Review

CROI 2018: Advances in Antiretroviral Therapy

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The 2018 Conference on Retroviruses and Opportunistic Infections (CROI) showcased exciting data on new investigational agents including MK-8591 and tri-specific antibody targeting 3 highly conserved epitopes on HIV-1 in a single antibody. Clinical trials of initial antiretroviral therapy (ART) and switch studies involving bictegravir/emtricitabine/tenofovir alafenamide were presented. Intensification of initial ART with integrase strand transfer inhibitors did not increase the risk of immune reconstitution inflammatory syndrome. Pharmacokinetic issues were discussed, including the substantial drug-drug interactions between efavirenz-based ART and hormonal contraception delivered via a vaginal ring. Studies on pre-ART drug resistance and emergence of drug resistance after initial and second-line ART in different settings and populations were highlighted. Novel technologies to identify drug resistance included a free, cloud-based web service for HIV genotyping analysis and a promising technology for point-of-care drug resistance mutations testing. New strategies to improve the HIV care continuum included home-based testing with initiation of same-day ART and stratified care with specialized clinics to serve those disengaged in care, but the data on financial incentives were not encouraging. Several studies provided insights into the impact of early ART on decreasing the size of the HIV reservoir in HIV-infected infants. Pertinent conference findings relating to women's health issues included similar clinical outcomes between breastfeeding and formula feeding HIV-infected women, the problem of viral rebound and ART nonadherence in pregnancy and postpartum.

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Investigational Antiretroviral Drugs

MK-8591 is a nucleoside reverse transcriptase translocation inhibitor that mimics deoxyadenosine and is incorporated into the viral DNA by reverse transcriptase. It promotes chain termination by inhibiting translocation. Although MK-8591 has an extremely long half-life, allowing for weekly dosing, Matthews and colleagues presented data on pharmacokinetics of daily dosing of MK-8591 in preparation for coadministration with doravirine as combination antiretroviral therapy (ART) (Abstract 26). They administered 0.25 mg, 0.75 mg, and 5 mg daily to 3 HIV-uninfected cohorts. MK-8591 was well tolerated. Target drug concentrations were achieved rapidly after the first dose in all three groups. After cessation of dosing, drug concentrations remained above target concentrations for more than 30 days in the 0.25 mg daily cohort. Vaginal and rectal biopsies were performed and the concentrations were supportive for use as preexposure prophylaxis (PrEP).

Tri-specific Antibody

Pegu and colleagues presented data on engineered antibodies that target 3 highly conserved epitopes on HIV-1 in a single antibody. (Abstract 113LB) The lead tri-specific antibody inhibited nearly 100% of viral strains tested at low micromolar concentrations. The pharmacokinetic profile of the antibody was similar to that of VRC01, allowing for infrequent dosing.[1] Although antiviral activity has not been established for the tri-specific antibody, it was shown to protect 8 of 8 macaques from simian-human immunodeficiency virus (SHIV) in a challenge model.

Clinical Trials of Initial Antiretroviral Therapy and Switch Studies

Bictegravir/Emtricitabine/Tenofovir Alafenamide

Molina and colleagues presented data from a clinical trial that enrolled 563 participants living with virologic suppression on dolutegravir/abacavir/lamivudine for at least 3 months and randomly assigned them to continue the regimen or switch to bictegravir/emtricitabine/tenofovir alafenamide (TAF) (Abstract 22). Virologic suppression was similar 48 weeks after randomization, with 95% suppression in the dolutegravir/abacavir/lamivudine group and 93.9% in the bictegravir/emtricitabine/TAF group: difference 0.7% (95% confidence interval [CI], -1.0%, 2.8%). Virologic non-suppression was mostly due to missing HIV-1 RNA measurements. Both regimens were well tolerated.

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Kityo and colleagues presented similar data from a clinical trial enrolling 470 women living with HIV who were receiving an elvitegravir-based single tablet regimen or a ritonavir-boosted (/r) atazanavir-based regimen (Abstract 500). Participants were randomly assigned to stay on their current ART or switch to bictegravir/emtricitabine/TAF. Both groups did extremely well, with 99.2% and 98.7% being virologically suppressed 24 weeks after randomization respectively. Both regimens were well tolerated.

Andreatta and colleagues presented data combining resistance data from bictegravir/emtricitabine/TAF studies (Abstract 506). They reviewed prestudy genotypes and performed sequencing of HIV-1 DNA in baseline samples from those with on-study viremia and a subset of those without viremia. No participants in the bictegravir/emtricitabine/TAF arms developed new mutations. The presence of archived emtricitabine or TAF resistance-associated mutations did not adversely affect virologic outcomes. No participants in the dolutegravir/abacavir/lamivudine group developed resistance. The only treatment-emergent resistance mutations occurred in a participant who received darunavir/r and abacavir/lamivudine who developed an L74V mutation. Similarly, no participants in 2 clinical trials comparing bictegravir with dolutegravir as initial therapy developed resistance (Abstract 536). Baseline resistance did not affect virologic outcomes and responses did not differ by HIV-1 subtype.

Gaur and colleagues presented data on 24 adolescents living with HIV (age 12-18 years) virologic suppression who changed their current ART to bictegravir/emtricitabine/TAF (Abstract 844). All 24 remained virologically suppressed through 24 weeks. Bictegravir exposure was similar to that observed in adults. TAF and emtricitabine exposures were higher in adolescents than in adults, but were similar to that reported for currently approved regimens for adolescents containing these drugs.

Two-Drug ART Regimens

Cahn and colleagues presented data from a clinical trial that randomized 145 treatment-naive adults living with HIV to receive darunavir/r plus lamivudine/tenofovir disoproxil fumarate (TDF) or a generic fixed-dose combination of darunavir/r plus lamivudine (Abstract 489). They found that 94% and 93% were virologically suppressed 48 weeks after randomization, with a difference of -1.0% (95% CI, -7.5%, 5.6%). The TDF-containing regimen tended to have better lipid outcomes, but safety and tolerability were otherwise similar. These results support the continued investigation of 2-drug regimens for initial therapy.

Few data exist on the outcomes of 2-drug ART regimens in clinical practice. Perone and colleagues presented data from the OPERA (Observational Pharmaco-Epidemiology Research and Analysis) cohort, a collaboration of 400 HIV practitioners at 79 health care facilities in the United States (Abstract 510). They compared virologic outcomes for patients switching to 2-drug with 3-drug regimens. Of note, a large majority of the 2-drug regimens included a protease inhibitor (PI); emerging 2-drug regimens (dolutegravir/rilpivirine, dolutegravir/lamivudine, or a PI/lamivudine) were rarely used. Patients switching to 2-drug regimens were older, had more ART experience, and more comorbidities. When considering patients who switched while viremic or while suppressed, the virologic outcomes were generally similar between those switching to 2-drug or 3-drug regimens when adjusted for baseline factors.

Gagliardini and colleagues presented data from the AIDS Research Consortium of Atlanta (ARCA) database on virologic outcomes to 2-drug regimens containing lamivudine in patients with (n=87) and without (n=349) a history of a M184V mutation within the ARCA database (Abstract 498). Those with a history of M184V were older, had a lower nadir CD4+ cell count, and were on ART for a longer time. The virologic failure rate on the 2-drug regimen was not statistically significantly higher for those with a M184V than those without that mutation. There was a significantly higher rate of low-level viremia or "viral blips" in the M184V group. These results should be interpreted with caution as the population of participants with the M184V mutation was relatively small and most participants received a PI/r and lamivudine.

Integrase Strand Transfer Inhibitors and Immune Reconstitution Inflammatory Syndrome

Gibb and colleagues presented data from the REALITY (Reduction of Early Mortality in HIV-Infected Adults and Children Starting Antiretroviral Therapy) trial on the impact of raltegravir intensification of initial ART therapy on the immune reconstitution inflammatory syndrome (IRIS) (Abstract 23). This was a clinical trial that randomized 1805 people living with HIV with a CD4+ cell count below 100/μL in a factorial design to test several strategies to reduce early mortality in this population. One strategy involved randomly assigning participants to an initial standard ART regimen with or without 12 weeks of raltegravir. Raltegravir did not reduce early mortality or World Health Organization (WHO) stage 3/4 events, but did lead to a more rapid decline in plasma HIV-1 RNA level. The analysis compared the risk of IRIS between arms. A blinded endpoint review committee adjudicated all suspected IRIS events. They found that the rate and timing of IRIS events were similar between arms. They concluded that integrase strand transfer inhibitors (InSTIs) do not impact the risk of IRIS despite achieving a faster viral load decline.

