Quantifying sexual exposure to HIV within an HIV-serodiscordant relationship: development of an algorithm

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Background: The risk of acquiring HIV from a single sexual contact varies enormously reflecting biological and behavioural characteristics of both infected and uninfected partners. Accurate information on HIV transmission risk is required to construct evidence-based risk reduction practices for individuals, to direct the provision of prevention strategies at the population level, and enable the definition, quantification and comparison of true exposure in individuals termed 'exposed uninfected' within clinical trials.

Methods: Following a systematic review of current literature on HIV transmission estimates, an HIV risk score was developed, incorporating weighted risk factors into a Bernoulli mathematical model, allowing quantification of overall risk of HIV acquisition within HIV-serodiscordant partnerships.

Results: The HIV risk score enumerates the relative risk of HIV acquisition from HIV-positive partners incorporating the type and frequency of specific sex acts, the index case HIV plasma viral load and stage of disease, and the presence of genital ulcer disease in either partner and pregnancy, HSV-2 seropositivity, and circumcision status (men only) in the HIV-negative partner.

Conclusion: Key determinants of HIV exposure risk can be incorporated into a mathematical model in order to quantify individual relative risks of HIV acquisition. Such a model can facilitate comparisons within clinical trials of exposed uninfected individuals and facilitate interventions to reduce HIV transmission.

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Background

Worldwide an estimated 33 million individuals are living with HIV [1], with approximately four million new HIV transmissions occurring in 2008 alone [1]. In the UK, almost one-quarter of new HIV diagnoses in 2009 amongst men having sex with men (MSM) were recently acquired infection [2]. With the successful introduction of antiretroviral therapy (ART) and onward HIV transmission continuing, the resulting increased HIV prevalence is accompanied by an increase in HIV-serodiscordant partnerships [3]. Sullivan *et al.* [4] estimated that in the USA 68% of HIV transmissions were from main sex partners. Reasons for this included increased exposure (over 10% more sexual acts with main than with casual partners); engagement in risky sexual

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behaviour [14% more likely to report receptive anal intercourse (RAI) with main than with casual partners] and less condom use with main partners (rates of anal intercourse without condoms being 16–31% higher than with casual partners). This is supported by data from London showing that HIV risk behaviour in MSM with main sexual partners is increasing [5]. This may reflect the increased provision of widespread ART and associated behavioural disinhibition [6].

The risk of HIV transmission reflects two distinct entities, the relative risk of HIV acquisition amongst HIV-uninfected individuals, which represents a composite of genetic factors [7,8], immunological factors [9], nature and frequency of sexual exposure [10], and presence of concurrent sexually transmitted infections (STIs) [11–14] and the onward transmission risk posed by HIV-infected individuals which is determined by HIV plasma and genital tract viral load [11,12,15], concomitant STIs [20,21], viral characteristics [16].

Accurate assessment of HIV transmission risk (susceptibility or infectiousness) may improve the application of such risk reduction strategies. In addition it may inform studies of individuals who despite repeated exposure to HIV remain uninfected, 'exposed uninfected'. Scientific investigation of such individuals is invaluable to inform potential mechanisms that may confer protection against HIV acquisition (e.g. identification of chemokine deletion d32 [7,8]) and as such enhance HIV prophylactic vaccine development. There is, however, currently no consensus definition of the level of HIV exposure upon which to identify exposed uninfected individuals, making cross-study comparisons difficult and adding controversy within this field [17]. Robust methodologies to quantify risk would enable analysis of this valuable area of research. Current transmission risk estimates [18,19] do not, however, take into account multiple co-factors (such as HIV viral load and STI) and are not available in a format that can directly inform clinicians, researchers and patients. Indeed a recent National Institutes of Health (NIH) meeting identified the lack of a unified definition of exposed uninfected as a key roadblock in research in the field [20].

Overall, a consensus and reliable tool to calculate HIV exposure risk is required to direct individuals, in particular those in HIV-serodiscordant relationships to construct evidence-based risk reduction practices; assess HIV transmission risk to direct the provision of post exposure prophylaxis (PEP); enable quantification and comparison of true exposure in exposed uninfected individuals for clinical trials, and enhance the interpretation of research in the field.

We have developed an exposure quantification tool to assess exposure, incorporating biological and behavioural factors associated with transmission to determine the overall estimated risk of HIV sexual transmission between sexual partners of known HIV status using a simple mathematical model.

Methods

A detailed literature review was carried out; the following sources were searched for systematic reviews, randomized controlled trials and cohort studies: Medline, ISI Web of Knowledge, Embase and the Cochrane Database of Systematic Reviews. Identification of robust studies published in the English language quantifying the extent to which a particular factor increased or decreased HIV transmission were included in the analysis. The following search terms were used: gonorrhoea, chlamydia, genital discharge, *Trichomonas vaginalis*, syphilis, candida, bacterial vaginosis, genital ulcer, genital wart, HSV, HIV viral load, HIV transmission, per coital act, condom use, age, hormonal contraception, pregnancy, oral, vaginal and anal sex. All databases were searched from January 1988 to July 2010. A total of 76 studies were selected for appraisal of which, $n = 72$ (95%) were successfully obtained. The following factors were taken into consideration: the impact factor of the journal, study design [randomized control trials (RCTs) in priority], sample size, statistical methods used, possibility of bias and reproducibility of findings. As a result 61 studies were included and nine studies excluded (Tables 1 and 2). In order to focus on actual rather than theoretical risk of HIV transmission risk, clinical studies were prioritized over biological plausibility and RCTs over cohort studies. For risk factors where there were a number of credible studies, priority was given to values obtained from studies of HIV-serodiscordant couples. In settings in which this was not possible, rigorous evaluation of available data was undertaken. A formal meta-analysis was not carried out due to the small number of studies per co-factor.

Development of a model of HIV exposure risk score

For factors consistently associated with HIV transmission, published adjusted odds ratios (ORs) and relative risk scores were incorporated into a Bernoulli mathematical model of STI/HIV transmission, to estimate the risk of acquiring HIV infection from an HIV-infected sexual partner [21,22].

Results

Clinical studies investigating HIV transmission risk are shown in Tables 1–3 and summarized in Table 3. Those incorporated into the risk score algorithm are

Table 1. Estimated risk ratios of biological factors contributing to HIV transmission.

