Antiretroviral Use for Prevention and Other Factors Affecting the Course of the HIV-1 Epidemic

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Antiretroviral therapy has tremendous potential to alter the HIV-1 epidemic trajectory. However, gaps in the continuum from HIV diagnosis, through linkage to care and uptake and adherence to antiretroviral therapy, are substantially limiting to the actual impact. In the United States, gaps in HIV diagnosis and care are greatest among African Americans, substance users, and persons living below the poverty line. Globally, HIV diagnosis rates are highest in women, but HIV incidence may be declining more rapidly in men, due to lower transmission rates from female partners and greater uptake of medical male circumcision. The 2012 Conference on Retroviruses and Opportunistic Infections explored gaps in the continuum of care and potential strategies to address them, and also addressed the disparate results from preexposure prophylaxis efficacy trials. The role of injectable contraceptives in increasing the risk of HIV acquisition in women was debated, as was the potential harm that could arise from limiting this contraceptive method due to increased maternal mortality. Similarly, the potential benefits and harms of serosorting were explored. Investigators explored scale-up of prevention strategies to have the biggest and most cost-effective impact on the global epidemic.

Antiretroviral Strategies for HIV Prevention

Antiretroviral Therapy

Following the announcement last year of the dramatic reduction in heterosexual transmission when antiretroviral therapy is initiated early in the course of HIV infection,[1] a great deal of attention was focused on using antiretroviral therapy as a method of reducing HIV infection rates at a population level at the 2012 Conference on Retroviruses and Opportunistic Infections (CROI). El-Sadr reviewed recent data demonstrating both the promise and the challenges of using antiretroviral therapy for HIV prevention (Abstract 18). She displayed gaps in the continuum of care from HIV diagnosis to linkage to care, retention in care, uptake of antiretroviral therapy, and

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suppression of viral load. In the United States, it is estimated that only 28% of HIV-1 infected persons have fully suppressed viral loads. In Mozambique, there are similar challenges with gaps in each step in the continuum of care. In one study, only 5% of 7000 HIV-seropositive persons had fully suppressed viral loads; this study did not take into account the large proportion of HIV-infected persons who may not yet be diagnosed. Other troubling data from Mozambique showed that 43% of those diagnosed with HIV were not enrolled in care, and 69% of persons eligible for antiretroviral therapy did not initiate treatment.

El-Sadr reviewed innovative strategies for addressing gaps at each stage in the continuum of care. Home-based voluntary HIV testing, in which health workers go door to door to offer HIV antibody testing, has been shown to increase the uptake and efficiency of HIV testing, uncovering a larger number of HIV-infected individuals than clinic-based strategies. HIV self-testing was shown to be accurate and highly acceptable in a study in Malawi. Couples-based HIV testing is another approach to delivery of testing. To enhance linkage to care, point-of-care CD4+ testing—particularly when paired with home-based testing—doubled the rate of uptake of antiretroviral therapy among eligible HIV-seropositive persons. However, a sizeable proportion of persons do not remain in care, and even if in care, some may not opt to take antiretroviral therapy. In a study of more than 7000 patients tested for HIV in South Africa, 35% were HIV-seropositive. Of the 743 patients eligible for antiretroviral therapy, 20% repeatedly refused treatment, despite a median CD4+ count of 110 cells/μL for the eligible group. The most common reason for refusal was the statement that the person was feeling well, suggesting additional education on the benefits of antiretroviral therapy among asymptomatic persons may be needed.

Failure to remain in care has hampered efforts to control the epidemic. In a meta-analysis of 36 African cohorts reviewed by El-Sadr, retention on antiretroviral therapy was 86% at 6 months but only 72% at 36 months. Although this rate of retention in therapy is higher than published data from North America, additional work must be done to improve the health of HIV-infected persons and decrease the risk of transmission to their uninfected partners. Text messaging has been used successfully in Kenya to modestly improve adherence to antiretroviral therapy and, in some cases, result in full viral suppression. Use of community treatment groups, in which one individual collects medications for other members of the group, has resulted in very low rates of attrition and excellent health outcomes. To obtain maximal individual and societal benefits from antiretroviral therapy, El-Sadr proposes that efforts focus on several different populations. Persons with the lowest

CD4+ cell counts may benefit most from early treatment, and the risk of HIV transmission among persons with low CD4+ cell counts appears to be substantially higher than the risk among persons with higher CD4 + cell counts. Given the HPTN (HIV Prevention Trials Network) 052 results,[1] treatment for HIV serodiscordant couples may be particularly effective. One strategy to efficiently identify serodiscordant couples is to test the partners of identified HIV-infected persons, as approximately half will have an HIV uninfected partner. HIV-seronegative pregnant women are at 4-fold higher risk of acquiring HIV infection than non-pregnant women, suggesting that particular attention should be focused on testing the male partners of pregnant women and offering treatment as necessary.

There are few data available about the effectiveness of antiretroviral therapy on HIV acquisition at a population level. Tanser and colleagues presented data from the Africa Centre for Health and Population Studies, a rural research community in Hlabisa, South Africa, that uses a unique population-level tracking of antiretroviral therapy uptake and HIV seroincidence (Abstract 136LB). The investigators demonstrated a strong dose-response relationship between antiretroviral therapy coverage and reduction in HIV acquisition. In geographic areas with 20% to 30% antiretroviral therapy coverage, HIV acquisition rates were 22% lower than in communities with lower rates of coverage. For communities with 30% to 40% coverage, HIV incidence was 38% lower. Future community randomized clinical trials will provide additional data on population-level impact of treatment as prevention.

