Review of the Evidence on Risk of HIV Transmission associated with Oral Sex

Report of a Working Group of the UK Chief Medical Officers' Expert Advisory Group on AIDS

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REVIEW OF THE EVIDENCE ON RISK OF HIV TRANSMISSION ASSOCIATED WITH ORAL SEX

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HIV Transmission through oral sex: current knowledge

1. There are well-documented reports of HIV transmission associated with oral sex

There is evidence, primarily from clinical case reports and some from epidemiological studies, that HIV can be transmitted through oral sex. The evidence is summarised in Annex 1 provided by the Public Health Laboratory Service Communicable Disease Surveillance Centre. Two recent review articles recognise also the importance of acknowledging the risk, which has been identified, and its potential for contribution to overall HIV transmission[1,2,3].

Not all of the case reports of orogenital transmission specify what kind of orogenital contact took place. Evidence suggests that there is a significant seroconversion risk associated with receptive fellatio[4]. It is plausible that receptive fellatio with ejaculation into the mouth from an HIV infected partner would involve exposure to the greatest amount of HIV.
It should be noted that there have been reports of HIV transmission associated with insertive as well as receptive fellatio and two reports of transmission associated with cunnilingus (see Annex 1). The relative rarity of cases of HIV infection which have been ascribed to oral transmission is likely to be influenced by the rarity with which oral exposure has occurred alone, and the tendency to ascribe HIV transmission to any higher risk exposure which can be identified[1].

2. As regards risk of HIV transmission, is oral sex safer than other forms of unprotected penetrative sex?

The evidence shows that oral sex is less risky than unprotected anal intercourse[5]. It is well established that receptive unprotected anal intercourse is the highest risk sexual activity for HIV transmission[4,5,6,7].

Because most heterosexual couples who practise oral sex also practise vaginal intercourse, it is not possible to compare the risks of these two types of sexual activity.
The risk associated with either of these activities can be increased - for example if there is inflammation or ulceration in the mouth or vagina[1,7,8] (see also Annex 3), but overall oral sex is probably safer than unprotected vaginal intercourse.

Oral sex is a common practice in both homosexual and heterosexual relationships[1,2,9,10]. Although unprotected oral sex may be a less efficient means of transmitting HIV than unprotected anal or vaginal sex, the frequency of its occurrence may serve to increase its relative contribution to overall HIV transmission[1,2,10] . The risk of a susceptible person acquiring HIV infection through sexual contact depends on the number of sexual contacts, and the probability of HIV transmission during each exposure[5]. The relative importance of oral sex as a route for transmission of HIV is likely to increase as other, higher risk sexual exposures are avoided[1,2,4,10]. A case-control study nested within a large international cohort study of HIV positive homosexual men has shown an increase in risk of HIV seroconversion associated with multiple partners for receptive oral sex[6].

3. Oral sex is more risky than non-penetrative sex

Oral sex poses more risk of HIV transmission than non-penetrative sexual acts such as mutual masturbation, mouth to mouth contact, body rubbing, hugging and massage where there is minimal opportunity for contact with potentially infectious body fluids. There are no reports of HIV transmission related to these activities. There are only two reports of HIV transmission associated with kissing[11,12] and in one of these, oral sex occurred too. Bleeding gums and deep kissing were relevant factors in one of the reports. Although HIV can be found in saliva[13], it is present in lower levels than in semen and vaginal fluids, and in normal circumstances it is not thought that kissing poses a risk of HIV infection.

4. HIV transmission through oral sex is biologically plausible

It is well established that HIV is present in semen, pre-ejaculatory fluid, vaginal and cervical secretions[14,15,16,17]. Current knowledge about the levels of virus in genital secretions and saliva indicate that some infectious material could be passed between partners if one partner was infected with HIV. **Annex 2** summarises research on viral load in body fluids.

Annex 3 gives a brief description of the normal healthy mouth and common oral pathology in the general population and in HIV disease. This indicates that there are potential entry routes for HIV in the mouth. We know that HIV can be transmitted through the vaginal and anal mucosae.

Thus, our current knowledge of both HIV and of the mouth indicates that transmission of HIV through oral sex is biologically plausible and supports the epidemiological conclusion that the risk is real, but less per exposure than for other forms of unprotected penetrative sex.

5. Avoiding ejaculation probably reduces but does not eliminate the risk of transmission

Some people practise oral sex without ejaculation as a risk reduction strategy. HIV has been isolated from pre-ejaculate[16] and there have been reports of HIV transmission to the receptive partner through oral sex without ejaculation[18,19,20]. However it would seem reasonable to assume that ejaculation increases the extent of exposure to HIV and that avoiding it may help reduce the risk of HIV transmission. The risk of a penile insertive partner acquiring HIV from an infected oral partner is likely to be increased if the penis is ulcerated or otherwise inflamed[1,7,8].

