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## Sexual Violence and HIV Transmission: Summary Proceedings of a Scientific Research Planning Meeting

**Jennifer F. Klot, MRP,**

Senior Advisor, Gender, Security & HIV/AIDS, Social Science Research Council

**Judith D. Auerbach, PhD,** and

Social Science Research Council

**Miranda R. Berry**

Social Science Research Council

### Abstract

This summarizes proceedings of a Scientific Research Planning Meeting on Sexual Violence and HIV transmission, convened by the Social Science Research Council on 19–20 March 2012 at the Greentree Foundation in New York. The Meeting brought together an interdisciplinary group of basic, clinical, epidemiological and social science researchers and policy makers with the aim of: (1) examining what is known about the physiology of sexual violence and its role in HIV transmission, acquisition and pathogenesis; (2) specifying factors that distinguish risks throughout the maturation of the female genital tract, the reproductive cycle and among post-menopausal women; and (3) developing a research agenda to explore unanswered questions. The Meeting resulted in a consensus Research Agenda and White Paper that identify priorities for HIV research, policy and practice as it pertains to the role of sexual violence and genital injury in HIV transmission, acquisition and pathogenesis, particularly among women and girls.

### Keywords

Adolescents; HIV/AIDS; genital trauma; sexual violence

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The Social Science Research Council convened a Scientific Research Planning meeting on the role of sexual violence and genital trauma in HIV transmission on 19–20 March 2012 at the Greentree Foundation in New York. The Meeting (hereafter referred to as the ‘Greentree Meeting’) brought together some 40 basic, clinical, epidemiological and social science researchers and policy makers to generate new insights about the physiology of sexual trauma and violence and its role in HIV transmission, acquisition and pathogenesis, particularly among women and girls. The meeting goals were to:

1. Examine what is known about the physiology of sexual trauma and injury, including gender-based violence, and its role in HIV transmission, acquisition and pathogenesis among women and girls;
2. Specify factors that may distinguish risks throughout the maturation of the female genital tract, the reproductive cycle, and among post-menopausal women;

3. Develop a research agenda to explore unanswered questions about the relationship between sexual violence and genital trauma, HIV transmission efficacy and host immunology.

The meeting was structured with formal presentations organized into topical panels and facilitated discussion. Following this, participants engaged in a research agenda-setting exercise that identified priority scientific questions and approaches important for bringing further insight into the complex relationships between sexual violence, genital trauma, and HIV transmission. All review articles from this meeting will be available online as a special issue of the American Journal of Reproductive Immunology in February 2013.

The Greentree Meeting resulted in a consensus White Paper that identifies priorities for HIV research, policy and practice as it pertains to the role of sexual violence and genital injury in HIV transmission, acquisition and pathogenesis, particularly among women and girls (1). Following is a brief summary of the meeting proceedings.

## Introduction

### Panel 1: The Social Epidemiology of HIV/AIDS and Sexual Violence

Chair: Judith D. Auerbach, Independent Consultant, San Francisco, CA, USA

This panel addressed what is currently known about the implications of different social patterns, forms and geographies of sexual violence and coercion for HIV transmission risk; the factors that shape exposure opportunities and access to services; and how perpetrator characteristics and motivations affect HIV transmission risks.

**Sexual Violence and HIV Risk**—Jennifer F. Klot, Senior Advisor, Gender, Security & HIV/AIDS, Social Science Research Council, USA

Sexual violence is a poorly-studied, yet potentially important risk factor in HIV transmission that may be significant in the overall expansion of the AIDS epidemic and its disproportionate geographic and gender distribution. This is especially so in sub-Saharan Africa, where 76% of all HIV positive women are located and where prevalence among young women 15–24 is two to three times higher than among young men in the same age group.

Although a growing body of behavioral and social science research documents a significant and reciprocal relationship between sexual violence and HIV transmission risk, far less attention has been given to the physiology of sexual violence as a co-factor in HIV transmission, acquisition and pathogenesis. These under-examined biological factors may help explain why rates of infection are disproportionately high among young women as compared to men, particularly in sub-Saharan Africa: (1) the type of injury, its location, severity and incidence; (2) age related anatomic factors, particularly among young adolescent girls; (3) co-factors such as STIs, co-infections, (4) perpetrator characteristics and motivation (e.g. likelihood of infectiousness, circumcision); and (5) access to emergency reproductive health services and other pharmacologic prevention modalities.

Different levels of transmission risk may be associated with different patterns and geographies of sexual violence, exploitation and coercion. For example, in some scenarios, conflict-related rape can increase transmission risk at both individual and population levels (2). Forced and early marriage or intimate partner violence have also been shown to increase transmission risk, for both physiological and social reasons (3,4). Understanding the biological and social co-factors that increase vulnerability and susceptibility to HIV among different sub-populations can improve understanding about who is at most risk of sexual

violence and HIV and why, as well as the conditions under which genital trauma can increase transmission probability. A central question arising from this discussion is the extent to which sexual violence prevention can also reduce HIV transmission.

**Sexual Violence & HIV: Global Evidence & Causal Paths**—Michele R. Decker, Assistant Professor of Population, Family and Reproductive Health, Bloomberg School of Public Health, Johns Hopkins University, USA

Consistent evidence links violence with HIV infection in multiple geographic settings and across HIV epidemic scenarios (5–7). Prospective research links violence with incident STI and HIV, confirming the temporal ordering of exposures (8,9). A recent meta-analysis that concluded no consistent effect of violence on HIV in developing countries should be noted, however this analysis surprisingly grouped women across disparate risk groups with regard to age and marital status (10).