Preexposure Prophylaxis

A major focus of this year's conference was preexposure prophylaxis (PrEP), which uses antiretrovirals in HIV-uninfected persons to lower the risk of HIV acquisition. Clinical trials to date have used either tenofovir disoproxil fumarate with or without emtricitabine. New results were released from several PrEP efficacy trials at CROI 2012.

To date, there has been only one efficacy trial of PrEP in MSM: the iPrEx (Chemoprophylaxis for HIV Prevention in Men) study, which was conducted in North and South America, Africa, and Asia. Most recently, Grant reported a 42% reduction in the risk of HIV acquisition through the end of study follow-up.[2] At CROI 2012, Anderson and colleagues presented data on iPrEx and the Strand study, a trial of tenofovir levels in peripheral blood mononuclear cells (PBMCs) when tenofovir was administered 2, 4, or 7 days per week under directly observed therapy (Abstract 31LB). In the Strand study, all participants receiving tenofovir had detectable drug in their PBMCs at the end of a 6-week course of the drug, regardless of randomization arm. In contrast, only 8% of participants in the iPrEx trial who were randomized to the emtricitabine/tenofovir arm who became HIV-1-infected had detectable drug at the time HIV infection was diagnosed, suggesting a high proportion were non-adherent or incompletely adherent to the daily regimen. Anderson then modeled the efficacy of different dosing regimens by combining data from iPrEx and Strand and concluded that 4 or more doses per week would be associated with a greater than 90 % reduction in HIV acquisition. However, the drug levels used to model these efficacy thresholds were based on data from dosing delivered under direct observation; efficacy would be projected to be lower with lower levels of adherence expected from unobserved dosing. Furthermore, these models use data from men who have sex with men (MSM); additional data are needed to confirm these findings and extrapolate to other populations.

Disparate results have been reported from PrEP efficacy trials in heterosexuals. Several presentations focused on the potential reasons for these results. Baeten and colleagues presented an update on the Partners PrEP study, an efficacy trial of daily oral tenofovir, emtricitabine/tenofovir, or placebo in 4758 serodiscordant heterosexual couples in Kenya and Uganda (Abstract 29). Final analysis of data from the pre-unblinding phase of this study confirmed high levels of efficacy in reducing HIV infections in the tenofovir (efficacy 67%; 95% confidence interval [CI], 44%-81%) and the emtricitabine/tenofovir (efficacy 75%; 95% CI, 55%-87%) arms. There were no statistically significant differences in efficacy between the 2 active medications, nor between women and men. Both drug regimens appeared safe and well-tolerated. Donnell and colleagues from the same study reported on the relative risk reduction associated with detectable tenofovir levels in women and men randomized to receive active drug who became infected, compared with those who remained uninfected (Abstract 30). Overall, 82% of the uninfected participants had detectable drug in plasma, a statistically significantly higher proportion than that among participants who became infected. Donnell calculated 86% and 90% relative risk reduction of HIV acquisition among those with detectable drug in the tenofovir and emtricitabine/tenofovir arms, respectively.

In the same session, Van Damme and colleagues presented data on the FEM-PrEP (Study to Assess the Role of Truvada in Preventing HIV Acquisition in Women) trial, a study of 2120 enrolled women at risk of HIV acquisition in Tanzania, Kenya, and South Africa (Abstract 32LB). This study was stopped early because the Data and Safety Monitoring Board (DSMB) determined that it was unlikely that efficacy would be demonstrated. This was the first scientific presentation of data from this study. In total, there were 68 post-enrollment infections, with 33 in the active treatment arm (receiving emtricitabine/tenofovir), and 35 in the placebo arm. One likely contributor to the lack of efficacy seen in this trial was the low rate of adherence to the study drug, although the magnitude of this factor is as yet unknown. Although 95% of the women reported that they always or usually took their study drug, only 26% of those who became infected and 35% of those who remained uninfected had detectable tenofovir in stored plasma specimens from their last preseroconversion time point.

Baeten discussed hypotheses for the difference in results between these studies (Abstract 67). He pointed out that 3 studies of oral tenofovir/emtricitabine (iPrEx, Partners PrEP, and TDF2 [FHI TDF West African trial]) and one of vaginal tenofovir gel (CAPRISA [Centre for the AIDS Programme of Research in South Africa] 004) have demonstrated efficacy in preventing HIV infection in MSM and heterosexuals, and 2 studies, 1 of oral tenofovir/emtricitabine (Partners PrEP) and 1 of vaginal tenofovir gel (VOICE [Vaginal and Oral Interventions to Control the Epidemic]), have not demonstrated efficacy in preventing HIV infection in women. Baeten categorized potential explanations as statistical, biologic, or behavioral, ruling out the first explanation based on the robustness of evidence from the trials that demonstrated efficacy. Potential biologic explanations for the lack of efficacy with oral PrEP include cofactors that could lower the threshold for infection, even in the presence of PrEP, such as sexually transmitted infections (STIs), genital inflammation, intravaginal practices, or the incidence of acute infection in partners. All of these cofactors may have been higher in the negative than in the positive trials. Potential biologic explanations for disparities in results of vaginal tenofovir gel may be related to dosing schedules. Whereas tenofovir was prescribed pericoitally in CAPRISA 004, it was recommended for daily use in VOICE. It is possible that these higher levels of this hyperosmolar vaginal gel could have caused epithelial disruption, overwhelming any potential efficacy of the drug. Adherence is frequently cited as a potential behavioral factor causing divergent results in different trials. This is supported by data from each of the positive trials that link higher level of adherence to greater degree of efficacy. Baeten emphasized that additional investigation is required to determine whether and to what extent each of these possible explanations contributed to different outcomes in different trials.