6. Other infections can be transmitted through oral sex

Other pathogens can be transmitted through oral sex[2,21]. Sexually transmitted infections such as gonorrhoea, chlamydia, syphilis, herpes simplex virus, human papilloma virus and hepatitis B can be transmitted in this way, as are other infections including the meningococcus and enteric pathogens. In the latter example the risk is increased particularly where there is oro-anal contact [21]. These other infections should be taken into account when considering sexual health aspects of oral sex.

7. Lesions of the mouth or throat may increase the risk

It is likely that diseases of the mouth, which lead to disruption or inflammation of the oral mucosa increase the risk of HIV transmission during oral sex. Examples would be mouth ulcers, severe gingivitis, periodontal disease, pharyngitis or bleeding gums after tooth brushing and dental flossing. More detail is given in Annex 3.

Any oral conditions associated with inflammation or bleeding will increase the risk of exposure to HIV in saliva and thus the chances of HIV transmission through oral sex. This is discussed in Annex 3.

The same would be expected to apply to the risk of transmitting other infections. The most common type of oral inflammation in people with HIV infection is caused by candidal infection (thrush). Some people at the time of HIV seroconversion have oral ulceration, which may be asymptomatic. This may further increase the likelihood that they may transmit HIV at a time when they are highly infectious and also unaware of this.

Some drugs used in the treatment of HIV (eg didanosine and zalcitabine) can result in dryness and ulceration of the mouth. Mouth dryness may increase the risk of transmission of infections because infectious material cannot be cleared as quickly as usual by saliva.

Tobacco smoking increases the incidence of all oral lesions including periodontal disease. Those who smoke crack cocaine are frequently affected by sores in their mouths and have been shown to have an increased risk of HIV transmission associated with oral sex[22].

Even where there is an apparently normal mouth it would be unwise to assume that HIV could **not** be transmitted through oral sex. Research has shown that tonsils of rhesus monkeys can be a non-

traumatic portal of entry for simian immunodeficiency virus[23] . Mucosal lesions are not a requirement for transmission of HIV through other sexual practices - there is good evidence that HIV can be transmitted across the intact healthy female genital tract. In addition people will not necessarily always be aware of lesions in their own mouths or in those of their partners.

8. Increased risk if co-infected with another sexually transmitted infection (STI)

Co-infection with other STIs increases susceptibility to and transmissibility of HIV infection[5,6,7,8,24]. This probably applies also to oral sex[2]. Some of these other sexually transmitted conditions may be asymptomatic and undiagnosed. Genital trauma increases the likelihood of HIV transmission[4] and it seems likely that this would be equally applicable if such trauma were associated with oral sex.

9. Possible increased risk during menstruation

HIV has been isolated from menstrual blood. There is limited evidence that sex during menses may increase the risk of female to male transmission of HIV through vaginal intercourse. It is plausible that cunnilingus during an HIV infected woman's menses (periods) could pose a greater risk of HIV transmission than at other times.

10. Possible increased risk at seroconversion and advanced disease stage

There is a very high viral load at the time of HIV seroconversion and when there is advanced HIV disease. This may be reflected in viral loads in semen and vaginal fluids. Increased viral load may increase the risk of HIV transmission through oral and other sex[5,7,25]. It seems likely that the converse may apply such as when viral load is maximally suppressed by highly active antiretroviral therapy. However, there is evidence that HIV can be found at times in the seminal cells of men receiving highly active anti-retroviral therapy, who have no detectable viral RNA in their plasma[7, 17, 26, 27].

Although some people experience a seroconversion illness, many do not and so would not be aware that they were potentially able to transmit HIV to a sexual partner, at that time or later. Oral ulcers or inflammation may also increase the risk of HIV transmission at the time of seroconversion (see also paragraph 7).

11. HIV can only be transmitted if one partner has the infection

Particular attention should be attached to the risks associated with oral sex when counselling an individual with HIV infection, or whose partner was likely to have HIV infection. As noted earlier many people are unaware that they have HIV infection at a time when they are particularly infectious to others. It is never possible to be sure that a prospective partner is not infected with HIV, but in some situations where HIV infection is more commonly encountered the chances of exposure to it will be relatively greater. Examples might be amongst some particularly vulnerable groups in this country or abroad where HIV prevalence is relatively higher than elsewhere.

