

## Invited Review

# CROI 2019: Complications and Coinfections in HIV Infection

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*The 2019 Conference on Retroviruses and Opportunistic Infections provided a considerable amount of new information on the progress in implementation of strategies to reduce morbidity and mortality from complications and coinfections that occur in people with HIV infection, and on the clinical management of these important problems. This review will address new insights into the prevention and treatment of tuberculosis, fungal infections, sexually transmitted infections, malignancies, and a range of metabolic complications and noncommunicable diseases*

**Keywords:** CROI, 2019, HIV, complications, coinfection, tuberculosis, multi-drug-resistant, STIs, fungal infection, metabolic, malignancies

### Tuberculosis: Women and Children

The call to ramp up isoniazid preventive therapy (IPT) for HIV-infected pregnant women to reduce the risk of tuberculosis (TB)-related complications during and after pregnancy was called into question after a recent study suggested worse maternal and infant outcomes when IPT was given to pregnant women during versus after delivery.<sup>1</sup> Salazar-Austin reported on a cohort of 155 pregnant women with HIV infection in South Africa observed between 2011 and 2014 who did (46%) or did not take IPT. Adverse pregnancy outcome, maternal or fetal death, or TB was present in 16% and 28% ( $P=.08$ ) of women exposed and not exposed to IPT, respectively (Abstract 77). There was only 1 case of TB, which occurred in a woman not receiving IPT. The authors suggested that these data are somewhat reassuring on the safety of IPT administered during pregnancy; however, features of this study (small and non-randomized; use of older antiretroviral therapy (ART) regimens in mothers and infants, inclusion of women beyond periconception only, differential follow-up), limit its ability to inform the ongoing policy discussion that weighs

the protective benefit of IPT versus potential safety issues.

Contraception efficacy during pregnancy for women with HIV is complicated by drug interactions with concomitant use of rifampin and efavirenz often used during TB treatment. In a pharmacokinetic study of HIV-infected women receiving efavirenz, rifampin, and depot medroxyprogesterone acetate (DMPA), 5 of 42 (11.9%) women had subtherapeutic medroxyprogesterone acetate (MPA) levels compared with 1 of 16 (6.3%) historical controls (HIV-infected, ART-naive) after 12 weeks (Abstract 78). Drug exposure to MPA was lower and clearance of MPA was faster in the women receiving rifampin and efavirenz than in historical controls. Although MPA levels were lower in the presence of efavirenz and rifampin, progesterone levels associated with ovulation were not present. The authors concluded that it may be prudent to decrease the interval of DMPA dosing in the presence of efavirenz and rifampin. They are now modelling data from various studies to identify optimal dosing frequencies for evaluation in future clinical studies.

Prevention and treatment for child contacts (HIV-infected or not infected) of adults with TB can reduce TB burden,

however, the implementation of this public health strategy is abysmal. Hirsch-Moverman evaluated a multi-component, community-based intervention in a cluster, randomized study of 10 clinics in Lesotho (Abstract 79). The intervention included enhanced teaching, mentorship for clinic staff, and TB education and reminders for community members by village health workers. There was no significant difference in the primary endpoint of the number of child contacts identified per adult TB case in the intervention (220/505, 44%) compared with the control (170/512, 33%) groups ( $P=.16$ ). The number of identified children screened for TB was 92% and 61% in the intervention and control arms, respectively ( $P=.07$ ). This study provides some insights on improving TB screening among children, but the main message is that current approaches are failing to reach and protect well over half of these children, which calls for more research in this area.

### TB and ART Drug Interactions

An important question in the TB prevention field is whether the proven short-course (12 week), isoniazid (INH), and rifapentine weekly regimen can be given in patients receiving a dolutegravir (DTG)-containing ART regimen. There are 2 major concerns with this combination. The first is that rifapentine's enzyme induction properties will lower DTG levels to subtherapeutic levels, jeopardizing viral suppression. The second concern is safety. A pharmacokinetic study in HIV-uninfected persons evaluating this combination was halted due to unexpected and serious systemic toxicity.<sup>2</sup> Investigators revisited this question in