Clinical Trials in Antiretroviral-Experienced Populations

Third-Line Antiretroviral Therapy

Few data exist on the outcomes of third-line ART in resource-limited settings. Grinsztejn and colleagues presented data from AIDS Clinical Trials Group (ACTG) Protocol A5288 that enrolled participants in whom first- and second-line ART had failed, with plasma HIV-1 RNA level above 1000 copies/mL after receiving a PI-based regimen for at least 24 weeks

(Abstract 30LB). Participants underwent real-time genotyping to select a new regimen. The study enrolled 545 participants who were divided into one of 4 cohorts based on resistance patterns. Overall, 47% were women, the median CD4+ cell count was 175/μL, the median plasma HIV-1 RNA level was 4.4 $\log_{10}$ copies/mL, and the median duration of ART use was 7.9 years. Nucleoside analogue reverse transcriptase inhibitor (nRTI)-associated resistance was observed in 62%, non-nucleoside analogue reverse transcriptase inhibitor (NNRTI)-associated resistance in 64%, and PI resistance in 36%. A total of 53% of participants enrolled into the trial had little resistance: no resistance to lopinavir/r and 1 or more active nRTI. These participants continued their second-line regimen. Participants in the other cohorts were placed on new ART regimens that generally included darunavir/r and raltegravir. These participants may have also received etravirine and an nRTI depending on their resistance pattern. Overall, a plasma HIV-1 RNA level below 200 copies/mL was achieved in 64% 48 weeks after entering the trial. Virologic suppression was lowest, 44%, in the group with the least resistance that continued their second-line therapy on study entry. Virologic suppression ranged from 74% in the cohort with the most extensive resistance to approximately 90% in the other cohorts. The authors concluded that darunavir/r and raltegravir with or without etravirine was highly effective as third-line therapy in those with resistance to lopinavir, and highlighted the need for real-time genotyping to select third-line ART in these settings. Additional strategies are needed for those in whom lopinavir/r is failing without resistance, a group challenged by adherence.

Subgroup Analyses of the DAWNING Trial

The DAWNING trial randomized people in whom their initial NNRTI plus 2 nRTIs was failing to LPV/r or dolutegravir plus 2 nRTIs. The study was stopped early for superiority of the dolutegravir arm.[2] Aboud and colleagues presented subgroup analyses from this trial examining the impact of choosing second-line nRTI components according to WHO recommendations on virologic outcomes (Abstract 508). Adherence to WHO-recommended, second-line nRTI was associated with better virologic outcomes. These results should be interpreted with caution as genotyping was used to select the second-line nRTI and at least 1 active nRTI was required.

Pharmacokinetic Considerations

Adherence Monitoring

Gandhi and colleagues presented data on the relationship between hair levels of antiretroviral drugs, a measure of longer term drug exposure, to virologic outcomes in ACTG A5257, a randomized clinical trial of 3 initial antiretroviral regimens (Abstract 24). Participants with hair drug levels in the lowest tertile had a much higher risk of virologic failure than the middle and highest tertile (26% vs 6% and 3%, respectively). On multivariable analysis, lower drug levels in hair were strongly associated with virologic failure. Interestingly, black race and lower educational status remained associated with virologic failure after controlling for hair drug levels.

Dried blood spot samples can be assayed for tenofovir diphosphate as a measure of longer term adherence. Castillo-Mancilla and colleagues presented results of a prospective cohort study that related tenofovir diphosphate concentrations in dried blood spots to virologic outcomes to ART (Abstract 25). They found that lower concentrations were associated with viremia. Among those with virologic suppression, lower concentrations were associated with black race, non-use of pharmacologic booster, and higher body mass indices. The authors concluded that tenofovir diphosphate concentrations in dried blood spot samples are a powerful predictor of virologic suppression.

ART Interactions With Vaginal Hormonal Contraception

Scarsi and colleagues presented results from ACTG A5316, a clinical trial that evaluated pharmacokinetic interactions between efavirenz or atazanavir/r-based ART and ethinyl estradiol/etonogestrol components of a vaginal contraceptive ring (Abstract 141). They enrolled cohorts of women living with HIV who were receiving efavirenz-based ART, atazanavir/r-based ART, or no ART. Approximately 25 premenopausal women were enrolled in each cohort. Compared with the control group of no ART, plasma ethinyl estradiol concentrations were reduced 53% to 57% among women receiving efavirenz and 29% to 35% among women receiving atazanavir/r. Plasma etonogestrol concentrations were reduced 76% to 79% among women receiving efavirenz and increased 71% to 79% among women receiving atazanavir/r. All control and atazanavir/r group participants achieved suppression of endogenous progesterone by 14 days of use and no participant had progesterone concentrations suggestive of ovulation. In contrast, efavirenz women were not suppressed until 21 days of use and 2 women had progesterone levels suggestive of ovulation. The authors concluded that the vaginal ring could be used effectively with atazanavir/r, but efavirenz-based ART may decrease the effectiveness of this contraceptive.

Dolutegravir Drug-Drug Interactions

Walimbwa and colleagues presented data on interactions of dolutegravir with 2 artemisinin-based antimalarial regimens, arthemether-lumefantrine and amodiaquine-artesunate (Abstract 459). Each regimen statistically significantly lowered dolutegravir trough concentrations, but this was deemed clinically insignificant given that the trough levels were still well above target concentrations and the short duration of antimalarial therapy. No meaningful interactions on the artemisinin-based regimens were observed and the authors concluded that standard doses can be used with dolutegravir.

Elliott and colleagues investigated the pharmacokinetics of darunavir/cobicistat and dolutegravir when dosed

concomitantly in 20 HIV-uninfected volunteers (Abstract 468). They found a 10% decrease in dolutegravir trough concentrations and a 7% decrease in darunavir trough concentrations. These interactions were felt to be clinically insignificant.

Long-Acting Antiretroviral Therapy

Ostermann and colleagues performed a survey of patients attending HIV clinics to understand patient interest in various strategies being considered for intermittent dosing of ART (Abstract 503). More patients were "very interested" in weekly oral dosing (66%) than were in injections every 2 months (38%) or subcutaneous implants every 6 months (18%).

The HIV Care Cascade: Achieving 90-90-90

The HIV care cascade models the sequential steps in effective care in and control of the epidemic: people living with HIV should move from diagnosis, to care engagement, to ART, to virologic suppression. The care cascade model, also called a continuum, was originally proposed at CROI by Carlos Del Rio in 2001,[3] and has been a focus of measuring effective HIV care since the Centers for Disease Control and Prevention (CDC) included it in national strategy in 2011.[4,5] In 2014, the Joint United Nations Programme on HIV/AIDS (UNAIDS) announced its ambitious 90-90-90 treatment goals: that 90% of people living with HIV will know their diagnosis, 90% of those will be on treatment, and that 90% of those will be virologically suppressed by 2020.[6] Encouraging new data on the care cascade across the globe presented at this year's CROI shed light on how close we are to reaching the 90-90-90 goals by 2020.

Perspectives on the US Care Cascade

A symposium entitled "Strategies for Improving the US Care Cascade" featured overviews from 4 researchers on specific aspects of the HIV care continuum. First, Del Rio (Abstract 60) provided an overview of the US HIV epidemic, with specific emphasis on disparities by race and ethnicity and by geography. Del Rio emphasized that social determinants of health, such as lack of health insurance, low educational attainment, poverty, and income inequality contribute to these disparities, which lead to the disproportionate HIV incidence in racial/ethnic minorities and in the US South. African Americans make up 12% of the US population but 44% of new HIV diagnoses. Similarly, the South, although it holds only 38% of the US population, is the venue for 50% of new HIV diagnoses. Even in settings with expanded access to care, such as San Francisco, racial and ethnic disparities exist in the care continuum, particularly when retention in care or virologic suppression are examined over time, rather than in cross-section.[7,8] Del Rio proposed that access to care and political commitment matter and called for all participants to retake our roles as activists.

Next, Scott and Mugavero (Abstracts 61 and 62) provided further insights into the importance of testing and linkage. Scott emphasized that programs involving real-time data sharing and direct outreach for linkage to care were most successful at post-diagnosis linkage to care. Mugavero focused on recent data demonstrating the rarity of sustained virologic suppression and that engagement in care is a dynamic process.[9,10] He proposed the use of missed clinic visits as an easily measurable marker of structural barriers to care and risk for disengagement and mortality.

Dombrowkski (Abstract 63) offered a different perspective on the care continuum, pointing out that public health investigations of "out of care" cases reveal that 50% are not actually out of care,[11] and that virologic suppression rates are often higher than cross-sectional estimates. She reviewed several studies of data to care initiatives where less than 15% of eligible cases were engaged in care through their interventions.[12-15] Dombrowksi proposed that asking patients who are disengaged to relink to the same system of care that failed to engage them in the first place is a failing strategy. Instead, she presented several innovative models of care that increased rates of virologic suppression for high-need patients. Examples include the Maximally Assisted Therapy program in Vancouver, which prioritizes immediate needs, such as housing, food security, and mental health; offers on-site directly observed therapy; and uses outreach teams to find those lost to care. Data from Seattle's Max Clinic, another example of innovative design for those neither engaged in care nor virologically suppressed (Abstract 1125), also suggest that walk-in access to care, immediate access to case management by phone, text, or in person, cross-agency coordinated care, financial incentives, and several other support services, can achieve high levels of virologic suppression compared with standard of care. Dombrowski argued that "tiered" approaches that identify high-need patients for enhanced care models can be a successful approach for achievement of virologic suppression and attainment of the final "90" of the care cascade.

