

Diagnostics as Prevention — A Rapid Testing-Based Strategy of Sex Workers against Sexual HIV Exposure

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Introduction: German sex workers have illegally established a prevention strategy, which consists of testing potential sexual partners with human immunodeficiency virus (HIV)-specific rapid diagnostic tests (RDTs) prior to engaging in unprotected sexual intercourse eventually performed in case of a negative test result. Based on a recently established modeling approach, the effectiveness of this strategy regarding the risk of HIV exposure was compared with protection provided by condom use.

Methods: Based on a literature search, the following assumptions were used for the calculations: an averaged 80% exposure risk reduction with a condom used during sexual intercourse, usage of a well-characterized 4th-generation HIV RDT, and a 10 day post-infection period without any measurable viral load in peripheral blood followed by a seroconversion period of about 3 weeks with 12.3% test sensitivity (antigen-specific) and only afterwards 97.3% (antibody-specific) test sensitivity.

Results: In most constellations, the HIV exposure risk in case of RDT-based prevention was lower than with condom use.

Conclusions: The RDT-based HIV exposure prevention as established by sex workers is effective in most situations. A notable weakness of the strategy is the RDTs' poor sensitivity in spite of a high transmission risk during the seroconversion stage.

Keywords: HIV, rapid testing, exposure risk, prevention, sex worker, risk assessment

Introduction

Recently, we have introduced a mathematical model for the comparison of prevention strategies against sexual transmission of the human immunodeficiency virus (HIV) [1] with a focus also on exposition prevention. Although condom use is the recommended procedure to prevent an HIV infection during risky sexual contacts, a Cochrane review [2] has estimated the effectiveness of condoms in reducing HIV transmission by 80% in heterosexual settings. However, the 95% confidence interval ranged from 35.4% to 94.2% [2] and more recent studies suggest a slightly lower protection [3] than the Cochrane analysis [2]. Furthermore, condom use of men having sex with men (MSM) is not represented [2], and studies assessing condom effectiveness are affected by numerous sources of bias [4–8]. In spite of these limitations, an estimated protection rate of 80% can be considered as widely accepted and was therefore used for further calculations. However, the main limitation is not technical failure of condom use, but rather its lacking acceptance in high-risk groups as extensively discussed elsewhere [1, 9].

In Germany, sex workers have illegally invented a strategy to protect themselves from exposure to HIV while avoiding condom

use, which is rather unpopular or even rejected by many of their clients. In detail, some sex workers offer unprotected intercourse if the client agrees to perform an HIV-1/2 rapid diagnostic test (RDT). This is discretely offered by a proportion of sex workers in Germany who expect higher wages when offering condom-free sex, which is forbidden in Germany in commercial sexual contacts (§32, sex worker protection law; *Prostitutionsschutzgesetz*). Further, it is not allowed to deliver HIV tests to private persons (§11, medical products law; *Medizinproduktegesetz*). As this approach is illegal and largely restricted either to the demimonde or private hedonistic parties, systematic scientific assessment of its effects and long-term consequences for both, the sex workers and their clientele, is yet missing.

In the very early stage of HIV infection known as the seroconversion period, however, the sensitivity of immunochromatographic RDTs for HIV detection is poor [10]. In detail, by modern 4th-generation serological HIV tests, p24 as the main viral marker protein can be detected not earlier than between the second or third week after infection. After 3 weeks or more, HIV-specific antibodies usually become measurable [11]. The use of 4th-generation RDT systems can narrow the diagnostic gap but cannot completely resolve this problem. Moreover, the sensitivity of p24 antigen detection by HIV RDT systems was shown to be poor in seroconversion panels as exemplarily demonstrated in Table 1 for the well-characterized 4th-generation

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Table 1. Performance characteristics of the “Determine HIV1/2 Ag/Ab combo test” (Alere Inc., Waltham, Massachusetts, USA) as assessed by a meta-analysis of studies comprising seroconverter panels from patients with early HIV infections [10]

	Sensitivity (95% confidence interval; CI)	Specificity (95% confidence interval; CI)
Pooled results	88.5% (80.1%–93.4%)	99.1% (97.3%–99.8%)
p24 antigen component	12.3% (1.1%–44.2%)	99.7% (96.8%–100%)
Antibody component	97.3% (60.7%–99.9%)	99.6% (99.0%–99.8%)

HIV RDT test “Determine HIV1/2 Ag/Ab combo test” (Alere Inc., Waltham, Massachusetts, USA) [10] and the successor product scored only moderately better [12].