12. HIV infected people can protect themselves from other infections by avoiding unprotected oral sex

The various oral lesions associated with HIV infection make those affected more vulnerable to contracting infections other than HIV through oral sex[1,2]. Not only is there benefit to HIV uninfected partners by avoiding unprotected oral sex, but also to the HIV infected people themselves by avoiding their own possible exposure to other infections (see paragraph 6).

13. Condoms and dental (rubber) dam decrease the risk of transmission

The use of condoms and dental (rubber) dam during oral sex will reduce the risk of transmission of HIV and other infections by acting as a barrier to exposure to potentially infectious material. This should be discussed with people who wish to minimise their risk of acquiring infection[2].

14. Can mouthwashes influence the risk of transmission?

It should be noted that the use of mouthwashes prior to, or after oral sex as a risk reduction strategy could compromise rather than increase protection by reducing the levels of protective substances normally found in the mouth.

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ANNEX 1

NOTES ON A REVIEW OF THE LITERATURE

Many of the early cohort studies and other case series have not shown orogenital contact to be a risk factor for HIV infection. Three potential reasons for this are:

(a) receptive and penetrative anal sex is so important compared with any other modes of transmission that this masks any other sexual practise risk;

(b) the increased risk is small and there have not been studies of sufficient power to demonstrate this small increased risk;

(c) there is no increased risk.

The problem with later studies especially cohort studies is that numbers of sero-conversions, other than those having receptive anal sex, are small and so it is likely that receptive anal sex is masking any effect that insertive anal sex, insertive oral sex and receptive oral sex might be having. Therefore it is difficult to differentiate what has caused the HIV transmission.

Cohort Studies (Table A* & A and Appendix A)

In a total of 16 cohorts, 6 provide some indication of risk associated with oral sex whilst 10 do not. A total of 23 individuals have been identified within the 6 cohorts as probably having acquired their HIV through oral sex. However these studies have not presented odds ratios, or any significant difference compared to other sexual behaviours. Those individuals who were sero-negative on enrolment to the cohort will have been counselled with regard to safer sex. Therefore any subsequent admission of unprotected anal sex may be difficult and this may lead to problems with honesty. For example, in the Amsterdam study (A3), of the 20 men who denied RAI at first questioning, 11 later admitted to RAI at face-to-face interview. In the 6 cohorts that have identified transmission of HIV from oral sex, the type of orogenital contact has either not been subdivided, or

has been identified as receptive or insertive oral sex. Both seem to present a risk, although receptive oral sex may have a greater risk. Most studies present the difficulty that few individuals practice entirely orogenital sex and so in homosexual men any anal sex that occurs is assumed to be the cause of the transmission, possibly masking the effect of other less risky behaviours. Receptive anal sex is known to be a high risk sexual activity. However if an individual rarely has anal sex and often has oral sex, it is assumed that the high risk activity is the route of the HIV transmission. It becomes even more difficult when comparing protected anal sex with unprotected oral sex. Heterosexual oral transmission is almost always confounded by vaginal sex. In gay men there has been a shift in behaviour resulting in more oral sex and less anal sex. Therefore it is usually easier to identify oral transmission in gay men. The 10 cohorts studies that do not show an increased risk of HIV transmission through oral sex have usually presented an odds ratio or relative risk and none of them indicated a risk. With all the cohorts studies there are differences in samples and methods that make comparisons difficult. In addition these studies may not have sufficient power to detect the small risks involved.

Case control studies and Cross-sectional studies (Table B and Appendix B)

There have been 4 case control studies nested within the cohort studies. One suggests a risk of transmission, 2 do not and the other shows an increase in those with multiple receptive oral sex and either no or one episode of receptive anal sex. The two studies that suggest a risk are presented in more detail as they are important amongst the new evidence - Samuel M.C. et al (B1), and Page-Schafer K. et al (B3). There are 3 case control studies carried out independently of cohorts. All 3 find no statistically evidence for an association after multivariate analysis. There are also 6 cross-sectional studies presented. Three of these indicate no significant relationship between seropositivity and oral sex. Of the remaining 3, one does not present any statistical information or make any claims on the size of the risk. Another suggests an independent association between seropositivity and oral sex but no statistical significance. The final study identifies 4 homosexual/ bisexual men (out of 30 studied) who probably acquired their infection through receptive oral sex.