Factor	HIV susceptibility	HIV infectiousness	Comments
Plasma HIV RNA Log10(copies/ml)			
<3.49		1.0 [11]	Quinn *et al.* [11]: $n=415$ heterosexual HIV-1 serodiscordant couples (HIV-1-negative partners constituted $n=228$ women and 187 men), retrospective identification of discordant couples during prospective community-based trial, Rakai, Uganda.
3.5–3.9		5.8aOR; 95% CI 2.26–17.80	
4.0–4.69		6.91aOR; 95% CI 2.96–20.15	
>4.70		11.87aOR; 95% CI 5.02–34.88	
Level per log increment		2.45aOR; 95% CI 1.85–3.26	
0–3.49		1.0 [15]	Wawer *et al.* [15]: $n=235$ heterosexual HIV-1 serodiscordant couples, retrospective identification of discordant couples during prospective community-based trial, Rakai, Uganda.
3.5–4.16		3.31aRR; 95% CI 1.01–10.80	
4.17–4.88		6.39aRR; 95% CI 2.10–19.42	
>4.88		7.06aRR; 95% CI 2.29–21.81	
<3.23		1.0 [12]	Gray *et al.* [12]: $n=174$ heterosexual HIV-1 serodiscordant couples. (HIV-1-negative partners constituted $n=97$ women and 77 men) retrospective identification of discordant couples during prospective community-based trial, Rakai, Uganda.
3.23–4.09		16.1aRR; 95% CI 3.11–295.71	
4.09–4.56		17.91aRR; 95% CI 3.44–328.65	
>4.56		27.7aRR; 95% CI 5.42–506.79	
CD4 cell count (cells per microlitre)			
<200		7.9OR; $P=0.03$ [81]	O'Brien *et al.* [81]: $n=39$ heterosexual HIV-1 serodiscordant couples (HIV-1-negative partners constituted $n=25$ women and 14 men), retrospective, Atlanta, USA. No multivariate analysis.
		17.6aOR; 95% CI 4.9–62.7 [82]	European Study group [82]: $n=563$ heterosexual HIV-1 serodiscordant couples, (HIV-1-negative partners constituted $n=404$ women and 159 men), muliticentre, prospective, Europe.
		16.81aORr; $P<0.001$ [83]	Seidlin *et al.* [83]: 158 heterosexual HIV-1 serodiscordant heterosexual HIV-1 serodiscordant couples (HIV-1-negative partners constituted $n=147$ women and 11 men), prospective, New York, US.
		6.1 to 17.6 aRR [85]	Royce *et al.* [85]: review.
<800		7OR [86]	Zunzunegui *et al.* [86] $n=130$ heterosexual HIV-1 serodiscordant couples (all women HIV-negative), prospective, Spain. Not significant on multivariate analysis.
Stage of HIV infection			
Primary (<5 months)		4.98aRR; 95% CI 2.00–12.39 [15]	Wawer *et al.* [15]: $n=235$ heterosexual HIV-1 serodiscordant couples, retrospective, Rakai, Uganda.
Late (6–35 months before death):		3.49aRR; 95% CI 1.76–6.92; independent of HIV-1 viral load	

Table 1 (*continued*)

Factor	HIV susceptibility	HIV infectiousness	Comments
Clinical stage 4		Clinical stage 4: 4.1 OR [86]	Zunzunegui: *et al.* [86]: $n=130$ heterosexual HIV-1 serodiscordant couples (all women HIV-negative), prospective. Spain. Not significant on multivariate analysis.
Circumcision	IRR 0.40; 95% CI 0.24–0.68 [25]		Auvert *et al.* [25]: $n=3274$ uncircumcised, HIV-1-negative men aged 18–24 years, RCT, South Africa.
	IRR 0.47; 95% CI 0.28–0.78 [24]		Bailey *et al.* [24]: $n=2784$ uncircumcised, HIV-1-negative men aged 18–24 years, RCT, Kenya.
	IRR 0.49; 95% CI 0.29–0.81 [26]		Gray *et al.* [26]: $n=4994$ uncircumcised, HIV-1-negative men aged 15–49 years, RCT, Uganda.
	$P>0.05$ [27]		Gray *et al.* [27]: $n=165$ female HIV-1-negative partners of uncircumcised, HIV-1-positive men, RCT of male circumcision, Uganda.
Genital ulcer	0.77aOR; 95% CI 0.33–1.60 [11]	0.93aOR; 95% CI, 0.48–1.66 [11]	Quinn *et al.* [11]: $n=415$ heterosexual HIV-1 serodiscordant couples, prospective, Rakai, Uganda.
	2.58 aOR; 95% CI 1.3–5.69 [12]		Gray *et al.* [12]: $n=174$ heterosexual HIV-1 serodiscordant couples. (HIV-1-negative partners constituted $n=97$ women and 77 men), retrospective, Rakai, Uganda.
		2.04aRR; 95% CI 1.04–3.99 [15]	Wawer *et al.* [15]: $n=235$ heterosexual HIV-1 serodiscordant couples, retrospective, Rakai, Uganda.
	5.3 aOR; 95% CI 1.4–19.5 [15]	5.3 aOR; 95% CI 1.4–19.5 [31]	Boily *et al.* [31]: systematic review, meta-analysis of 25 heterosexual studies.
Chlamydia/ NSU	1.06 aRR; 95% CI 0.61–1.84 [12]		Gray *et al.* [12]: $n=174$ heterosexual HIV-1 serodiscordant couples. (HIV-1-negative partners constituted $n=97$ women and 77 men), retrospective, Rakai, Uganda.
	0.22aOR; 95% CI 0.01–0.97 [11]	0.22aOR; 95% CI 0.01–0.97 [11]	Quinn *et al.* [11]: $n=415$ heterosexual HIV-1 serodiscordant couples (HIV-1-negative partners constituted $n=228$ women and 187 men), prospective, Rakai, Uganda.
	3.6aOR; 95% CI 1.4–9.1 [35]		Laga *et al.* [35]: $n=431$ female CSW, retrospective nested case ($n=68$ HIV-1 incident female CSW) control ($n=126$ HIV negative CSW), Kinshasa, Congo.
	3.6 aOR; 95% CI 1.3–11.0 [40]		Plummer *et al.* [40]: $n=124$ female CSW prospective. Nested case ($n=83$ HIV-incident cases) control ($n=41$ HIV negative) controls, Nairobi, Kenya.
	5.2aHR; 95% CI 1.9–14.4 [32]		Kapiga *et al.* [32]: $n=845$ bar/hotel female workers, prospective, Moshi, Tanzania.

Table 1 (*continued*)