New Data on the Care Cascade in Low- and Middle-Income Countries

Two notable sessions presented data on targeted and rapid scale-up of comprehensive HIV testing and treatment strategies in low- and middle-income countries. Kagaayi and colleagues presented data on the impact of a comprehensive HIV prevention program in an HIV hyperendemic mobile fishing community in Uganda (Abstract 90). The interventions deployed during a targeted and rapid scale-up in this community beginning in 2011 included: free HIV testing, male circumcision, condoms and behavioral prevention counseling, and linkage to HIV care and treatment. Investigators collected data in a series of 5 surveys between 2011 and 2017, interviewing 5,005 participants. Data on the impact of this program on sexual risk behavior, male circumcision coverage, and HIV incidence are reviewed elsewhere in this issue of *Topics in Antiviral Medicine* https://www.iasusa.org/sites/default/files/uploads/26-1-buchbinder-liu.pdf. Between

December 2011 and December 2016, self-reported ART coverage increased from 19% to 81% among people living with HIV, and virologic suppression to below 1000 copies/mL increased from 33% to 78%, although ART coverage was lower in younger age groups and in men over time. Study findings were limited by the high prevalence of out-migration in this community, but the authors conducted appropriate sensitivity analyses and the differences remained statistically significant. These results on the positive impact of this comprehensive HIV prevention, diagnosis and linkage to care strategy in a highly mobile and hyperendemic community are very encouraging.

Another piece of encouraging news came from Thin and colleagues (Abstract 91), who presented country-level data on 90-90-90 targets from the Lesotho Population-based HIV Impact Assessment (LePHIA) study, a national household-based survey including HIV and viral load (HIV-1 quantitative RNA) testing conducted between November 2016 and May 2017. Data on the care cascade showed that: 77.2% of people living with HIV were diagnosed, 90.2% of those were on ART, and 88.3% of those were virologically suppressed. There were clear disparities by age and sex, with better outcomes for women and those of older age.

Several presentations covered what is often the most challenging component of the care cascade, the transition from awareness of HIV diagnosis to linkage to care. Sibanda and colleagues (Abstract 150LB) presented data from a cluster randomized trial within the STAR (HIV Self Testing Africa) initiative exploring the impact of conditional incentives, given to lay HIV self-test distributors, on linkage within 6 weeks of the completion of the testing campaign by their self-testing clients. They found no impact of these financial incentives on linkage to any service: 28.7% in the intervention arm and 31.2% in the control arm. They were surprised to find that most people testing positive for HIV in this study were already on ART, and they did see a small impact of the intervention (adjusted odds ratio [aOR] 1.59; 95% CI, 1.05, 2.39) when they restricted their analysis to those who were newly diagnosed with HIV. They also conducted a nested nonrandomized differences-in-differences study on the impact of HIV self-testing on demand for ART, which did show a statistically significant increase in demand for ART in community health facilities during the self-testing campaign period, though not before and after.

Further highlighting challenges of linkage, Steele and colleagues found that only 36% of those newly diagnosed after community-based testing in KwaZulu-Natal were linked to care within 6 months (Abstract 1089). Ayieko and colleagues used a structured patient-centered phone call from a clinical officer following HIV testing to improve linkage for those newly diagnosed or re-engagement in care for those out of care in 5 Kenyan communities (Abstract 1090). In a randomized controlled trial of 130 participants, they found increased linkage in the intervention arm (41%) compared with the control arm (24%, $P<.05$). It is concerning that less than half of the population was linked to care, even with intervention, across all 3 of these studies.

HIV Treatment Strategies and Outcomes Including Life Expectancy and Mortality

Treatment Strategies: Rapid ART Initiation, Financial Incentives, and Other Services

Several investigators presented data on the impact of innovative treatment strategies on virologic suppression and other treatment outcomes. Highlights included new data on the impact of rapid ART start programs, financial incentives, and integration of substance use treatment.

Rapid ART initiation became standard of care in San Francisco in 2015 as part of the San Francisco Getting to Zero Consortium. The program included linkage to care within 5 or fewer days for all new confirmed HIV diagnoses and initiation of ART at the first care visit. Bacon and colleagues compared San Francisco Department of Public Health HIV case registry data between 2013 and 2016 to examine the impact of this program (Abstract 93). The number of people living with HIV who went from diagnosis to care within 5 days and started ART within 1 day of their first clinic visit increased from 23 (6% of new diagnoses) in 2013 to 80 (30% of new diagnoses in 2016). The time between diagnosis and achieving an HIV-1 plasma RNA level below 200 copies/mL decreased from 134 days in 2013 to 61 days in 2016. Latinos and individuals who were homeless had the greatest improvements in time from diagnosis to initiation of ART and to achieving virologic suppression. Despite these efforts, 16% of those newly diagnosed in 2016 remain without ART. They are analyzing data on long-term retention and durability of virologic suppression but have found retention above 90% at a median of 1.1 years follow-up at San Francisco General Hospital.

Labhardt and colleagues pursued an alternative approach for rapid initiation of ART in the CASCADE trial, which determined the impact of same day home-based HIV testing and initiation of ART in Lesotho.[16] This randomized clinical trial compared standard of care, home-based HIV testing and linkage to care, with the intervention—home-based testing with same-day initiation of ART with a 30-day medication supply. Linkage to care within 3 months was more common in the intervention arm (69%) than in the control (43%, $P<.001$), as was virologic suppression at 12 months: 50% in the intervention arm and 34% in the control ($P<.007$). Retention in care remained statistically significantly higher in the intervention group throughout the 1-year study period. These encouraging results, which achieved higher rates of linkage to care than other interventions presented at CROI, will no doubt lead to similar efforts to collapse the care cascade in other settings.

Several studies explored the impact of financial incentives on virologic suppression in highly divergent contexts. Thirumurthy and colleagues conducted a randomized clinical trial in Uganda, testing the impact of an intervention, unconditional cash transfers as escalating financial incentives to achieve viral suppression to below 400 copies/mL, compared with a control group that received a single unconditional cash transfer at enrollment (Abstract 95). They did not find any impact of the intervention on virologic suppression at 24 or 48 weeks. Investigators believe these findings

may be influenced by high rates of engagement and virologic suppression at baseline in the cohort, although when they limited their findings to those participants who were not virologically suppressed at baseline, there was still no impact of the intervention.

Feaster and colleagues presented long-term outcomes from the Project Hope study, which was a 3-armed randomized clinical trial of hospitalized substance users with HIV infection comparing: 1) 6 months of patient navigation, 2) patient navigation and financial incentives, and 3) treatment as usual. Previous studies showed that the participants randomly assigned to patient navigation and financial incentives had higher rates of viral suppression at 6 but not 12 months after randomization, compared with treatment as usual.[17] Investigators presented follow-up data for 422 participants (53% of the original cohort) who consented to long term follow-up (median observation time, 3.3 years) and found overall low rates of viral suppression (33%). Substance use, determined by urine drug screening, remained high throughout the followup period (60%-71%) and rates of death were high (26% since randomization), but neither differed by study arm. Neither the data presented by Thirumurthy nor Feaster encourage the use of financial incentives as leverage to increase rates of virologic suppression.

In contrast, Springer and colleagues examined the impact of naltrexone use in incarcerated individuals with opioid or alcohol use disorders who were transitioning back into the community (Abstract 96). Investigators conducted 2 separate double-blind placebo-controlled randomized trials, in which those with either opioid use disorders in the NEW HOPE (Needing Extended-Release Wellness Helping Opioid-Dependent People Excel trial) or those with alcohol use disorders in Project INSPIRE were randomly assigned to the intervention of a naltrexone injection within 7 days of release from incarceration followed by 6 monthly injections, or the placebo injections (control group). In NEW HOPE, 37.9% of those receiving naltrexone were virally suppressed (to <50 copies/mL) at baseline and 60.6% at 6 months ($P = .002$). In the placebo arm 55.6% were virologically suppressed at baseline and 40.7% were suppressed at 6 months ($P = .294$). The results of Project INSPIRE were similarly encouraging, with viral suppression increasing from 31% to 56.7% between baseline and 6 months in the intervention arm but decreasing from 42% to 30.3% over 6 months in the placebo arm. The investigators conclude that naltrexone can help maintain or achieve virologic suppression in a context in which maintenance of suppression is rare: those with opioid or alcohol use disorders being released from incarceration.