Case Reports (Table C and Appendix C)

Case reports are essential to the identification of risks, which are either 'hidden' by other greater risks, or do in fact only present a small risk. There have been a number of case reports in the literature over the last 15 years suggesting a risk associated with oral sex and HIV transmission. Thirteen case reports are presented here - 9 of which are male-to-male, 2 female-to-male and 2 male-to-female. They provide evidence that transmission is occurring and that certain situations might increase the risk e.g. concomitant sexually transmitted infections, allergy, oral trauma or sores, ejaculation in the mouth etc. One of the case reports denies having ejaculate in the mouth and so raises the issue of transmission via pre-ejaculatory fluid. However there are sometimes factors that cast doubt on the method of transmission and case reports need to be interpreted carefully. Unless a previous negative test has been carried out, it may be difficult to date the seroconversion. Other viral infections may be confused with seroconversion illness since the symptoms can be very non-specific. Admission of a riskier activity, e.g. unprotected anal sex, may be difficult and so reports may have problems with honesty of admission of sexual practice, especially if the person has been previously counselled with regard to the risks of anal sex.

Related Studies (Appendix D)

Other case reports support the biological plausibility of transmission via mucous membranes. One report identifies HIV transmission via deep kissing. Another case probably acquired HIV through either deep kissing or oral sex (without ejaculation), with gingivitis and bleeding gums contributing to transmission. Bite related instances of HIV transmission, probably from exposure to saliva contaminated with blood, have also occurred. One study highlighted the high frequency of blood in saliva after teeth brushing. Two studies suggest that crack smoking, which causes oral sores and fissures, increases the transmission of HIV through oral sex.

When discussing the risks of HIV transmission via oral sex, it is important to mention the studies reporting the frequency of oral sex and whether the contact is protected or not. The National Sexual Attitudes and Lifestyle Survey highlights how frequently oral sex is practised. Whilst a number of other studies have looked at the frequency of condom use in oral sex, especially among gay men, and this ranges from only 6% to 12%. Therefore even if the overall risk is small, the population attributable risk could be significant, if the sexual practice is common.

Female to Female Transmission (Table E and Appendix E)

There are two case reports presented where the risk behaviour appears to be only oro-genital contact. The other case reports include other sexual behaviours which may present additional risk e.g. during menstruation or traumatic sex. Other high risk activities e.g. IVDU, blood transfusion, were denied in these reports. Analysis of national surveillance data in the United States has ascribed the majority of HIV transmission in women, who have sex with women, to be mainly by injecting drug use, and the remaining proportion has been ascribed to receipt of blood or blood products.

Oro-anal Transmission (Appendix F)

The published literature related to oro-anal sex and HIV transmission is small, although there is a substantial amount relating to oro-anal contact and Kaposi's Sarcoma (KS), some of which is included below. Much of this debate following Beral's analysis in 1992 (F2) is now less relevant since the discovery of HHV8 (human herpes virus 8), widely recognised to be the viral cause of KS. There has only been one case report identifying oro-anal sex as the probable cause of transmission.

The source case was insertive with his tongue and had gingivitis at the time. Nine other studies (case control, cohort and cross-sectional) have also commented on the risk of transmission with oro-anal contact. All 9 studies found no increased risk.

HIV reports to CDSC (Table G)

There have been 13 case reports of oro-genital transmission reported to the HIV and STD division at the Communicable Disease Surveillance Centre (CDSC). Five of these have been published and are included in the numbers quoted. In 2 of the 13 reports to CDSC where the only admitted HIV risk was oral sex, the clinician reporting the case was not convinced that this was the only risk. (e.g. failure to give detail, or talk about the risk, etc.). Of the remaining 11 reports, 9 were male-to-male but for the majority of these whether receptive, insertive or both was not specified. One was male-to-female and one was female-to-male although the last case was a complex one said to have involved oral sex in Thailand.

Conclusion

Cases of HIV transmission do occur through oro-genital contact . In fact there will be more than have been published in the literature. We have identified 39 published case reports (the total number in and out of cohort studies, and female-to-female). Only five of these relate to cases in the UK. However a total of 13 reports (including the 5 published reports) have been made to the HIV and STD division at CDSC. In addition, there is likely to be some under-reporting of risk by physicians. Although there may be reluctance to disclose higher risk behaviour amongst cases, it is very unlikely that this would be a factor in all of the reports (published and not). These case reports provide evidence of transmission and highlight possible factors that increase the risk. The cohort studies presenting risk measures have not substantiated this transmission risk. Often these studies do not have sufficient power to detect the small increases in risk that might be occurring. The evidence for HIV transmission through oro-genital contact is important, as several studies have indicated that this is a common sexual behaviour and is frequently unprotected. There has only been one case report of HIV transmission through oro-anal sexual contact.