In summary, positive reactions of HIV RDTs in case of early HIV infections are delayed by approximately 1 week compared to serological 4th-generation bench-top devices in the laboratory as demonstrated by comparing the principles using a seroconverter panel [13]. As polymerase chain reaction (PCR), in contrast, can identify viruses even 2 weeks earlier than 4th-generation bench-top devices [14] and positive HIV RDT results were demonstrated between 10 days and 19 days after the initial positive PCR results in a previous assessment [15], it is reasonable to assume that the diagnostic gap between first transmissibility as indicated by detection of viral RNA in the PCR and reliably positive HIV RDT results is approximately 3 weeks. The practical relevance of this 3 week gap on real exposure risks by sex workers who apply RDTs for HIV exposure prophylaxis instead of condom use depends on the incidence of new HIV infections in their suitors.

Here, the HIV exposure risks (ERs) in the case of RDT use and exclusion of sexual partners with a correct or false-positive test from unprotected sex as preventive strategy was compared to the ERs in the case of condom use without knowledge about the HIV status of the sexual partners in a bio-statistical model considering effects of different HIV prevalences and incidences.

Methods

Risk modeling was based on the following assumptions:

1. Sexual HIV ER can be reduced through condom use by about 80% [2].
2. Fourth-generation RDTs targeting the p24 antigen and HIV-specific antibodies are considered the gold standard. As the best described system [10], the Determine HIV1/2 Ag/Ab combo test was the reference for this assessment.
3. Sexual ERs start at the time of first positive PCR approximately 10 days after infection. For an approximate seroconversion period of 3 weeks between the first positive PCR and positive results in antibody-based RDTs, a p24-antigen-based sensitivity of 12.3% was assumed. Subsequently, an antibody-based sensitivity of 97.3% was used for the calculations [10].
4. HIV prevalence and incidence for Germany was derived from the annual report of the National Reference Center for Infectious Diseases, RKI, for 2016 [16].

Based on these assumptions and our recently published modeling approach [1], the model presented here was established as described in Results section.

Ethics. Ethical approval was not necessary in line with national laws and regulations, because the study described a mathematical model only. Neither patient data nor patient-related materials were used.

Results

For infection risks through sexual exposure, the following factors are relevant:

- prevalence and incidence of HIV among sexual partners,
- preventive effects of precaution/protection measures, and
- frequency of sexual contacts.

Based on the literature quoted above, the following assumptions apply. Recently infected individuals are virtually not infectious in spite of viral spread in tissues during a latency period of about 10 days without any measurable viral load in the peripheral blood [17]. Thereafter, individuals become infectious in the absence of HIV-specific antibodies detectable by common RDTs. Antigens are poorly detectable by RDTs. We assumed a sensitivity of 12.3% for antigen detection. About 1 month after infection, RDT-detectable antibodies circulate in the peripheral blood. We assumed a sensitivity of 97.3% for antibody detection. A simplified visualization of the process is provided in Figure 1.

For modeling the ER with the HIV prevalence ($Prev_{HIV}$) and the cumulative incidence (CI_{HIV}), we distinguish relevant periods:

- incidence frequency F_{dn} , which is not detectable by the antibody or the antigen detecting component of the test;
- incidence frequency F_{Abn} , where the infection is not detectable by the test's antibody component, and
- incidence frequency F_{Ag} , where the infection is detectable only by the test's antigen component, while the individual is infectious.

