STATE OF THE ART AND SCIENCE
Will Risk Compensation Accompany Pre-Exposure Prophylaxis for HIV?
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Thirty years into the HIV epidemic, feasible and effective prevention strategies that can be implemented in populations with high incidences of new infection are still needed. An ideal prevention package should meet the needs of each subgroup in a population and be acceptable, accessible, and effective. Control of HIV will be best accomplished by combining several proven prevention strategies, including condom use, medical male circumcision, HIV antibody testing, antiretroviral therapy (ART) for treatment as prevention (TasP) for those infected with HIV, pre-exposure prophylaxis (PrEP) for those not infected with HIV [1], and postexposure prophylaxis. Biomedical interventions incorporating ART are most likely to have the greatest impact on the epidemic: they have been shown to be effective in several randomized placebo control trials [2-6] and open-label extensions, in which researchers and participants knew the active drug was being used [7].

Risk Compensation
As the evidence for the success of these HIV prevention interventions increases, concern has emerged about how users of these interventions, particularly TasP and PrEP, may change their HIV sexual risk behaviors. This concern is best explained by the prevailing theory about how individuals manage their personal risks. Risk "homeostasis" is defined as "a system in which individuals accept a certain level of subjectively estimated [or "perceived"] risk to their health in exchange for benefits they expect to receive from [an]... activity" [8]. In short, individuals maintain an approximate risk "set point." However, introduction of an intervention that reduces the perceived risk of the behavior or activity may cause a person to increase risky behavior—this is called "risk compensation" [9]—so that the discrepancy between the level of risk the person takes and the perceived risk increases. While taking ART, for example, individuals perceive that they are protected from transmitting or acquiring HIV. Risk compensation thus may occur when prophylactic technologies are used to prevent HIV acquisition. If risk compensation does indeed occur, it has the ability to mitigate the potential benefits of ART-based HIV prevention strategies.

Has Risk Compensation Occurred in Other Realms?
Historically, similar arguments have been raised regarding risk compensation after introduction of other interventions that lessen the consequences of risky behavior. The extensive availability of female contraceptives has been criticized for promoting risky sexual behavior, but studies have not supported the contention that contraceptive provision leads to increased risk behavior. Just this year, Secura et al. found that giving women free birth control did not result in increased promiscuity

[10]. Needle exchange programs (NEP) for injection drug use (IDU) were met with similar arguments about enabling and prolonging IDU [11], but subsequent studies found that associations between NEP use and HIV risk could be explained by the fact that NEPs attract high-risk injection drug users [12, 13]. More recently, there was concern that earlier sexual debut and greater numbers of sexual partners would follow use of the human papillomavirus vaccination, but increased sexual activity has not been observed [14-19].

Risk Compensation around HIV
HIV may be different from these previous examples. Unlike hepatitis C and cervical cancer, HIV is fatal without lifelong therapy. Moreover, HIV acquisition through sexual activity is often conceptualized as a direct consequence of risky sexual behavior. Accordingly, if the perceived threat of HIV infection is reduced, more risk compensation is likely to occur. But *is* HIV different—namely, has risk compensation been observed to follow HIV-related interventions in ways that it has not been observed to follow, for example, HPV-prevention interventions? Let us examine the three applications of antiretroviral therapy individually.

nPEP. In theory, giving HIV medications after a risky sexual encounter, also known as nonoccupational postexposure prophylaxis or nPEP, could unintentionally increase an individual's sexual risk behavior by giving the individual a sense of postrisk protection. However, a cohort study in England that followed participants longitudinally found no overall increase in sexual risk behaviors among individuals who were provided an advance supply of nPEP [20].

Treatment with ART. Risk compensation could also theoretically result from the widespread dissemination of ART to those already infected with HIV, which has been proposed to reduce the overall population likelihood of HIV transmission by suppressing population plasma HIV RNA levels. In the developing world, however, this appears not to have occurred. Current data from cross-sectional and observational cohort studies in developing countries suggest that better access to ART has not led to significant risk compensation [21].

