the same participants using the Xpert MTB/RIF Ultra assay, alongside participant acceptability. Among 520 participants (47% PWH), compared with a culture-based reference standard (7% prevalence), HCWC and SC tongue swabs had identical sensitivity (68.3%; 95% CI, 51.9-81.9), high specificity (HCWC, 99.4%; SC, 99.8%), and low error rates (HCWC, 3.2%; SC, 3.4%). Most participants (89%) reported comfort with tongue swab collection and confidence in self-collection; 22% preferred SC, 34% preferred HCWC, and 43% had no preference. These findings support tongue swabs as an acceptable specimen type for TB diagnosis, with both self- and HCW-collection offering flexible, person-centered options in those unable to provide sputum.

Current sputum-based TB diagnostics and compartment-specific sampling approaches frequently miss disseminated TB among people with AHD, who are at high risk of mortality. Le Phuong and colleagues (Abstract 966) conducted a prospective study in Vietnam to evaluate the diagnostic and prognostic utility of blood Xpert Ultra and Myco/F Lytic blood culture among adults with AHD hospitalized for any reason. Among 825 participants (median CD4+ count, 18 cells/µL), 28% (n = 239) had microbiologically confirmed TB, including 26.5% (n = 63) diagnosed solely through blood-based testing. Notably, 71.1% (42/59) of these blood-only cases were rapidly identified by Xpert Ultra. Detection of TB in blood (via culture or Xpert) was independently associated with a 2.14-fold increased risk of 24-week mortality (95% CI, 1.09–4.20). These findings build on studies from sub-Saharan Africa and further support the role of blood-based Xpert Ultra testing, where available, to rapidly diagnose disseminated TB and initiate treatment among hospitalized patients with AHD at high risk of poor outcomes.

Community-based TB active case finding (ACF) remains underutilized in high-burden settings, partly due to its low efficiency and the high costs associated with large numbers needed to screen (NNS). To address this, Kerkhoff and colleagues (Abstract 959) conducted a pilot study of a highly targeted TB ACF strategy at social drinking venues in Zambia where individuals with unhealthy alcohol use and greatly elevated TB risk congregate. All participants were tested for TB using sputum Xpert Ultra regardless of symptoms, and those with negative or unknown HIV status were offered HIV testing. Among 440 participants (30.5% with known HIV), 3.3% (95% CI, 1.8–5.9) had newly diagnosed HIV (NNS = 30), and 5.2% (95% CI, 3.5–7.7) had newly diagnosed TB (NNS = 19). Nearly all participants (99.8%) reported they would participate in a similar ACF activity again. These findings demonstrate that a targeted TB-HIV screening strategy at social drinking venues is acceptable, feasible, and highly efficient; evaluation at scale is warranted to assess effectiveness and implementability.

Mpox

Although the number of worldwide cases has decreased, mpox remains a global public health challenge shaped by viral evolution, immunity, and syndemic interactions with HIV. At CROI 2025, investigators presented new data spanning molecular virology, immune response durability, reinfection risk, treatment outcomes, and cost-effectiveness. Together, these studies offer a more nuanced understanding of the shifting clinical and epidemiologic landscape of mpox, while underscoring the urgent need for integrated strategies that reflect both individual- and population-level vulnerabilities.

Syndemic Dynamics, Reinfection, and the Persistent Burden

Several studies presented at CROI 2025 deepened our understanding of the ongoing syndemic of mpox and HIV, highlighting reinfection risk, behavior change over time, long-term consequences, and the partial protection offered by vaccination.

Behavioral risk factors for mpox were explored by Saadeh and colleagues (Abstract 1093), who analyzed sexual behavior patterns among gay, bisexual, and other men who have sex with men (GBMSM) with mpox in California before, during, and after the August 2022 state of emergency (SOE). Rates of group sex, multiple partners, and meeting partners in sex-on-premises venues declined during the SOE and increased again afterward, although they remained below pre-SOE levels. These shifts likely reflect the impact of targeted public health messaging and evolving individual risk perception but also point to continued vulnerability in the face of ongoing community transmission and the need for vaccination.