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a phase I/II study with the rationale that hypersensitivity reactions with TB drugs such as rifamycins may be less in an HIV-infected versus uninfected person (Abstract 80). In interim results of the first 60 subjects, DTG bioavailability was 29% lower in the presence of INH and rifapentine. Trough levels in the presence of INH and rifapentine were lower, but exceeded, the DTG 90% inhibitory concentrations ( $IC_{90}$ ) in all cases but one, and all participants maintained viral suppression during the period of observation. The serious toxicities seen in the HIV-uninfected study exposed to this combination were not observed among these HIV-infected study subjects. To date, only 1 patient had a possible hypersensitivity grade II reaction and was able to resume dosing. These data are reassuring, but represent only a small group of individuals that differ

***DRV/r dose and frequency adjustments among persons receiving rifampin to compensate for drug interactions are associated with serious hepatotoxicity and reduced DRV levels, these combinations should not be used in clinical practice***

from the original study by both ethnicity and HIV status. Continued vigilance will be required with the planned expansion of this regimen globally.

For TB treatment, lopinavir/ritonavir (LPV/r) is the recommended protease inhibitor (PI) with rifampin-containing regimens, but the data are sparse for darunavir/ritonavir (DRV/r), a recommended PI regimen from the standpoint of HIV treatment. Maartens and colleagues reported findings from a pharmacokinetic study that provided a clear, but disappointing answer for the use of DRV/r with rifampin (Abstract 81). Both of the 2 dose-adjusted regimens of DRV/r (1600 mg/200 mg daily and 800 mg/100 mg given every 12 hours) to

HIV-infected persons without TB were associated with unacceptable toxic effects. Six of the first 17 participants developed grade 3 or greater hepatotoxicity, a finding that prompted cessation of the study. In addition, subtherapeutic DRV levels were uniformly present with daily dosing and among some patients on the twice daily regimen. Thus at present, for patients requiring a PI and rifampin, LPV/r is the safest choice, and DRV/r should not be used.

**Multi-Drug-Resistant Tuberculosis**

Combinations of promising investigational agents such as bedaquiline and delamanid for treatment of multi-drug-resistant (MDR) TB require rigorous assessment of potential life-threatening toxic effects, such as serious QT interval prolongation, which occurred with both drugs, prior to large-scale use. In a much anticipated phase II study that randomly assigned adults with MDR TB to bedaquiline, delamanid, or both, the mean millisecond increase (95% confidence interval [CI]) in QT interval was 11.9 (7.4, 16.5); 8.6 (4.0, 13.2) and 20.7 (16.1, 25.4) in the 3 arms, respectively (Abstract 84). The increases in QT interval were all less than grade 3, and no cardiac events were observed. Thus, QT prolongation with the combination of bedaquiline and delamanid in this trial setting was moderate and not more than additive with this 2-drug combination. It is important to note that if use of this combination goes forward, that the safety established in this trial was in the setting where persons with baseline electrocardiogram abnormalities, receiving moxifloxacin or clofazimine (drugs causing QT prolongation and used in MDR TB treatment) were excluded. In addition, careful monitoring and replacement of electrolytes (eg, magnesium, potassium) was conducted.

High-dose isoniazid (INH) is included in short-course MDR TB treatment regimens, but the optimal dosing and contribution to microbiologic efficacy is not known. Dooley and colleagues conducted a study to inform this question in a phase II randomized evaluation of INH doses of 5, 10, or 15 mg/kg for the first 7 days of treatment (n=43)

in HIV-infected persons with MDR TB and inhibin alpha (inhA)-mediated (low-level) INH resistance (Abstract 82). Microbiologic efficacy was compared with a parallel evaluation of standard-dose INH in persons with non-MDR TB (n=16). The reduction in TB burden measured in solid or liquid culture sys-

***Bedaquiline and delamanid each increase QT interval, but even in combination the magnitude remains moderate suggesting future MDR TB regimens may include this combination with close monitoring***

tems was comparable between the 2 high-dose INH regimens and that seen with standard dose INH for drug-sensitive TB. In this short-term, selected population with inhA mutation and unknown acetylase status, high-dose INH appeared efficacious. More information and data are needed to understand the role of this regimen in contemporary and evolving INH mono-resistant and MDR TB regimens.