In the same session, Buchbinder presented what is known about the potential for intermittent dosing of PrEP (Abstract 68). She pointed out that, although treatment of HIV-seropositive persons may substantially lower the risk of HIV transmission, there have been substantial challenges in the United States and globally with HIV testing, linkage to care, and uptake and adherence to antiretroviral therapy, as outlined in El-Sadr's presentation described above. The best way to substantially reduce HIV infections globally involves treatment as well as prevention, and PrEP may play a role in this effort. She reviewed 4 types of "intermittent PrEP": (1) fixed dosing (on a regular schedule, but less than daily); (2) event-based dosing (pericoitally); (3) combined fixed and event-based dosing (regular dosing less than daily, with postcoital doses to augment drug levels); and (4) periodic dosing (daily dosing, but only during periods of risk). Less than daily dosing has the potential to reduce cost and toxicity, as well as improve adherence and tolerability. Potential downsides of less than daily dosing include increased potential for antiretroviral drug resistance, decreased efficacy, and potential worsening of adherence or tolerability. After reviewing what is known to date about these issues, she pointed out that all PrEP regimens require ruling out HIV infection before (re)initiation of PrEP, and monitoring for renal toxicity on an ongoing basis. Fixed intermittent dosing may be feasible for preventing HIV infection, given data from trials indicating that high levels of efficacy may be achievable with less than daily dosing. However, the substantial hazard with fixed intermittent dosing is that, if doses are missed, there is less "forgiveness," and drug levels may not be sufficient to prevent infection. She posited that episode-driven regimens may be successful if they are built into all sexual acts (eg, microbicides), but are unlikely to be successful if they are not, because individuals may not leave adequate time before sexual exposure to take PrEP, and may not recognize which sexual episodes contain risk. She noted the questions about the likely success of intermittent PrEP, and suggested that long-acting agents and extended delivery methods may obviate the need for intermittent PrEP.

Microbicides

Delivering antiretrovirals topically (eg, microbicides) rather than systemically (eg, oral PrEP) has the potential to increase drug levels at the locations where infection occurs, while also reducing the risk of systemic toxic effects. On the other hand, because tenofovir may be detectable in cervicovaginal lavage fluid (CVL) for up to 30 days after vaginal administration, there is concern that resistance to tenofovir could emerge in the vaginal compartment, either during the "tail" of tenofovir postdosing, or when tenofovir is delivered postinfection but prior to diagnosis. Johnson presented the results of sensitive resistance screening of HIV-1 from genital tract samples of women participating in the CAPRISA 004 efficacy trial, on behalf of Wei and colleagues (Abstract 33). In this trial of 899 women enrolled in South Africa, topically administered 1% tenofovir gel was associated with a 39% reduction in HIV-1 infection rates (95% CI, 6%-60%). This trial used a "BAT 24" dosing regimen. Women were instructed to use the gel within 12 hours Before and up to 12 hours After sexual intercourse, but no more than Twice per 24-hour period. As in previously described studies of oral tenofovir, efficacy in this microbicide trial was highly associated with adherence. Only 40% of women who became HIV-infected had any tenofovir detectable in CVL specimens at the seroconversion visit, compared with 96% of the women remaining uninfected. No tenofovir resistance was detected in the plasma of infected women from the CAPRISA 004 trial. In evaluating tenofovir resistance in CVL specimens, only 3 of the 21 specimens with detectable HIV-1 had detectable tenofovir, and only 1 of these had a K65R mutation detectable. The woman with the K65R mutation had very high levels of tenofovir and recent HIV infection; the investigators suggested that this indicated that tenofovir was administered shortly after infection. None of the resistant virus was detectable in expressed RNA,

only in the proviral DNA. Johnson suggested that this implies a low risk of resistance emergence in the vaginal compartment, but acknowledged that these women were closely monitored to decrease the likelihood of using the gel postinfection.

McGowan and colleagues presented data from MTN (Microbicide Trials Network) 007, a randomized controlled trial (RCT) of a reduced glycerin (RG) formulation of 1% tenofovir gel for rectal use (Abstract 34LB). A previous phase I study (MTN 006) had demonstrated substantial gastrointestinal symptoms with a hyperosmolar preparation of tenofovir gel ($>$ 3000 mOsm/kg). With the RG formulation used in the MTN 007 trial, the osmolarity was substantially reduced, to 836 mOsm/kg, which is closer to iso-osmolar levels (290 mOsm/kg) and therefore potentially less likely to induce the abdominal pain, bloating, and diarrhea reported in the previous study. In MTN 007, 65 HIV-seronegative men and women were randomly assigned to receive a single dose followed by 7 consecutive daily doses of 2% nonoxynol-9 (N-9), the "positive" control; 1% RG tenofovir gel; hydroxyethyl cellulose (HEC), the placebo; or no product. Tolerability was high in all study arms, with rare grade 3 symptoms, and rare evidence of mucosal toxicity, except in the nonoxynol-9 arm. McGowan noted significant differences in the cytokine/chemokine profile, T-cell phenotype, and rectal microflora between the nonoxynol-9 and tenofovir arms, and hypothesized that these may contribute to differences in toxicity profiles between these agents.

Making a case for the relevance of rectal microbicides for heterosexuals, DiNenno and colleagues presented data on the prevalence and factors associated with unprotected anal intercourse in more than 10,000 heterosexual men and women enrolled in the 2010 US National HIV Behavioral Surveillance System (NHBS; Abstract 1100). After excluding persons who reported ever having used injection drugs, 28% of the remaining women and 33% of the remaining men reported heterosexual unprotected anal intercourse in the prior 12 months. For both men and women, factors associated with unprotected anal intercourse on multivariate analysis were household income at or below poverty, use of noninjection drugs, and exchange of sex with their partner.