Factor	HIV susceptibility	HIV infectiousness	Comments
	0.44aOR; 95% CI 0.17–1.13 [14]		Macdonald *et al.* [14]: $n=232$ MSM, unmatched case control ($n=75$ incident HIV cases and $n=157$ controls), UK.
Gonorrhoea	4.8aOR; 95% CI 2.4–9.8 [35]	1.17aOR; 95% CI 0.23–3.83 [35]	Laga *et al.* [35] $n=431$ female CSW, retrospective nested case ($n=68$ HIV-1-incident female CSW) control ($n=126$ HIV negative CSW), Kinshasa, Congo.
	1.01aOR; 95% CI 0.86–1.19 [11]		Quinn *et al.* [11]: $n=415$ heterosexual HIV-1 serodiscordant couples (HIV-1-negative partners constituted $n=228$ women and 187 men), prospective, Rakai, Uganda.
	0 aOR [12]		Gray *et al.* [12]: $n=174$ HIV-1 serodiscordant couples (HIV-1-negative partners constituted $n=97$ women and 77 men) prospective, Rakai, Uganda.
	2.5aOR; 95% CI 1.1–5.7 [33]		Kassler *et al.* [33]: $n=6175$ attendees at STI clinic. Nested retrospective case ($n=49$ men and women incident HIV-1 and 98 HIV-negative controls), Baltimore, US.
	1.7 aHR; 95% CI 1.1–2.6 [34]		Martin *et al.* [34]: $n=675$ female HIV-1-negative CSW, prospective, Mombasa, Kenya.
	4.22aOR; 95% CI 1.82–9.74 [14]		Macdonald *et al.* [14]: $n=232$ MSM, unmatched case control ($n=75$ incident HIV cases and $n=157$ controls), UK.
Trichomonas vaginalis	1.9aOR; 95% CI 0.9–4.1 [35]	1.84aOR; 95% CI 0.84–3.89 [11]	Laga *et al.* [35]: $n=431$ female CSW, retrospective nested case ($n=68$ HIV-1-incident female CSW) control ($n=126$ HIV-negative CSW), Kinshasa, Congo.
	1.27aOR; 95% CI 0.65–2.35 [11]		Quinn *et al.* [11]: $n=415$ heterosexual HIV-1 serodiscordant couples, prospective, Rakai, Uganda.
	0 aOR [12]		Gray *et al.* [12]: $n=174$ HIV-1 serodiscordant couples. (HIV-1-negative partners constituted $n=97$ women and 77 men) prospective, Rakai, Uganda.
	1.53aOR; 95% CI 1.04–2.24 [36]		McClelland *et al.* [36]: $n=1335$ HIV-1-negative female CSW, prospective, Mombasa, Kenya.
	2.74aOR; 95% CI 1.25–6.00 [37]		Van Der Pol *et al.* [37]: $n=639$ HIV-1 negative women, nested case control study ($n=213$ incident HIV-1, $n=426$ HIV-negative controls), prospective, Uganda and Zimbabwe.

Table 1 (*continued*)

Factor	HIV susceptibility	HIV infectiousness	Comments
Infectious syphilis	4.44aOR; 95% CI 2.96–6.65 [38]	pVL increases by 0.22 Log_{10} compared to presyphilis ($P=0.02$) [39]	Reynolds *et al.* [38]: $n=2732$ HIV-1-negative men and women attending STI clinic, prospective, India. Bichacz *et al.* [39]: $n=52$ HIV-1 infected men diagnosed with primary or secondary syphilis, retrospective case note review, three clinics in San Francisco and Los Angeles, US.
	4.85aOR; 95% CI 0.86–27.41 [14]		Macdonald *et al.* [14]: $n=232$ MSM, unmatched case control ($n=75$ incident HIV cases and $n=157$ controls), UK.
Bacterial vaginosis	2.3aOR; $P=0.04$ [44]		Taha *et al.* [44]: $n=1196$ HIV-1-negative pregnant women, prospective, Malawi.
	0.77aOR; 95% CI 0.44–1.36 [11]	0.91aOR; 95% CI, 0.45–1.80 [11]	Quinn *et al.* [11]: $n=415$ heterosexual HIV-1 serodiscordant couples, prospective, Rakai, Uganda.
	$P>0.05$ [12]		Gray *et al.* [12]: $n=305$ heterosexual HIV-1 serodiscordant couples (HIV-1-negative partners constituted $n=196$ women and 108 men), retrospective Rakai, Uganda.
	2.01aOR; 95% CI 1.12–3.62 [45]		Myer *et al.* [45]: $n=409$ HIV-1-negative women, retrospective nested case ($n=85$ HIV-1 incident infected women) control ($n=324$ HIV-1 negative) South Africa.
Genital warts	1.02 OR; 95% CI 0.60–1.60 [46]		Mayaud *et al.* [46]: $n=607$ pregnant women HIV-positive ($n=96$) and HIV-negative ($n=511$), prospective, Tanzania.
	1.14OR; 95% CI 0.41–3.18 [14]		Macdonald *et al.* [14]: $n=232$ MSM, unmatched case control ($n=75$ incident HIV cases and $n=157$ controls), UK.
Candidiasis	0.11OR; 95% CI 0.04–0.36 [47]		Hester *et al.* [47]: heterosexual HIV-1 serodiscordant couples study, prospective, nested case ($n=45$ HIV-1-incident infected women) control ($n=45$ HIV-1-negative women), Luska, Zambia. No multivariate analysis.
HSV-2 seroconversion	5.5 aHR; 95% CI 1.2–25.4 [32]		Kapiga *et al.* [32]: $n=845$ bar/hotel female workers, prospective, Moshi, Tanzania.
HSV seropositive	Women: 4.3 aRR; 95% CI 1.5–12.4 [32]	HIV-1 genital shedding is not altered by HSV-2 genital shedding and nonshedding: 0.8aOR; 95% CI, 0.2–3.3 [90]	Kapiga *et al.* [32]: $n=845$ bar/hotel female workers, prospective, Moshi, Tanzania. Cowan *et al.* [90]: $n=214$ CSW ($n=124$ co-infected with HIV-1 and HSV-2), prospective, rural Zimbabwe.

Table 1 (*continued*)

Factor	HIV susceptibility	HIV infectiousness	Comments
	Women: 3.1 aRR; 95% CI 1.7–5.6 [13] Heterosexual men: 2.7aRR; 95% CI 1–9–3.9 [13] MSM: 1.7aRR; 95% CI 1.2–2.4 [13]		Freeman *et al.* [13]: meta-analysis of 19 studies where relative timing of HSV-2 infection and incident HIV-1 infection were known.
	Acyclovir HSV suppressive therapy does not reduce HIV-1 acquisition in women 1.16; 95% CI 0.83–1.62 [87] 1.08; 95% CI 0.64 to 1.83 [88]	Valacyclovir HSV suppressive therapy significantly reduces genital HIV-1 RNA levels in women aOR-0.29; 95% CI −0.44 to −0.15) [89]	Celum *et al.* [87]: $n=3277$ HIV-1 negative, HSV-2 seropositive women and MSM. Double blind RCT of suppressive treatment with acyclovir 400 mg twice daily, Peru and USA. Watson-Jones *et al.* [88]: $n=821$ HIV-1-negative, HSV-2 seropositive women working in recreational facilities. Double-blind RCT of suppressive treatment with acyclovir 400 mg twice daily, northwestern Tanzania. Nagot *et al.* [89]: $n=140$ CSW co-infected with HIV-1 and HSV-2, double-blind RCT of suppressive treatment with valacyclovir 500 mg twice daily, Burkina Faso, West Africa.
Syphilis seroposiitve	1.20aOR; 95% CI 0.59–2.23 [11]	0.72aOR; 95% CI 0.34–1.32 [11]	Quinn *et al.* [11]: $n=415$ heterosexual HIV-1 serodiscordant couples, prospective, Rakai, Uganda.
Combined oral contraceptive	0.5 aOR; 95% CI 0.3–1.0 [48]		Lazzarin *et al.* [48]: $n=368$ HIV-1-negative women in HIV-1 serodiscordant relationships. Cross-sectional, Italy.
	0.99aHR; 95% CI 0.69–1.42 [30]		Morrison *et al.* [30]: $n=4439$ HIV-1-negative women aged 18–35 years attending family planning clinics, prospective. Uganda, Zimbabwe, Thailand. Retrospective analysis comparing: pregnant women, nonpregnant lactating women, and women neither pregnant nor lactating who were either using or not using hormonal contraception.
DMPA	1.25aHR; 95% CI 0.89–1.78 [49]	No effect on pVL; $P=0.9$ [92]	Richardson *et al.* [49]: 6109 HIV-1-negative women aged 18–35 years, prospective. Uganda, Zimbabwe, Thailand.
		1.62aOR; 95% CI 1.03–2.63 [50]	Wang *et al.* [50]: $n=101$ HIV-1-positive women, family planning clinic, prospective, Kenya.
Age <30 years		2.38aRR; 95% CI 1.30–4.38 [15]	Wawer *et al.* [15]: $n=235$ heterosexual HIV-1 serodiscordant couples, retrospective, Rakai, Uganda.