Abbreviations RR relative risk OR odds ratio

Table A* - Case Reports in Cohorts

Number	From ® To	Cohort/ City/ Country	Sexual Factors	Testing Factors	Other factors
A1	M → M **5 cases**	French Cohort	All 5 had insertive oral sex 3 were receptive (two with swallowing) and had deep kissing; None had anal sex for 3 months prior to seroconversion (one 6 months ago, one 3 years, one 10 years and two never)	Mean period since sero-negative result and positive = 5.4 months (3-14 months)	
A2	M → M **2 cases**	San Francisco City Clinic	No anal sex for over 5 years; Multiple oral sex, receptive and insertive, with ejaculation; One also oro-anal contact	One 4.5 months between negative and positive. One 11 months.	Both had gingival recession.
A3	M → M **4 cases**	Amsterdam	No anal sex in preceding 6 months; receptive and insertive oral sex.	Study of 102 sero-convertors	
A4	M → M **6 cases**	Stockholm	Oral sex with ejaculation; Time period not stated	Study of 60 sero-convertors	
A5	Not stated **4 cases**	Washington Clinic	Only oral sex	Confirmed seroconversion; negative within 12 months of seroconversion.	OR not significant for oral sex or oro-anal contact.
A6	M → M **2 cases**	Multi-centre AIDS Cohort Study (MACS) (Chicago/ Baltimore/ Los Angeles/ Pittsburgh)	No anal sex for 12 months (one could have sero-converted after 6 months)	6 monthly testing	
A7	M → M	Toronto/ Canada	No significant association with oral sex or oro-anal contact; Odds Ratio (adjusted for no. of receptive anal sex contacts): insertive - 1.11; receptive - 0.61 receptive with ejaculation - 0.83 swallowing - 0.72		

Table A – Cohorts continued

Number	From ® To	Cohort/ City/ Country	Sexual Factors	Testing Factors	Other factors
A8	M → M	Denmark	Neither receptive nor insertive significant association; Relative risk with freq. Of receptive oral sex: none – 1.0; seldom - 0.6; moderate - 0.9; frequent - 0.8		
A9	M → F (1987) F → M (1991)	HIV testing sites throughout California	No association with oral sex shown in 1987 findings - RR 1.2, p not sig.; no mention of oral sex in 1991 findings.		
A10	M → M	San Francisco City Clinic	No cases of oral sex only; Univariate RR with a steady partner: insertive - 2.9, receptive - 2.1; with a non-steady partner: insertive - 2.0, receptive - 3.1; Multivariate - not significant.		
A11	M → M	MACS	No oral sex only in sero-converters; No HIV in 147 who had oral sex only.		
A12	M → M	Vancouver Lymphadeno-pathy - AIDS study	Neither oral sex nor ingestion of sperm associated with seroconversion.	6 monthly tests	
A13	M → M	San Francisco's Men's Health Study	No increase in seroconversion associated with oral sex; HIV positive in those who have oral sex - 41/171; and in those do not - 8/44; RR = 1.0 (p = 0.97)	6 monthly tests	
A14	M → M	Amsterdam AIDS study	Oral sex not significant; No risk information or p-value given.		
A15	M → M	New York City	Oral sex not mentioned as a significant risk.		
A16	M → M	Manhatten, NYC	ROI, IOI & IOA all associated with less serconverisions. ROA associated with more seroconversions, but p=0.1. Overall no statistically significant association found with either oro-genital or oro-anal contact and seroconversions (1.2% per month).		RAI and number of partners were the main risk factors.
A17	M → M	San Francisco – Options Study	8 of 102 only oral sex or protected anal sex, Recent seroconvertors		

Table B - Case Control and Cross-sectional Studies

Number	From ® To	Cohort/ City/ Country	Sexual Factors	Testing Factors	Other factors
B1	M → M	Cases from 3 San Francisco cohorts: Men's Health; City Clinic; and General Hospital	Receptive oral sex important but not significant; appeared more important than insertive anal sex	Men's Health - 7 months City Clinic - 18 months General Hospital - 14 months	Issues with the regression models used.
B2	M → M	Cases from MACS (Chicago) and Coping & Change Study (CCS)	Univariate: receptive oral sex associated in the later time period; but this disappears in the multivariate analysis.	6 monthly testing	Receptive anal sex the main issue; non-condom use and drug use also important.
B3	M → M	Cases from Amsterdam; San Francisco - Men's Health & General Hospital; Vancouver; Sydney	Univariate: receptive oral sex OR 1.05 and remains after adjusting for no. of receptive anal sex contacts (although p=0.06); Multivariate: not clear from the paper.	<2 years between last negative and first positive	
B4	M → M	Cases from San Francisco – AIDS surveillance data	No association with oral sex (or oro-anal)	Not stated	
B5	M → M	Cross-sectional study from GP and dermato-venereologist attenders in Paris/ France	Univariate analyses - no association between HIV seropositivity and oro-genital or oro-anal sex.	45 sero-positive and 201 sero-negative.	
B6	M → M	Cross-sectional study of male homosexual GUM clinic attenders in West London.	No evidence of an association between seropositivity and oro-genital or oro-anal contact.		
B7	M → M	Case control study. Cases - KS & PCP patients on file. Controls - matched friends and clinic attenders in New York City, San Francisco, Atlanta and Los Angeles.	IAI occurred among 78% of cases and 62-64% of controls. ROI occurred among 98% of cases and 99-100% of controls. No statistical comparisons were made.	Before HIV testing available.	
B8	M → M	Case control study. Cases - KS patients. Controls - patients from medical records of gay male clinic population.	Univariate - ROI RR 1.5 (p=0.01); with swallowing RR 1.9 (0.003); IOI RR 1.3 (p=0.05). Multivariate - none of these remained significant.	Before HIV testing available.	