**Fungal Infections**

The risk of cryptococcal disease among persons with HIV infection presenting with low CD4+ cell counts is well established, and the basis for current recommendations to screen and treat those with asymptomatic and symptomatic disease. There is another population, which has received little attention (those on ART with virologic failure), that may be also be at high risk of cryptococcal disease. Mpoza and colleagues tested 1186 persons who had samples of viral loads sent to assess and confirm virologic failure in 2017 and 2018 (Abstract 708). Cryptococemia was present in 35 of 1186 (3.0%). The median prior ART duration was 42 months. Nearly all (32/35) cases were among those with HIV RNA levels above 5000 copies/mL, and median HIV RNA

levels were higher among those with (53,700 copies/mL) than without (11,650 copies/mL) cryptococcal antigenemia. Among the subset of 21 persons with cryptococemia in whom follow-up data were available, meningitis-free survival was 62% at 6 months. This analysis is interesting and important in light of the evolving treatment landscape in sub-Saharan Africa where HIV RNA testing is ramping up, and CD4+ cell count testing is being scaled back, including among individuals with virologic failure. With the rollout of ART, there will be a growing population of persons with virologic failure that this study suggests could benefit from cryptococcal antigen screening and treatment to reduce morbidity and mortality.

In Southeast Asia, *Talormyces marneffei* (Tm) infection has a high mortality, and is the major common serious fungal opportunistic infection. A new Tm antigen (TmAg) test Mp1p has higher sensitivity than blood culture for the diagnosis of clinical disease, but the assay has not been evaluated as a screening tool for asymptomatic disease in persons with advanced HIV disease. Thu and colleagues in Vietnam evaluated 1082 patients with CD4+ count below 100 cell/ $\mu$ L followed up between 2015 and 2017 (Abstract 710). TmAg was detected in 45 (4.2%). Risk for TmAg was 3.5-fold higher in those with CD4+ count below 50 cell/ $\mu$ L, and 3.4-fold higher in those living in highland regions. The probability of death was 12.7% in the cohort, and was higher (30.0%) in the TmAg-positive patients than the TmAg-negative patients (11.9%); log rank,  $P=.002$ . This study would suggest that preemptive therapy for Tm should be evaluated in this high-risk, low CD4+ cell count population in Southeast Asia.

### Sexually Transmitted Infections

Ranchandani evaluated the relationship between syphilis and hearing loss in a convenience sample of 362 individuals with syphilis who had cerebrospinal fluid (CSF) evaluated, regardless of syphilis disease stage (Abstract 1013). The odds of high-frequency hearing loss were greater in the presence of CSF pleocytosis, *Treponema pallidum*

detection by polymerase chain reaction (PCR) in the blood, and older age. The odds of low or medium frequency hearing loss were greater in those with *T. pallidum* in CSF, history of injection drug use, and older age. Syphilis stage, ART

**Adjusted rates of presumed SCD and of autopsy-defined sudden arrhythmic deaths were 82% and 83% higher, respectively, in HIV infection than in the uninfected population. Importantly, occult drug overdose accounted for 34% of SCD in people living with HIV and for 14% in the general population**

use, HIV RNA level, and CD4+ cell count were not associated with any form of hearing loss. The authors noted the high incidence of hearing loss in this population, and postulate pathophysiology for high frequency and low frequency hearing loss may differ based on different levels of CSF inflammation. In a second report on syphilis, Robertson and colleagues performed formal cognitive function evaluations on 186 individuals with syphilis (Abstract 1014). The study population was young (median age, 35 years) and largely male (98%); 82% had primary syphilis, and 19% and 21% reported using stimulants or cannabis, respectively. Cognitive impairment was mild (39%), moderate (10%), or severe (10%) in the study population. Rapid plasma reagin titer of 1:32 or above in these 3 groups was 72%, 79%, and 100%, respectively ( $P=.02$ ). Moderate or severe cognitive impairment was more frequent among those with asymptomatic early latent or late latent (34%) than those with primary or secondary disease (21%;  $P=.05$ ). HIV status was not associated with cognitive impairment. The authors' interpretation of these results was that bacterial burden may

contribute to cognitive impairment with syphilis and is most commonly detected in latent disease.

The standard treatment for lymphogranuloma venereum (LGV) is doxycycline 100 mg twice daily for 21 days. The authors evaluated the efficacy of the standard doxycycline regimen versus 1 gram azithromycin once weekly for 3 weeks (Abstract 1011). All subjects received a single dose of ceftriaxone. There were 136 men (95% were HIV infected) with confirmed LGV proctitis in the study. Clinical (12 week) and microbiologic cure (4 week) were high in both arms: 99% and 97% for the azithromycin group and 95% and 100% for the doxycycline group. Diagnosis and treatment of LGV remains challenging due to lack of rapid diagnostic tests, and treatment of persons with sexually transmitted infections are complicated by presence of numerous pathogens. Larger randomized studies will be needed to determine benefits and risks of azithromycin compared with doxycycline in populations with sexually transmitted infections and suspected LGV.