There are multiple, complex and causal pathways between sexual violence, coercion and fear of abuse and increased HIV risk. Violence victims often have limited ability to refuse unwanted sex, and negotiate safe sex. Genital trauma during forced or unwanted intercourse can facilitate HIV transmission. Anal sex has recently emerged as an important and understudied risk mechanism. Qualitative evidence demonstrates that violence and coercion are a common context for anal intercourse, and quantitative evidence from India suggests a strong association of violence with anal sex (11–14).

The HIV risk associated with violence does not stem from victims' exposures alone. On the contrary, violence perpetrators have been found to engage in higher levels of sexual risk behavior, for example, multiple sex partners, engagement in transactional sex, and condom non-use (15–18). In turn, violence perpetrators are more likely to be HIV infected, with violence enhancing the likelihood of subsequent transmission (19).

This emerging evidence base linking violence with sexual risk and STI/HIV infection enables for the first time the application of epidemiological modeling to estimate the HIV epidemic impact of reducing gender-based violence. Preliminary findings from a modeling exercise with the Futures Institute suggests that significant cumulative HIV infections may be averted by reducing violence against female sex workers.

**The Social Epidemiology of HIV/AIDS and Sexual Violence in an Endemic Setting: South Africa**—Kristin Dunkle, Assistant Professor of Behavioral Sciences and Health Education, Rollins School of Public Health, Emory University, USA

There are two main pathways through which gender-based violence can lead to HIV infection: (1) direct transmission from an HIV-infected perpetrator to an HIV-negative victim, or (2) indirect long-term increase in risk resulting from the impact of the violence on survivors. Both pathways begin in a cycle of mutually reinforcing association between gender inequality—including such forms as 'compulsory heterosexuality' and 'high-risk masculinities' (which often characterize perpetrators) and the violence which both arises from and reinforces inequalities of gender and sexual orientation. South Africa is an excellent place to understand how these dynamics impact HIV risk in an endemic setting, and also an excellent case study for understanding the global 'syndemic' (i.e. mutually reinforcing epidemics) of violence perpetration, high risk sexual behaviors, and substance use. South Africa is a country with both endemic HIV prevalence (the highest number of HIV cases in the world), and endemic gender-based violence – 25% of women in the general population and 40% in targeted studies report physical violence from their partners.

The first, direct transmission risk pathway depends on whether men who perpetrate GBV are more likely to be HIV infected than other men. One in three South African men report rape perpetration and over 40% of men report physical violence against a female partner. Men who report perpetrating such violence have more sexual partners, more concurrent partners, are more likely to engage in transactional sex and have sex with sex workers, use more alcohol and other drugs (15,20–24). Additionally, men who perpetrate physical violence against female partners are more likely to be HIV infected (4). Because some perpetrators are more likely to be HIV infected, women who experience intimate partner violence are more likely to become HIV infected, regardless of their other risks. There is currently no evidence to support a major impact of rape on HIV risk at a population level, although individual cases unquestionably occur (25,26).

The second, indirect pathway increases women's HIV risk through the psychosocial impact of rape and intimate partner violence on survivors. Violence reduces the likelihood that victims will be able to influence the timing and circumstances of sex, resulting in more unwanted sex and less condom use (15,27,28). Exposure to violence from a sexual partner is also consistently associated with subsequent high-risk sexual behaviors including multiple and concurrent sexual partnerships, increased numbers of overall partners, lower levels of condom use, increased substance use and sex while intoxicated, and increased participation in transactional sex and sex work (16,24,29–35). Thus, preventing HIV infection resulting from gender-based violence must include long term psychosocial support for survivors to mitigate against the long term impact of violence.

## **Panel II: The Physiology of Genital Trauma: Implications for HIV Transmission, Acquisition, and Pathogenesis**

Chair: Papa Salif Sow, Professor of Infectious Diseases, University of Dakar, Senegal

This panel addressed what is known and not known about the measurement and impact of genito-anal injury and coital trauma in relation to HIV transmission, acquisition, and pathogenesis. Presenters identified how factors affecting injury and trauma change throughout the reproductive and life cycle and may be influenced further by endogenous hormones, female genital mutilation, and co-infections.

### **Forced Sex and HIV Risk in Violent Relationships**

Jacquelyn Campbell, Anna D. Wolf Chair and Professor, School of Nursing, Johns Hopkins University, USA

The contribution of intimate partner violence (IPV) to HIV transmission and progression is highly under-researched. The overlap between physical, sexual and psychological abuse can be discerned in relation to early sexual debut, anal sex, disease progression and immune system effects. Data from the 2012 African Caribbean and African American Women's Study associates physically abusive relationships with repeated acts of forced sex acts, including a substantial proportion of anal sex, as well as higher rates of forced unprotected anal sex. And data from 11 regions examined in the WHO Multi-Country Study On Women's Health and Domestic Violence against Women show that the younger a women's age of first sex, the higher risk of her experiencing a forced encounter (36). A growing body of research also points to the immune system effects of IPV, through altered hypothalamic, pituitary and adrenal gland interactions and the suppression of Th1 cell cytokine production (which fights bacteria and viruses). Post traumatic stress disorder (PTSD) and depression – co-morbidities associated with IPV – can also contribute to immune suppression and pro-inflammatory responses (37–39). The physiological effects of IPV on the immune system have been under-researched, particularly in relation to interactions with other STIs, chronic

pain, inflammation-related friability of urinary and vaginal tissues, and issues relating to age and reproductive and menstrual cycles.