Findings continue to support the need for integrated HIV, sexually transmitted infection, and mpox services, especially for those with advanced disease or poor care engagement

Silva and colleagues (Abstract 1090) presented data from a large prospective mpox cohort in Brazil, in which 50% of individuals were PWH. Those with HIV had significantly higher rates of fever, proctitis, active syphilis, and hepatitis C virus coinfection, and were more likely to test positive for mpox virus from anorectal specimens. All mpox-related deaths occurred in individuals with CD4+ counts below 350 cells/µL. The findings highlight the layered vulnerabilities faced by PWH, and continue to support the need for integrated HIV, sexually transmitted infection, and mpox services, especially for those with advanced disease or poor care engagement.

Watson and colleagues (Abstract 1092) identified 9 probable or confirmed cases of mpox reinfection in California, representing 0.14% of all reported infections. All individuals were GBMSM, and 4 were PWH.

Whole-genome sequencing confirmed distinct clade IIb lineages in 3 cases, with reinfections occurring 266 to 778 days after initial diagnosis. Although symptoms were not detailed, the authors noted that reinfections may be underrecognized, particularly when mild, an observation consistent with prior literature.

Schäfer and colleagues (Abstract 1095) evaluated mpox severity and viral load in a cohort from Hamburg, Germany, comparing individuals by modified vaccinia Ankara-Bavarian Nordic (MVA-BN) vaccine status and HIV infection. Complete and incomplete vaccination regimens were associated with significantly lower mpox severity scores and reduced rates of systemic symptoms like fever and headache. However, polymerase chain reaction (PCR) cycle threshold values, used as a proxy for viral load, did not differ by vaccine status or HIV serostatus. These findings suggest that MVA-BN vaccination reduces symptom severity but may not substantially impact viral shedding.

The morbidity of mpox infection extends beyond acute illness, as demonstrated by Bulnes and colleagues (Abstract 1094), who conducted a longitudinal follow-up of 64 individuals from 2 tertiary care centers approximately 20 months after infection. A total of 15.6% reported persistent symptoms such as fatigue, and more than 45% experienced work or school absenteeism, highlighting the socioeconomic impact of mpox. Nearly half had persistent scarring, and 18.6% experienced severe scarring as measured by a Dermatology Life Quality Index above 10. Scarring severity was associated with HIV viremia, CD4+ count below 200 cells/μL, hospitalization, and Black race, reflecting intersections between clinical immunocompromise and structural inequities. Together, these findings underscore that mpox is not solely a viral outbreak but part of a syndemic shaped by overlapping biologic, social, and structural drivers. Addressing its long-term impact will require coordinated public health strategies that expand vaccination, integration of HIV and sexually transmitted infection services, and support for surveillance in vulnerable populations.

Mpox is not solely a viral outbreak but part of a syndemic shaped by overlapping biologic, social, and structural drivers

Clade Ib Emergence and Mpox Spread in Uganda

Two oral presentations from Uganda provided a detailed view of the country's 2024 mpox outbreak, highlighting the cross-border origins and widespread domestic dissemination of clade Ib mpox virus. These findings serve as a stark reminder of the substantial, ongoing outbreak in Africa that contributed to the WHO declaration of mpox as a Public Health Emergency of International Concern.

Bbosa and colleagues (Abstract 131) from Uganda described enhanced genomic surveillance following the country's first confirmed mpox cases in July 2024. Of 597 suspected cases, 24 tested positive by PCR, and whole-genome sequencing of 8 samples yielded above 99% coverage. Phylogenetic analysis demonstrated close genetic relatedness to clade Ib mpox virus strains from recent South Kivu outbreaks in the neighboring Democratic Republic of Congo (DRC), suggesting regional cross-border spillover. Notably, metagenomic sequencing of PCR-negative cases identified varicella-zoster virus (VZV) as a frequent cause of rash illness, highlighting the diagnostic overlap between mpox and other viral infections, and the challenges of syndromic surveillance in the absence of widespread diagnostic testing.

Namusoosa and colleagues (Abstract 132) reported a national epidemiologic assessment of mpox cases in Uganda from July to October 2024. Specimens from 1991 suspected mpox cases underwent diagnostic testing, from which a total of 323 were positive for mpox virus by PCR (16% positivity). These were identified across 35 districts, with Kampala accounting for 41%. The median age of confirmed cases was 24 years, with 28% of cases in children. Atypical genital lesions were observed in 25% of cases within sexually mediated clusters, and close contact with a known case was reported in 60% of infections. All sequenced viruses were clade Ib, with 5 subclades identified; notably, apolipoprotein B mRNA-editing enzyme catalytic polypeptide-3 (APOBEC-3)-like mutations were absent. Transmission was not associated with geographic, demographic, or batch-level clustering, suggesting widespread community transmission beyond discrete networks.