### Noncommunicable Diseases

#### Cardiovascular Disease

Two studies focused on sudden cardiac death (SCD) this year, a topic that has received little attention in the past. Friberg and colleagues from the Veterans Aging Cohort Study meticulously reviewed medical records and death certificates to assess the occurrence of SCD in people living with HIV (PLWH) compared with a well matched control population. They found that PLWH had a 14% higher risk of SCD and that uncontrolled HIV infection appeared to increase this risk (Abstract 32). Tseng and colleagues in San Francisco conducted an impressive population-based prospective study evaluating all incident out-of-hospital death cardiac arrests in San Francisco with full autopsies, histology, toxicology, and record reviews between 2011 and 2016. These complete evaluations allowed them to identify which deaths were actual sudden arrhythmic deaths (Abstract 33). The adjusted rates of both presumed SCDs

and autopsy-defined sudden arrhythmic death syndrome (SAD) were 82% and 83% higher, respectively, in the HIV-infected and the uninfected populations. Importantly, occult drug overdose accounted for 34% of SCD in PLWH and 14% in the general population. Histologic studies identified higher rates of cardiac fibrosis in PLWH, which may underlie the excess risk for SAD. Collectively these studies highlight the need for better screening modalities for substance use and for cardiac fibrosis in PLWH.

### Myocardial Infarction

Studies presented this year continued to focus on identifying and quantifying risk factors for myocardial infarction (MI) in PLWH. Using a large commercial database, O'Halloran and colleagues compared the rates of major cardiovascular endpoints (MI, ischemic stroke, coronary artery bypass grafting, or percutaneous coronary interventions) among adults who initiated ART with integrase strand transfer inhibitors (INSTIs), PIs, or nonnucleoside reverse transcriptase inhibitors (NNRTIs) (Abstract 680). The population was relatively young (mean age, 40 years) and was predominantly men with a median follow-up of 561 days. Treatment with an INSTI-based regimen was associated with a 43% reduction in major adverse cardiovascular events; most notable MI (acute MI occurred in 11 [0.21%] in the INSTI group and in 55 [0.36%] among those who received non-INSTI treatment.) Although the event rate is small and follow-up is short, these data supplement data on virologic outcomes that underlie the choice of INSTIs as preferred agents for initial therapy.

Previous studies have suggested that HIV increases the risk of atherosclerosis in women to a greater extent than in men. Hanna and colleagues previously reported higher rates of HIV-related cardiovascular mortality in women than in men across New York City, but concerns lingered about confounding. In a new analysis they focused on women from the Bronx where socioeconomic status was less variable, and found that the sex difference was attenuated (Abstract 663). Whether the higher rates of cardiovascular mortality in women

were due to access to preventive care or other biologic mechanisms remains to be defined.

Several studies examined the relationship between specific biomarkers and measures of atherosclerosis. Higher levels of interleukin-10, an anti-inflammatory cytokine, were associated with less coronary plaque (specifically non-calcified plaque) as measured by computerized tomography (CT) angiography in PLWH, after control for other risk factors and biomarkers including MCP-1 and CD163 (Abstract 631). The mechanism that underlies this association remains poorly defined.

### Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is thought to be increased in PLWH and may be underdiagnosed. Crothers and colleagues used data from more than 25,000 PLWH followed upon the Center for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) cohort to link the presence of COPD (which was diagnosed in 423 participants based on treatment information) with an increased risk of MI, most notably Type 2 MI (thought to be caused by supply-demand mismatch). The association persisted after control for traditional risk factors for MI. These findings highlight the importance of early recognition and treatment for COPD in PLWH (Abstract 31).