### **Anogenital and Oral Injuries in Sexual Assault**

Kathryn Laughon, Associate Professor of Nursing, University Of Virginia, USA

The types and frequency of genital injuries sustained by sexual assault victims are typically classified in relation to tears, ecchymosis, abrasions, and redness. Each may contribute to increased HIV risk through bleeding, breaks in skin and inflammation. Although there is no standardized reporting, most genital injuries identified in non-consensual sex occur in the posterior fourchette, the hymen, labia minora, cervix, urethra/periurethral, anus, vagina and rectum. Rates of injury vary immensely, with studies estimating between 32% and 94% in sexual assault patients (40). Although some studies associate higher rates (up to three times higher) of injury, abrasions and bruises in non-consensual sex than consensual sex, others have found no difference. Most studies find that sexually assaulted adolescents sustain more injuries than adult women (41). Although very little data are available regarding incidence of genital injury in children, pre-pubescent girls may be at greater risk of injury – as estrogen levels fall (from infancy), the hymen becomes thin and will tear instead of stretch, and skin bleeds profusely with minor trauma (42).

### **Female Genital Mutilation/Cutting**

Khady Diouf, M.D., Associate Obstetrician Gynecologist, Brigham and Women's Hospital, USA; Clinical Instructor, Harvard Medical School, USA and Nawal Nour, MD, MPH, Director, African Women's Health Center, Brigham and Women's Hospital; Associate Professor, Harvard Medical School, USA

Female Genital Mutilation/Cutting (FGM/C) is practiced in many countries in Africa and Asia for a variety of reasons: (1) psychosexual: to decrease sexual desire in women, to ensure chastity and fidelity and to enhance male sexual pleasure; (2) sociocultural: as an initiation into womanhood; to preserve fertility; (3) hygienic and aesthetic reasons; and (4) socioeconomic: to raise social status and to ensure marriageability. There are 4 types of FGM/C, ranging from nicking or piercing the external genitalia (type IV) to removing part or all of the clitoris and/or the labia minora (type I and II), to removing most of the external genitalia, re-approximating the remnant tissue thus leaving a small opening for urine and menses (type III). There are numerous short and long-term genitourinary complications associated with the procedure including infection, hemorrhage, vulvar swelling, dyspareunia, pelvic inflammatory disease, infertility, as well as obstetric complications (43). Although there is little evidence linking FGM/C and HIV transmission, the few studies that have been carried out point to the potential role of non-sterile/soiled equipment, transfusion with potentially contaminated blood following hemorrhage, reported increased prevalence of reproductive tract infections associated with HIV transmission and acquisition, and inflammation/abrasion of vaginal tissue from the physical trauma of FGM (44). Other potential risk factors include earlier sexual debut, polygamous relationships, and male preference for 'uncut' women and higher rates of anal intercourse (due to difficult and painful vaginal intercourse) (45). However, there remain few rigorous studies exploring FGM/C and HIV, and more research is needed to identify the direct and indirect pathways linking HIV transmission with FGM/C, namely in relation to the sexual practices of cut women and their partners, including the prevalence of anal intercourse, extramarital relationships, and the frequency/quality of sexual intercourse.

## **Rape and Sexual Violence: Case of East Democratic Republic of Congo**

Gilbert Utshudienyema Wembodinga, Department of Obstetrics and Gynecology, Panzi General Referral Hospital, and Evangelical University in Africa/Bukavu, Democratic Republic of the Congo (DRC), Dennis Mukwege, Department of Surgery, Panzi General Referral Hospital and Evangelical University in Africa/Bukavu, DRC; Ahuka O. Longombe, Department of Obstetrics and Gynecology, VSV Service/General Reference Hospital Panzi/Bukavu, DRC; and Dr. Irene Tchangou, MD, Obstetrician & Gynecologist, Fistula Care Project Assistant, Panzi Hospital

In the Democratic Republic of Congo (DRC), sexual violence has become a tactic of war, a means to propagate HIV, wipe out ethnic groups through forced pregnancies, and as a means to ensure that people are forced to flee from their homes. In conflict, the main perpetrators are men and victims are predominantly women (46).

In the DRC, data from survivors seeking treatment at Panzi Clinic showed that rape was one of the most serious forms of violence, with women comprising 98% of the victims. Women reported having been assaulted by rebels, the army, relatives and robbers. Fifty-three percent of the rapes took place in the victim's house or village, with 60% of the victims reporting more than two perpetrators per assault. The impact on individual victims of such violence included physical lacerations, wounds, sexually transmitted infections (including HIV), pregnancy, psychosocial trauma and social rejection and stigma (47). From a sample of 781 sexual and gender-based violence (SGBV) victims treated at Panzi, 1% tested positive for HIV, over 3% were positive for syphilis, 10% had unwanted pregnancies, and only 10% were considered to have no signs of psychological trauma.

The impact of assaults extends beyond the individual victim to their families and to the community at large; this is more pronounced when the sexual violence perpetrated systematically against tens or hundreds of people within one community. The main social consequences of sexual violence are increased morbidity and mortality, population displacement and the destruction of family and social structures among survivors and their families and communities (48).

### **Panel III: Clinical and Field Perspectives: Risk Groups and Risk Factors**

Chair: Kathryn Anastos, Professor of Medicine, Epidemiology and Population Health, Albert Einstein College of Medicine, USA

This panel described various clinical presentations of sexual violence and the current state of treatment and care provided to survivors of it, as well as challenges and opportunities for implementing HIV prevention (including pre- and post-exposure prophylaxis (PrEP and PEP)) in clinical settings where such patients present.