Together, these findings illustrate how clade Ib mpox virus, previously linked to outbreaks in Central Africa, has expanded regionally and adapted to diverse transmission contexts in Uganda. The co-circulation of mpox virus and VZV, along with high rates of sexual and household transmission (including frequent pediatric infection), calls for integrated surveillance, rapid diagnostic capacity, and targeted prevention strategies.

Testing

Lumembe-Numbi and colleagues (Abstract 1197) evaluated the differentiation in real time by high-resolution melting (DIRASH) multiplex PCR assay, designed for simultaneous detection of mpox virus, VZV, herpes simplex virus-1, and herpes simplex virus-2. Retrospective testing of 850 samples from France and the DRC showed high sensitivity (≥94%) and 100% specificity across all pathogens. The test is lyophilized, stable at room temperature, and paired with automated interpretation software, making it particularly well suited for use in resource-limited settings. These findings support the DIRASH assay as a valuable tool for differential diagnosis of vesicular rashes in the context of overlapping mpox and varicella outbreaks in Central Africa.

> ***In a randomized trial, tecovirimat did not improve outcomes in people with clade II mpox***

Treatment

In a highly anticipated presentation, Wilkin and colleagues (Abstract 201) reported the primary results of the ACTG (AIDS Clinical Trials Group) A5418/STOMP (Study of Tecovirimat for Mpox), the first phase III, randomized, placebo-controlled trial evaluating tecovirimat for clade II mpox. Among 412 participants, clinical resolution by day 29 occurred in 83% of tecovirimat recipients and 84% of those receiving placebo (incidence rate ratio, 0.98; $P = .89$). Pain reduction over the first 5 days was similar between groups. Although a greater proportion of tecovirimat recipients had undetectable lesion DNA at day 8 (48% vs 33%), this difference was not statistically significant and was no longer observed by day 15. AEs were infrequent and balanced across study arms. Based on these findings, the trial was stopped early for futility. These results, together with those from PALM007 (Tecovirimat for Treatment of Monkeypox Virus) in clade I mpox (presented at IDWeek 2024), do not support the continued use of tecovirimat monotherapy for mpox.

In a paired abstract, Fischer and colleagues (Abstract 159) presented interim results from the open-label arm of ACTG A5418/STOMP. Among participants treated with tecovirimat, no baseline clinical or demographic characteristics — including HIV status or symptom duration — were associated with time to clinical resolution or virologic clearance. This exploratory analysis did not identify predictors of clinical improvement. Compared with participants in the PALM007 trial with clade I mpox, those in STOMP with clade II mpox had lower lesion counts and slower clinical resolution, underscoring potential differences in disease dynamics across viral clades.

Virology

Genomic analyses from South Korea and Japan highlighted evolving viral dynamics that may support sustained mpox virus transmission and adaptation. Choi and colleagues (Abstract 300) described ongoing local transmission of the clade IIb, C.1 lineage in South Korea, with 151 locally acquired cases in 2023. Transmission, as was seen globally, was most frequently linked to GBMSM with anonymous sexual contact, complicating containment efforts. Genomic sequencing revealed 8 subclusters, including TC.2 as the predominant strain (53 cases) in 2023 and TC.8 emerging in 2024. APOBEC-3-mediated mutations were commonly observed and may facilitate immune evasion. Building on these findings, Lee and colleagues (Abstract 301) identified 5 novel genomic deletions in genes associated with immune regulation, including interleukin-18 binding and nuclear factor kappa B inhibition proteins. These deletions may promote viral persistence through immune regulation and viral adaptation. In Japan, Ishige and colleagues (Abstract 302) detected a large-scale genomic rearrangement in 1 of 3 mpox virus strains. Despite large structural changes, the virus remained replication competent and could result in more rapid evolution of mpox virus.

Summer and colleagues (Abstract 140) compared the phenotypic properties of clade IIb lineage A mpox virus, which is endemic to Africa, with clade IIb lineage B mpox virus, which is responsible for the recent global outbreak. Both lineages replicate similarly in various cell types, but lineage B (global strain) exhibited lower extracellular virus production and defective long-range spread. Clinically, lineage A-infected individuals typically show more severe disease, with extensive viral dissemination (more than 100 lesions), than the milder, localized presentations seen in lineage B infections (fewer than 10 anogenital lesions). Both lineages showed strong induction of inflammatory cytokines, unlike other orthopoxviruses, but did not activate interferon or antiviral gene pathways.