### Obesity

At this year's conference there was a substantial focus on obesity. HIV infection occurs in populations with high background rates of obesity globally (Abstract 677). Therefore a key question is whether ART drugs increase the risk of excessive weight gain. Although it is clear that INSTIs have a favorable profile with respect to lipids, there is a lingering concern about weight gain with this class of drugs. It has been challenging to sort out the contributions of the "return to health" phenomenon to increases in weight in those initiating ART from a direct effect of specific ART agents. Limited data are available from the randomized registrational trials of INSTIs beyond what has been reported from AIDS

Clinical Trials Group (ACTG) 5257 (comparing raltegravir with atazanavir/r and darunavir/r).<sup>3</sup> In this study, women, blacks, and people with lower CD4+ cell count and higher HIV RNA level appeared at greater risk. Several observational trials examined these issues (Abstracts 669, 670, 671, 672, 673, 674, 675).

McComsey and colleagues, in a study sponsored by Gilead Sciences, examined electronic medical records of 3468 adults to identify factors associated with changes in weight among virally suppressed PLWH who received different initial ART regimens (Abstract 671). A number of factors were associated with weight gain of more than 3% in this analysis, specifically being underweight or normal body mass index at baseline, female sex, and a history of psychiatric disorders. Although use of INSTIs was more prevalent in the group that gained more than 3% weight, this difference did not persist after controlling for the other risk factors, highlighting the complex interaction between many factors and changes in weight over time.

In one of the largest studies reported to date on the topic of weight changes and ART, NA-ACCORD (North American AIDS Cohort Collaboration on Research and Design) investigators also examined the issue of weight gain and ART among 21,886 adults (87% men) with a median age of 42 years and follow-up out to 5 years for each drug class, and with individual INSTI drug exposures at 1 and 2 years (Abstract 670). The analyses controlled for several important measures including baseline CD4+ count, HIV RNA level, sex, race, and baseline weight, but no information on diet or activity were reported. Weight gain was greatest in the INSTI group (n = 4,112) with gains 5.8 kg at 5 years, respectively, compared with 4.1 kg for NNRTI and 5.0 kg for NNRTI and PI users. The difference was statistically significant when comparing INSTI users with NNRTI users but not with PI users. After 2 years of follow-up, raltegravir and DTG users gained more weight than those on NNRTIs, whereas elvitegravir use was associated with less weight gain than with PIs.

Examining the impact of a switch to an INSTI regimen in virologically

suppressed PLWH removes the complexity of examining weight gain among those initiating ART. Lake and colleagues examined changes in weight and waist circumference in virologically suppressed adults in an ACTG cohort who switched to an InSTI-containing regimen by comparing the trajectories (change of weight per year) 2 years before and after the switch. They found that the rate of change in weight was greater for women, blacks, and those older than 60 years. Baseline rates of weight change were on average less than 1 kg per year; however, after the switch to an InSTI (raltegravir, DTG, or elvitegravir) these high-risk groups gained on average 1.5 kg per year. The relatively small sample size limited comparison by specific ART agents in this study (Abstract 669). Another important factor that may influence the quantity of visceral adipose tissue (VAT) is prior exposure to thymidine analogues and didanosine (Abstract 676). In carefully selected participants in a Danish cohort, investigators reported greater VAT area in PLWH with and without prior thymidine analogue or didanosine exposure that persisted for years after these drugs were discontinued.

Are weight changes with InSTIs associated with other health consequences? Kerchberger and colleagues led a WIHS (Women's Interagency HIV Study) analysis comparing women who added or switched to an InSTI with those who remained on non-InSTI ART (Abstract 672). The group that switched or added an InSTI experienced a 2.14-kg greater increase in weight, a 0.78 kg/m<sup>2</sup> greater increase in body mass index, and a 1.35% greater increase in percent body fat. Additionally, those who switched or added an InSTI had a few mm HG higher measures of systolic blood pressure and a higher rate of new onset diabetes (4.5% vs 2.2% those not on an InSTI). Although there may be unmeasured confounders between those who changed treatment and those who did not, these results signal possible negative health consequences associated with this modest weight gain that require further study. Consistent with earlier studies that identified lower CD4+ cell count and higher HIV RNA level with greater weight gain,

it was not surprising to see that higher levels of immune activation prior to starting ART were associated in more weight gain (Abstract 673). Importantly, women who gained weight on ART had smaller declines in measures

### *There is an urgent need for more evaluation of weight changes with specific InSTIs in diverse populations with HIV infection*

of immune activation on ART. The impact of this residual immune activation on longer-term outcomes may portend future complications.