Table B - Case Control and Cross-sectional Studies continued

Number	From ® To	Cohort/ City/ Country	Sexual Factors	Testing Factors	Other factors
B9	M → M	Case control study. Cases - KS & opportunistic infection patients. Controls - symptom free referrals at a clinic in Texas.	No significant association found between oro-genital or oro-anal contact and seropositivity.	Before HIV testing available.	Smoking, marijuana use, nitrite use, bath house use, prior syphilis, fist-rectal sex, all associated with cases.
B10	M → M	Cross-sectional study. Men attending a health centre in Boston.	No significant association between sero-positivity and oro-genital or oro-anal contact.		
B11	M → M	Cross-sectional study of partners of AIDS cases in San Francisco.	ROI OR 2.1 (CI 0.8-5.6) but not statistically significant.		
B12	M → M	Nested case control study in the Sydney AIDS Project (gay men from general practice and out-patient departments).	7 men denied RAI within the last 6 months: 3 IAI, 1 RAI in last 8 months, 1 fisting, 1 NSU & ano-genital herpes and 1 no other risk factor identified. No significant association between oro-genital or oro-anal contact, but ROA RR 2.1 (p=0.07).	6 monthly testing. 55 seroconverted.	
B13	M → F F → M	Cross-sectional survey of sexual partners of AIDS patients (who acquired their HIV from blood product receipt)	No statistical information given and small numbers involved. Fellatio & cunnilingus were reported with similar frequencies between seropositives and seronegatives.		

Table C - Case Reports

Number	From ® To	Country (City)	Sexual Factors	Testing Factors	Other factors
C1	M → M	UK (Glasgow)	Oral sex only - receptive with known positive; never had anal sex		
C2	F → M	US (Burlington)	Oral sex with prostitute; wife regular partner	No previous negative; wife negative	
C3	F → M	Italy (Bari)	Oral sex with occasional partner; regular partner neg.		Possible seroconversion illness after exposure
C4	M → M	UK (London)	No anal sex for 8 years; oral sex with casual contact - receptive		Possible seroconversion; transmission of gonorrhoea
C5	M → M	US (Atlanta)	Oral sex with a positive partner plus deep kissing and protected anal sex. ; receptive and without ejaculation No other contacts for at least one month preceding this one.	Testing revealed seroconversion	Confirmed seroconversion illness one month after contact.
C6	M → M M → M	UK (London) UK (London)	Protected anal sex; regular oral sex with multiple partners with ejaculation. Protected anal sex; regular oral sex with multiple partners with ejaculation.	Negative in 1987 Positive in 1989 Negative in 1987 Positive in 1990	Allergies Allergies
C7	M → F M → F	Italy (Rome) Italy (Rome)	Oral sex only with positive partner Oral sex only	Negative in Feb 1989 Positive in Aug 1989	Possible seroconversion illness in May 1989; 'lesions' on penis
C8	M → M	UK (Durham)	Oral sex only for 7 months		Possible seroconversion illness; receiving chemotherapy for lymphoma
C9	M → M M → M	Sweden (Stockholm) Sweden (Stockholm)	8 partners: 2 protected anal sex, otherwise oral sex (insertive and receptive) Insertive oral sex only; Oct 1994 bitten during oral sex with anonymous partner. No anal sex for 5 years.	Negative in 1989 Positive in 1993 Negative in Mar 1993 Positive in Dec 1994	
C10	M → M	US (Washington)	Between negative and positive: 20 oral sex partners without ejaculation (but pre-ejaculatory fluid) and one partner protected anal sex infrequently	Negative in Jun 1996 Seroconversion in Sept 1996	Confirmed seroconversion illness; oral surgery in June 1996 (resumed sex shortly after)