Lineages A and B differ by 51 nucleotides, most consistent with host APOBEC-3-mediated mutations.

Although the full biologic implications of these mutations are still unclear, they likely contribute to the observed attenuation of lineage B, aligning with clinical observations of milder disease. These findings also support the idea that APOBEC-3 mutagenesis is not only a marker of human-to-human mpox virus transmission but also a driver of phenotypic change.

Together, these studies underscore the importance of genomic surveillance to detect viral adaptations that may influence transmission dynamics, alter virulence, or impact disease severity.

Immunology

Several studies at CROI 2025 evaluated the durability and quality of immune responses to mpox infection as well as to MVA-BN vaccination, with a notable focus on PWH and other vulnerable populations.

Liu and colleagues (Abstract 438) and Byrne and colleagues (Abstract 439) documented a rapid decline in antibody levels following MVA-BN vaccination, with fewer than one-third of vaccine recipients remaining seropositive by 2 years. In contrast, individuals with prior mpox had more varied antibody responses. Prior smallpox vaccination was associated with more sustained serological responses, particularly to the anti-H3 immunoglobulin G target, which also correlated better with neutralizing activity than other vaccine targets. Among PWH, antibody durability was significantly reduced (OR, 0.18; $P = .01$), raising concern about long-term protection in immunocompromised populations.

Cellular immunity studies offered a more nuanced picture. De la Calle-Jiménez and colleagues (Abstract 440) found that mpox disease generated robust and sustained CD4+ and CD8+ T-cell responses in PWH and in those using HIV preexposure prophylaxis, whereas MVA-BN vaccination produced minimal T-cell activation, comparable to that seen in unexposed individuals. In contrast, Khan and colleagues (Abstract 441) reported that vaccinated, virally suppressed PWH exhibited stronger CD4+ and CD8+ T-cell responses to vaccinia antigens than those with prior infection, despite similar antibody levels. Notably, 2 vaccinated individuals without detectable antibodies still had robust T-cell responses, underscoring the potential value of cellular immunity even in the absence of seroconversion.

Finally, Mazzotta and colleagues (Abstract 443) confirmed that humoral and cellular responses waned substantially 2 years after vaccination. Neutralizing antibodies were detectable in fewer than 25% of participants, and T-cell responses, though still measurable, had declined significantly.

Taken together, these findings underscore the need for larger studies to better characterize correlates of immune protection and to inform epidemiologic surveillance for reinfection and assess the need for booster vaccination for vulnerable populations.

Vaccine Cost-Effectiveness

Zhang and colleagues (Abstract 1208) evaluated vaccination strategies to prevent future mpox outbreaks among GBMSM in England using a dynamic transmission model. All vaccination strategies, preemptive, reactive, or a combination, were cost-saving and gained quality-adjusted life years (QALYs) compared with no vaccination. The most favorable approach was a combined strategy of low-rate routine vaccination with intensified reactive vaccination during outbreaks, which remained cost-effective under most assumptions (unless vaccine cost exceeded £576/dose). Even when factoring in varying outbreak severity, behavior change, and importation rates, the combined approach consistently minimizes mpox-related morbidity and economic burden. These findings reinforce the value of sustained preemptive vaccination efforts in vulnerable populations, especially with ongoing global transmission and the possibility of waning immunity over time.

Other Opportunistic Infections

To assess recent trends in ART initiation and the prevalence and impact of opportunistic infections (OIs) at ART initiation, Kulkarni and colleagues (Abstract 981) analyzed data from the NA-ACCORD (North American AIDS Cohort Collaboration on Research and Design) from 2017 to 2021. Among 6923 adults with detectable HIV viral loads (>200 copies/mL), 27% had a CD4+ count below 200 cells/µL, and 5.4% (n = 374) had an OI diagnosed within 6 months before or 2 weeks after ART initiation. The most common OIs were *Pneumocystis* pneumonia (44%), esophageal candidiasis (23%), pulmonary TB (6%), and cryptococcal meningitis (5%). The 1-year cumulative incidence of death was 5.5% (95% CI,

> ***One in 20 people in a large North American cohort were diagnosed with an OI when starting ART***

3.5–8.3) among those with an OI, compared with 1.3% (95% CI, 1.0–1.6) among those without. Having an OI at ART initiation was independently associated with a 1.85-fold increased risk of 1-year mortality (95% CI, 1.03–3.34) after adjustment for confounders. These findings highlight that 1 in 20 PWH in the longitudinal US and Canadian cohort are starting ART with an OI, underscoring the need for targeted test-and-treat strategies to facilitate earlier diagnosis and ART initiation to reduce OIs and associated mortality.