We define relevant frequencies:

- frequency of infected individuals who are not detectable: $Freq_{dn} = \frac{F_{dn}I_{HIV}}{Prev_{HIV}}$,
- frequency, where infection is only detectable by the antigen detecting component of the test: $Freq_{Ag} = \frac{F_{Ag}I_{HIV}}{Prev_{HIV}}$, and
- frequency, during which the infection is detectable by the antibody detecting component of the test: $Freq_{Ab} = \frac{Prev_{HIV} - (F_{Abn} + F_{dn})I_{HIV}}{Prev_{HIV}}$.

For these frequencies holds $Freq_{Ab} + Freq_{Ag} + Freq_{dn} = 1$.

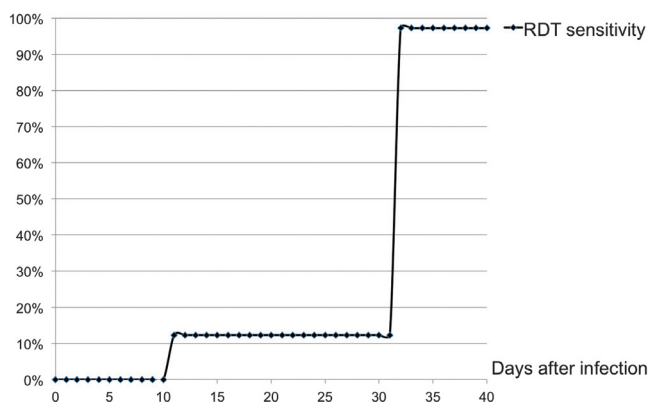


Figure 1. Simplified sensitivity of the RDT during the first 40 days of infection as used for our modeling approach. The first 10 days represent the stage without detectable viral load in the peripheral blood. Days 11 until 31 represent 3 weeks of seroconversion without measurable antibodies and only poorly detectable antigens. After day 31, antibodies become detectable. The figure demonstrates the artificial aspect of the calculation as a continuous transition would be expected in vivo

HIV prevalence is the basis for estimating the risk of getting in contact with HIV through a random sexual contact. ER per unprotected contact, ER_U :

$$ER_U = \text{Prev}_{\text{HIV}}$$

We assume a 10 day latency (d_{ni}) after a new infection, during which the newly infected individual is not infectious and there is virtually no ER. We further assume that condom use reduces the ER by around 80%. To estimate the ER with condom (ER_C), we therefore multiply the ER per unprotected contact (ER_U) with $1 - 0.8 = 0.2$:

$$ER_C = 0.2 * ER_U$$

Here, we intend to estimate the HIV ER if an RDT is used to exclude that a partner is infected and abstains from intercourse if the test is positive, correctly or falsely. We address this ER as exposure risk per unprotected contact after testing (ER_{UT}).

For the ER per unprotected contact after testing (ER_{UT}), we conclude:

$$ER_{\text{UT}} = ER_U \left((1 - \text{Sens}_{\text{Ag}}) \text{Freq}_{\text{Ag}} + (1 - \text{Sens}_{\text{Ab}}) \text{Freq}_{\text{Ab}} + \text{Freq}_{\text{dn}} \right).$$

ER_{UT} thus consists of exposure to infectious individuals who test false negative and are therefore accepted for intercourse, including exposures to infectious individuals during the period of reduced test sensitivity in the seroconversion period.

For condom use, one has to consider:

$$ER_{\text{UT}} < ER_C \Leftrightarrow \left((1 - \text{Sens}_{\text{Ag}}) \text{Freq}_{\text{Ag}} + (1 - \text{Sens}_{\text{Ab}}) \text{Freq}_{\text{Ab}} + \text{Freq}_{\text{dn}} \right) < 0.2.$$

We assume that antibody titers remain below the detection threshold of RDT-based antibody testing for 1 month (31 days, comprising 10 days without circulating virus and about 21 days of circulating viruses without detectable antibodies) with the newly infected individual posing virtually no HIV ER to others for the first 10 days after infection. Thus, the period during which the infection is not detectable by RDTs targeting antibodies only while an ER exists and the infected individual is infectious is 21 days.