Table 1 (*continued*)

Factor	HIV susceptibility	HIV infectiousness	Comments
15–24 years	2.15aOR; 95% CI 0.80–6.43 [12]		Gray *et al.* [12]: $n=174$ HIV-1 serodiscordant couples. (HIV-1-negative partners constituted $n=97$ women and 77 men), retrospective, Rakai, Uganda.
25–29 years	2.06aOR; 95% CI, 0.83–5.86 [12]		
30–34 years	0.62aOR; 95% CI 0.18–2.08 [12]		
35–59 years	1 [12]		
>30 years		3.1 OR [86]	Zunzunegui *et al.* [86]: $n=130$ heterosexual HIV-1 serodiscordant couples (all women HIV-negative), prospective, Spain. Not significant on multivariate analysis.
Breastfeeding	1.16aRR; 95% CI 0.82–1.63 [12]		Gray *et al.* [12]: $n=174$ heterosexual HIV-1 serodiscordant couples. (HIV-1-negative partners constituted $n=97$ women and 77 men), retrospective, Rakai, Uganda.
Pregnancy	1.14aHR; 95% CI 0.47–2.80 [30]		Morrison *et al.* [30]: $n=4439$ HIV-1-negative women aged 18–35 years attending family planning clinics, prospective. Uganda, Zimbabwe, Thailand. Retrospective analysis comparing: pregnant women, nonpregnant lactating women, and women neither pregnant nor lactating who were either using or not using hormonal contraception.
	2.16aRR; 95% CI 1.39–3.37 [12]		Gray *et al.* [12]: $n=174$ heterosexual HIV-1 serodiscordant couples. (HIV-1-negative partners constituted $n=97$ women and 77 men), retrospective, Rakai, Uganda.

aHR, adjusted hazard ratio; aOR, adjusted odds ratio; aRR, adjusted rate ratio; CI, confidence interval; CSW, commercial sex workers; IRR, incidence rate ratio; NSU, non-specific urethritis; OR, odds ratio; pVL, plasma viral load; RCT, randomized controlled trial; RR, rate ratio; STI, sexually transmitted infection.

Table 2. Summary of studies addressing risk of transmission for different sex acts.

Type of sex act	Risk of HIV transmission per exposure	95% Confidence interval	Reference	Risk group studied
Receptive anal			Mastro *et al.* [62]	Review
	0.00102		Grant *et al.* [51]	*N* = 343 high risk MSM and bisexual HIV-1-negative men, prospective, San Francisco, USA
			Royce *et al.* [85]	Review
	0.00042–0.0012		Samuel *et al.* [52]	*N* = 329 HIV-1-negative MSM in three prospective studies. Nested case (*n* = 83 incident HIV-1), control (*n* = 246 HIV negative controls), USA
	0.0082		Vittinghoff *et al.* [53]	*N* = 1583 high risk HIV-1 negative MSM and bisexual HIV-1-negative men prospective USA
	0.005–0.03		De Gruttola *et al.* [54]	*N* = 155 HIV-1 serodiscordant MSM couples, retrospective, Boston, USA
	0.005		Varghese *et al.* [18]	Review
			Kaplan *et al.* [51]	*N* = 1034 MSM mathematical modelling using data from Grant *JID* 1987
	0.001–0.03		Fisher *et al.* [19]	British Association for Sexual Health and HIV guidelines
	0.014	0.002–0.025	Baggaley *et al.* [76]	Systematic review, meta-analysis of heterosexual and MKSM studies
	0.0143	0.0048–0.0285	Jin *et al.* [84]	*N* = 1427 Prospective community-based HIV negative MSM, Sydney, Australia
	0.017	0.003–0.089	Boily *et al.* [31]	Systematic review, meta-analysis of heterosexual studies only
Receptive anal with no ejaculation	0.0065	0.0015–0.0153	Jin *et al.* [84]	*N* = 1427 Prospective community-based HIV negative MSM, Sydney, Australia
Receptive vaginal			Royce *et al.* [85]	Review
	0.001		De Vincenzi *et al.* [55]	*N* = 305 heterosexual HIV-1 serodiscordant couples (HIV-1-negative partners *n* = 163 women and 93 men), prospective, prospective, European multicentre study
	0.001		Varghese *et al.* [18]	Review
	0.0009		Gray *et al.* [12]	*N* = 525 heterosexual HIV-1 serodiscordant couples prospective, (HIV-1 negative partners *n* = 97 females and 428 males Rakai, Uganda
	0.0007		Leynaert *et al.* [56]	*N* = 359 heterosexual HIV-1 serodiscordant, prospective, European multicentre (HIV-1 negative partners *n* = 359 women)
	0.0006–0.0009		Shiboski *et al.* [57]	*N* = 384 heterosexual HIV-1 serodiscordant couples, retrospective (HIV-1-negative partners *n* = 384 females), multicentre retrospective, California, USA
	0.0005		Downs *et al.* [58]	*N* = 563 heterosexual HIV-1 serodiscordant couples within European study group (HIV-1-negative partners *n* = 148 women and 377 men), retrospective
	0.0015			*N* = 563 heterosexual HIV-1 serodiscordant couples within European study group (HIV-1 negative partners *n* = 73 females and 73 males), prospective
	0.0004–0.006		Donnelly *et al.* [91]	*N* = 425 HIV-1 negative female CSW, prospective, Dakar, Senegal

Table 2 (*continued*)