Table E - Female-to-Female Transmission

Number	Study type/ sample	Country/ City	Sexual factors	Testing Factors	Other Factors
E1	Case report	New York City/ USA	Oral and digital vaginal contact; oro-anal contact; during menses; traumatic bleeding;	No previous negative test stated; unwell 4-6 weeks after starting relationship with IVDU - status unknown.	2 low risk heterosexual contacts (one negative); plus protected sex with bisexual man.
E2	Case report	Philippines	Oro-genital contact only; no heterosexual contact.	No previous negative test stated.	No IVDU; no blood transfusion.
E3	Case report	New York City/ USA	Homosexual female. No male partners with risk factors.	No previous negative test stated.	No IVDU; blood transfusion, but after symptoms began.
E4	Case report	New York City/ USA	Oro-genital contact only with women since 1980 (1 IVDU).	No previous negative; HIV positive test 1988.	
E5	Surveillance data 1980-91	USA	Women who only have sex with women (164)	AIDS cases	152 IVDUs; 12 blood transfusion recipient
E6	Surveillance data 1980-89	USA	Women who only have sex with women (79)	AIDS cases	95% IVDUs; 5% blood transfusion recipient
E7	Special surveillance project	USA - 9 States	Of women with HIV/AIDS (1122): 55 bisexual; 10 homosexual - 8 IVDUs, 1 blood transfusion recipient, 1 unknown		
E8	Sero-prevalence, behaviour and attitudes survey (snowball sample)	Italy/ Turin	181 lesbians	11 HIV positive (10 IVDU)	multivariate analysis - HIV associated with IVDU and bisexual behaviour
E9	HIV testers at STD and women's health clinics between 1989-91	USA	women who have sex with women (since 1978) = 511 470 bisexual and 41 lesbian	13 bisexuals HIV positive; no lesbian HIV positive	
E10	960,000 female blood donors	USA	None of positives exclusively female-to-female	144 HIV positive	106 interviewed

Number	Study type/ sample	Country/ City	Sexual factors	Testing Factors	Other Factors
E11	28 HIV discordant lesbian couples (1998)	Italy	Wide variety of sexual behaviour - mutual masturbation (14%), oro-genital (12.6) and oro-anal contact (10%), digital anal (9%), sex toys (4%) and sex during menses (1%).	10 infected partners - no transmission	
E12	Lesbians from: national magazine readership (162 - 42% response rate) and OP clinic attenders (101)	New York City clinic and USA magazine	Magazine lesbian reader; clinic attenders - women who have sexual contact with women.	76 of magazine readers have tested for HIV - 4 HIV positive; 101 of OP attenders agreed to testing - 13 HIV positive	Positive readers: all were IVDUs +/- sex with male IVDUs; Positive attenders 12 IVDUs, 1 sex with male IVDU
E13	Summary of 2 studies at 1994: discordant lesbian couples (E11) and lesbians in Turin (E8)	Italy	Despite theoretically high risk sexual activity, no risk of transmission found through lesbian sex, but larger samples needed.		Comment from E14: 40% probability of not finding no transmission
E15	Case report	Spain	Female homosexual, described herself as an active sexual partner; never had heterosexual contact.	HIV positive	No history of IVDU or blood transfusion.
E16	Case report	Sweden	Female homosexual; sex during menses.	Partner probably positive but not tested; case seroconversion confirmed.	Assistance at road traffic accident.
E17	Case report	Boston/ USA	Female homosexual; oral and digital genital contact; shared vibrator; sex with low risk males 10 years previously	HIV positive partner	Refer to 4 other reports associated with sex between women; 2 who had HIV positive female partners and sex with low risk males.

Table F - Summary of cases reported to CDSC with oral sex as probable/possible route of transmission

Year of report (date diagnosed**)**	**Gender**	**Previous negative**	**Seroconversion illness**	**Published**	**Probable route**	**Possible route - with reservations**
1988	M→M	n/k	n/k	Lancet 1988; (ii):1363		
1989	M→M	1987	n/k	Lancet 1992; 339:627	allergic pharyngitis	
1990 (Oct 1990)	M→M	1987	Yes	Lancet 1992; 339:627	allergic pharyngitis	
1991 (March 1991)	M→M	No	3 wks after episode (Seroconversion documented on blood)	Lancet 1991; 338:830	Yes	
1993 (July 1993)	M→M	Nov 1992	Sero-converting spec July 93	Int J STD + AIDS 1995;6:50-1	Yes	
1994 – 1998	M → M 6 F → M 1 M → F 1		4 possible	Case reports to CDSC only, not published.	1 bleeding disorder 1 mouth abscess	In 2 clinician not convinced.