Perspectives on Living with HIV

In 2018, 50% of adults living with HIV in the United States are over 50 years of age, and people living with HIV are living longer, healthier lives. However, the burden of non-HIV related comorbidities in this aging population is growing, and subpopulations with HIV in the United States and in low- and middle-income countries still experience late presentations to care with advanced HIV disease and early mortality. This year's CROI provided new data on what it means to live with HIV in 2018, and included a symposium entitled "Life Expectancy at 25" that reviewed data on life expectancy, the impact of comorbidities, and the implications of chronic inflammation for people living with HIV (Symposium S-6).

Data from the Veterans Aging Cohort Study (VACS), which includes national Veterans Administration electronic health records, consistently provides insights into the impact of aging with HIV. Justice and colleagues pooled data from the VACS, the CDC HIV surveillance report, and a public HIV clinic based at Yale New Haven Hospital to explore the presentation of HIV by age and whether non-HIV related conditions should trigger diagnostic testing for HIV (Abstract 92). They found that from 2010 to 2015, those 50 years of age or older comprised 48% of new diagnoses in the VACS, 24% at the public HIV clinic, and 18% in the CDC surveillance report. In the VACS and the public HIV clinic cohorts, those over 60 years of age were more than twice as likely as those under 40 years of age to be diagnosed with a concomitant AIDS-defining illness, a CD4+ cell count under 200/μL, or an AIDS diagnosis.

Finally, they used VACS cohort data to demonstrate that age-associated non-AIDS diagnoses of bacterial pneumonia, herpes zoster, anemia, lymphocytopenia, or thrombocytopenia were all more common in older individuals with HIV infection. These 5 diagnoses raised the relative risk of HIV diagnosis in all age groups, although the association was less strong for those over 60 years of age for anemia and lymphocytopenia. The investigators suggest that anyone presenting with bacterial pneumonia, herpes zoster, or thrombocytopenia should be tested for HIV, regardless of the current age-based guidelines that recommend routine HIV testing up to 65 years of age.

There were many notable presentations on mortality in people living with HIV. Gaolathe and colleagues compared mortality rates in those living with HIV with those without HIV who were participating in the Botswana Combination Prevention Project, a pair-matched community-randomized HIV prevention trial in 30 rural and peri-urban communities throughout the country (Abstract 97). This trial has rigorous ascertainment of cause of mortality through household interviews, medical record data, and death certificate review. Among 12,156 participants with a mean duration of vital status follow-up of 2.1 years, morality rates were 257/100,000 person years (py) in those without HIV and 957/100,000 py in those with HIV. Compared with those who were HIV-uninfected, infectious causes of death were more common for those not receiving or in their first year of ART, but nearly half of deaths among those with HIV infection were from non-infectious causes. Cancer led to 24% of deaths in those with HIV and 19% of those without.

Late presentation to care and HIV-related mortality, particularly in key populations, remain a challenge in the global fight to end AIDS. In the past 12 months, the WHO, Médecins Sans Frontières, and ICAP (the International Center for AIDS Care and Treatment Programs) of Columbia University released guidelines relevant to the care of people with

advanced HIV disease,[18-20] and a Themed Discussion led by Nathan Ford provided an excellent overview and discussed new data on this topic (Themed Discussion 11).

Three presenters examined life expectancy within United States- and Canadian- based cohorts. Althoff and colleagues used data from the NA-ACCORD (North American AIDS Cohort Collaboration on Research and Design) to examine life expectancy in key populations living with HIV in the United States and Canada (Abstract 903). For people who inject drugs, life expectancy between 2012 and 2015 was 16 years lower than those not injecting drugs, and for black men who have sex with men (MSM), life expectancy was 14 years lower than for white MSM. Both these disparities persisted when analysis was restricted to those initiating ART with a CD4+ cell count above 350/μL. Black and white women had similar life expectancies, but when analysis was restricted to those initiating ART with a CD4+ cell count above 350/μL, black women had higher life expectancy, likely due to increased risk of deaths from drug or alcohol use in white women.

Sun and colleagues also examined mortality in injection drug users (IDUs) in the ALIVE (AIDS Linked to the Intravenous Experience) cohort in Baltimore (Abstract 891). Overall mortality increased in the 4794 individuals in the cohort (25.8% of whom were living with HIV) from cohort inception in 1988 through the introduction of combination ART in 1997. As expected, for people living with HIV, AIDS- and infectious diseases-related mortality increased until 2000, and then dropped precipitously as the median CD4+ count rose. Mortality from chronic diseases increased throughout the observation period. Mortality from drug overdose or drug-related causes increased from 1988 to 1999 and decreased from 2000 to 2010 as injection drug use prevalence decreased. Of concern, mortality in injection drug users has increased again between 2010 and 2015. The investigators speculate that the recent increase in drug overdose and drug-related deaths is linked to the opioid epidemic.

Palella and colleagues explored a different aspect of mortality risk in people living with HIV by using data from the HOPS (HIV Outpatient Study) to explore the association between long-term HIV viral exposure and mortality (Abstract 901). After examining the associations between overall mortality and several different measures of viral exposure, the most effective model to predict mortality included the most recent HIV RNA value and the percentage of person years with an HIV RNA level above 200 copies/mL. However, each measure of viral load exposure they tested was associated with mortality.

Two presentations in this session explored mortality in the context of hospitalization or advanced HIV disease in low- and middle-income countries. Hoffman and colleagues characterized mortality, readmission, and engagement in care following inpatient hospitalization in 121 individuals in a hospital in South Africa (Abstract 902). They found high rates of mortality (26%) and readmission (53%) 6 months after hospitalization. Factors associated with readmission or death in a multivariate analysis included: skipping clinic visits because it was "hard to get to" and having no recorded post-hospitalization clinic visit, but no specific clinical criteria were associated with death. These data suggest that a systems approach to support outpatient followup after hospital discharge could help reduce the high rates of mortality for hospitalized people with HIV infection.

Teasdale and colleagues used data from ICAP-supported HIV care sites in Ethiopia, Kenya, Mozambique, and Tanzania to determine loss to follow up and death for 3 CD4+ cell count strata within those qualifying as having advanced disease: fewer than 50/μL, 50 to 100/μL, and 101 to 200/μL (Abstract 898). They found that those with fewer than 50 CD4+ cells/μL had a 40% increased risk of loss to follow up or death, and those with CD4+ cell counts of 101 to 200/μL had similar risk to that of those with CD4+ cell count above 200/μL. Considering this heightened risk for poor outcomes, they propose the creation of differentiated service delivery models for those living with HIV who have CD4+ cell counts below 100/μL. Considering that other data from low- and middle-income countries at CROI show that 1 in 5 patients not on ART have a CD4+ cell count below 200/μL (Abstract 887), it is likely that efforts to increase movement through the HIV care cascade will result in more individuals presenting to care with advanced disease, requiring specialized attention and services.

HIV Resistance

Epidemiologic Studies of Drug Resistance

With the international scale-up of ART, epidemiologic surveillance of drug resistance remains crucial to ensure that recommended ART regimens are regionally appropriate and that public health interventions can be initiated if rates of drug resistance mutations (DRMs) are unacceptably high.

Identifying Networks of Transmitted Drug Resistance

In an effort to track transmitted drug resistance (TDR) among patients newly diagnosed with HIV in Mexico City, Matías-Florentino and colleagues (Abstract 523) combined results from baseline HIV-1 resistance tests with genetic network analysis of patients newly diagnosed with HIV infection seen at the Condesa Clinic, the largest HIV clinic in Mexico. Network analysis demonstrated that 39% (747/1916) of sequences had a putative linkage with at least 1 other sequence forming 264 clusters. In 84 sequences, the same DRM was shared (>5% cutoff) with a linked sequence in 33 distinct clusters. The K103N mutation was the most frequently encountered DRM among the linked sequences at 61%. The linked sequences with common DRMs may represent TDR. These findings highlight the need to prevent initiation of TDF transmission chains by improving retention in care and minimizing the turnaround time for clinicians to receive and act on resistance results. They also posited that next generation sequencing (NGS) to detect DRMs at a cutoff of above 5% had a moderate advantage over Sanger-like sequencing (>20% cutoff) as there were a few cases of linked low-frequency DRMs identified.

In a similar analysis of 714 HIV-1 infected ART-naive individuals in the Cologne-Bonn region of Germany (Abstract 524), genetic network, geospatial, and drug resistance mutation analyses were combined to detect and characterize putative transmission clusters of TDR. The researchers identified 77 transmission clusters and the frequency of DRMs was comparable in clustering (17.5%) and non-clustering individuals (17.1%). Of the 133 linked, DRM-containing sequences, 17.3% were between genetically linked partners with shared DRMs. Clustering individuals with or without DRMs were mostly located in the city centers and among men who have sex with men. This methodology could be used to identify hotspots of transmission and TDR to target prevention and treatment interventions.