Type of sex act	Risk of HIV transmission per exposure	95% Confidence interval	Reference	Risk group studied
	0.0014		Wiley *et al.* [59]	$N=55$ HIV-1-negative female partners of male index cases from the prospective California partner study, USA. Data from Peterman *JAMA* 1988
	0.0009		Padian *et al.* [60]	$N=442$ heterosexual HIV-1 serodiscordant couples, retrospective (HIV-1-negative partners $n=360$ women and 82 men), California, USA
	0.0032		Plummer *et al.* [40]	$N=49$ HIV-1-negative female CSW, prospective, Nairobi, Kenya
	0.001–0.002		Fisher *et al.* [19]	British Association for Sexual Health and HIV guidelines
	0.0008	0.0006–0.0011	Boily *et al.* [31]	Systematic review and meta-analysis of observational studies in high-income countries
	0.003	0.0014–0.0063	Boily *et al.* [31]	Systematic review and meta-analysis of observational studies in low-income countries
Insertive vaginal	0.0013		Gray *et al.* [12]	$N=305$ heterosexual HIV-1 serodiscordant couples (HIV-1-negative partners $n=196$ women and 108 men), prospective, Rakai, Uganda
	0.0001125		Padian *et al.* [60]	$N=442$ heterosexual HIV-1 serodiscordant couples, retrospective (HIV-1-negative partners $n=360$ women and 82 men), California, USA
	0.00082		Cameron *et al.* [61]	$N=73$ men attending an STI clinic following a single exposure to a cohort of female CSWs. All men initially seronegative and seroconverted over following 12 weeks. Serostatus of CSWs inferred from prevalence data (85% prevalence), cross-sectional, Nairobi, Kenya
			Royce *et al.* [82]	Review
	0.001		De Vincenzi *et al.* [55]	$N=305$ heterosexual HIV-1 serodiscordant couples (HIV-1 negative partners $n=163$ women and 93 men), prospective, European multicentre study
	0.0005		Varghese *et al.* [18]	Review
	0.056		Mastro *et al.* [62]	$N=1115$ military conscripts having sex with CSW of known HIV-1 seroprevalence, cross-sectional, Thailand
	0.0005		Leynaert *et al.* [56]	$N=359$ heterosexual HIV-1 serodiscordant, prospective, European multicentre (HIV-1-negative partners $n=359$ women)
	0.0014		Peterman *et al.* [63]	$N=80$ heterosexual HIV-1 serodiscordant couples (HIV-1 negative partners $n=10$ women and 25 men), prospective, Atlanta, USA
	0.0003		Downs *et al.* [58]	$N=563$ heterosexual HIV-1 serodiscordant couples within European study group (HIV-1-negative partners $n=148$ women and 377 men), retrospective
	0.0015			$N=563$ heterosexual HIV-1 serodiscordant couples within European study group (HIV-1-negative partners $n=73$ women and 73 men), prospective
	0.0003–0.0009		Fisher *et al.* [19]	BASSH guidelines
	0.0004	0.0001–0.0014	Boily *et al.* [31]	Systematic review and meta-analysis of observational studies in high-income countries

Table 2 (*continued*)

Type of sex act	Risk of HIV transmission per exposure	95% Confidence interval	Reference	Risk group studied
	0.0038	0.0013–0.011	Boily *et al.* [31]	Systematic review and meta-analysis of observational studies in low-income countries
Insertive anal	0.0006		Vittinghoff *et al.* [53]	$N=2189$ HIV-1-negative high-risk MSM and bisexual men, prospective, USA
	0.00065		Varghese *et al.* [18]	Review
			Samuel *et al.* [52]	$N=329$ HIV-1 negative MSM in 3 prospective San Francisco cohort studies. Nested case control study ($n=83$ incident HIV-1, $n=246$ HIV-negative controls), USA
			De Gruttola *et al.* [54]	$N=58$ HIV-1 serodiscordant MSM couples, Boston, USA
	0.0006		Fisher *et al.* [19]	BASSH guidelines
	Uncircumcised 0.0062	0.0007–0.0168	Jin *et al.* [84]	$N=1427$ Prospective community based HIV negative MSM, Sydney, Australia
	Circumcised 0.0011	0.0002–0.0024	Jin *et al.* [84]	$N=1427$ Prospective community-based HIV negative MSM, Sydney, Australia
Receptive oral	0–0.0004		Vittinghoff *et al.* [53]	$N=1583$ HIV-1-negative high-risk MSM and bisexual men prospective USA
	0		Del Romero *et al.* [64]	$N=135$ heterosexual HIV-1 serodiscordant, prospective, (HIV-1-negative partners constituted $n=110$ women and 25 men), Madrid, Spain
Insertive oral	0		Samuel *et al.* [52]	$N=329$ HIV-1-negative MSM in 3 prospective San Francisco cohort studies. Nested case ($n=83$ incident HIV-1), control ($n=246$ HIV-negative controls), USA
	0		Del Romero *et al.* [64]	$N=135$ heterosexual HIV-1 serodiscordant, prospective, (HIV-1-negative partners $n=110$ women $n=25$ men), Madrid, Spain. Case reports of women acquiring HIV from IOI exist

Table 3. Summary of types of sex-act affected by the risk multipliers for HIV transmission.

Factor	Subscript	Mechanism of increased transmission risk	Routes of transmission affected				
			ROI	IVI	RVI	IAI	RAI
Viral load	VL	Infectivity	Yes	Yes	Yes	Yes	Yes
Stage	Stage	Infectivity	Yes	Yes	Yes	Yes	Yes
GUD	GUD	Infectivity	Yes	Yes	Yes	Yes	Yes
GUD	GUD	Susceptibility	No	Yes	Yes	Yes	Yes
HSV-2 seropositivity	HSV-2	Susceptibility	No	Yes	Yes	Yes	Yes
Circumcision	Circ	Susceptibility	No	Yes	No	No	No
Pregnant	Preg	Susceptibility	No	No	Yes	No	No

GUD, genital ulcer disease; IAI, insertive anal intercourse; IVI, insertive vaginal intercourse; RAI, receptive anal intercourse; ROI, receptive oral intercourse; RVI, receptive vaginal intercourse.

summarized in Table 4. The tables are divided into those factors affecting the HIV susceptibility of uninfected individuals and those factors affecting the HIV infectivity of infected individuals.

Factors determining HIV transmission and incorporated into the risk transmission score

Biological risk score

For HIV-serodiscordant couples, the index case viral load [11] and the stage of HIV disease (primary and late stage) [15] were the most important independent biological factors conferring enhanced risk of onward transmission.

The presence of genital ulcer disease (GUD) [11,12,15] in either partner and for HIV-negative individual's pregnancy [23], HSV-2 seropositivity [13] and lack of circumcision (men only) [24–27] in the HIV-negative partner conferred an increased risk of HIV transmission. For the risk score, the authors suggest that previous genital HSV-2 is used as a surrogate marker of HSV-2 seropositivity as routine serological screening for HSV-2 is not generally available.

Summary of evidence

There are both HIV-serodiscordant couple data and population data to support HIV plasma viral load and stage of HIV infection in HIV transmission [15,28,29]. For male circumcision, HIV-serodiscordant couple data are not available; however, three RCTs confirmed unequivocally that it is protective for heterosexual HIV-negative men [24–26]. Pregnancy has been associated with HIV acquisition in a HIV-serodiscordant study [23] but not in a cohort study [30]. Despite no data from HIV-serodiscordant studies, a large meta-analysis of 19 clinical studies showed a strong association of seropositive HSV-2 serology with HIV acquisition [13].

A role for GUD in HIV acquisition and transmission was found in two out of three HIV-serodiscordant studies [11,12,15] and a large meta-analysis of 25 heterosexual cohorts [31]. Although HSV-2 seroconversion is associated with HIV acquisition in a cohort study [32], it was not included as a factor as there were no data from HIV-serodiscordant studies, longitudinal testing for HSV-2 is not routine practice and there is an overlap

Table 4. The risk factors and odds ratios used in the HIV exposure risk score.