New Antiretroviral Agents, New Delivery Methods

Romano presented an overview of new strategies and agents for oral and topical PrEP (Abstract 69). The limitations of the current tenofovir-based regimens are that they focus on one mechanism of action (ie, reverse transcriptase inhibition), with mixed results potentially caused by potency or adherence issues. The next generation of PrEP regimens may include combination antiretroviral approaches and new delivery methods to increase potency and adherence, which could be combined with agents to prevent other STIs or with contraceptives. Romano gave examples of trials focused on HIV prevention, including: (1) HPTN 069: oral daily regimens of maraviroc (an entry inhibitor) with or without emtricitabine, tenofovir, or emtricitabine/tenofovir (a nucleoside analogue reverse transcriptase inhibitor [nRTI]); (2) MTN-013/IPM (International Partnership for Microbicides) 026: combination dapivirine (a nonnucleoside analogue reverse transcriptase inhibitor [NNRTI]) and maraviroc delivered as an intravaginal ring; and (3) SSAT (St Stephen's AIDS Trust) 040: injectable rilpivirine long-acting (NNRTI). Of note, Jackson and colleagues reported that the rilpivirine long-acting intramuscular (IM) injection appeared to be safe and well-tolerated when given as a single dose, with prolonged plasma and genital tract exposure (Abstract 35). This trial also pointed to the importance of understanding how drugs penetrate different genital tract compartments. Rilpivirine levels in CVL were equal to or higher than plasma, levels in rectal tissue were equivalent to levels in plasma, and vaginal tissues had somewhat lower levels than in plasma.

Nel and colleagues presented data from an RCT of the investigational drug dapivirine (TMC120) vaginal microbicide rings in 280 African HIV–seronegative women (Abstract 1089). In this trial, women inserted active or placebo vaginal rings once every 28 days over a 12–week period. Safety was excellent, with infrequent adverse events that were balanced between the 2 arms. Acceptability was high, with more than 90% of women reporting no ring removals, and 97% reporting comfort and intent to use the vaginal ring in the future if safe and effective.

Non-Antiretroviral Prevention Strategies

Medical Male Circumcision

Three previously reported RCTs had demonstrated that medical male circumcision (MMC) resulted in a 50% to 60% reduction in HIV acquisition among men. No substantial protective effect has been seen for the female partners of circumcised HIV-infected men. Two presentations at this year's conference addressed the population-level impact of MMC. First, Gray and colleagues presented population-level data on the impact of voluntary MMC on HIV infection rates in Uganda (Abstract 36). Comparing the HIV incidence from the period prior to the MMC RCT, during which non-Muslim men had very low MMC rates (1999), to the period post-trial (2004-2011), the study found substantial reductions in HIV incidence among non-Muslim men, with no corresponding reduction among Muslim men or non-Muslim women. After adjusting for secular changes in the distribution of age and sexual risk practices, the study found a 27% reduction in HIV incidence (95% CI, 10%-40%) among non-Muslim men, likely attributable to the uptake of MMC.

Auvert and colleagues measured the population-level impact of MMC on herpes simplex virus type-2 (HSV-2) in Orange Farm, South Africa (Abstract 37). The prevalence of HSV-2 among circumcised men was 16.5% in comparison with HSV-2 prevalence of 31% among uncircumcised males, leading

to a weighted prevalence reduction (adjusting for age) of 23% (95% CI, 9%-35%). This reduction was significantly lower than the reduction in HIV prevalence (50%; 95% CI, 44%-62%; $P < .001$), suggesting that MMC may be more effective in preventing HIV than HSV-2 acquisition.

Seroadaptive Sexual Practices

Vallabhaneni and colleagues presented an analysis of the impact of seroadaptive practices (changing sexual practices based on the perceived HIV serostatus of sex partners) on the risk of HIV acquisition (Abstract 140). She and her colleagues pooled data from more than 12,000 HIV-seronegative MSM recruited from US or Canadian sites, participating in 1 of 4 longitudinal cohort studies conducted from 1995 to 2007. In this analysis, Vallabhaneni categorized participants for each 6-month interval based on their highest reported risk during that interval. Seroadaptive practices included having unprotected anal sex, but with the following limitations (in hierarchical order): (1) having only 1 HIV-seronegative partner, (2) engaging only in insertive anal sex with all partners, (3) having only (numerous) HIV-seronegative partners, and (4) restricting sexual activity with partners who were HIV-seropositive or of unknown serostatus to insertive anal sex. A total of 663 infections occurred during more than 60,000 6-month intervals of follow-up. Compared with having unprotected anal sex without any seroadaptive practices, each of the seroadaptive practices was associated with a lower risk of HIV-1 seroconversion. However, compared with reporting no unprotected anal sex, serosorting (having only HIV-negative partners) was associated with a doubling of risk, and having unprotected anal sex without seroadaptive practices with more than a 3-fold increased risk. Vallabhaneni suggested that seroadaptive practices may be recommended as a harm reduction strategy for men engaging in unprotected receptive anal sex with HIV-seropositive partners or partners with unknown serostatus. However,

men should be counseled that serosorting is associated with a doubling of risk compared with not reporting any unprotected anal sex, and serosorting should not be relied upon as a "safe" alternative to 100% condom use.