#### **Clinical & Field Perspectives: Eastern Democratic Republic of Congo**

Nancy Glass, Associate Professor, Johns Hopkins University School of Nursing and Associate Director, Johns Hopkins Center for Global Health, USA

More than sixteen years of armed conflict in eastern Democratic Republic of Congo has created an environment of increased risk for HIV/AIDS characterized by limited infrastructure, economic insecurity and sexual and gender based violence. In rural areas, the absence of essential health infrastructure, supplies, and trained health care providers limits the access of survivors of sexual violence to health care and post-exposure prophylaxis.



In this context, an interdisciplinary and participatory action research collaboration is being supported by the National Institutes of Health (NIH)/National Institute for Minority Health and Health Disparities (NIMHD). The partnership includes two academic institutions, Johns Hopkins University School of Nursing, the Kaiser Centre for Health Research, and two Congolese-led community development organizations: Foundation RamaLevina, an integrated health, economic and social program for survivors of sexual and gender-based violence (SGBV) and their families, and PAIDEK Microfinance (49).

Between July 2010 and June 2011, 657 (85%) of 772 women receiving health services in 6 rural villages in the Eastern South Kivu province were identified as survivors of sexual violence. Among these, 89% had been assaulted in their homes with 25% reporting 4 or more male perpetrators. Nearly half did not receive health services and, even among those who did receive care, fewer than 5% reached care within one week. Ninety-three percent of survivors accepted HIV testing – 3.2% were positive – double the national prevalence for women. Eighty percent of survivors took STI treatment to their partners with more than half reporting that their husband/partners completed full or partial treatment. This collaboration provides an excellent model for implementing and scaling up locally led integrated approaches to providing quality care to survivors and for engaging male partners in HIV and STI testing, treatment and follow up care. Challenges include the need to ensure sustained access to essential supplies and medications for survivors, partners and their children as well as socio-cultural and economic issues regarding fear of disclosure, extreme poverty, gender inequality and impunity for perpetrators – both civilian and armed combatants.

### **Clinical and Field Perspectives: Risk Groups and Risk Factors**

Velda Mushangwe-Mtisi, Department of Obstetrics and Gynaecology, University of Zimbabwe Medical School, Zimbabwe

Seventy percent of the survivors reporting to a Harare-based Sexual Violence Clinic, which takes care of adult rape survivors, were between the ages of 16 and 25. In most cases, there are no visible injuries following sexual assault. This is likely due to the duration between the incident and the report and also depends on the nature and circumstances of the sexual assault. Fear, stigma and factors such as limited infrastructure and transportation limit the ability of survivors to access healthcare and follow-up treatment. Only 32% come to the clinic within the first 72 hours after assault and this diminishes the effectiveness of PEP and emergency contraception. While all of those requiring PEP actually receive it, many do not return for follow-up treatment, and it is unknown if they finish the course of medication. The Harare clinic takes an integrated approach to service delivery, combining medical care with counseling and referral to other services such as social welfare, safe houses, and legal support. Between March 2009 and March 2010, 88% of those seeking treatment received an emergency contraceptive pill. Among the 85% who agreed to get tested for HIV, 10.9 percent were positive. Challenges to providing comprehensive care include the poor follow-up rate – only 30% – and the lack of screening and diagnostic equipment. Sexual violence and HIV programs tend to be located in different clinical settings. More awareness-raising is needed to sensitize communities about the risks of HIV and sexual violence and for multisectoral approaches to training district level health teams.<sup>1</sup>

### **Sexual Violence and Traumatic Fistula in Precarious Situations**

Serigne Magueye Gueye, Professor of Surgery and Urology, Université Cheikh Anta DIOP and Grand Yoff General Hospital, Director, IFRU-SU, Senegal

<sup>1</sup>Data in presentation is unpublished and based on internal clinic records.

While sexual violence is very common in conflict zones, its magnitude is not fully known, and there is even less information about the intersection of sexual violence, HIV and traumatic fistula. Risk factors in conflict-affected settings in Africa include low health expenditures, poverty, rapid population growth, mobility, and unstable family situations. Alcohol and substance abuse are aggravating factors in the context of sexual violence, and perpetrators include the militia, rebels, regular armed forces, civilians, and family and community members. Traumatic fistula occurs due to sexual violence, and obstetric fistula occurs during childbirth. Medical doctors working in conflict affected settings, including DRC, Darfur, Chad, Somalia, Burundi, Guinea Bissau, Cote d'Ivoire, Rwanda, Liberia, Sierra Leone, Angola, Central African Republic and Eritrea, have observed and attended to survivors of individual and group rape, injuries resulting from the use of instruments in the genital organs such as firearms, knives, sticks and other septic tools. The medical and health consequences often include vesico-vaginal and recto-vaginal fistula, as well as pelvic floor trauma, HIV infection and psychosocial distress. Most traumatic fistulae are deemed incurable and are accompanied by severe loss of bladder capacity, complete vaginal stenosis, total destruction of urethra and irreparable damage to continence mechanism, among other harms. Many of the women affected by fistula also have experienced FGM, further increasing the severity of their injuries. Consequently these women need reconstruction of the genito-urinary tract or palliative surgery, psycho-social support, ongoing management of sexual and reproductive health issues and economic and social re-integration support. Multidisciplinary collaborations are urgently needed to develop research and practice protocols for assessing the linkages between traumatic fistula, FGM, sexual violence and HIV.