The impact of ART on sexual risk compensation in *developed* countries, however, may not be the same. Mathematical modeling studies have suggested that HIV incidence in men who have sex with men (MSM) in the United States and other industrialized nations may be increasing because of increased risk behavior in the era of ART [22]. Furthermore, there has been an increase in syphilis and gonorrhea rates in MSM across the United States [23], particularly among HIV-infected people, which could be an unintended consequence of risk compensation associated with greater access to and use of ART. In a large meta-analysis of HIV therapy and risk behavior literature, it was found that individuals who thought ART reduced the likelihood of HIV transmission or for whom the availability of ART reduced concerns about having unsafe sex were more likely to engage in unprotected sex. Additionally, unprotected sex was associated with the belief that an undetectable viral load affords protection against transmission of HIV [24]. Finally, several

studies in developed countries have found increases in unprotected anal intercourse after ART with casual partners in both HIV-infected and uninfected individuals [25-27]. Findings from these studies suggest that some risk compensation has occurred in the United States with increased use of ART for treatment.

PrEP. Given the evidence of risk compensation seen with readily accessible ART in the United States and other developed countries, it is reasonable to posit that PrEP used to prevent HIV in uninfected individuals could have a similar effect on sexual behavior. Prior to the FDA approval of PrEP, potential users were surveyed and reported that they believed taking PrEP could decrease their use of condoms [28-30]. But risk compensation after PrEP implementation has been examined in several trials and to date has not been associated with increased sexual risk behavior or sexually transmitted infections in the majority of these studies [3-5, 7, 31-34]. In the iPrEx trial, in which subjects receive blinded PrEP medication or placebo, there was no change in reported sexual practices from baseline through followup and no difference in overall syphilis incidence in the perceived treatment group [34]. Qualitative findings from the iPrEx open-label extension parallel these results, with participants reporting no significant changes in their sexual practices [35].

However, assessments of risk compensation within clinical trials, including open-label extension programs, must be viewed cautiously. Notably, all randomized and open-label trials of PrEP medications have provided and emphasized the use of condoms, as well as HIV testing; this model may not be fully implemented in clinical practice. As noted above, sexual risk behaviors have been shown to increase following significant HIV biomedical breakthroughs, particularly in the industrialized world, and few rigorous data have been collected to definitively answer risk compensation concerns for biomedical HIV prevention.

Based on studies looking at risk behaviors after widely available ART and newly introduced PrEP, it is certainly possible that risk compensation could occur with PrEP implementation. It will be necessary to examine the degree to which individuals change their risk behaviors as PrEP advances from randomized trials to implementation in the community, particularly as more evidence for PrEP efficacy emerges.

It must be emphasized that behavioral disinhibition will only increase HIV transmission if the prevention strategy has low efficacy, which has not been seen in most of the oral-medication PrEP studies [3-7]. The efficacy of PrEP medications has been shown to be as high as 100 percent if taken daily as prescribed, even with occasional missed doses [7]. In other words, even if riskier sexual behavior does occur, the added protection of PrEP, correctly used, should still lower HIV incidence.

Further Investigation
Although risk compensation can be studied, the most rigorous methodological designs are ethically flawed and would be difficult to implement [36]. The ideal

study design for assessing risk compensation would be a randomized control trial in which one arm was made to believe the intervention would lower their risk and the other was made to believe that it would not change their risk. Under this design, any behavioral differences seen between arms would be attributable to the messages that participants receive, not to the intervention itself [36]. However, this design would require deceiving some or all participants and feigning uncertainty about the merits of two conditions in a randomized trial. Problems of deception and clinical equipoise limit precise methodological testing for risk compensation [37]. Moreover, it may be challenging to evaluate whether potential PrEP-related risk compensation has the ability to reverse gains made in HIV prevention at a population level, which is ultimately the most important question.

As PrEP rolls out into the real world, there must be an open channel of communication between policymakers, health care professionals, advocates, and PrEP users, and the discussion around HIV prevention with PrEP needs to become less punitive and derogatory and more nonjudgmental and understanding. It will be essential to monitor STI rates, HIV seroconversions on PrEP, and drug resistance mutations expected from PrEP medications to determine possible consequences of risk compensation. The numerous PrEP demonstration projects throughout the United States will evaluate risk compensation in various populations and will include methodological strategies designed to assess changes in risk behavior. Clearly, an overall strategy will require clinicians to implement combination prevention packages, promote condom use and other risk reduction strategies, test regularly for HIV and STIs, and monitor PrEP adherence. The uniqueness of each demonstration project will allow us to better understand the factors associated with PrEP-related risk compensation and tailor risk reduction strategies to meet the needs of different subgroups.

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Disclosure
Richard H. Haubrich receives honoraria or consultant fees from BMS, Gilead Sciences, Janssen, and Merck and research support (to UCSD) from Abbott, GlaxoSmithKline, Pfizer, and Merck.

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