Regional Variation in Pretreatment Drug Resistance

Several studies highlighted the importance of monitoring pretreatment drug resistance as rates of TDR can be affected by system-wide changes including introduction of new ART to the market, changes in national or regional treatment guidelines, changes in ART accessibility, and introduction of new interventions such as test and treat and PrEP.

A study of the French National Agency for AIDS/HIV Research (ANRS) program for HIV-1 resistance surveillance among 1121 ART-naive patients in 2014 to 2016 (Abstract 529) showed a stable prevalence of overall pretreatment drug resistance (PDR) (10.8%) but a high level of NNRTI-associated PDR (12.9%) and relatively high prevalence of InSTI-associated PDR (5.3%) suggesting that additional public health interventions to prevent TDR are warranted. In Florida, HIV-1 genotype sequences reported to the Florida Department of Health HIV/AIDS Surveillance System were analyzed for patients with newly diagnosed HIV infection (n = 3970; Abstract 526). Overall rates of PDR remained relatively stable from 2015 to 2016 (12.7% and 11.0%, respectively) but NNRTI-associated PDR decreased from 10.2% to 7.8% and InSTI-associated PDR increased from 1.4% to 2.3%. Ongoing surveillance is needed to further delineate trends in this area.

A study of PDR among 5484 ART-naive patients in Spain (Abstract 528) showed that from 2007 to 2017, rates of PDR remained stable around 8%, with a peak in 2013 to 2014 that correlated with inclusion of rilpivirine as an initial agent for ART in the Spanish Grupo de Estudio del SIDA-SEIMC (GESIDA) guidelines. In 2015, recommendations changed to include only InSTI-based regimens in conjunction with nRTIs as initial regimens and subsequently there was a sharp decline in rates of baseline resistance to initial ART (11.8% in 2014 vs 2.2% in 2015-2017). This highlights the positive impact epidemiologic surveillance with appropriate intervention can have on TDR.

Impact of Pretreatment Drug Resistance on Clinical Outcomes

In a study of 564 patients enrolled in a randomized clinical trial of routine virologic monitoring versus targeted monitoring in Vietnam from 2011 to 2017 (Abstract 525), rates of PDR were stable (<10%) and there was no difference in rates of virologic failure (HIV RNA >200 copies/mL) over 36 months in those with and without baseline PDR (aOR, 1.45; 95% CI, 0.41-3.98) nor between those who were randomly assigned to routine virologic monitoring and those who were not (aOR, 0.87; 95% CI, 0.49-1.52).

In a substudy (Abstract 533) of patients the HIV Prevention Trials Network (HPTN) 052 in which serodiscordant couples were enrolled and the HIV-infected index patients were randomly assigned early ART (ART initiation with a CD4+ cell count 250-550 cells/μL) or delayed ART (ART initiation delayed until a CD4+ cell count ≤250 cells/μL), an analysis of PDR among patients with virologic failure in the early (n = 151) and delayed (n = 98) arms was performed. In total, 4.7% of participants had resistance at baseline and 35.5% had new resistance at the time of treatment failure. New resistance at treatment failure was more common among those randomly assigned to the delayed treatment arm (43.4% vs 30.5%; $P = .06$), those on a regimen of efavirenz, lamivudine, and zidovudine (40.5% vs 20.8%; $P = .0074$), and those who had a higher baseline HIV RNA level (per unit $\log_{10}$ copy/mL increment OR, 2.54; 95% CI, 1.63-3.98).

Substantial variation in disease progression among HIV subtypes has been described but variation among non-B HIV-1 subtypes with respect to viral suppression with initial ART has been limited by small sample sizes. Poon and colleagues (Abstract 540) combined HIV-1 sequence and clinical data records from several study cohorts and clinical sites in Uganda to create the largest database of initial treatment failures in Uganda studied to date. In their analysis, they found there were no associations of HIV-1 subtype with treatment failures regardless of subtype. Subtype A and D recombinants, however, were significantly less likely to be among treatment failures and the authors suggest intersubtype recombinations may be an important barrier to the emergence of drug resistance.

Development of Resistance after Initial and Second-Line ART

In resource-limited settings, availability of viral load testing and resistance testing is often limited or nonexistent, which can result in patients with virologic failure remaining on compromised regimens leading to the emergence and accumulation of DRMs.

WHO guidelines do not include resistance testing in the algorithm for patients on a failing initial ART regimen. Rather the recommendation is to continue the regimen, provide adherence counseling, and if the repeat HIV RNA level is above 1000 copies/mL in 3 months, to change to a second-line regimen. In an argument to include resistance testing in the algorithm, McCluskey and colleagues (Abstract 530) conducted a retrospective genotype analysis of Ugandan patients on at least 4 months of an initial ART regimen with an HIV-1 RNA level above 1000 copies/mL. They found intermediate- to high-level resistance in 52% (47/90) of these patients and

in a majority the second-line regimen failed to resuppress regardless of the level of adherence.

Meloni and colleagues (Abstract 538) conducted a retrospective analysis of patients in Nigeria who had virologic failure on an initial regimen containing zidovudine (n=103) versus TDF (n=88) and of the impact of DRMs on second-line options. Patients on zidovudine were almost 10 times more likely to have a compromised second-line option compared those on TDF (aOR, 9.90; 95% CI, 2.58-37.99). Accumulation of DRMs was higher among those who had a delayed switch to a second-line regimen and the delayed switch magnified the effect of zidovudine to limit effectiveness of second-line options. These data reinforce the benefits of a TDF-based regimen over one including zidovudine and support limiting the amount of time between detection of virologic failure and ART switch to limit accumulation of DRMs and increase the likelihood that second-line ART will be effective.

In a study of Ethiopian children enrolled in the EPHIC (Ethiopia Pediatric HIV Cohort; Abstract 539), 12% (94/780) of children on an initial ART regimen experienced virologic failure. Of the participants with virologic failure and successful genotyping, 81% had at least 1 DRM: 69% to nRTI and NNRTI; 10% to NNRTI alone; 1% to nRTI alone; 1% to PI, nRTI, and NNRTI. These mutations had a substantial impact on second-line ART regimens; 100% of those with NNRTI resistance were resistant to the 2 WHO-recommended NNRTIs (efavirenz and nevirapine) and 42% had resistance to all 4 WHO-recommended nRTIs (abacavir, lamivudine, zidovudine, and tenofovir). Resistance testing was performed using dried-blood spot-based genotyping demonstrating its use in settings such as this, where plasma HIV-1 RNA genotyping is not feasible.

In a retrospective analysis of patients enrolled in a cluster-randomized trial of HIV viral load monitoring in Lusaka, Zambia (n=1973; Abstract 537), only 8.4% of patients on an NNRTI-based regimen (efavirenz or nevirapine) had virologic failure over 4446 person years. 23% of those with virologic failure had major NNRTI-associated DRMs at baseline, but in a Kaplan-Meier survival analysis, the presence of these mutations did not affect overall mean time to failure. At virologic failure, 82% had a major nRTI or NNRTI DRM. More DRMs were detected in patients who had a longer time to ART switch after first detection of virologic failure. Among patients on TDF-based regimens that failed, prevalence of TDF-associated resistance increased from 42% at time of failure to 58% for those who had not made a switch until 30 months after failure was first detected. Prevalence of resistance to second-generation NNRTIs in the delayed switch group was 70%. These high rates of failure show the consequences of remaining nonadherent to ART or remaining on a failing regimen. Without viral load and genotype testing, clinicians are hampered from identifying patients who need adherence interventions and/or a change in regimen.

Kityo and colleagues (Abstract 531) investigated the impact of raltegravir intensification on HIV resistance for patients enrolled in the REALITY trial, a randomized controlled trial in Kenya, Uganda, Zimbabwe, and Malawi in which ART-naive patients with a CD4+ cell count below 100 /μL were randomly assigned to 12 weeks of standard ART (2 nRTIs + an NNRTI; Std) or standard ART plus RAL (Std+RAL). At 12 weeks, 6.6% (45/677) of patients randomized to Std+RAL had an HIV-1 RNA level above 1000 copies/mL. Fifteen percent of patients with virologic failure and successful InSTI genotype testing (5/33) had InSTI-associated DRMs, 9% had intermediate- or high-level raltegravir resistance, and none had intermediate- or high-level dolutegravir resistance. At 48 weeks, 11.6% (76/654) in the Std+RAL group and 14% (90/642) in the Std group had an HIV-1 RNA level above 1000 copies/mL. K219E/Q, K101E/P, and P225H mutations were less common in the Std+RAL group and no difference was seen between the groups with other reverse transcriptase mutations, nor with predicted intermediate- or high-level resistance to the most commonly used NNRTIs and nRTIs. The authors concluded that at 48 weeks there was no clinical benefit to raltegravir intensification and it did not substantially protect against clinically relevant nRTI or NNRTI resistance.