### **Modulators of HIV Risk: From Bench to Bedside and Back Again**

*Betsy Herold, Professor of Pediatrics (Infectious Diseases), Microbiology & Immunology and Obstetrics & Gynecology, Albert Einstein College of Medicine, USA<sup>2</sup>*

Factors associated with increased risk of HIV transmission include viral load, stage of HIV infection, virulence, tropism and the number and activation status of target immune cells in the uninfected partner. Protective modulators include an intact epithelial barrier, antimicrobial proteins, mucus, healthy vaginal microbiota and host genetics. Injuries, microabrasions and inflammation resulting from sexual violence are more likely than consensual sex to disrupt the epithelial barrier, allowing HIV-1 to reach submucosal immune target cells. The inflammatory responses to injury may also increase the number of activated target cells or promote HIV replication through activation of the viral promoter. The risk of HIV acquisition is also associated with barrier unprotected sex, anal sex, and other sexually transmitted infections. Semen, the primary source of HIV, interferes with normal host defenses. For example, semen buffers the normally protective acidic pH of the female genital tract and seminal proteins may promote HIV binding to cells (50), recruit new HIV targets (51), or enhance HIV replication. HPV and other viral and bacterial sexually transmitted infections (STI), which may be acquired in the setting of sexual violence, are also associated with increased risk of HIV acquisition by similar mechanisms (52). Unfortunately, STI treatment or suppressive therapy is not effective in reducing the risk of HIV transmission or acquisition in controlled clinical trials highlighting the need for novel approaches.

Adolescent girls and pregnant women are more susceptible to HIV in part because of increased cervical ectopy (single layered columnar epithelium), and because they may have increased concentrations of inflammatory immune mediators in their genital tract, reduced

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<sup>2</sup>Co-Authored with Rebecca Pellet Madan, MD (Department of Pediatrics, Albert Einstein College of Medicine).



levels of protective mediators including immunoglobulins, and fewer protective lactobacilli. Strategies to reduce inflammation and augment natural host defense are currently being evaluated and could help protect vulnerable populations from HIV and other sexually transmitted infections.

## **Panel IV: Genitoanal Trauma and Sexual Violence: Implications for Mucosal Immunology**

Chair: Fulvia Veronese, Assistant Director for Translational Research, Prevention Science Program, United States National Institutes of Health, USA

This panel examined aspects of host immunity of the female reproductive tracts that may facilitate or protect against genitoanal injury and violence-related HIV transmission, acquisition and pathogenesis, and the role of inflammation in this regard.

### **Sexual Violence and HIV Transmission: Endocrine Regulation of Immune Protection in the Female Reproductive Tract against HIV**

Charles Wira, Professor of Physiology, Dartmouth Medical School, USA

Sex hormones regulate all levels of immune protection against HIV acquisition throughout the course of the menstrual cycle in the female reproductive tract. Ovulation is the key window of viral vulnerability for transmission of HIV due to hormone-mediated suppression of immune events that optimize the conditions for fertilization and implantation. Hormonal changes mediate cell immunity through the decreased activity of cytotoxic T lymphocyte (CTL) cells, which recognize foreign cells, including those infected with HIV. CTL activity is present during the first half of the menstrual cycle and absent during the second half, pointing to the increased likelihood of infection in the menstrual cycle (53). An understudied factor affecting host immunology and susceptibility is cervical ectopy, a normal characteristic of female reproductive tract development in adolescence. Others have shown that protein levels of cervical vaginal cytokines/chemokines are higher in women with immature cervical epithelium, implying a higher level of risk for those with cervical ectopy (54). Cervical ectopy is also more likely to occur during pregnancy and with oral contraceptive use and is positively associated with HIV and other STIs. More research is needed regarding the innate and adaptive immune systems in the female reproductive tract as it applies to girls before and during puberty, the impact of genital trauma and FGM/C, and the relationship between cervical ectopy and HIV acquisition.

### **The Role of Female Genital Tract Epithelial Lining in HIV Transmission: Barrier Functions and Local Microenvironment**

Charu Kaushic, Associate Professor of Pathology and Molecular Medicine, McMaster University, Canada

Epithelial cells in the genital tract function as a barrier against HIV transmission; they are the first cells that initiate immune responses to the presence of pathogens and changes in the genital microenvironment (55). Seminal plasma and bacterial and viral co-infections can also induce inflammatory responses from epithelial cells, driving HIV replication (56). Exposure to HIV-1 directly impairs mucosal epithelia barrier integrity and function, allowing microbial translocation (57). HIV-1 can manipulate the innate response in the female genital tract to gain entry and induce local inflammation. This increases the chance of HIV infection, since HIV can leak paracellularly. Bacterial and viral co-infections can induce inflammatory responses from epithelial cells and drive HIV replication. Local regulatory cytokines can help protect barrier disruption. Questions remain about the role of

the epithelial barrier in HIV pathogenesis in vivo, and the impact of genital trauma on its function and immune responses. Can strengthening the barrier protect against HIV infection? Should anti-inflammatory treatments be considered in addition to anti-virals for prophylaxis? Under inflammatory conditions, can dormant HIV start to replicate in epithelial cells and how does this affect transmission dynamics?