To round out the story of weight changes and InSTI use, Landovitz and colleagues reported results of retrospective analysis of weight changes during a randomized HIV prevention study (conducted in HIV-uninfected men and women) comparing the investigational InSTI cabotegravir (given initially in oral form followed by long-acting injection every 2 to 3 months) (Abstract 34). This analysis found no significant increase in weight after exposure to cabotegravir in any sub-group. These results suggest that there may be an interaction between the effective treatment of HIV infection and the weight gain observed.

As future studies are considered on the topic of weight gain and changes in fat depots, the question arises how best to measure changes in visceral fat. New software now allows for the estimation of visceral fat on dual-energy X-ray absorptiometry (DXA) scans; however, an analysis comparing DXA VAT with CT-measured VAT suggests that although they are correlated, longitudinal DXA measures may come up short when estimating changes in VAT over time in PLWH (Abstract 682). Additionally, measures of fat density by CT may reveal important changes in the quality of fat tissue, whether this varies by ART drug exposure should be evaluated in larger trials (Abstract 681).

Collectively, the large number of studies examining weight changes on InSTIs highlight the urgent need for more

evaluation of weight changes with specific InSTI in diverse populations of PLWH and underscore the importance of data from randomized trials to complement the information from observational data. Additional information on other factors that impact weight such as diet and exercise will be needed to sort out the direct and indirect effects of specific ART agents on weight.

### **Renal and Bone Disease**

Tenofovir disoproxil fumarate (TDF) has been associated with a decline of the estimated glomerular filtration rate (eGFR), but less is known about the recovery after switch to other agents (Abstract 694). Investigators from the Netherlands conducted 2 studies to examine the recovery of eGFR after a switch to either tenofovir alafenamide (TAF) or abacavir. The studies excluded participants with other comorbidities that would contribute to renal dysfunction (ie, diabetes or hypertension). A more than 50% eGFR recovery from the participants' baseline was observed in fewer than 30% of participants (28/100 [28%] who switched to TAF and 23/85 [27%] switched to abacavir, respectively;  $P > .1$ ). In another post TDF observational study of PLWH who switched to TAF, eGFR returned to normal levels in less than half of the participants at 1 year; those receiving an unboosted PI had a higher probability of improving (Abstract 693).

A cross-sectional study of older adults in 4 different ART exposure groups including different combinations of TDF and PIs (no TDF/no PI, TDF/PI, no TDF/PI, TDF/no PI) explored the relationship between renal tubular dysfunction and low bone mineral density (BMD) (Abstract 689). Lumbar spine BMD was lower in female participants, those with a lower body mass index, and a higher retinal-binding protein: creatinine ratio, but the association between lower BMD and renal tubular dysfunction was attenuated after adjustment for TDF exposure.

DTG, cobicistat, and rilpivirine each inhibit proximal tubular creatinine secretion with very modest declines in eGFR in clinical trials. Elias and col-

leagues examined changes in eGFR in a large observational study conducted in 21 Spanish sites. Participants who were taking 2 or more inhibitors of creatinine secretion had a greater decline in eGFR than those taking 1, suggesting an additive effect of these agents on measures of eGFR (Abstract 692).

HIV Outpatient Study (HOPS) investigators reported that 7% of adults experienced incident bone fracture between 2000 and 2017. Incident bone fracture was associated with a 50% increase in mortality. Not surprisingly, other factors associated with mortality included CD4+ count below 200 cells/ $\mu$ L, non-AIDS cancer, hepatitis C virus (HCV) infection, and chronic liver, renal, and cardiovascular disease. Among those with incident fracture, chronic renal disease and HCV infection remained independently associated with all-cause mortality. Although it is not possible to assess the causative role of fracture in mortality, these results confirm that fracture may be a poor prognostic sign (Abstract 30).

## Malignancies Among People Living with HIV

### Breast Cancer

Sadigh and colleagues presented a prospective cohort study of women diagnosed with breast cancer in Botswana (Abstract 16). The study enrolled 430 women, including 31% women living with HIV (WLWH). WLWH were younger than the women without HIV, but receptor status, cancer stage at diagnosis, and treatment plans were similar between groups. They found that the 2-year survival was lower for WLWH than those

### Administering the quadrivalent HPV vaccine prior to LEEP treatment of cervical HSILs did not improve HSIL outcomes

without HIV (57% and 73%, respectively). The vast majority of deaths were due to cancer and none were due to consequences of HIV infection. The reasons for this marked increase in breast cancer mortality are unclear.