In a study of patients with virologic failure on a lopinavir/r-based, second-line ART regimen from 15 clinics in Namibia (Abstract 541), 160 (67%) had genotypes available and 70% had evidence of any DRM, 51% with any nRTI DRM, 63% with any NNRTI DRM, and 13% any DRM. The authors suggest that given the high proportion of patients without PI-associated resistance, many may achieve viral suppression with enhanced adherence strategies and no change in ART. Epidemiologic surveillance of DRMs in patients in whom second-line regimens are failing is important to determine whether or not virologic failure is more of an adherence issue or a resistance issue, to ensure that effective ART is available for patients in whom second-line regimens are failing, and to determine if changes should be made in recommended second-line regimens.

In Abstract 554, Abela and colleagues conducted a case-control study of risk factors for acquired drug resistance (ADR) in patients enrolled in the SHCS (Swiss HIV Cohort Study). There were 115 patients with ADR who were randomly matched with 115 patients without ADR. Patients with difficult psychosocial barriers to adherence such as unemployment (OR, 2.1; 95% CI, 1.9-8.6), limited education (OR, 3.1; 95% CI, 1.1-8.1), and psychiatric comorbidities or adverse effects (OR, 2.1; 95% CI, 1.1-4.3) were at a higher risk for ADR, suggesting that identifying and addressing these barriers may prevent ADR.

Prevalence of DRMs in Different Settings

Zhang and colleagues (Abstract 550) evaluated the prevalence of DRMs among HIV-infected men who have sex with men (MSM) living in sub-Saharan Africa. Baseline laboratory test results of men enrolled in HPTN 075 were analyzed for presence of antiretroviral drugs, HIV-1 RNA level, and HIV-1 resistance. Sixty-five point six percent (120/183) of the men were not on ART, 17.4% (11/63) of men on ART were not virally suppressed, and 54.5% (6/11) of those men had at least 1 DRM, with M184I or M184V being the most common DRMs

identified, followed by K103N. The high percentage of HIV-infected men not on ART, high number men on ART who are not virally suppressed, and high rates of DRMs among those who are not virally suppressed emphasize the importance of improving HIV care for African MSM.

In a similar study of young women enrolled in HPTN 068 (Abstract 551), a prospective cohort study of South African high school women who received annual HIV testing until expected graduation date, enrollment samples and samples from the first clinical visit for women who became infected with HIV-1 after enrollment were studied for the presence of antiretroviral drugs, HIV-1 RNA level, and HIV-1 genotype. Of women with HIV-1 at enrollment, 12.5% (10/80) had antiretroviral drugs detected, and 13.4% (9/67) of the women who had resistance testing had resistance detected. For women who seroconverted during the study, antiretroviral medications were detected at first HIV clinical visit in 9.9% (16/162) and 5.6% (9/162) had major resistance mutations.

Botswana was one of the first countries to implement a test and treat strategy, and in 2016 became the first sub-Saharan African country to use dolutegravir-based ART as the initial regimen. In the context of this countrywide scale-up, prevalence of nRTI- and NNRTI-associated DRMs (Abstract 552) and InSTI-associated DRMs (Abstract 542) was evaluated through a random sample of 2998 HIV-infected individuals enrolled in the Botswana Combination Prevention Project. HIV-1 RNA and proviral DNA templates were used for amplification for genotyping. Overall prevalence of nRTI and NNRTI DRMs was 7.9%, and rates of nRTI-associated and NNRTI-associated DRMs was 2.7% and 6.9%, respectively. 96.7% of patients on ART were virologically suppressed and rates of resistance among those on ART without viral suppression was 17.1% for nRTI-associated DRMs and 27.6% for NNRTI-associated DRMs. Among patients not on ART, overall prevalence of nRTI and NNRTI DRMs was 5.8%, and rates of nRTI- and NNRTI-associated DRMs were 1.6% and 4.8%, respectively. In the evaluation of InSTI-associated resistance (Abstract 542), prevalence of any InSTI-associated DRM was 2.43% and rates of resistance were similar between those who were on ART and those who were ART-naive. The low prevalence of DRMs is reassuring but there was a trend toward moderate but increasing rates of nRTI-associated and NNRTI-associated DRMs over time. These findings highlight the importance of on-going public health surveillance of DRMs to measure treatment success and monitor for concerning trends.

Through the HOPE in Action study, the first successful HIV-positive-to-HIV-positive kidney and liver transplants have occurred in the United States. There is a theoretical risk of superinfection with an ART-resistant or CXCR4-tropic virus from HIV-infected deceased donors (HIVDDs) to HIV-positive transplant recipients. Bismut and colleagues (Abstract 553) evaluated the genotypes and coreceptor tropism in potential HIVDDs and found that rates of ART-resistance and CXCR4-tropism to be comparable to levels in the general population. Twenty-six percent (8/31) of those with samples that were successfully genotyped had at least 1 DRM. The most common DRMs found were associated with NNRTIs (n = 4), followed by nRTIs (n = 3), PIs (n = 2), and InSTIs (n = 1). Successful coreceptor tropism phenotype was performed in 25 participants and a majority had dual/mixed virus (n = 12) followed by exclusive CCR5-tropic virus (n = 10); none had CXCR4-tropic virus identified. These are preliminary results and to fully appreciate if HIVDD drug resistance or tropism status affects the HIV-infected transplant recipient outcomes, surveillance of resistance and HIV tropism should continue in this population.

Low-Frequency HIV-1 Drug Resistance Mutations

The prevalence and clinical impact of minority resistant variants (MRVs), DRMs that occur in less than 20% of the viral population, remain an area of active research.

A study of PDR detected using NGS was performed (Abstract 527) using baseline stored plasma specimens from 3365 patients who enrolled in the START (Strategic timing of Antiretroviral Treatment) study, an international trial of immediate versus deferred ART in ART-naive individuals with CD4+ cell counts above 500/μL. The investigators found that a detection threshold of 2% or higher identified more PDR than a higher than 20% threshold, with prevalence for PDR as follows: any 19.7% versus 8.3%; nRTI-associated 6.1% versus 2.7%; NNRTI-associated 7.0% versus 4.3%; PI-associated 9.0% versus 2.1%; and InSTI-associated 0.9% versus less than 0.1%. The clinical impact of these MRVs is unknown and warrants further investigation.

In a study (Abstract 545) of the impact of MRVs on virologic response to InSTI-based regimens, Sanger sequencing and ultra-deep sequencing (UDS) were performed on samples from 134 patients in whom an InSTI-based regimen (with raltegravir, elvitegravir, or dolutegravir) was failing. At least 1 InSTI-related DRM was identified in 40% of subjects. In addition to DRMs identified through Sanger sequencing, UDS detected additional InSTI-related DRMs in 9% (>5% cutoff) and 18% (>1% cutoff) of sequences leading to a change in the InSTI-resistance interpretation among 7% and 13% using greater than 5% and 1% cutoffs, respectively. Prevalence of MRVs at baseline was similar among patients with virologic failure (14.7%) and those with virologic success (12.9%). The MRVs present at baseline were not associated with virologic failure and did not emerge with virologic failure.

Boltz and colleagues (Abstract 536) hypothesized that MRVs with dual-class resistance are associated with virologic failure but that MRVs with single-class resistance are not. Using a novel, ultrasensitive, NGS assay that can detect rare variants with linked DRMs, the researchers sequenced baseline samples from women in the nevirapine/emtricitabine/TDF arm of the ACTG A5208/OCTANE trials. The study supported their hypothesis as the percent of patients with linked DRMs on the same genome was statistically significantly higher in the virologic failure group than the virologic success group whereas linked single-class DRMs were not associated with failure in either trial.

Using a case-control study nested in the multi-country PASER (Pan-African Studies to Evaluate Resistance) cohort,

Inzaule and colleagues (Abstract 534) evaluated different detection thresholds of PDR to predict risk of virologic failure. They concluded that a 5% cutoff appears adequate as the sensitivity to detect cases was higher than that 20% (standard) and 10% cutoff with minimal compromise to specificity, but the marginal gain to the 20% cutoff is small.

Characterization of Drug Resistance Mutations

InSTI Drug Resistance Mutations

T97A is a polymorphism found infrequently in (InSTI)-naive individuals that also emerges in patients in whom InSTI-based regimens are failing. T97A by itself has minimal effects on InSTI susceptibility but in combination with major InSTI DRMs, it synergistically reduces susceptibility to elvitegravir and raltegravir. The contribution of T97A to dolutegravir resistance in the setting of other InSTI DRMs is poorly characterized. Kuriakose and colleagues (Abstract 543) described 2 highly treatment-experienced individuals with pre-existing multidrug resistant (MDR) HIV-1 including with the Q148H and G140S integrase DRMs who developed virologic failure while on dolutegravir as part of a salvage regimen. Both patients had isolated emergence of T97A that led to a greater than 10-fold increase in dolutegravir 50% inhibitory concentration (IC50) suggesting a synergistic effect of T97A on the susceptibility of dolutegravir in the setting of Q148H and G140S.