Golden and colleagues reported on trends in serosorting and their relationship to HIV, syphilis, and gonorrhea incidence over time among patients attending the Seattle King County Sexually Transmitted Diseases (STDs) clinic (Abstract 1092). Both HIV-seropositive and seronegative men have been engaging in statistically significantly less serodiscordant unprotected anal sex, but significantly more seroconcordant unprotected anal sex (serosorting) over time in their clinic. These trends correlate with increased rates of early syphilis in HIV-seropositive men and gonorrhea in both HIV-seropositive and -seronegative MSM. In accordance with Vallabhaneni's previously described results, Golden found that HIV-seronegative men reporting serosorting were at intermediate risk of seroconversion—lower than men reporting unprotected anal sex with an HIV-seropositive or unknown serostatus partner, but higher than men reporting no unprotected anal sex. In a separate longitudinal analysis of a cohort of almost 800 MSM recruited in San Francisco, Vallabhaneni reported that 61% of the HIV-seronegative men and 35% of the HIV-seropositive men said they intended to serosort (Abstract 1093). However, when the men who intended to serosort were seen 6 months after enrollment, HIV-seropositive and -seronegative men using substances (eg, methamphetamines, alcohol, poppers, downers) were statistically significantly more likely to report having had unprotected anal sex with a partner of unknown or discordant serostatus to their own. This highlights the role that substance use plays in disinhibition of safer sex plans.

Heffelfinger and colleagues reported on the proportion of HIV-seropositive MSM who were unaware of their HIV serostatus and risk factors for unprotected anal sex with a potentially serodiscordant partner (Abstract 1091). Of the 1562 HIV-seropositive men en-

rolled in the NHBS in 2008, 56% were aware of their HIV-seropositive status, and 44% were not. Predictors of being unaware of an HIV-seropositive status included being non-white, being younger than 30 years of age, ever having used injection drugs, and several measures of lower socioeconomic status (eg, being uninsured, having less education, and income at or below poverty). Independent predictors of engaging in unprotected anal sex with an HIV-seronegative or unknown serostatus partner were being unaware of HIV-seropositive status, binge drinking in the last 30 days, and being US-born. Freedman and colleagues, using data from the Medical Monitoring Project (MMP) conducted by the US Centers for Disease Control and Prevention (CDC), reported that only 5% of HIV-infected patients in clinical care reporting unprotected sex with an HIV-seronegative or unknown serostatus partner were not virally suppressed (Abstract 1090).

Superinfection

Serosorting for HIV-infected persons will limit the spread of new HIV infections, but may also result in increased rates of superinfection. This may in turn lead to worsened clinical outcome in HIV-infected persons. Two presentations measured rates of HIV-1 superinfection, based on deep sequencing strategies. Redd and colleagues presented data on superinfection rates among men and women within the longitudinal cohort in Rakai, Uganda (Abstract 58). In the analysis of 149 participants who seroconverted from 1997 to 2002 with a follow-up specimen available in 2008, 7 superinfection events were detected. All superinfection events were observed in the gp41 region. All initial infections were subtype D, with 3 superinfections being intersubtype (all type subtype A), and the other 4 being intrasubtype. The incidence of superinfection (1.44/100 person-years) was similar to the rate of initial HIV infection in the same cohort (1.15/100 person-years). Ronen and colleagues presented data on superinfection in the Mombasa,

Kenya, female sex worker cohort (Abstract 59LB). This analysis is still underway, with 117 of 149 qualifying specimens having been tested. At the time of the presentation, the incidence of superinfection in this cohort was 3.25/100 person-years, with HIV incidence in the same cohort of 3.06/100 person-years. Audience members pointed out that these are likely to be underestimates of superinfection, as they will not identify transient cases of superinfection or differences that occur in regions of the genome that were not sequenced. Although previous studies suggested that the risk of superinfection may be greatest soon after HIV infection, Ronen's data captured episodes that occurred up to 5 years after initial infection. Both investigators have plans to examine the impact of superinfection on the clinical course of HIV disease. The implication of these results for the development of HIV vaccines is not yet clear.

Trends in HIV Diagnosis and Factors Contributing to HIV Outcomes

HIV Testing

Branson reviewed the current algorithm for HIV testing, pointing to its problems (Abstract 114). The current testing algorithm has been in use since 1989 and requires repeat screening antibody tests, confirmed by a specific test, typically a Western blot or enzyme immunoassay (EIA). This system means that the confirmatory test (a first-generation assay) is being used to confirm a third- or fourth-generation assay, despite the fact that third-generation assays turn positive on average 2 weeks earlier than a Western blot, and fourth-generation assays 5 days earlier than third. Another problem with the current algorithm is that it does not adequately differentiate HIV-1 from HIV-2 infection. NNRTIs and some protease inhibitors (PIs) are ineffective in treating HIV-2 infection, and HIV-2 is not detectable with current viral load testing. Therefore, HIV-2-infected persons who are treated and monitored as though they have HIV-1 infection

are often not correctly diagnosed until their condition inexplicably deteriorates, despite an undetectable viral load. In fact, in New York City, 93% of HIV-2 cases had been read as HIV-1 positive on Western blot, as had 60% of HIV-2 cases reported to the CDC.

The CDC and Public Health Laboratories developed a new testing algorithm (Figure 1). In this algorithm, patients should be screened with a fourth-generation HIV-1/2 immunoassay. If that test is negative, patients are determined to be negative for both antibody and p24 antigen. Positive tests are then tested using an assay to differentiate IgG for HIV-1 from HIV-2. This will confirm a positive result. If this confirmatory test is negative, RNA testing is done to detect acute HIV-1 infection. If negative, HIV-1 infection has been ruled out. The new algorithm has been validated to be both more sensitive and more specific than the current algorithm, and to produce fewer indeterminate test results. This leads to yet another benefit: the current algorithm can take days to weeks to produce a definitive diagnosis, but running a test through the new algorithm can provide definitive results within 2 hours.

In the same session, Sullivan provided an overview of what is known about the impact of disclosure of serostatus to one's sexual partners (Abstract 117). He differentiated 3 types of disclosure.