Factor (symbol)	HIV-negative susceptibility to HIV	HIV-infected individuals infectiousness (95% CI)
Viral load Log_{10} [20] [α_{VL}]		Adjusted OR for risk score
0–3.49		0.14 (0.06–0.34)
3.50–3.9		0.84 (0.24–2.98)
4.0–4.69		1
>4.70		1.72 (0.51–5.75)
Stage of HIV infection [21] [α_{stage}]		
Primary		4.98 (2.00–12.39)
Chronic		1
Late		3.49 (1.76–6.92)
Male circumcised [41–43] [γ_{circ}]	0.47 (0.28–0.78)	1
GUD [20,21,69,82] [γ_{GUD}; α_{GUD}]	2.58 (1.3–5.69)	2.04 (0.93–5.3)
HSV-2 seropositivity [34] [γ_{HSV-2}]		
Heterosexual female	3.1 (1.7–5.6)	
2.7 (1.9–3.9)		
1.7 (1.2–2.4)	1	
Heterosexual male		1
MSM		1
Pregnant [37,77] [γ_{preg}]	2.16 (1.39–3.37)	1

Data from HIV-serodiscordant couples studies were prioritized. Baseline probabilities per sex act are (Varghese): insertive oral intercourse: 0; receptive oral intercourse: 0.0004; insertive vaginal intercourse: 0.0005; receptive vaginal intercourse: 0.001; insertive anal intercourse: 0.00065; receptive anal intercourse: 0.005. CI, confidence interval; OR, odds ratio.

with GUD which is an independent risk factor in the risk score.

The role of bacterial STI in HIV transmission is complex and lacks consistent agreement between studies. Two large HIV-serodiscordant couples studies found no association of any individual STI with HIV transmission; however, incident rates of STI in these studies was low [11,12]. In contrast, the majority of cohort studies have shown an association of STI, in particular gonorrhoea and *Trichomonas vaginalis*, with HIV transmission. Gonorrhoea was not associated with HIV transmission in two HIV-serodiscordant studies [11,12] but was associated with HIV acquisition in three cohort studies [14,33,34]. Trichomonas was not associated with HIV transmission in two HIV-serodiscordant studies [11,12] and one cohort study [35] but was associated with HIV acquisition in two further cohort studies [36,37]. Two cohort studies have shown nonconcordant results in an association of infections syphilis with HIV acquisition [14,38]; however, GUD, the primary stage of the infection, is associated with acquisition [12,31]. For HIV infectiousness the affect appears to be mediated by an increase in plasma viral load (pVL) [39]. Chlamydia was not associated with HIV transmission in two HIV-serodiscordant studies [11,12] and one cohort study [14] but was associated in three further cohort studies [32,35,40]. In addition, several large, well conducted trials of enhanced STI treatment and care have failed to show a consistent impact on HIV incidence [15,41–43]. Bacterial vaginosis was not associated with HIV acquisition in two HIV-serodiscordant couple studies [11,12] but was significant in two cohort studies [44,45]. Neither genital warts [14,46] nor Candida [47] have been associated with HIV transmission.

In regard to hormonal influences, the combined oral contraceptive (COCP) was not associated with HIV acquisition in a HIV serodiscordant or a cohort study [30,48] and the depot medroxyprogesterone acetate (DMPA) was not associated with HIV acquisition in two cohort studies [49,50]. Breast feeding was not associated with HIV acquisition in a HIV-serodiscordant couple study [23].

Behavioural risk score

Risk estimates for the type of sex act were derived from a review publication [18] and concurred closely with estimates from other large well designed studies. Most estimates show that the risk of HIV acquisition per coital act is highest in receptive anal intercourse (RAI) (range 0.04–3.0%) [51–54], followed by receptive vaginal intercourse (RVI) (range 0.04–0.0.32%) [12,15,18,55–60], insertive anal intercourse (IAI) (range 0.06–0.056%) [18,52–54], insertive vaginal intercourse (IVI) (0.01–0.14%) [15,18,55,56,58,60–63], receptive oral intercourse (ROI) (range 0–0.04) [55,64] and finally insertive oral intercourse (IOI) (range 0–0) [52,64].

The estimates are, however, limited by the fact that the majority of anal intercourse estimates derive from MSM cohorts, with little data for anal intercourse amongst heterosexuals. In addition, estimates are not stratified according to HIV-infected partner viral load. However, as the majority of sex act HIV transmission studies were carried out prior to the widespread availability of ART, estimates obtained can be assumed to correspond to an 'average' or mean viral load set point of a chronically HIV-infected untreated individual [65–67].

To incorporate the effect of viral load on transmission risk per sex act, we had to adjust for the relative risks calculated for different viral loads assuming transmission estimates for type of sex act represented the risk for an 'average' viral load. A set point viral load calculated by Mei *et al.* [67] was used for the risk score. This estimate derived from individuals prospectively evaluated from primary HIV infection and the data were analysed using four methodologies and calculated a mean viral load set point of 4.20 Log_{10} copies/ml [67]. For the risk score, the viral load category containing 4.20 Log_{10} copies/ml [11] was used as a reference point for the typical viral load of participants in studies that measured the transmission risk associated with different types of sex act.

By incorporating the biological and behavioural risk score, an overall evaluation of exposure is obtained.

The Bernoulli model

HIV exposure risk score for HIV-serodiscordant couples

Biological factors discussed are incorporated into the model as 'risk multipliers', represented by α, with subscripts denoting the particular factor. If a particular condition applies, then the multiplier takes the appropriate value determined from the literature; if the condition does not apply then the multiplier takes the value 1, so that the per-sex-act risk is not modified. Missing values were scored as 1.

β_{type} represents the risk of acquisition of HIV by an HIV-negative person who does not have an STI, is not pregnant or circumcised and does not have a history of HSV-2, during one unprotected sex act of a particular type with an HIV-positive partner who is in the 'reference' viral load category, is not in early-stage HIV infection, and does not have GUD. The value of β_{type} depends upon the type of unprotected sex act, with insertive and receptive sex acts being distinct. The practice of insertive oral intercourse was not considered a transmission risk and therefore not included in the model [52,64].

The following multipliers pertain to the HIV-infected partner: α_{VL} represents the effect of the viral load being different from the 'reference' category of 4.20 Log_{10} copies/ml if this is the case (risk is reduced or

increased if viral load is in a lower or higher category, respectively); α_{stage} represents the effect of the stage of HIV infection, with infectivity being increased in primary HIV infection, defined as within 6 months of HIV acquisition, and late-stage infection, defined as 6–35 months before death; and α_{GUD} represents the increased risk associated with the presence of GUD irrespective of causal organism.

The following multipliers pertain to the HIV-negative partner: γ_{GUD}, $\gamma_{HSV\text{-}2}$, γ_{preg}, γ_{circ}, which represent the effects of GUD, HSV-2 seropositivity, pregnancy, and male circumcision: the first three increase susceptibility, whereas the last reduces susceptibility.

