Diversification of the prevention of sexually transmitted infections

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“With a technically well evaluated diagnostics-as-prevention approach covering a broad spectrum of STIs, sexual risk-taking populations could greatly reduce their STI transmission risk.”

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Traditional condom-based STI prevention

In June 2019, the Spanish Ministry of Health launched a promotion campaign for condom use among adolescents. Gonorrhea incidence in Spain had increased by 26% within the last 4 years and syphilis incidence by a factor of 4.2 within the last 22 years [1]. The decreasing acceptance of traditional preventative methods against sexually transmitted infections (STIs) can also be seen in other countries, for example, exemplified by the marked increase of the incidence of syphilis in Germany within the last 20 years [2]. As estimated by the World Health Organization (WHO), at present, more than a million individuals per day get infected with *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Treponema pallidum* or *Trichomonas vaginalis* [3].

Lack of effectiveness, however, cannot be made responsible for the obvious neglect of STI prevention by condom use. The risk reduction of human immunodeficiency virus (HIV) transmission in the case of condom use with heterosexual serodiscordant partners has been estimated at about 80% in a meta-analysis [4]. Considering that, theoretically, there is a relatively low sexual transmission probability of HIV [5], an 80% decrease represents acceptable protection. For comparison, transmission risks for STIs in the case of unprotected vaginal sex vary over a wide range, for example, 0.1% for herpes simplex virus type 2, 0.1–1% for HIV, 20–35% for *C. trachomatis*, 40–60% for human papilloma virus, 50% for *N. gonorrhoeae*, 60% for *T. pallidum* and 80% for *Haemophilus ducreyi* per case of unprotected sexual contact [6].

Of course, it should be kept in mind that the protective effect of condoms is significantly better for body fluid-borne sexually transmitted diseases (e.g., gonorrhea, chlamydial urethritis) than for smear infections (e.g., genital herpes, condyloma) [7]. However, even in the latter case, condom protection is still better than unprotected contact [8]. However, 100% safety cannot be expected from condom use and this should not be claimed, in order to avoid exaggerated and therefore easy-to-disappoint expectations of users.

HIV-PrEP: a new trend with risks & side effects

As an alternative to condom use in terms of HIV prevention, pre-exposure prophylaxis (PrEP) is based on a fixed combination of the nucleoside analog reverse transcriptase inhibitors tenofovir and emtricitabine, and is increasingly used in populations showing sexual risk behavior [9]. Despite the undeniable preventative effectiveness of the HIV PrEP concept, this option should not lead to undifferentiated carelessness. On the one hand, it has become obvious that HIV-PrEP-based prevention and concomitant renouncement of condoms are associated with a higher risk of acquiring other STIs [10,11]. The underlying mechanism is also referred to as ‘risk compensation’ or the ‘Peltzman effect’: The feeling of higher security leads to riskier behavior than would have been shown without the preventative measure and thus with a higher risk perception. In the PROUD study [12], one of the two most frequently quoted PrEP approval studies [12,13], this effect was not visible, as the study was conducted to demonstrate the efficacy

of HIV PrEP in populations rejecting condom use *per se* and showing correspondingly high STI prevalence rates of 50% and more in both study groups [12]. HIV-PrEP protects against HIV transmission, but not against the transmission of other STIs if condoms are omitted.

Although the idea seems obvious, the concept of a combined PrEP, which also includes antibacterial agents, has not yet been adequately evaluated in terms of risk–benefit assessments. A previous study on doxycycline-based post-exposure prophylaxis (PEP) after risky sexual encounters has demonstrated protection against *T. pallidum* and *C. trachomatis* but, as expected, not against other bacterial pathogens with nonmatching resistance patterns like gonococci [14]. This finding stresses the challenge that various bacterial STI agents would require customized antimicrobial preventative approaches. A ‘one-size-fits-all’ preventative antimicrobial solution is currently out of sight beyond the experimental combination of PEP or PrEP comprising multiple drugs. However, such theoretical poly-pharmaceutical preventative PEP or PrEP approaches would be highly likely to be associated with undesired side effects for the users, for which it is presently hard to say whether or not their application would still be ethically justified, not to mention less obvious problems for the users such as potential drug interactions, microbiome depletion and resistance selection.