Firstly, for newly HIV-diagnosed individuals, partner notification by health departments has been shown to identify other HIV-seropositive persons who were unaware of their HIV infection. Most data suggest that health care practitioners play an important role in successful notification; individuals notify substantially fewer partners without the help of a practitioner, even when the newly diagnosed person has access to other tools, such as online anonymous notification. Secondly, in evaluating strategies to reduce the risk of HIV transmission from known HIV-infected persons, data show that knowledge of HIV-seropositive status is the most important predictor of safer sex practices. The benefits of disclosure per se are not consistently documented. Finally, Sullivan pointed to the potential hazard of serodisclosure of HIV-seronegative status to sex partners, if that encourages persons to have unprotected sex with others also believed to be HIV-seronegative. Several studies have demonstrated the important role of presumed HIV-seronegative partners in driving new infections, as some of these partners are newly infected and therefore may be highly infectious. Sullivan closed with promising data on the potential role of voluntary couples-based counseling and testing as a way to disclose serostatus within a partnership and
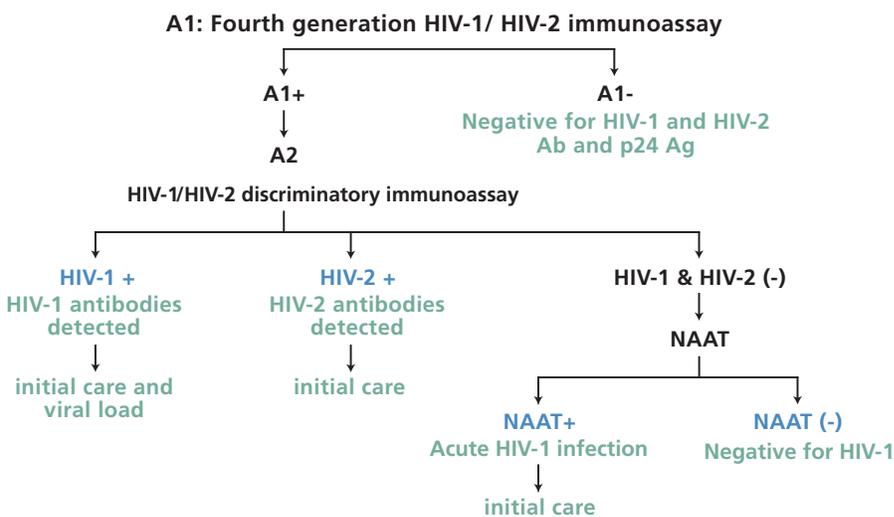
A1: Fourth generation HIV-1/ HIV-2 immunoassay

A1+ → **A2**

A1-
Negative for HIV-1 and HIV-2
Ab and p24 Ag

HIV-1/HIV-2 discriminatory immunoassay

HIV-1 +
HIV-1 antibodies detected
↓
initial care and viral load

HIV-2 +
HIV-2 antibodies detected
↓
initial care

HIV-1 & HIV-2 (-)
↓
NAAT

NAAT+
Acute HIV-1 infection
↓
initial care

NAAT (-)
Negative for HIV-1

Figure **1**. HIV Testing Algorithm from the 2010 Centers for Disease Control and Prevention American Public Health Laboratories HIV Diagnostic Conference. Ab indicates antibody; Ag, antigen; NAAT, nucleic acid amplification test.

encourage strategies to reduce the risk of HIV transmission.

McNairy introduced a themed discussion session focused on novel testing and linkage to care (Session 29). She pointed to the differences in HIV diagnosis rates in the United States (now up to 80%) compared with resource-limited settings (estimated at less than 40%). There is substantial heterogeneity in the proportion of diagnosed persons who are linked to care. In the United States, estimates range from 69% to 77%, and in resource-limited settings, they range from 33% to 88%. Two presentations focused on new strategies to provide HIV testing outside of clinical care settings. Katz and colleagues presented on the acceptability and ease of use of home self-testing among MSM in Seattle (Abstract 1131). Of 133 participants enrolled to date, 89% stated that they would test more frequently if the home test were available. Cost of the test was a determinant of whether or not the person anticipated testing at all, as well as the frequency of testing; more than half of the participants stated that they would only pay $20 or less for a test kit. More than 90% of the men stated that the oral fluid-based self-test kit was easy to use. Katz also described a case of a participant who tested a sex partner (despite all participants being instructed not to test partners); the sex partner was newly diagnosed by this test as HIV-seropositive. The HIV-seropositive sex partner stated to the clinic staff that he thought it was acceptable to learn of his HIV status in that way. He waited 2 months before seeking confirmatory testing, but stated that knowledge of his possible HIV-seropositive status motivated him to use condoms with his sex partners.

Van Rooyen and colleagues presented data from a study of home-based voluntary counseling and testing, combined with point-of-care CD4+ testing in KwaZulu-Natal, South Africa (Abstract 1135). Their team was able to perform HIV testing on 91% of the adults living in the targeted households. Of the 673 men and women tested, nearly 32% were being tested

for the first time. Test results showed 30% were HIV-seropositive, of whom 37% were newly diagnosed. Median CD4+ count at diagnosis was 425 cells/µL, substantially higher than reported in clinic-based testing. By 3 months after testing, 88% of the HIV-seropositive men and women were linked into care. Fatch and colleagues evaluated factors associated with never having received an HIV antibody test in rural Uganda (Abstract 1137). Overall, 60% of the populations sampled had never been HIV tested. Lower socioeconomic status (eg, lack of education, low income) was significantly associated with lack of testing for both men and women. Women were also at increased risk if they suffered from food insecurity or drank alcohol.