For a single unprotected sex act, the risk of transmission is the product of the 'baseline' transmission probability for that type of sex act and the relevant risk-modifier coefficients (i.e. HIV viral load category, STI co-infection status), that is

$$\beta_{type}\alpha_{VL}\alpha_{stage}\alpha_{GUD}\gamma_{GUD}\gamma_{HSV\text{-}2}\gamma_{preg}\gamma_{circ} \quad \text{(I)}$$

When a risk multiplier does not affect a particular sex-act type it takes the value 1 so it does not affect the calculated risk – this is why multipliers for the effects of both pregnancy and circumcision on susceptibility appear in the generic formula, despite it being impossible for them to apply to the same individual.

When the number of unprotected sex acts exceeds 1, to calculate the risk of acquisition, it is necessary to consider the 'escape probability'. The 'escape probability' is the probability of not becoming infected, which, for a single unprotected sex act, is 1 minus the per-act transmission probability. The escape probability for several sex acts of the same type with the same partner is the escape probability for a single act of that type with that partner raised to the power of the number of acts of that type. The risk of acquisition during those sex acts is 1 minus the total escape probability (as there are only two outcomes – acquiring infection or escaping it – the probability of those two outcomes must sum to 1). Therefore, the risk of HIV acquisition over all unprotected sex acts of a particular type with an HIV-infected partner is the following:

$$1-\left(1-\beta_{type}\alpha_{VL}\alpha_{stage}\alpha_{GUD}\gamma_{GUD}\gamma_{HSV\text{-}2}\gamma_{preg}\gamma_{circ}\right)^{N_{type}} \quad \text{(II)}$$

where N_{type} is the number of sex acts of the particular type.

When a person has different types of unprotected sex acts with one partner, the escape probability for all sex acts of all types is the product of the escape probabilities for each type of sex act (considering the number of sex acts of each particular type). The transmission probability for all unprotected sex acts of all types with that partner is 1 minus the escape probability for all sex acts of all types, that is

for an uninfected woman having sex with an HIV-infected male partner,

$$1-\left[\begin{array}{l}\left(1-\beta_{ROI}\alpha_{VL}\alpha_{stage}\alpha_{GUD}\right)^{N_{ROI}}\\ \times\left(1-\beta_{RVI}\alpha_{VL}\alpha_{stage}\alpha_{GUD}\gamma_{GUD}\gamma_{HSV\text{-}2}\gamma_{preg}\right)^{N_{RVI}}\\ \times\left(1-\beta_{RAI}\alpha_{VL}\alpha_{stage}\alpha_{GUD}\gamma_{GUD}\gamma_{HSV\text{-}2}\right)^{N_{RAI}}\end{array}\right] \quad \text{(III)}$$

for an uninfected man having sex with an HIV-infected female partner,

$$1-\left[\begin{array}{l}\left(1-\beta_{IVI}\alpha_{VL}\alpha_{stage}\alpha_{GUD}\gamma_{GUD}\gamma_{HSV\text{-}2}\gamma_{circ}\right)^{N_{IVI}}\\ \times\left(1-\beta_{IAI}\alpha_{VL}\alpha_{stage}\alpha_{GUD}\gamma_{GUD}\gamma_{HSV\text{-}2}\gamma_{circ}\right)^{N_{IAI}}\end{array}\right] \quad \text{(IV)}$$

for an uninfected man having sex with an HIV-infected male partner,

$$1-\left[\begin{array}{l}\left(1-\beta_{ROI}\alpha_{VL}\alpha_{stage}\alpha_{GUD}\right)^{N_{ROI}}\\ \times\left(1-\beta_{IAI}\alpha_{VL}\alpha_{stage}\alpha_{GUD}\gamma_{GUD}\gamma_{HSV\text{-}2}\gamma_{circ}\right)^{N_{IAI}}\\ \times\left(1-\beta_{RAI}\alpha_{VL}\alpha_{stage}\alpha_{GUD}\gamma_{GUD}\gamma_{HSV\text{-}2}\right)^{N_{RAI}}\end{array}\right] \quad \text{(V)}$$

These formulae apply to having one HIV-positive partner. When an individual has more than one HIV-infected sexual partner, the escape probabilities must be calculated for each partner and then multiplied together to calculate the escape probability for all sex acts of all types with all partners. The risk of acquisition is then 1 minus the escape probability for all sex acts of all types with all HIV-positive partners.

For example, for an uninfected man with an HIV-infected male partner and an HIV-infected female partner, the risk of HIV acquisition is,

$$1-\left\{\begin{array}{l}\left[\begin{array}{l}\left(1-\beta_{IVI}\alpha_{VL}\alpha_{stage}\alpha_{GUD}\gamma_{GUD}\gamma_{HSV\text{-}2}\gamma_{circ}\right)^{N_{IVI}}\\ \times\left(1-\beta_{IAI}\alpha_{VL}\alpha_{stage}\alpha_{GUD}\gamma_{GUD}\gamma_{HSV\text{-}2}\gamma_{circ}\right)^{N_{IAI,F}}\end{array}\right]\\ \times\left[\begin{array}{l}\left(1-\beta_{ROI}\alpha_{VL}\alpha_{stage}\alpha_{GUD}\right)^{N_{ROI}}\\ \times\left(1-\beta_{IAI}\alpha_{VL}\alpha_{stage}\alpha_{GUD}\gamma_{GUD}\gamma_{HSV\text{-}2}\gamma_{circ}\right)^{N_{IAI,M}}\\ \times\left(1-\beta_{RAI}\alpha_{VL}\alpha_{stage}\alpha_{GUD}\gamma_{GUD}\gamma_{HSV\text{-}2}\right)^{N_{RAI}}\end{array}\right]\end{array}\right\} \quad \text{(VI)}$$

where the number of unprotected acts of insertive anal intercourse with the female and males partners, respectively, are $N_{IAI,F}$ and $N_{IAI,M}$.

Characteristics of the partner(s) that affect the risk score may not always be known. If the partner is known to be HIV-positive then there is a transmission risk, but if the status of the partner with respect to viral load, stage of HIV infection and GUD are not known then the multipliers can be varied between their values if present and 1 (the value if absent) to calculate the range of uncertainty in the estimate of risk that arises from the lack of information. Figure 1 shows a plot of possible scenarios