The E157Q polymorphism is present in about 3% to 5% of ART-naive patients but in 2 case reports has been associated with virologic failure in the setting of raltegravir-based regimens and non-suppression to a dolutegravir-based regimen in a patient with a baseline E157Q mutation. Charpentier and colleagues (Abstract 547) evaluated more than 8500 integrase sequences from InSTI-naive patients in routine clinical care and found an overall prevalence of E157Q of 2.7%, with a higher prevalence among the CRF02_AG subtype (5.6%) than the subtype B (1.7%). In vitro analysis of E157Q site-directed mutants demonstrated minimal fold change to raltegravir, elvitegravir, and dolutegravir with the greatest impact found on elvitegravir especially in CRF02_AG subtypes (2.4-fold decrease in susceptibility). Based on these data, the authors suggest avoiding elvitegravir in patients with the baseline E157Q polymorphism, with particular caution in patients with subtype CRF02_AG.

Pham et al (Abstract 548) described the emergence of the S230R integrase substitution in 2 patients who experienced virologic failure while on dolutegravir monotherapy and further characterized the effects of this mutation on activity, infectivity, replication capacity, and InSTI susceptibility. The investigators noted that compared with wild-type virus, this mutation resulted in a 63% reduction in strand transfer efficiency, a 1.29-fold decrease in infectivity, no change in replication capacity, and a variable effect on InSTI susceptibility with a decreased fold change of 3.85, 3.72, 1.52, and 1.21 on dolutegravir, cabotegravir, raltegravir, and elvitegravir, respectively.

Brenner and colleagues (Abstract 549) evaluated the relative emergence of DRMs in response to increasing concentrations of dolutegravir, elvitegravir, bictegravir, and cabotegravir in vitro among HIV subtype B (n = 7) and non-B subtypes (n = 5) isolates amplified from peripheral blood mononuclear cells (PBMCs) of individuals with primary HIV infection. The time to resistance and number of strains that developed resistance was faster and higher in isolates exposed to elvitegravir, followed by cabotegravir, and then by bictegravir and dolutegravir. Furthermore, elvitegravir and cabotegravir selected for strains with complicated patterns of high-level resistance, which led to viral escape whereas the dolutegravir- and bictegravir-exposed mutants were singleton mutations that conferred low level resistance and reduced replicative fitness. These findings support evidence of a high genetic barrier to resistance for bictegravir and dolutegravir, compared with cabotegravir or elvitegravir.

Abstract 544 described selection of mutations by dolutegravir in vitro located in the 3'-PPT (polypurine tract), a region located outside of the integrase gene, that confer very high level resistance to all InSTIs. They report that these mutants replicated efficiently with or without dolutegravir and hypothesized that replication occurs without integration through unintegrated viral DNA via 1-LTR circles. These results warrant further investigation as HIV-1 DR mutants that skip the integration step in replication have not previously been described. Furthermore, during the oral abstract presentation, there was substantial controversy regarding the measurement of 1-LTR circles in this study, calling to question whether or not these mutants truly replicate without integration.

Through a series of ex vivo and in vivo experiments, (Abstract 546) bictegravir resistance pathways were further characterized and provide evidence that bictegravir has a high genetic barrier to resistance. After extended culture of wild-type HIV-1 with bictegravir, 2 patterns of integrase region resistance that conferred no to low-level reduced susceptibility to bictegravir were identified: R263K with or without M50I (<3-fold reduced susceptibility), and S153F or S153Y (2-fold susceptibility to bictegravir). Extended culture of InSTI-resistant HIV-1 with bictegravir led to no to slow development of additional integrase substitutions and all selected viral pools remained sensitive to bictegravir and dolutegravir aside from 1 variant that had high-level resistance to all InSTIs but had very low replication capacity and may not be viable in vivo.

Protease Inhibitor Resistance Mutations Outside of the Protease Gene

In clinical trials, virologic failure in patients on initial, ritonavir-boosted PI-based regimens is rarely associated with selection of resistance mutations in the protease region (PR). Two studies (Abstracts 558 and 559) sought to identify mutations outside of the PR that might contribute to virologic failure with boosted PIs. Perrier and colleagues (Abstract 558) evaluated the baseline sequences in the protease, Gag, and gp41 regions of ART-naive patients initiated on a PI-based regimen. Of 154 individuals enrolled, 36 experienced virologic failure.

Through ultra-deep sequencing, 4 PR-associated (T4A, S37T, I72M, E21D), 3 Gag (G62d, n315h, y441s), and 1 gp41 (I270T) region mutations correlated with virologic failure. One gp41 mutation (I4L) was associated with virologic success. These findings require further investigation to determine whether or not these mutations have a direct impact on PI activity.

In Abstract 559, Blanch-Lombarte and colleagues investigated HIV-1 Gag mutational patterns related to virologic failure in patients on darunavir or lopinavir monotherapy without PI-associated resistance mutations. They evaluated Gag-PR amplified sequences from 9 plasma samples and found a novel set of Gag mutations (K95R, E203D, V215M, R286K) related to PI-associated resistance and that Gag acted as a direct contributor to PI resistance in the absence of PI-associated resistance mutations. The authors suggest that these findings could be used to optimize genotype analysis of resistance and that additional studies in non-B clade viruses are warranted.

Relative In Vitro Efficacy of ART in the Setting of Resistance Mutations

Margot and colleagues (Abstract 560) compared the in vitro efficacy of TDF and TAF on site-directed and patient-derived mutants containing varying numbers of thymidine analogue mutations (TAMs) with or without M184V. The authors found that TAF susceptibility decreased with increasing number of TAMs, M184V increased antiviral activity of TAF similarly to tenofovir, TAF inhibited viral breakthrough (>28 days without breakthrough) of most TAM-containing HIV-1 (11/14) compared with 0/14 with TFV suggesting that TAF has a higher genetic barrier to resistance than TDF.

White and colleagues (Abstract 532) presented an integrated analysis of resistance from 2 phase III studies of bictegravir, emtricitabine, and TAF in treatment naive individuals. In this pooled analysis, PDR did not affect efficacy and no drug resistance emerged through week 48 in any of the study arms (bictegravir/emtricitabine/tenofovir alafenamide, dolutegravir/abacavir/lamivudine, emtricitabine/TAF plus dolutegravir). One patient with pretreatment G140S and Q148A mutations and virus that was phenotypically sensitive to bictegravir and partially sensitive to dolutegravir achieved an HIV-1 RNA level below 50 copies/mL on bictegravir/emtricitabine/TAF at week 4, which was sustained through week 72. These results support other studies that show InSTI-based regimens maintain a high barrier to resistance.

New Technologies to Identify HIV Drug Resistance

Herms and colleagues (Abstract 555) noted that cost-effective, scalable tools for epidemiologic surveillance of HIV drug resistance in low- and middle-income countries are needed to address the increasing prevalence of resistance in these areas. They described the performance of PASeq.org, a free, cloud-based web service for HIV genotyping analysis of NGS data that could address this need as it is inexpensive, simple to use, web-accessible, secured, and can be scaled up to thousands of samples with a short turn-around time (<1 hour). The investigators compared the genotyping analysis of 12 HIV plasma samples using routine Sanger-based technology and manual analysis using ViroSeq System software v2.8 to PASeq.org analysis of NGS. They concluded that PASeq.org analysis of NGS data provided Sanger-like information with improved resolution and increased sensitivity and provides a cost-effective alternative to multi-sample, high-throughput genotyping.

Abstract 556 described a deep-sequencing platform (long-read Single Molecule Real Time [SMRT], Pacific Biosciences) that can identify DRMs in HIV-1 from full-length pol amplicons. Through full-length sequencing, the authors found evidence of minority DRMs during acute or early infection, the role of which in treatment failure requires further investigation.

Clutter and colleagues (Abstract 557) described a methodology in development for point-of-care genotypic resistance testing. Using a solid-phase nucleic acid melt-curve analysis platform, nucleic acid target sequences are identified through analysis of hybridization kinetics of nucleic acid targets to surface-bound oligonucleotide probes. They validated this technique with in vitro experimentation and demonstrated good sensitivity and specificity in a large set of diverse global HIV-1 samples. This promising technology for point-of-care DRM testing will require further modifications before this will be useable in real-world settings.

Issues Related to HIV Maternal and Infant Health

ART in Pregnancy

Zash and colleagues investigated the relationship between gestational hypertension, ART use, and adverse pregnancy outcomes (Abstract 803). Nevirapine use was strongly associated with gestational hypertension and this relationship was not modified based on nRTI use. They found that hypertensive women receiving nevirapine accounted for 30% of stillbirths, even though only 13% of women received nevirapine.