> ***Data suggest a similar risk of AIDS-defining conditions between those with and without perinatal HIV but underscore the importance of long-term retention in care***

Adults with perinatally acquired HIV may be at increased risk for AIDS-defining conditions (ADCs) compared with those with non-perinatally acquired HIV due to chronic inflammation, early immune system disruption, and long-term ART exposure but this is poorly characterized. Burchell and colleagues (Abstract 1135) analyzed data from the NA-ACCORD among participants aged 18 to 40 years during follow-up from 2000 to 2022 to compare ADC burden by mode of HIV acquisition. Among 22,950 PWH, 455 (2.0%) had perinatally acquired HIV. Across the cohort, there were 5715 ADCs, including 109 among adults with perinatally acquired HIV. The weighted mean cumulative number (MCC) of ADCs declined from the period 2000 to 2011, to the period 2012 to 2022; in both periods the MCC of ADCs among adults with perinatally acquired HIV was comparable to that of each nonperinatally acquired HIV risk group (male-to-male sex contact, injection drug use, and heterosexual contact). These data suggest a similar risk of ADC between those with and without perinatal HIV but underscore the importance of long-term retention in care for ADC prevention.

It is not well understood if cytomegalovirus (CMV) and Epstein-Barr virus (EBV) coinfection contribute to poor outcomes in people with AHD and cryptococcal meningitis (CM). To address this, Ellis and colleagues (Abstract 977) assessed the prevalence of CMV and EBV in plasma and cerebrospinal fluid (CSF), and their association with mortality among PWH with CM in AMBITION-CM (Intermittent High-Dose AmBisome on a High-Dose Fluconazole Backbone for Cryptococcal Meningitis Induction Therapy in Sub-Saharan Africa: An Adaptive Randomized Controlled Noninferiority Trial),[2] a multicountry randomized trial investigating the efficacy of a single dose of liposomal amphotericin for CM. Among 811 participants (median CD4+ count, 27 cells/µL), EBV plasma viremia was present in 73% (n = 395/804) and CMV viremia in 49% (n = 585/804), and central nervous system EBV and CMV were detectable in 27% (n = 191/708) and 5% (n = 39/707), respectively. EBV viremia was associated with a proinflammatory phenotype (higher CD4+ counts and increased CSF inflammation), and CMV viremia was associated with a pauci-inflammatory phenotype (lower CD4+ counts, reduced CSF inflammation, and higher CSF fungal burdens). Notably, CMV viremia at or above 1000 copies/mL was independently associated with greater 2-week mortality (aOR, 2.31; 95% CI, 1.12-4.75) and greater 10-week mortality, whereas EBV viremia and detectable central nervous system EBV and CMV were not. This study suggests that CMV viremia may represent a modifiable risk factor to reduce mortality in HIV-associated CM, warranting evaluation in interventional trials to assess the impact of CMV treatment on outcomes.

As global syphilis rates rise, neurosyphilis (NS) remains a serious complication requiring timely treatment — traditionally, intravenous penicillin (PCN) for 10 to 14 days, which poses challenges in resource-limited settings due to cost, shortages, and need for hospitalization. To address limited data for the effectiveness of ceftriaxone (CTX) for NS, especially in resource-limited settings where CTX may be more cost-effective and feasible than PCN, Villa-Benavides and colleagues (Abstract 982) conducted a multicenter retrospective study in Mexico comparing these 2 agents for NS treatment. Among 201 patients (94% PWH; median CD4+ count, 270 cells/µL), 144 (72%) received PCN (16–24 million units/d) and 57 (28%) received CTX (1–2 g/d intramuscularly or intravenously). At 6 months, univariate analyses showed similar serologic response rates (≥4-fold reduction in serum venereal disease research laboratory or rapid plasma reagin titers) between CTX and PCN (47% vs 42%), but a lower clinical response rate (resolution of ophthalmic, otologic, or neuropsychiatric symptoms or pleocytosis) in the CTX group (28% vs 58%; $P < .01$). However, in multivariable analyses, treatment type was not associated with differences in either outcome. Independent predictors of lower clinical response included AHD (OR, 0.35; 95% CI, 0.12–0.97) and hepatitis B virus coinfection (OR, 0.08; 95% CI, 0.01–0.45). Although the retrospective design and dosing variability limit interpretation, these findings add to growing evidence that CTX may be a reasonable alternative to PCN for NS treatment when PCN is not available.