### **Proposed Mechanisms for HIV Transmission across Epithelium**

Thomas Hope, Professor of Cell and Molecular Biology, Northwestern University, USA

Direct observation of the interactions of HIV with mucosal barriers is crucial to fully understanding the mechanisms of HIV transmission. Fluorescent tagging can enable this visualization of individual virions, which are then administered onto tissues or in the context of primate models. Sections from exposed tissue are evaluated to show where the virus goes after entering the host. Though current research focuses on the increased vulnerability of single layer columnar epithelium, the images from these experiments show that virus can also enter through intact squamous epithelium. Approximately 10 times more virus was found in places where more water (from inoculate) entered, indicating that HIV can penetrate more deeply in natural weak points in the barrier. However, for infection to occur, the viral particles must come into contact with a cell they can infect. Inflammation aids this process by bringing T cells to the surface of the epithelium and thus not requiring the virus to have to penetrate as deeply into the epithelium in order to reach a target cell.

Inflammation is a key driver of transmission/acquisition. Sexual violence leads to local inflammation, thus facilitating this process of infection. In terms of modeling trauma, one can use the edges of biopsies as proxies. Data from 40 scans show that the exposed connective tissue on these edges of biopsies acts as a virus magnet although the viral particles did not penetrate very deeply. There is also the possibility for injuries to be protective; for example, no virus was found in a blood clot that developed following biopsy.

### **Panel V: Data Gaps and Measurement Challenges**

Chair: Carel Pretorius, Researcher, Futures Institute, USA

This panel addressed the kinds of data needed to establish the link between sexual violence, genital trauma, and HIV infection, including how best to collect such data and measure important indicators, particularly in contexts not conducive to research, such as conflict situations.

### **From the Laboratory to Clinical Trials and Back Again: Lessons Learned from HIV Prevention Trials**

Sengeziwe Sibeko, Nuffield Medical Fellow, Oxford University, UK

The increasingly perplexing outcomes of the recent HIV prevention trials, and particularly vaccine, PrEP, and circumcision trials, have underscored the importance of laboratory sciences in delineating mechanisms that mediate the association between HIV exposure and acquisition and explaining contradictory outcomes. For instance, the results of the two trials testing the topical pre-exposure prophylaxis (PrEP) strategy in women using the same drug, 1% tenofovir gel, have been conflicting. Likewise, HIV envelope proteins targeted at the humoral immune system failed to protect against HIV acquisition. The Merck vaccine targeting the cell-mediated immune system was halted for futility. While the Thai RV144 trial yielded a positive result, it was only marginally positive failing to reach statistical significance. The reasons for these conflicting results have yet to be identified. Clinical trials must incorporate basic science protocols that aim to answer not only the questions of the

impact of the preventive strategy on HIV acquisition/protection but also to enhance our understanding of natural correlates of protection/harm at the portal of entry. In order to enhance these immune-physiological studies, appropriate biological specimens ought to be collected, and in the context of sexually transmitted HIV, these specimens must be collected from the genital tract. However, if the biological specimens collected are not appropriate, adequate, timed or processed correctly, understanding about these immunological correlates may be compromised. Moreover, understanding how immune responses are affected by genital trauma, including sexual violence, will require the simultaneous collection of behavioral data about the nature and circumstances of specific sex acts (58–60).

### **Challenges in Virological Diagnosis of HIV Transmission from Sexual Abuse**

Anneka Ehrnst, Professor of Clinical Immunology, Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet, Sweden

Virological diagnosis of blood samples can be used to identify the chain of HIV transmission in cases of sexual violence. Close epidemiological links have been discerned in cases where HIV-1 genes from a sexual violence victim and the rape suspect shared rare genetic features (61). Phylogenetic analysis of samples taken 2–12 years after infection has been able to reconstruct the chain of transmission among 11 HIV-1 infected individuals (62). The clonal expansion of HIV strains provides a high resolution among genetic ties. Virological methods can aid investigation of sexual abuse, particularly when children are involved but also through contact tracing (63). Using filter paper, blood samples can be stored for long periods, upwards of 12 years. This might also be a way to increase sample collection in areas with limited resources.

In the case of child sexual abuse, diagnosing through virological analysis of HIV is relatively straight-forward. It is more controversial and ethically ambiguous in cases of infection among adults. However, the work in virology on HIV transmission in older cases shows the wealth of information yielded from older samples and methods of storage that can be used in a variety of settings.

### **Conflict-Related Sexual Violence and the Spread of HIV**

Ragnhild Nordås, Senior Researcher, Centre for the Study of Civil War, Peace Research Institute Oslo, Norway

Comparative analysis of the link between conflict-related sexual violence and HIV is limited. In part, this is due to the absence of reliable measurement of sexual violence, and challenges related to data collection, such as reporting and source biases. Most research on conflict-related sexual violence is single case studies focused on high profile/prevalence cases, such as Bosnia, Rwanda and the DRC. However, to understand conflict-related sexual violence and its consequences, we also need to map cases of relative absence.

Key factors relevant for understanding the link between conflict-related sexual violence and HIV include: (1) Prevalence of sexual violence and the degree of violence/force; (2) Targeting, i.e. varying infection risks across different populations or geographic locations; (3) Perpetrator characteristics – e.g. physical, psychological and social. Additional information is needed about post-infection patterns of exposure to violence and thereby the risk of spreading of HIV. Future research should attempt to identify geographic and sub-national patterns in variation of sexual violence, as well as social and other factors that contribute to risk of spreading HIV. Future research opportunities include coupling data on conflict sexual violence with geographically and temporally disaggregated data on conflict events and displacement/migration data, identifying pre-war baselines of sexual violence through specialized individual and household surveys, and studying the spread of HIV by

using indicators of sexual violence in conflict in network analysis in conflict-affected countries.