### Cervical Cancer Prevention

Firnhaber and colleagues presented a double-blind, placebo-controlled, randomized trial of the quadrivalent human papillomavirus (HPV) vaccine in WLWH being treated with loop electrosurgical excision procedure (LEEP) for cervical high grade squamous intraepithelial lesions (HSILs) (Abstract 14). One hundred eighty were randomly assigned to receive vaccine or saline placebo at entry, week 4, and week 24. LEEP was performed on all women at week 4. Cervical colposcopy with biopsies and cervical cytology were performed for endpoint assessment at week 26 and 52. The investigators found no difference in the primary endpoint, cervical HSILs on cytology or cervical biopsy at week 26 or 52, between the vaccine and placebo arms (53% vs 45%, respectively; relative risk, 1.16; 95% CI, .87-1.6). This study does not support HPV vaccination to improve HSIL treatment outcomes in WLWH.

McGrath and colleagues evaluated HPV outcomes in a study that randomly assigned WLWH from Kenya who were diagnosed with cervical HSILs to either cervical cryotherapy or LEEP (Abstract 278). They found that women were more likely to clear cervical HPV infections after treatment with LEEP than after cryotherapy (36% vs 24%, respectively). The rates of reinfection with HPV were similar between arms. These results suggest that availability of LEEP should be expanded in cervical cancer screening programs in low- and middle-income countries.

Kuhn and colleagues presented data on the use of the Gene Xpert test for high-risk HPV for cervical cancer screening, a point-of-care diagnostic test (Abstract 279). They enrolled 586 women without HIV and 535 WLWH from South Africa. The WLWH had a higher prevalence of high-risk HPV than those without HIV (49% vs. 16%, respectively) and a higher prevalence of cervical HSILs on histology (17% vs 5.3%, respectively). For WLWH, they found a sensitivity for Xpert of 93% and a specificity of 60%. Limiting the test to 3 channels that test for 8 of 14 high-risk HPV types improved the specificity to 68% with preserving

sensitivity at 91%. Furthermore, they investigated higher HPV DNA thresholds for test positivity that reduced sensitivity to 85% and increased specificity to 77%.

### United States Preventive Services Task Force clinical criteria for lung cancer screening (age 55-80 and greater than 30-pack per year smoking history) perform poorly in PLWH

Higher specificity is essential if using primary HPV testing for cervical cancer screening.

### Lung Cancer

Sellers and colleagues reviewed participants who developed lung cancer in the MACS (Multicenter AIDS Cohort Study) and WIHS, and whether these cancers may have been detected using the United States Preventive Services Task Force recommended lung cancer screening of adults ages 55 to 80 years with a more than 30-pack per year history of tobacco use with low-dose CT scans (Abstract 15). They found that the criteria performed poorly in PLWH: only 16% of cancers in women and 24% of cancers in men would have been potentially diagnosed by these screening criteria. They found that the optimal criteria for WLWH were ages 49 to 75 years and a greater than 16-pack per year history. For men living with HIV, the optimal criteria were ages 43 to 75 years and a greater than 18-pack per year history.

### Kaposi Sarcoma

Histopathology services are limited in sub-Saharan Africa, but this is required for diagnosis of Kaposi sarcoma (KS). Semeere and colleagues presented data on the use of quantitative PCR of Kaposi sarcoma herpesvirus (KSHV) of skin biopsies as an alternative to histopathology for the diagnosis of KS in 506 participants undergoing skin biopsies (Abstract 20). Using a US-based pathology consensus panel as the gold

standard, they found that local interpretation had a sensitivity of 95% and a specificity of 70%. Using an optimized cutoff for KSHV detection in skin biopsy samples, they found that this test had 98% sensitivity and a specificity of 90%. The authors noted the potential for this test to be simplified and implemented in low- and middle-income countries resource constrained settings to improve KS diagnosis.

### Conclusion

The work presented at this year's CROI reminds us that we still have work to do to reduce the morbidity associated with long-term HIV treatment, including ending the high impact of TB infection on HIV outcomes. 

**All cited abstracts appear in the CROI 2019 Abstracts eBook, available online at [www.CROIconference.org](http://www.CROIconference.org)**

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