Another problem of HIV-PrEP has already emerged in the approval studies, both for continuous [12] and for discontinuous ‘on-demand’ [13] PrEP, which achieved protection rates of 86% each in men-having-sex-with-men with affinity to high-risk sexual contacts. HIV breakthrough infections in the subjects under PrEP were mainly due to lack of adherence to the drug intake. Thus, HIV-PrEP, if it is to work reliably, requires a high degree of discipline with regard to adherence to medication. Even a hypothetical PrEP with long-acting injectable substances such as the integrase inhibitor carbogravir [15] or new long-acting non-nucleoside reverse transcriptase translocation inhibitors requires discipline regarding concomitant use of oral co-medication. Oral co-medication is needed to prevent the development of viral resistance due to potential HIV infection in the period of slowly decreasing drug levels, if PrEP is finally discontinued in spite of ongoing sexual risk behavior of the PrEP user or the PrEP user’s sexual partners.

The diagnostics-as-prevention concept

Another concept for the prevention of sexual transmission of HIV, widely neglected by preventative medical science, was semi-legally implemented by sex workers [16]. Sex workers, who offered unprotected sexual intercourse to maximize profitability, protected themselves from HIV transmission by performing HIV rapid tests on their clients and engaging in unprotected intercourse only in the event of a negative test result. This prevention approach is referred to as ‘diagnostics-as-prevention’.

Theoretically, there are some valid arguments against this prevention approach. In particular, traditional immunochromatographic rapid tests have great difficulty detecting early HIV infection stages, which are already associated with a high risk of transmission [17]. Since legal concerns make it hard to empirically investigate the diagnostics-as-prevention concept as applied by sex workers, evaluation by mathematical modeling has been performed. This is possible, because first, there are very good prevalence and incidence data on HIV infection available, and second, the infectiousness of the virus is very well characterized as a function of the situational context, and third, from evaluation studies, very exact results on the performance of diagnostic HIV tests exist [16,17].

Interestingly, it became obvious from modeling that the diagnostics-as-prevention concept as implemented by sex workers allows an even greater reduction of the exposure risk to HIV than the mere use of condoms in most situations [16]. The weakness of the immunochromatographic rapid tests in the early infection phase can be partially compensated if additional PCR-based rapid tests are used, which are increasingly available as point-of-care-testing options [17].

The big advantage of the diagnostics-as-prevention approach compared with HIV-PrEP is that it is not necessarily limited to HIV prevention. Depending on the availability and affordability of reliable rapid test systems, multi-test prevention approaches can be conducted including other STIs, reducing the overall exposure risk even further for methodological reasons due to multiple testing [18]. With a technically well evaluated diagnostics-as-prevention approach covering a broad spectrum of STIs, sexual risk-taking populations could greatly reduce their STI transmission risk. However, test characteristics have to be considered and beyond HIV testing, presently available rapid tests score poorly compared with the diagnostic gold standard assays [19].

It remains unclear how broad the diagnostics-as-prevention concept has been implemented in sex workers’ lifestyles. However, the KABP-Surv STI study among German sex workers of the Robert Koch Institute (Germany)

from 2011 reported an HIV prevalence of only 0.2% in German sex workers, thus only twice as high as in comparison with the average German population [20].

Nevertheless, the application of the diagnostics-as-prevention approach will presumably stay restricted to a small risk group, as rapid testing options are usually not readily available in case of a spontaneous risky sexual encounter, but require considerable preparation.

Conclusion

With condom use, PrEP approaches and the diagnostics-as-prevention concept, a number of strategies for the prevention of STI transmission is available. Each of them has different pros and cons and it ultimately remains to be seen whether and how far they will be practiced and accepted by the public. Nevertheless, a diversification of the prevention strategies for sexual STI transmission is good news for individuals with reservations against specific approaches. In particular, this applies to individuals with risky sexual behavior who deny traditional condom use but are nevertheless risk-aware, open-minded and ready to accept alternative preventative options.

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