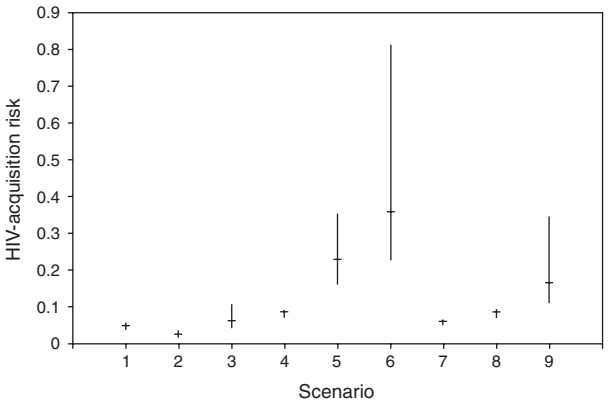

Fig. 1. Plot of example scenarios using HIV risk score. Graph to illustrate the range of variation in risk estimates for scenarios concerning male–male, male–female, and female–male transmission: point estimates and 95% intervals are shown. For each of these examples a 'baseline' scenario has been shown in which the HIV-infected partner is in the chronic stage with an 'average' viral load and the effect of adding additional risk factors depicted. The scenarios are (1) HIV– male with HIV+ female partner: 100 unprotected acts of insertive vaginal intercourse. (2) As scenario 1 except male is circumcised. (3) As scenario 1 except male is circumcised and is HSV-2 seropositive. (4) HIV– female with HIV+ male partner: 80 unprotected acts of receptive vaginal intercourse, 20 unprotected acts of receptive oral intercourse. (5) As scenario 4 except female is HSV-2 seropositive. (6) As scenario 4 except female is HSV-2 seropositive and male has $\log_{10}$ viral load of 4.7 or more. (7) HIV– male with HIV+ male partner: 10 unprotected acts of each of receptive oral intercourse, receptive anal intercourse, insertive anal intercourse. (8) As scenario 7 except HIV– male is circumcised. (9) As scenario 7 except HIV– male is circumcised and HIV+ male has genital ulcer disease.

using the HIV risk score and illustrates the range of variation in risk estimates obtained. If it is not known if the partner is HIV-infected or not then this additional uncertainty can be accounted for by estimating the probability that the partner is infected, given the prevalence in the relevant local population group.

Discussion

In this study we present a formularized approach to synthesizing findings from HIV transmission studies (in particular HIV-serodiscordant couple studies) with potential practical applications. The model enables estimation of an individual's risk of HIV acquisition based on reported sexual practises, STI status and partners infectiousness. As such it could be used as an adjunct in safe sex counselling, for both HIV-infected and uninfected individuals to guide couple-specific evidence-based risk reduction practices and direct the provision of PEP. Importantly it may also inform on the debate in the field of HIV-serodiscordant couple studies by providing a clear definition of exposure; without such a tool comparisons between studies have been impossible. The behaviour score also enables comparison of uninfected unexposed control couples of studies to match sexual practices.

As a transmission model, a Bernoulli model is easily described and manipulated, requires few parameters, has clinical relevance and has been empirically verified in an HIV seroconversion study in Africa [68]. However, as with any model, there are limitations due to its assumptions and supporting data. Firstly, the model assumes that all viral loads have a transmission risk, rather than a threshold below which no transmission is possible. This concurs with models of HIV transmission [69] and reports of sexual and vertical transmission occurring from individuals with an undetectable viral load [70,71] but contrasts with two studies of HIV-serodiscordant couples, in which no transmission events occurred with viral load below 1500 copies/ml both on ART and ART naive [72,73]. However, the absence of transmission in a study does not rule out the possibility of a low transmission risk. Mathematical models suggest that although the risk of transmission on effective suppressive ART is not zero it is very low [69]. The exact risk of transmission between HIV-serodiscordant couples is currently under investigation in the International Partners study [74].

Secondly, the model assumes that only a limited number of factors affect susceptibility to HIV infection. This is untrue given the multiple mechanisms contributing to HIV susceptibility (genetic [7,8] and biological [9] and infectiousness (viral phenotype, load and stage of infection [11,15,16]); if such risks are quantified then they can be incorporated into the model providing the status of the individual which is known. Specifically in the context of HIV-serodiscordant research in which evaluation of CCR5 haplotype of the exposed uninfected and viral co-receptor phenotype of the HIV-infected individual may be available, manipulation of the model could more accurately reflect HIV transmission risk. Finally, due to a lack of data available, the model assumes that all risk factors are independent co-factors of HIV transmission and that the presence of a co-factor affects equally all relevant types of sex act. It was not able to specifically evaluate sex or infection-site-specific (i.e. pharynx, rectum or urethra) risks for incident STI, except for HSV-2 seropositivity [13] and was also unable to account for interactions of STI, circumcision status and genital tract HIV viral load on HIV infectivity. As such the viral load transmission data used in the risk score were derived from vaginal sex within HIV-serodiscordant couples in Africa [11] and therefore may not be directly applicable to non-African settings or MSM. To enhance the accuracy of the model more data are required on the role of HIV co-factors specifically within MSM

populations, the impact of site-specific STI and the possible amplifying effects of biological co-factors.

In order to ensure that robust data were used to develop the HIV risk model an in-depth literature review was carried out and in contrast to previous publications this review focused on both MSM and heterosexual transmission of HIV. [31,75,76] Effort was made to identify confounding factors, such as HIV viral load, heterogeneity in study design, differences in population characteristics, including STI rates, circumcision rates and sexual behaviour and/or insufficient power due to small sample size. Many studies (especially cross-sectional studies) are limited by the use of historical data as a proxy HIV acquisition, a lack of sexual behaviour data and an inability to detect the co-transmission of HIV and STI. Hence such studies conferred lower priority in developing the risk score.

Studies of HIV-serodiscordant couples were prioritized as they are able to assess the effect of STI on both the infectiousness and susceptibility to HIV, whilst controlling for infectivity mediated via plasma viral load, sex act type and sex frequency. It is accepted, however, that all estimates are affected by unadjusted inclusion of condom-protected acts in the count of sex acts.

The HIV risk score may underestimate risk for a number of reasons: Firstly, the exclusion of bacterial STI; secondly, the lack of information concerning actual risk per site; thirdly the potential for two factors to exponentially increase transmission risk; fourthly, the use of plasma viral load as a surrogate for genital tract HIV viral load. The fact that different ART agents have differential penetration into genital tract mucosae [77] means that the two sites may reflect one another and has contributed towards the controversy surrounding the Swiss statement [78]. Finally, the viral load set point used in the model (4.2 RNA copies/ml) fits into the second highest viral load category in the Quinn *et al.* [11] transmission data (4.17–4.88 RNA copies/ml). This means that viral load up to 0.68 Log_{10} higher are categorized as set point (i.e. transmission risk, which may lead to further underestimation in HIV transmission risk).

The accuracy of the HIV exposure risk score is dependent on the quality of the sexual behaviour information collected (e.g. over-reporting of coital frequency leads to over-estimation of the overall risk) and the quality of the STI screens performed. Further work is underway to elucidate accurate sexual behaviour information in a format appropriate to the model and acceptable to participants [20].

Validation and assessment of the practical utility of the HIV exposure risk score is required from prospective cohorts of heterosexual [79] (e.g. HPTN052 study) and MSM HIV-serodiscordant couples. In testing the model, sensitivity analysis will need to be carried out to quantify uncertainty in calculated individual risk arising from uncertainty in parameter estimates from literature (represented by 95% CIs) and uncertainty in the reported behaviour of individuals [80]. Subsequently, the score has potential to be used both in HIV research and HIV (both primary and secondary) prevention. It could also be modified to incorporate partners of known HIV status but unknown HIV viral load using population data (on ART usage, HSV-2 seroprevalence, circumcision status, and STI rates) to numerate the algorithm.

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