HIV-Related Disparities in the United States

Several abstracts focused on temporal trends in receipt of medical care, antiretroviral therapy, and clinical outcomes. Hogg and colleagues reported on data from the NA-ACCORD (North American AIDS Cohort Collaborative on Research and Design) (Abstract 137). They noted increases in total life expectancy for HIV-infected 20-year-olds from 54 years to 67 years in the period from 1996 to 2007. Total life expectancy for HIV-seronegative persons in North America was approximately 80 years. Factors associated with lower life expectancy for HIV-infected persons included African American race, injection drug use, and lower CD4+ cell count. There were no substantial differences in life expectancy between HIV-infected men and women.

Skarbinski and colleagues at the CDC reported data from the MMP, a probability-based estimate from 23 US cities, states, and territories to estimate the proportion of HIV-seropositive persons in care who are on antiretroviral treatment and virally suppressed (Abstract 138). From these data, researchers estimated that 89% of HIV-infected persons in the United States who are in care have been prescribed antiretroviral therapy in the previous year, and 72% are virally suppressed. In a

multivariate model, factors associated with lower rates of treatment included younger age (18 years–29 years), being black, being a woman who has sex with men, having a more recent HIV diagnosis, or having a higher CD4+ cell count. Factors associated with lack of viral suppression included younger age (18 years–49 years), being black or of "other" race, having CD4+ count greater than 500 cells/µL, and having income at or below the poverty line. Presenters also estimated that expanding national guidelines for initiating antiretroviral therapy to all HIV-infected patients would only increase the proportion of persons in care on antiretroviral therapy by 3%. The conclusion from these data was that gaps in effective treatments exist for particular subpopulations (eg, young, black, women who have sex with men, and persons of low socioeconomic status). These disparities must be addressed, and increasing awareness of HIV serostatus, linkage to care, and retention in care need to be addressed as well.

Truong and colleagues also noted disparities in early antiretroviral initiation among patients in San Francisco, as measured through a citywide surveillance unit (Abstract 139). In 2010, the San Francisco Department of Public Health and the Positive Health Program of the San Francisco General Hospital recommended that all HIV-infected patients be offered antiretroviral therapy, regardless of CD4+ cell count. Truong documented the substantial increase in earlier diagnosis and treatment of HIV-seropositive persons in San Francisco from 2004 to 2010. The most dramatic change in 2010 was in the proportion of persons initiating antiretroviral therapy at the time of diagnosis. The mean difference in CD4 + count between diagnosis and treatment was 44 cells/µL in 2009 and 7/µL in 2010. However, substantial disparities were noted in the proportion not receiving antiretroviral therapy, with lower proportions among younger HIV-seropositive persons, non-white races, those with income at or below the poverty line, and persons not having private insurance.

Millett built on his earlier work by

presenting a meta-analysis of racial disparities in HIV risk, infection, and care among MSM in the United States (Abstract 1094). He and colleagues reported data from more than 145 US studies that included more than 150,000 black MSM and more than 500,000 MSM of other races. Despite reporting substantially significantly fewer male sex partners, less substance use, and similar rates of partner concurrency and serodiscordant unprotected anal sex compared with other MSM, black MSM were found to have double the risk of HIV infection. Among MSM with known HIV infection, black MSM reported fewer clinical visits, less antiretroviral therapy utilization, lower antiretroviral therapy adherence, and lower CD4+ cell counts than other MSM. Among MSM less than 30 years old, black MSM reported earlier sexual debut, and greater likelihood of having older male sex partners or having been sexually abused as a child. Millett pointed to the need to move beyond risk-based interventions in black MSM populations and address structural issues, engagement in care, and intergenerational sex.

Trends in the Global HIV Epidemic

Wawer and colleagues presented data on temporal trends in HIV incidence, prevalence, and prevention services in Rakai, Uganda, from 1994 through 2011 (Abstract 141). In parallel with the rise in uptake of antiretroviral therapy and MMC after 2005, there was an overall steep decline in HIV incidence and a lesser decline in HIV prevalence. The decline in incidence was greater in men than in women (10-fold vs 2-fold, respectively). Moreover, although HIV prevalence in men has leveled off in recent years, HIV prevalence in women appears to be rising. Wawer highlighted 2 possible explanations for these sex-based differences. MMC reduces HIV incidence primarily in men. Antiretroviral therapy uptake is greater in women than men, leading to a more substantial reduction in transmission to male partners, but an increased life expectancy for women, compared with men. In combination, antiretroviral

therapy and MMC would likely lead to a greater decline in HIV incidence in men, with the rising prevalence of HIV in women reflecting decreased mortality rates. Wawer ended by pointing out the substantial deficit in delivery of services to all who need them in Rakai, and argued that these population-level benefits of antiretroviral therapy and MMC make increased provision of services imperative.

Justman presented data on behalf of Nkambule and colleagues on the SHIMS (Swaziland HIV Incidence Measurement Survey), conducted in 2011, which compared HIV prevalence with levels measured in 2005 (Abstract 142). HIV prevalence in 2011 was highest among men aged 35 years to 39 years (48%) and women aged 30 years to 34 years (54%). Age-specific prevalence appears to have declined for younger ages and increased at older ages in both men and women. Justman and colleagues hypothesized that this may reflect increased uptake of antiretroviral therapy, with the resulting declines in HIV incidence reflected particularly among younger persons, and increased survival rates among older persons.