Kaposi Sarcoma

Accurate and timely diagnosis of Kaposi sarcoma (KS) remains a major challenge in Africa due to reliance on histopathology, which is often unavailable or limited in capacity. To address this, Semeere and colleagues (Abstract 789) evaluated a quantitative PCR (qPCR) assay that measures lesional KS-associated herpesvirus (KSHV) DNA to distinguish KS from non-KS lesions. Mucocutaneous biopsies were collected from individuals in Uganda with suspected KS, and US-based histopathologic interpretation served as the reference standard against which qPCR was evaluated in a training and subsequent validation population. Among 506 participants in the training group (94% PWH, 67% with histologically confirmed KS), the optimal qPCR threshold was 161 KSHV DNA copies/5 μL input, which was associated with a sensitivity of 91% and a specificity of 91%. Among 439 participants in the validation group (94% PWH; 76% with KS), the same threshold achieved sensitivity of 93% and specificity of 93%. These findings validate lesional KSHV qPCR as a promising alternative to histopathology for KS diagnosis, and efforts are underway to develop a point-of-care version of this assay.

Immune checkpoint inhibitors like nivolumab are a promising strategy for KS but their immunologic effects, particularly among PWH, are not well characterized. Wang and colleagues (Abstract 792) conducted a prospective, single-center, nonrandomized phase I trial evaluating low-dose intralesional nivolumab in adults with KS. Eligible participants had fewer than 25 KS skin lesions and received intralesional nivolumab (concentration, 10 mg/mL) across 4 doses at weeks 0, 2, 4, and 6. At 26 weeks, participants who tolerated treatment were eligible to receive 4 additional doses, with final assessments at week 52. Among 12 participants (50% PWH; median CD4+ count, 630 cells/μL), intralesional nivolumab was well tolerated, 10 opted to receive 4 additional doses, and 3 participants without HIV achieved complete remission. Treatment was associated with reduced PD-1 expression on circulating CD4+ and CD8+ T cells, as well as increased frequencies of Ki67+ (cell cycling) terminally differential CD8+ T cells; the effects were not impacted by HIV status. Additionally, increases in central memory and effector CD4+ and CD8+ T-cell phenotypes were observed. These findings demonstrate that low-dose intralesional nivolumab is safe and immunologically active in adults with KS — with or without HIV — and may enhance antiviral and antitumor immune responses while minimizing systemic toxicity. Larger studies are needed to further assess clinical outcomes and immunologic effects.

KS remains an important HIV-associated malignancy with limited effective treatment options. Mercado-Matos and colleagues (Abstract 124) presented results from an ongoing phase I/II study of abemaciclib, a potentially T-cell sparing oral cyclin-dependent kinase (CDK4/6) inhibitor US Food and Drug Administration-approved for metastatic breast cancer, in adult participants with KS and measurable skin disease; PWH (on ≥8 weeks of ART) or PWoH were included. The study used a 3+3 dose de-escalation design to identify a maximum tolerated dose (MTD) in phase I (n = 6), and assessed overall response rate in phase II (n = 28), stratified by previously treated (2a; n = 17) or untreated KS (2b; n = 11). Overall, 34 participants were enrolled (25 PWH: median CD4+ count, 427 cells/μL; median HIV-RNA level, >20 copies/mL) and 82% had stage T1 KS disease. In phase I, 6 participants with prior KS therapy were prescribed 200 mg BID and there were no dose-limiting toxicities. In phase II, 81% of all participants achieved at least a partial response, including 77% and 90% of those with (2a) and without prior KS therapy (2b). Neutropenia (80%) was common, with 13 participants requiring dose reductions for grade 3 or 4 neutropenia. Notably, there were no significant changes in the median CD4+ count from baseline to cycle 3 and some evidence of significant improvement by the end of treatment ($P = .03$). Abemaciclib is a promising novel therapeutic in the clinical pipeline for KS in PWH and PWoH, that unlike other chemotherapies for KS does not adversely impact CD4+ cell counts.