The Determine HIV1/2 Ag/Ab combo test combines antibody and antigen detection and can, in principle, detect newly acquired infections before antiviral antibodies are synthesized and detectable. Unfortunately, the sensitivity for detecting antigens in this early phase is only about 12.3%.

The general risk of becoming exposed with n sexual contacts (with n individual exposure risks) is:

$$ER^n = 1 - \prod_{k=1}^n (1 - ER_k).$$

The differential ERs per individual contact depending on prevalence and incidence of HIV in a sexually active community are shown in Figures 2–5. Notably, the dimensions of the Y axis are adapted to the respective situations to allow better visibility of the relation of exposure risk to incidence and prevalence.

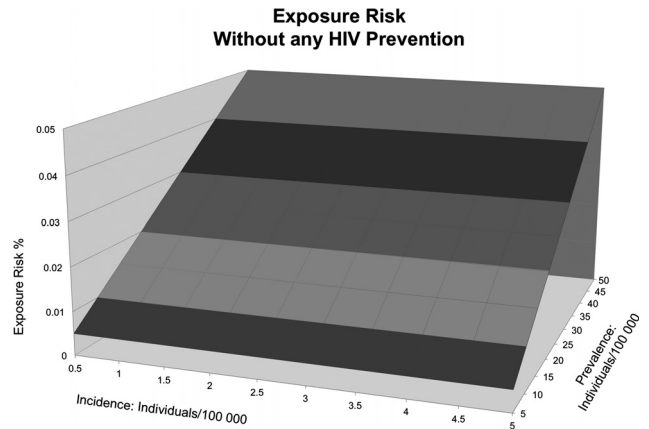


Figure 2. Exposure risk without any HIV prevention. X axis: incidence per 100,000 individuals. Y axis: exposure risk in percent. Z axis: prevalence per 100,000 individuals

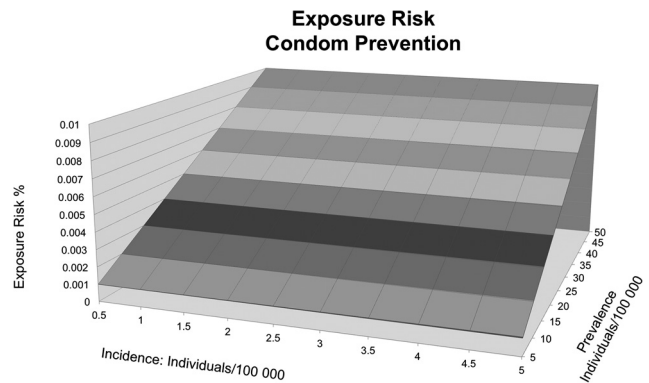


Figure 3. Exposure risk with condom-based HIV prevention. X axis: incidence per 100,000 individuals. Y axis: exposure risk in percent. Z axis: prevalence per 100,000 individuals

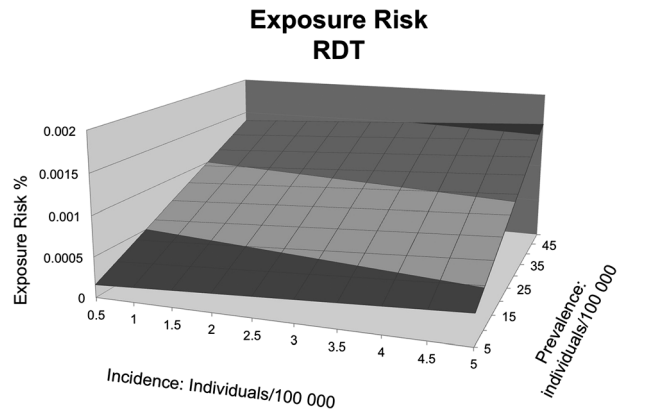


Figure 4. Exposure risk with RDT-based HIV prevention. X axis: incidence per 100,000 individuals. Y axis: exposure risk in percent. Z axis: prevalence per 100,000 individuals

The risk of getting infected within n contacts is given with:

$$IR^n = 1 - \prod_{k=1}^n (1 - \text{TR}_k ER_k)$$

where TR_k is the individual transmission risk per contact k .