Injectable Hormonal Contraception

Similar to the literature, this year's CROI presented conflicting data on the impact of injectable hormonal contraception (IHC) on the risk of HIV acquisition. McCoy and colleagues presented data on the impact of different types of hormonal contraception on the risk of HIV acquisition (Abstract 20LB). McCoy performed her secondary data analysis on the MIRA (Methods for Improving Reproductive Health in Africa) study, a randomized controlled efficacy trial of the use of a diaphragm and lubricant gel on reducing the risk of HIV-1 acquisition. In this analysis of 4866 women, the use of IHC was associated with a 37% increase in the risk of HIV-1 acquisition; oral contraceptives had no effect on HIV-1 acquisition. The mechanism for this increased risk is not clear, and the increased risk could not be attributed to a specific type of injectable hormonal contraceptive.

McCoy presented data from a large number of studies analyzing the effects of contraception on HIV acquisition rates, which show a trend toward increased risk of HIV-1 acquisition associated with use of IHC. However, a number of other studies have found no such association. At the conference, Lutalo and colleagues presented data on more than 500 serodiscordant heterosexual couples in Rakai, Uganda, in 288 of which the woman was the HIV-1-uninfected partner (Abstract 563). The study found no evidence of increased HIV acquisition risk associated with use of IHC, either overall or stratified by type of injectable.

Butler and colleagues addressed the potential benefits and risks of reducing IHC use globally (Abstract 1074). The study compared the potential benefit of reduced HIV-1 infections with the increased rates of pregnancy and maternal deaths likely to result from substituting other forms of contraception. The analysis found that only southern African countries where IHC could be contributing substantial numbers of infections have any potential for public health benefit, assuming the increased relative risk among IHC users is significant. In other parts of the world, the effects of reducing IHC use could potentially be harmful, because of the potential for increased maternal mortality rates.

Modeling the Impact of Increased Testing, Treatment, and Prevention Interventions

Several investigators presented data on how best to prioritize population-level interventions to avert new infections and deaths, while remaining cost-effective. Birger and colleagues presented the relative benefit of different components of test-and-treat interventions on the HIV epidemic in Newark, New Jersey (Abstract 1075). The data model indicated that interventions aimed at retaining HIV-1-infected patients in care would have the greatest impact. However, retention was projected to lead to only a 16% reduction in new HIV-1infections and a 19% reduction in deaths by 2050. Combining retention in care with increased testing

coverage would reduce new infections by 25%, and the model predicted the further addition of increased rates of viral suppression would lead to a 39% reduction in new infections and a 46% reduction in deaths by 2050. Kessler and colleagues presented modeled data for New York City (Abstract 1076). Their model also suggested that care coordination (efforts to retain patients in care and enhance adherence to medication) would have the largest impact on infection rates, but also incurred the most expense. The model estimated that increased testing, linkage to care, and care coordination would cost $1 billion per year for New York City, and would result in a 23% reduction in new HIV infection rates. Expanding treatment to all HIV-infected persons at the time of diagnosis would only decrease new infections by 3% in the model.

Several investigators focused on the relative impact of expanded testing with various prevention interventions on the HIV epidemic in sub-Saharan Africa. Alsallaq and colleagues presented data on the impact of home-based counseling and testing (HBCT), with linkage to prevention services in KwaZulu-Natal, South Africa (Abstract 1079). The model indicated that 90 % coverage of HBCT, coupled with behavior change, MMC (for HIV-uninfected men) and antiretroviral therapy, could result in a 47% decrease in new HIV infections within 4 years of implementation. Behavior change interventions introduced short-term reductions in HIV infections, while MMC (which reduces susceptibility to infection) and antiretroviral therapy (which reduces transmissibility of infection) had long-term impacts. In the model, the expansion of treatment from those with

CD4+ counts less than 200 cells/μL to all newly diagnosed persons, regardless of CD4+ cell count, could further reduce HIV incidence by 63% at year 4 and 76% at year 15. Nichols and colleagues presented data modeled for rural Zambia on the relative cost-effectiveness of increased testing and antiretroviral therapy for HIV-infected persons, compared with to providing PrEP in a targeted (high-risk groups) or non-targeted (general population) fashion (Abstract 1080). In this model, increased HIV-1 testing (assumed coverage of 70%-90%) and linkage to care (assumed coverage of 70%) could result in a 50% reduction in incidence over 10 years, at a cost of $134 for each quality-adjusted life–year (QALY) gained. In this model, targeted PrEP was somewhat less effective, with a projected 31% reduction in HIV-1 incidence at a cost of $323 per QALY. Non-targeted PrEP was the least effective (23% reduction in incidence) and most costly ($1843 per QALY) approach. Alistar and colleagues also evaluated increased rates of treatment, focused PrEP, and generalized PrEP administration for South African adults (Abstract 1081). As in the previous study, the greatest benefit comes from scaling up treatment. Increasing antiretroviral coverage to 50% of persons eligible under existing guidelines could result in 1.5 million infections averted over the next 20 years, while universal treatment could result in 3.6 million infections averted. Universal access to treatment was more cost-effective than providing treatment according to existing guidelines ($310-$340 per QALY gained vs $410-$420 per QALY gained, respectively). Targeting PrEP to those at greatest risk could actu-

ally be cost-saving if universal access were to reach fewer than 70% of the HIV-1-infected population. Generalized PrEP would be most expensive if antiretroviral therapy coverage were high ($1050-$2800 per QALY gained). Buchbinder and colleagues explored different strategies for targeting PrEP in the MSM global epidemic, based on data from the iPrEx study (Abstract 1066). In that analysis, the total number needed to treat (NNT) to prevent 1 HIV infection was 60. However, men reporting unprotected receptive anal sex, regardless of partner serostatus, accounted for two-thirds of all new HIV infections, and the NNT for this subset was only 35. All of these abstracts point to a primary need to expand coverage of antiretroviral therapy to HIV-infected populations, with a supportive role of targeted PrEP to further reduce HIV-1 infection.

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