### **Bad Data, Good Ways Forward: The Evolving Empirics of Sexual Violence**

Amelia Hoover Green, Assistant Professor of Political Science, Drexel University, USA

The types, patterns and magnitudes of bias in current research on sexual violence in armed conflict are definitional as well as psychological, political and logistical. Seemingly innocuous changes in research methods can dramatically impact findings; in one randomized survey experiment in the US, changing the initial round of screening question changed the estimated prevalence of forced sex by nearly ten-fold (64). The reliability and validity of data describing different types and patterns of sexual violence — their absolute and relative frequencies, their role in conflict versus non-conflict settings, etc. — is questionable at best. In addition, the lack of pre-conflict baseline data makes existing data impossible to interpret: both the role of conflict in sexual violence and the role of sexual violence in HIV transmission remain unclear. Thus, methodological research on reporting patterns is essential. Promising research agendas in this area include qualitative interviews and focus groups, survey experimentation, neighborhood or “sisterhood” survey methods, and comprehensive sensitivity analyses of existing data (65). Other methodological developments include perpetrator interviews regarding causes and dynamics of sexual violence, and multi-method local investigations. All this work must consider carefully the ethical questions associated with investigating sensitive topics under insecure circumstances. Ultimately, understanding the causes and consequences of conflict-related sexual violence requires understanding varying patterns of access to, and decisions about, reporting.

### **Panel VI: Methodological Challenges and Opportunities: Implications for Modeling**

Chair: Catherine Hankins, Consultant, Joint United Nations Programme on HIV/AIDS, Switzerland

Presenters on this panel described challenges and opportunities in determining biological, behavioral, and social-demographic parameters for models of HIV transmission that factor in the role of sexual violence and genital trauma to better inform surveillance efforts and intervention strategies.

#### **Sexual Violence & HIV: What Can Modeling Do?**

Charlotte Watts, Sigrid Rausing Professor in Gender, Violence and Health, London School of Hygiene and Tropical Medicine, UK

Mathematical and epidemiological models are imperfect yet powerful tools to explore the contribution of key risk factors to HIV transmission, to explore the potential impact of behavior change, and to estimate the broader population impacts of interventions that have been shown to be effective in a specific setting. Models rely on biological data, e.g. on HIV transmission probabilities per sex act, co-factors (such as STI effects), the duration of time in different HIV phases, and on behavioral, social, and demographic data, including the number of sex acts in a given timeframe, how consistently condoms are used, and the size of subpopulations. A key building block of these models is the force of infection – i.e. the rate at which susceptible individuals become infected per unit time. This rate is determined by a number of variables for which accurate estimates do not exist, namely, (1) per-act transmission probabilities; (2) probability that the partner is infected with HIV; (3) the

partner's stage of infection; (4) the number of sex acts within an infectious period; (5) the efficacy and frequency of condom use; and (6) the presence of co-factors.

For models to estimate the contribution of sexual violence to HIV risk, behavioral and biological data are needed for a number of key inputs. Although prospective research in South Africa and India and some cross-sectional studies demonstrate an association between physical and/or sexual violence and HIV/STI risk, there remains little conceptual clarity regarding the direct and indirect pathways of association. Given the influence of multiple factors, methodological challenges arise in identifying which forms of violence to consider (e.g. the typology and severity of exposure), what outcomes to use, how to construct comparison groups, and what to control for in the analysis. More accurate estimates are needed regarding prevalence and the relative probability of risk of different forms of exposure, the duration of effect, HIV and STI prevalence among higher risk violent males as compared to other males, the probability of male-to-female infection per vaginal and anal sex act, and the impact of genital trauma on per-sex-act probabilities. Clarity is also needed regarding the relative importance of various risk factors – how to estimate them and which to include in models – e.g. in relation to forced, early, and anal sex and the impact of female genital mutilation/cutting. Advancing this agenda will benefit from systematic reviews of current evidence on the relationship between early sex and HIV risk in different settings and of potential intervention models to delay first sex, influence the age difference between partners and the likelihood of condom use. Further analyses and qualitative research is also needed to clarify the pathways of association between key risk factors, such as sexual violence and anal sex. Additional priorities include secondary analysis of existing epidemiological data to explore evidence of increased transmission risk among adolescent girls in generalized HIV epidemics, age-disaggregated modeling and new intervention research.

### **Approaches to Measuring Sexual Violence in Conflict-Affected Settings: Cluster RCT of a Male-Focused Violence Prevention Intervention in Rural Côte d'Ivoire**

*Mazeda Hossain, Lecturer in Social Epidemiology, Department of Global Health and Development, London School of Hygiene and Tropical Medicine, UK<sup>3</sup>*

In conflict-affected settings, there is little reliable data about the causes and risk factors associated with sexual and gender-based violence (SGBV), and prevalence and patterns of trauma exposures among women and men. Comparative analyses within conflict-affected settings are limited by the use of different indicators and definitions of what constitutes sexual violence. There are also few rigorous evaluations of partner violence prevention strategies, especially in conflict-affected settings. Innovative programs in low-income settings are still in their early development and focus on male behavior, concepts of masculinities and gender norms. Preliminary findings from a cluster randomized controlled trial in Côte d'Ivoire assessing the impact of a male-focused violence prevention intervention found similar overall levels of partner and non-partner violence across the six intervention and six control sites but significant differences in the types of violence reported by women and men (66). Exposure to traumatic events was relative to the conflict period but highlighted that traumatic events are not limited to the conflict period. Building a strong evidence base will require standard measures across settings, while also adapting to the specific context and ensuring that data collection does not increase women's risk of violence. Sexual violence reporting needs to be contextualized within the broader socio-cultural environment. Determining the relative contribution of sexual violence and rape to

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<sup>3</sup>Contributors: Cathy Zimmerman, Ligia Kiss, Charlotte Watts

HIV risk must also be contextualized within broader experiences of violence and locally specific gender dynamics.