The consequences of these mathematical assumptions are demonstrated in two examples suggesting higher exposure risks in the case of condom use than in the case of RDT-based prevention under typical circumstances. Finally, the limitations of the RDT-based approach are outlined.

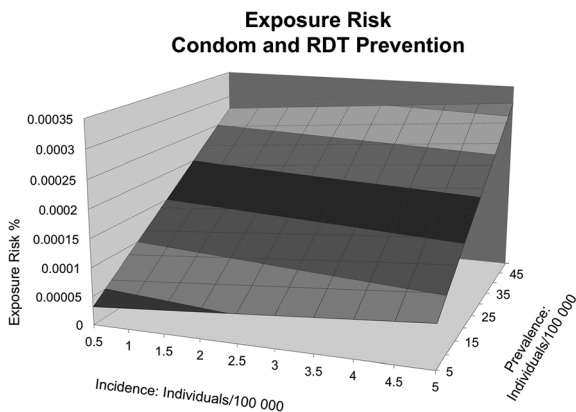


Figure 5. Exposure risk with combined condom- and RDT-based HIV prevention. X axis: incidence per 100,000 individuals. Y axis: exposure risk in percent. Z axis: prevalence per 100,000 individuals

Example 1

With a number of 84,700 HIV-infected individuals living in Germany in 2015 and an estimated number of 3200 new infections in that same year among a population of 82.2 million as stated by Robert Koch Institute (RKI) [16], we calculate a prevalence (prev) of 0.001 and a cumulative incidence (CI) of 0.00004. Assuming that new infections are not associated with an ER within the first 10 days and an antigen sensitivity of 0.123 and an antibody sensitivity of 0.973, we conclude for different ERs:

$$ER_U = 0.001; ER_U^{1000} = 0.64; ER_C = 0.0002; ER_C^{1000} = 0.19$$

$$ER_T = 0.00003, ER_T^{1000} = 0.03; ER_{TC} = 0.000006; ER_{TC}^{1000} = 0.006$$

When ranking the ERs, the order is:

$$ER_{Unprotected} > ER_{Condom} > ER_{negative\ Test\ and\ unprotected} > ER_{negative\ Test\ and\ Condom}$$

Table 2 summarizes the ER for the total population, heterosexuals and MSM, depending on contact frequencies and protective strategies. Condom effects in MSM contacts have to be interpreted cautiously, as the underlying meta-analysis suggesting a protection rate of 80% was focused on heterosexual contacts only [2].

Table 2. Exposure risks depending on the frequency of sexual contacts and protective strategies for the total population as well as for heterosexual and MSM contacts

Population	Number of sexual contacts	Exposure risk (ER) in %			
		Unprotected	Condom	RDT negative	RDT negative and condom
Total	1	0.1 ^a	0.02	0.003	0.0006
	50	5.0	1.0	0.15	0.03
	100	9.8	2.0	0.3	0.06
	1000	64.3	18.6	2.9	0.6
Heterosexuals	1	0.01 ^b	0.003	0.0004	0.000008
	50	0.66	0.13	0.02	0.004
	100	1.3	0.27	0.04	0.008
	1000	12.5	2.7	0.4	0.08
MSM	1	13.5 ^c	2.7	0.4	0.08
	50	99.9	74.5	17.8	3.8
	100	100	93.5	32.5	7.5
	1000	100	100	98.0	54.3

^aAverage HIV infection rate in the German population as stated by the RKI.

^bArbitrarily assumed HIV infection rate in an exemption-free heterosexual collective in Germany assuming a 10% proportion of heterosexual transmission.

^cArbitrarily assumed HIV infection rate in a German MSM club, assuming 1% to 3% unknown and untreated HIV infections in such collectives [19], and an estimated 80% rate of known and treated HIV infections.

Example 2

It is assumed that two sexually highly active individuals have 1000 random casual heterosexual contacts each in the same population as described in example 1. The first individual uses exclusively condoms for prevention. The second individual uses condoms in 80% of contacts. In 20%, condoms are not used but a negative RDT result is mandatory.