Sibiude and colleagues reviewed a cohort of 2837 women receiving raltegravir or 1 of 3 PI/r regimens (atazanavir, darunavir, lopinavir) when becoming pregnant (Abstract 805). No obvious differences in pregnancy outcomes, neonatal outcomes, or virologic control based on regimen received were found, although the number of women on raltegravir-based regimens was limited. The proportion with plasma HIV-1 RNA level above 50 copies/mL at delivery was 4.7% for women receiving raltegravir and ranged from 9.8% to 14.5% for women receiving the one of the 3 different PI regimens.

Early ART Effects on the HIV Reservoir in HIV-Infected Infants

Two oral abstracts described the impact of early ART on the size of the HIV reservoir in infants infected with HIV as a result of mother-to-child transmission. Using data from 2 Thai cohorts (HIVNAT 194, a cross-sectional cohort with n = 46, and HIVNAT 209, a longitudinal cohort with n = 42), Massanella and colleagues (Abstract 135) evaluated markers of

HIV persistence in infants and children who received antiretroviral prophylaxis followed by ART continuously without interruption since birth and compared them with those of children who had antiretroviral prophylaxis with an interruption interval prior to ART initiation. The researchers measured total and integrated HIV DNA in CD4+ T cells using real-time polymerase chain reaction (PCR), and used the Tat/rev Induced Limiting Deleting Assay (TILDA) to measure the size of inducible reservoir by determining the frequency of latently infected CD4+ T cells that generate multiply spliced RNA. Total and integrated HIV DNA levels decreased substantially during the first year of ART but remained detectable after that timepoint in almost all the children. In half of the children, the TILDA measures of inducible reservoir decreased rapidly after commencement of ART, and were undetectable in half of the children after 1 year of treatment. Children who had received ART without interruption since birth, with direct conversion from ARV prophylaxis to ART, had lower levels of total and integrated HIV DNA (ie, lower HIV reservoir) compared with those who had a delay. They also noted a positive correlation between age at ART initiation and levels of total and integrated HIV DNA and frequency of CD4+ T cells with inducible reservoir:infants who started ART before 6 weeks of age had lower levels of HIV persistence markers.

Shapiro and colleagues (Abstract 136) assessed markers of HIV reservoir size and development of early immune responses in HIV-infected children in Botswana's Early Infant Treatment Study (EIT) who were immediately commenced on ART within 7 days of age (median, 2 days; range 1-5 days), and compared them with children who started ART at a later age ranging from 30 to 365 days (control group). Quantitative HIV DNA testing was performed on PBMCs at various visits, along with qualitative DNA PCR testing on PBMCs and HIV-1 and -2 antibody dual enzyme linked immunosorbent assay (ELISA) at 84 weeks. Compared with controls, children who were treated within 7 days after birth had low HIV viral reservoir at enrollment and after 84 weeks of ART. Qualitative DNA PCR reversion from detectable to undetectable and negative HIV ELISA were seen in those children with consistent viral suppression, with 6 of the children (67%) having reversion and 5 of the children (56%) having negative EIA. The authors suggested that qualitative HIV DNA PCR and EIA HIV antibody tests could be employed as markers of HIV reservoir size in HIV-infected children who receive early ART.

Clinical Outcomes in Breastfeeding HIV-Infected Women

Hoffman and colleagues (Abstract 138) performed a cross-study analysis to compare the clinical outcomes of HIV-infected women who were predominantly breastfeeding in the multi-center, multi-country, randomized PROMISE (Promoting Maternal and Infant Survival Everywhere) 1077BF/FF trial with those reported in formula feeding women in the PROMISE 1077HS study. In the PROMISE 1077BF/FF study, 1612 HIV-infected women with baseline CD4+ cell counts above 350/μL and who initiated 3-drug ART during pregnancy were randomly assigned to continue ART or discontinue ART during the postpartum period (though discontinuation of ART during the postpartum period based on CD4+ cell count level is no longer recommended by the WHO and other guidelines). The preferred ART regimen in the study was lopinavir/ritonavir and TDF/emtricitabine. The primary efficacy endpoint was a composite of time to an AIDS event (defined as WHO Stage 4 clinical event) or death. Secondary endpoints included time to a composite endpoint of an HIV/AIDS-related event (defined as WHO stage 4 clinical event, pulmonary tuberculosis, or other serious bacterial infections) or a WHO stage 2 or 3 event, time to stage 2 or 3 event, and grade 2 to 4 safety endpoint. The median age at entry into the PROMISE 1077BF/FF trial was 26 years, and the median CD4+ cell count was 698/μL. A vast majority (95%) of the women were breastfeeding. The median follow-up period was 1.6 years. The authors did not find any statistically significant difference in the primary efficacy endpoint of clinical disease progression between the ART continuation and discontinuation arms (hazard ratio [HR], 0.55; 95% CI, 0.14, 2.08), as well as rates of safety events (HR, 0.95; 95% CI, 0.76, 1.17). Rates of WHO stage 2 and 3 events were significantly lower in those who continued ART than in those who discontinued ART (HR, 0.60; 95% CI, 0.39, 0.90). In cross-study comparison, the rates of the primary efficacy endpoint, WHO stage 2 and 3 events, and safety endpoints in the women in the PROMISE 1077BF/FF trial were similar to those previously reported in each of arms of the formula feeding women in the PROMISE 1077HS study. Based on these findings, the authors concluded that prolonged breastfeeding in the postpartum period had no adverse effects on clinical and safety outcomes in HIV-infected women with CD4+ cell counts of above 350/μL and had comparable clinical outcomes to those among formula feeding women.

Clinical efficacy and laboratory safety outcomes were further compared in 557 HIV-infected women in the PROMISE trial who had maintained CD4+ level at or above 350 cells/μL and who were randomly assigned to continue (n = 289) or discontinue ART (n = 268) post cessation of breastfeeding during the postpartum period (Abstract 139). As noted previously, the preferred ART regimen was lopinavir/r and TDF/emtricitabine. Women assigned to the discontinuation arm received the standard of care in the local country, with resumption of ART as needed during follow up. The primary composite efficacy endpoint was similar to that described in Abstract 138, namely a composite endpoint of time to progression to an AIDS-defining illness (defined as WHO stage 4 clinical event) or death. Secondary endpoints were grade 3 or higher laboratory and clinical findings and some grade 2 renal and hepatic laboratory findings. The baseline characteristics of the women were similar across both arms, with a median age of 28 years, 93% being WHO clinical stage 1, and 95% of the women having a CD4+ cell count of above 500 cells/μL. The median follow-up period was 84 weeks. Overall, the rate of primary efficacy endpoint across both arms was very low, with an incidence rate of 0.23%/100 py, with no statistically significant difference between the 2 arms (HR, 1.04; 95% CI, 0.06, 16.59) and with 1 maternal death reported in

each arm (causes of death were ruptured ectopic pregnancy and chronic renal insufficiency). Higher rates of grade 2 or higher adverse events were observed in the ART continuation arm although this finding was not statistically significant ($P = .08$). When restricting the analysis to include only grade 3 or 4 clinical adverse events, there were higher adverse event rates observed in the ART continuation arm than in the discontinuation arm (incidence rate, 4.9; 95% CI 3.8, 6.3 vs incidence rate, 1.7; 95% CI 1.1, 2.6; $P = .01$), with the most common clinical event being weight loss.

HIV Rebound Viremia and ART Nonadherence in Pregnant and Breastfeeding Women

ART adherence and resistance during HIV viremic episodes (defined as >1000 HIV RNA copies/mL) after initial viral suppression (<50 HIV RNA copies/mL) in pregnant and breastfeeding HIV-infected South African women were analyzed in Abstract 140. In this nested case-control study comparing women with viremic episodes after initial suppression (cases, n = 107) with those with continuously maintained suppression (controls, n = 124), the women were started on ART consisting of efavirenz/TDF/emtricitabine and underwent intensive viral load testing, starting from the initial antenatal visit through 12 months postpartum. Presence of antiretrovirals in plasma samples was assessed in cases and controls, as was drug resistance mutations. Overall, 30% of the women had a viremic episode after virologic suppression by 12 months postpartum. Presence of any antiretroviral drug was detected in 18% of cases at time of viremic episode and in 94% of controls at matched time points ($P < .001$). The authors calculated a 36.8-fold increased odds of ART nonadherence in women who had viremic episodes compared to controls (OR, 36., 95% CI, 15.5, 90.5) and an attributable fraction of 97% for viremic episodes due to ART nonadherence. Before the initiation of ART, detected drug resistance mutations were all NNRTI-related, with 11% in cases and 5% in controls ($P = .15$) with most being major NNRTI mutations. At the viremic episode timepoint, 45% of cases had any drug resistance mutation detected, with a majority being NNRTI mutations. Merely 18% of cases with drug resistance mutations detected at the time of a viremic episode had drug resistance mutations pre-ART, suggesting emergence of drug resistance mutations during 12 months postpartum while on ART. The authors highlighted the importance of addressing barriers to ART adherence in pregnant and postpartum HIV-infected women.

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