### **Heterosexual anal intercourse: a neglected risk factor for HIV?<sup>4</sup>**

Marie-Claude Boily, Senior Lecturer, Infectious Disease Ecology, Imperial College, UK

The risk of HIV transmission is greater during receptive anal intercourse (RAI) than receptive vaginal intercourse (RVI) because the rectal mucosa lack the protective humoral immune barrier present in cervico-vaginal secretions and are more susceptible to traumatic abrasions that may facilitate transmission (67). Determining the contribution of RAI in heterosexual transmission at the population level requires information on who and how many individuals practice unprotected AI, how often they do so, and with whom, as well as quantitative estimates of the probability of HIV transmission per type of sexual act. Current evidence suggests that the risk of HIV acquisition is 1.4% [95% CI 0.2–2.5] during RAI compared to 0.08% [95% CI 0.06–0.11] during RVI acts in developed countries (68). AI seems to be ubiquitous across populations, age groups and countries with some studies reporting that up to 20% and more of selected populations in America, Africa and elsewhere have ever engaged in AI (67). However, more data is required on the frequency of AI, when it is practiced and why? For example, one study in South Africa reported that 10.4 % women and 14.6% men practiced AI in 40–50% (67) of all their sex acts in the past three months, suggesting that overall, 6%–10% of all unprotected sex acts reported by study participants (townships, STI clinics) in Cape Town were AI (68,69). Results from mathematical model of heterosexual HIV transmission parameterized with Kalishman’s data suggest that a small fraction of RAI (i.e. 5–10%) may be as, or more, important to overall HIV transmission (approximately 8 – 48% of all HIV transmission in the general population) than the acute phase of HIV infection (~ 7–31% of all HIV transmission); this is worse for women (70). In these simulations, HIV risk during insertive anal intercourse (IAI) was increased by 1–4 and 4–20-fold during unprotected IAI and RAI compared to VI, respectively, whereas the HIV risk during the primary and late phase of HIV infection was increased by 5–19 and 5–12 fold, respectively. These findings have important implications for interpreting model results on the population-level effectiveness of vaginal microbicides (VMB) in heterosexual population since VMB cannot be used during AI. One model predicts that even if only 5% of all unprotected sex acts are AI, this could be sufficient to reduce the impact of VMB (in terms of cumulative fraction of HIV infections averted) by 17–39% over 25 years (68).

In order to gain a more precise understanding of the role of AI in the heterosexual epidemic in different contexts, and to design effective prevention, it is important to more precisely quantify the frequency of unprotected anal sex and to understand when it is practiced. It remains to be known how sexual violence might influence the prevalence and frequency of AI and the transmission probability during AI (perhaps more trauma during violent AI increases HIV risk), and subsequent implications for intervention. Heterosexual anal intercourse has seldom been considered in current HIV models that estimate the impact of prevention interventions, potentially leading to overestimation of the impact of some types of interventions (e.g. VMB). Drawing attention to heterosexual anal intercourse adds a new pathway through which sexual violence can influence HIV incidence and prevalence – as well as impede prevention efforts.

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## Biology as Population Dynamics: Heuristics for Transmission Risk

Alex Welte, Director, South Africa Centre for Epidemiological Modelling and Analysis, South Africa

Population type models, accounting for lifetimes, mixing and recruiting patterns, genetic evolution, and environmental conditions, can be applied to the biology of HIV infection. A simple hypothetical model is used to demonstrate the effect of a vaccine-like stimulus on mortality and fertility of invading virions, mortality of freshly infected cells and availability of infectable cells, all of which impact the probability of infection. The dynamical insights and assumptions of models such as this are compatible with the continuum of inter- and intra-variability of risk in sexual violence, and may be helpful for making sense of the sparse data available on sexual violence. These models also capture the importance of timing and duration of different events in viral replication. This type of cellular modeling could be applied to the mucosal immunology questions of basic scientists, particularly questions regarding adolescents, epithelium barrier, cervical ectopy and the differences in viral replication due to site of infection.

## Conclusions and Implications for Research: Priority Scientific Research Questions and Approaches

It was clear from the rich array of presentations that there remain significant gaps in research to clarify and assess the role and significance of sexual violence and genital trauma in HIV transmission, acquisition, and disease progression among women and girls globally. Meeting participants acknowledged the complexity of causal pathways between sexual violence, genital trauma, and HIV transmission, and felt that these can only be elucidated by an integrated bio-social approach. Following the panel presentations and discussions, meeting participants identified a set of priority research questions and approaches spanning basic, laboratory science, clinical investigation, and behavioral and social research. Specific research questions related to:

- the role of ano-genital injury in HIV transmission, acquisition and pathogenesis;
- the influence of age-related anatomic characteristics in shaping HIV transmission, acquisition, and pathogenesis ; and
- the role of heterosexual anal intercourse in the epidemiology of HIV/AIDS.

And methodological issues related to:

- primate models;
- biological plausibility/proof-of-concept studies;
- sociological plausibility studies;
- natural experiments;
- virological approaches;
- cross-sectional studies and secondary analyses of existing data;
- longitudinal cohort studies (prospective/retrospective);
- systematic reviews;
- mathematical and epidemiological models; and
- new intervention research.

The complete list of research priorities and approaches, as well proposed directions for policy, and practice, may be found in The Greentree White Paper (1).

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