The ER through a single contact with condom in a population with a prevalence of 0.001 and a cumulative incidence of 0.00004 is:

$$ER_c = 0.2 * 0.001 = 0.0002$$

The ER through a single contact without condom, but after negative RDT in a population with a prevalence of 0.001 and a cumulative incidence of 0.00004, is:

$$ER_{UT} = 0.001 * ((1 - 0.123) * 0.0023 + (1 - 0.973) * 0.9966 + 0.0011) = 0.00003.$$

The cumulative ER after 1000 sexual contacts for the first individual is:

$$ER^{1000} = 1 - (1 - 0.0002)^{1000} = 0.18.$$

The cumulative ER after 1000 contacts for the second individual is:

$$ER^{1000} = 1 - (1 - 0.0002)^{800} (1 - 0.00003)^{200} = 0.15.$$

The higher preventive effect of the negative RDT compared to condom use causes a cumulative ER that is 16% lower in the second, compared to the first individual.

Limitations of the Reliability of the RDT Approach

Due to the low sensitivity of the RDT in very early infections, it may fail as preventive strategy in risk groups with high proportions of newly infected individuals. A risk group of very high proportions of recently infected HIV-positive potential sex partners is theoretically possible, e.g., in a hedonistic club, although unlikely. Given the 3 weeks of the antigen-only stage with 12.3% RDT sensitivity only, and the later infection stages as antibody stage with 97.3% RDT

Table 3. Estimations of average sexual HIV transmission risks in case of unprotected contacts depending on individual sexual activities and practices including risk factors beyond considering only the viral load

Sexual practice	Average sexual HIV transmission risk per unprotected serological discordant contact [19]
Receptive vaginal intercourse	0.05%–0.15% [19]
Insertive vaginal intercourse	0.03%–5.6% [19]
Receptive anal intercourse	0.1%–7.5% [19]
Insertive anal intercourse	0.07%–1.68% [19]
Oral intercourse	Exceptional cases of transmission, mainly associated with oral intake of ejaculate [19]
Risk factor	Estimated effect on the sexual HIV transmission risk compared to baseline (vaginal intercourse) [18, 20–24]
Male circumcision	Risk reduction by 50% to 67% [20]
Effect of rape for genocidal purposes in sub-Saharan African conflict areas	Slight reduction of HIV transmission on population level in spite of presumed contact bleeding with increased individual transmission risk due to a reduced number of casual sexual contacts during the conflicts [21, 22]
“Dry sex,” for which the vagina is dried with cloth or paper or narrowed and dried by additional objects with the goal of increasing friction during penetration	Increase of the risk by less than factor 1.5 [23]
Genital mutilation in women (so-called female circumcision)	Increase of the risk by factor 2 [24]
Concomitant STDs	Increase of the risk by factor 2.5 (by factor 10 in case of genital herpes) [20]
Moderate viral load of >2,500,000 copies/L	Increase of the risk by factor 10 to 30 [20]
Very early HIV infection (seroconversion)	Increase of the risk by factor 10 to 100 [18, 20]

sensitivity, the theoretical maximum risk of exposure per sexual contact will be 87.8% in a risk group of 100% HIV-positive potential sexual partners in the antigen-only stage. This risk declines with increasing proportions of individuals in the antibody stage and increasing proportions of HIV-negative partners. In contrast to the RDT approach, the ER for condom use remains at 20%, even under most unfavorable conditions.