Human Papillomavirus and Associated Malignancies

Although HIV infection is known to significantly increase the risk of cervical cancer following human papillomavirus (HPV) infection, far less is known about HPV-related noncervical cancers among PWH including anal, oropharyngeal, vaginal, vulvar, and penile cancers as well as the potential impact of improved global HPV vaccine coverage among PWH on these cancers. To address these gaps, Wongkalasin and colleagues (Abstract 165) conducted a modeling study to evaluate the global burden of HPV-related noncervical cancers in PWH and assess the potential impact of improved sex-neutral HPV vaccine coverage worldwide.

Using publicly available data from 185 countries, the researchers estimated the population-attributable fraction of cancers attributable to HIV and modeled the impact of improved country-specific vaccine coverage. Overall, the study estimated that worldwide, approximately 12% of anal cancer, 8% of vaginal cancer, 6% of vulvar cancer, 4% of penile cancer, and 1% of oropharyngeal cancer cases may be attributable to HIV — that is, they may not have occurred in the absence of HIV-related immunosuppression among people co-infected with HPV. There was substantial geographic variation in these estimates: in Africa, 29% of all HPV-related noncervical cancers may be attributable to HIV, compared with only 5% globally. For anal cancer specifically (n = 35,719 cases in 2022), they estimated that 12.4% were attributable to HIV; the attributable fraction ranged from 1.5% in Southeast Asia to 10.6% in the Americas to 41.8% in Africa. Notably, among the 10 countries with the highest number of HIV-attributable cancers, only 2 had HPV vaccine coverage rates exceeding 50%. Modeling showed that increasing vaccine coverage to the WHO current 90% target among girls and boys (compared with current levels of 21% for girls and 7% for boys) could prevent 6854 cancer cases in PWH—more than doubling the number currently prevented. These findings suggest that both VSS and urine sampling are highly acceptable screening approaches among WWH, but that VSS offers better sensitivity, especially at low viral loads. Although acceptability is high, further evaluation of diagnostic performance and cost-effectiveness is needed before widespread adoption.

WHO guidelines now recommend 1- or 2-dose HPV vaccine schedules for girls and women aged 9 to 20 years, with many countries implementing single-dose strategies based on evidence of comparable and durable protection. However, for women with HIV (WWH), 2 doses, and 3, if possible, are recommended regardless of age. Kapeu and colleagues (Abstract 807) conducted a prospective, randomized, non-inferiority trial comparing the immunogenicity of 2 (months 0 and 6) vs 3 (months 0, 2, and 6) doses of the 9-valent HPV vaccine among WWH. Among 167 participants (81% from sub-Saharan Africa; median CD4+ count, 649 cells/µL; IQR, 492-831) on ART with suppressed viral load (<400 copies/mL), seroconversion rates for all vaccine genotypes were noninferior with 2 vs 3 doses in the modified intention-to-treat (97.7% vs 97.9%; *P*<.001 for noninferiority) and per-protocol analyses (96.8% vs 98.9%; *P* = .57). Antibody titers at month 7 were high in both arms. Injection-site reactions were significantly less frequent in the 2-dose group (60% vs 82%; *P* = .027). These findings suggest that a 2-dose 9-valent HPV vaccine schedule is immunogenically noninferior to 3 doses in women with well-controlled HIV, supporting a simplified approach aligned with current WHO guidance.

Cervical cancer screening is a key priority for WWH, but clinic-based approaches reliant on Papanicolaou (Pap) smears can limit coverage. Although vaginal self-sampling (VSS) is gaining traction, urine sampling is a less invasive and understudied alternative, particularly for those uncomfortable with genital sampling. Mailhe and colleagues (Abstract 805) evaluated the acceptability and performance of VSS and urine sampling among WWH in France. Among 201 participants (median CD4+ count, 770 cells/µL), 87% found VSS acceptable, and 74% and 80% preferred VSS and urine sampling, respectively, over clinician-collected cervical samples. Among 167 participants with paired samples, only 1 unsatisfactory sample occurred for VSS and urine sampling, respectively. High-risk HPV (HR-HPV) was detected by VSS in 43.4% of participants. Urine sampling showed 83% agreement with VSS ($\kappa = 0.64$), and discordant results were mostly (79%) due to low HR-HPV DNA levels. These findings suggest that both VSS and urine sampling are highly acceptable screening approaches among WWH, but that VSS offers better sensitivity, especially at low viral loads. Although acceptability is high, further evaluation of diagnostic performance and cost-effectiveness is needed before widespread adoption.