If we assume that in this setting the frequency of infected individuals without antibodies and without detectable viral load is 0, the underlying formula for the individual exposure risk is then simplified as follows:

$$ER_{UT} = \text{Prev}_{HIV} \left((1 - \text{Sens}_{Ag}) \text{Freq}_{Ag} + (1 - \text{Sens}_{Ab}) \text{Freq}_{Ab} \right)$$

With the assumption depicted in the example above, namely that the frequency of potential partners without antibodies or HIV viremia is 0% and there is a sensitivity of 0.123 in the antigen-only phase as well as 0.973 in the antibody-only phase, the consequence is that, for $ER_{UT} < ER_C$, a frequency of antibody-positive individuals (antigen-only positive individuals) of $\text{Freq}_{Ab} > 0.796$ ($\Rightarrow \text{Freq}_{Ag} < 0.204$) is required. The contrary situation is described by $ER_{UT} > ER_C$ if $\text{Freq}_{Ab} < 0.796$. If, in contrast, we assume that $\text{Freq}_{Ab} < 0.796$ and $\text{Freq}_{Ag} < 0.204$, then it follows that $((1 - \text{Sens}_{Ag}) \text{Freq}_{Ag} + (1 - \text{Sens}_{Ab}) \text{Freq}_{Ab}) = 0.2$ and therefore $ER_{UT} = ER_U((1 - \text{Sens}_{Ag}) \text{Freq}_{Ag} + (1 - \text{Sens}_{Ab}) \text{Freq}_{Ab}) = ER_U * 0.2 = ER_C$ describes identical ERs in RDT-only- and condom-only-based prevention.

Discussion

In most conditions, the risk of HIV exposure per risky contact is lower with an RDT-based approach than with condom use as suggested by the presented exposure risk estimates. In contrast, condom use yields a better protection against an HIV-infection than the RDT-based approach, if considerably more than 20% of risky potential contacts involve HIV-infected individuals who are newly infected and still in the antigen-only phase. Although such a situation is rather unlikely, it may occur, e.g., if HIV is newly introduced in a very promiscuous and sexually highly active community. Unprotected sexual contact with HIV-infected individuals in the seroconversion stage is particularly dangerous because the transmission risk is increased by factor 10 to 100

compared to the baseline risk during the chronic stage of infection due to very high viral loads [18]. As this study models exposition risks and not transmission risks, respective estimations would be beyond its scope but are described in detail elsewhere [1]. As also detailed there [1], molecular RDT systems based on nucleic acid amplification (NAT) might be applied to solve the problem of lacking sensitivity in the early infection stages. Due to financial and logistic reasons, however, the application of NAT-based RDT systems for leisure purposes will be restricted to well-equipped and resource-rich hedonistic communities and appears less likely to be deployed. In addition to the effects of viral load [1], several other factors can interfere with the risk of HIV transmission in the case of unprotected sexual exposure as shown in Table 3. Furthermore, acquisition of other STDs is facilitated by a prevention strategy solely based on a system to disclose an HIV infection in an individual. A combination of a test-based strategy with condom use can further reduce HIV exposure, compared to applying either one strategy alone.

Residual protection against STD transmission can remain even in the case of broken condoms. Based on material testing of condoms and calculations of the ejaculate volume compared to condom-free sex, relative STD transmission risks were calculated as 6‰ in cases of condom bursts, 0.008‰ (0.8/100000) in condoms with a visible leakage, and 0.00004‰ (0.004/100000) in condoms invisibly perforated [25]. Such considerations are superfluous if the condom is totally disrupted, as this can be the case during continuous hard sexual intercourse or if the condom is deliberately omitted under the influence of drugs or alcohol [26, 27]. Under such circumstances, decline of sexual partners who are not RDT tested may be the safer alternative.

The presented modeling approach demonstrates that preventive strategies should not basically be rejected as inefficient just because they are established within risk groups and not by prevention specialists. As recently suggested, punitive laws are likely to impede HIV prevention [28, 29]. This may also affect the here described legally banned prevention approach of sex workers in Germany.

Conclusions

In spite of the good performance of RDT-based pre-screening of potential sex partners for an HIV infection prior to unprotected sexual contacts, there remain limitations of this approach with a particular focus on the early phases of the infection and on the risk of getting infected with other STDs.

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Authors' Contribution

A.H. performed the mathematical modeling. A.H., R.H., T.M., U.L., O.H., C.G.M., N.G.S. and H.F. jointly performed the literature research and wrote and reviewed the manuscript. H.F. provided the concept.

Conflicts of Interest

The authors declare no conflict of interest.

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