Optimizing screening for anal cancer among PWH remains a challenge due to the low specificity of anal cytology leading to a large number of individuals requiring unnecessary high-resolution anoscopy (HRA), which is often unavailable or centralized. Bello-Perez and colleagues (Abstract 808) evaluated whether adenosine deaminases acting on RNA (ADAR1) mRNA levels, which are expressed in cervical and other cancers, could improve the specificity of screening approaches and safely reduce the number of PWH with abnormal anal cytology requiring HRA. In this prospective single-center study, PWH with abnormal anal cytology (atypical squamous cells of undetermined significance, low-grade squamous intraepithelial lesion, or high-grade squamous intraepithelial lesion [HSIL]) underwent HRA-directed biopsies, and anal samples were tested for HPV genotypes and ADAR1 mRNA was quantified. Among 171 participants, 40 (23.3%) had biopsy-confirmed HSIL. Participants with HSIL had a higher median number of HPV genotypes than those without HSIL (5 vs 3; *P* < .001), and significantly elevated ADAR1 mRNA levels (49.4 vs 4.1; *P* < .0 01). A model incorporating ADAR1 expression showed good discrimination for HSIL (AUC, 0.83; 95% CI, 0.75–0.92). Using an ADAR1 threshold of 24.7 and higher, only 22.8% of participants with abnormal cytology would be referred for HRA, detecting 72.5% of HSIL cases. A combined model using ADAR1 above 4 and HPV genotype quantification would refer 46.2% of participants while detecting 95% of HSIL cases. These findings suggest that ADAR1 mRNA quantification could improve the efficiency of anal cancer screening in PWH by reducing unnecessary HRAs, although further evaluation of accuracy and cost-effectiveness is warranted.

Anal cancer screening is recommended for GBMSM with HIV age 35 years and older; its value in younger GBMSM remains under debate. Appelbaum and colleagues (Abstract 810) retrospectively analyzed screening outcomes (2013 to 2023) at a single center among 18– to 34-year-old GBMSM with HIV. Among 216 individuals (5% with CD4+ count <200 cells/µL; 46% HPV vaccinated), 127 (58.7%) had at least 1 anal Pap test (246 total Pap tests). Of the 246 total Pap tests, 19% were unsatisfactory, and 31% (n = 76) showed high-grade cytologic abnormalities; however, only 30% of these individuals (n = 23/76) underwent HRA, and 14% (n = 11/76) had high-grade dysplasia on biopsy. Two cases of squamous cell carcinoma of the anus (SCCA) were diagnosed outside the screening window, leading the authors to question the utility of screening in this age group. However, low uptake of follow-up procedures and small sample size limit these conclusions. These findings underscore the need for prospective, adequately powered studies to clarify the benefits and implementation of screening in younger populations.

Prior studies have shown that PWH are at an increased risk of oropharyngeal cancer (OPC) and have poorer outcomes compared with PWoH, but these differences may, in part, be confounded by differential patient and treatment characteristics. To address the potential limitations of prior studies, Chiao and colleagues (Abstract 125) conducted a matched retrospective cohort study to evaluate OPC treatment initiation and survival among adult PWH and PWoH receiving care within the Veterans Affairs (VA) or Kaiser Permanente California between 2008 and 2019. PWH and PWoH with OPC were matched 1:1 on sex, age, race, year of OPC diagnosis, stage, and HPV tumor status and followed up from the time of treatment initiation (chemotherapy, radiation, or surgery) until death, loss to follow up, or censure (December 31, 2021). Overall, 260 participants were included (50% PWH, 52% with CD4+ count <500 cells/µL), with 20% diagnosed at stage 1 or 2, and 80% stage 3 or 4a/b (69% HPV positive). Treatment initiation within 180 days (65% vs 72%; $P = .17$) and median time to treatment initiation (57 days vs 60 days; $P = .76$) were similar among PWH and PWoH, respectively; however, mean survival was lower in PWH (3.4 years vs 3.9 years; $P = .03$). In analyses adjusting for potential confounders including HPV status, a status of being HIV positive was associated with higher mortality (hazard ratio [HR], 1.7; 95% CI, 1.1-2.6; $P = .027$). Despite similar baseline demographics and treatment uptake, PWH experienced lower survival. This could be due to tumoral and immunological differences that merit further study.

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