Appendix A - Cohort Studies

Cases of sero-conversions in participants of cohort studies have been reported where the only risk admitted was oro-genital contact.

A1. **Rozenbaum W. et al** - HIV transmission by oral sex. Lancet 1988; (i):1395.

French Cohort Study of initially sero-negative homosexual men: 5 seroconverted who denied anal sex or other risk factors for at least 3 months prior to seroconversion. Since previous negative test all 5 closely questioned about sexual practice - all 5 insertive fellatio, 3/5 receptive, 3/5 deep kissing 2/5 swallowing sperm.

Following this Lancet report the following correspondence appeared:
Dassey D.E. HIV and Oro-genital transmission. Lancet 1988; (ii):1023. Raises subject of longer seroconversion interval than 3 months, especially question the 2/5 who only took part in insertive fellatio (i.e. not receptive).
Detels R. - Lancet 1988 (ii) 1023
Long seroconversion interval possibilities
Reply to these:
Rozenbaum W.. - Lancet 1988 (ii) 1023
In 5 cases last anal intercourse before first positive test was six months; 3yrs; 10yrs and two had never had anal intercourse.'

A2. **Lifson A.R. et al** - HIV seroconversion in two homosexual men after receptive oral intercourse with ejaculation. American Journal of Public Health 1990: 80; 1509-11.

San Francisco Cohort of homosexual men - Two case reports in men who had reported no anal intercourse for greater than 5 years but both prior to their positive HIV test had multiple episodes of oral intercourse with ejaculation including some with known HIV positive persons. Both had previous negative tests (antibody negative, antigen negative and PCR negative). Both had "gingival recession" but no other significant oral pathology. Oral insertive and receptive for both; one also oro-anal.

A3. **Keet I.P.M. et al** - Oro-genital sex and the transmission of HIV among homosexual men. AIDS 1992; 6: 223-6.

Amsterdam Cohort Study - 102 with known date of seroconversion. Receptive anal intercourse in 6-9 months before seroconversion denied by 20 seroconvertors in their written questionnaires, but in face to face interviews 11 later reported this, i.e. 9/102 study participants for whom HIV sero-conversion dates were known admitted only oro-genital sex as the exposure for HIV. Only 4 of the 9 had not had IAI in the preceding 6 months.

A4. **Grutzmoler S. et al** - HIV transmission in gay men in Stockholm 1990-92. Six cases of HIV infection through oral sex. 1993 International Conference on AIDS, Berlin.

Of 28 known sero-conversions 6 were presumed infected through oral sex. All were questioned by a clinician and counsellor independently. The authors conclude that unprotected receptive oral sex may play a relatively more important role as a route of infection as unprotected anal intercourse becomes less frequent.

A5 **Schacker T. et al** - Clinical and epidemiologic features of primary HIV infection. Ann Int Med 1996; 125 (4): 257-264.

Cohort of 46 sero-converters (43 men + 3 women). 4 patients had only reported oral-genital contact during lead up to HIV infection, all had to be negative within 12 months before and documented retroviral syndrome.

Protected	1607 episodes of oral intercourse	36%
	711 " anal intercourse	42%

Unprotected oral most commonly reported activity but no control group so no odds ratio. Odds ratio adjusted for number of RAI contacts was not significant, for oral-genital or oro-anal contact.

A6 **Detels R. et al** - Seroconversion, sexual activity, and condom use among 2915 HIV sero-negative men followed up for two years. J AIDS;1989:2:77-83

2915 sero-negative homo/bi-sexual men (MACS) - 6 months testing 8% (232) seroconverted over 24 months.
Two men no ano-genital intercourse (one ano-genital contact about 12 months previously; other - receptive oral intercourse with ejaculation).

A7 **Coates R.A. et al** - Risk factors for HIV infection in male sexual contacts of men with AIDS or an AIDS-related condition. Am J Epi;1988:128:4:729-739

246 healthy male sexual contacts of men with AIDS (127) or an AIDS Related Complex (ARC) (122): 102 - negative; 144 - positive. Oral sex odds ratio below one for univariate analysis. No multivariate analysis with those who do have ano-genital intercourse.

A8 **Melbye M et al** - Sero-epidemiology of HTLV-III antibody in Danish homosexual men: prevalence, transmission, and disease outcome. BMJ;1984:289:573-575

250 Danish homosexual men, sera in Dec. '81 showed antibody in 22 (8.8%), followed until Feb. '83 5 sero-conversions. Receptive AI important but not ROI, IOI nor in this study IAI.

A9 **Padian N.S. et al** - Male-to-female (JAMA;1987:258:6:788-790) and female-to-male (JAMA;1991 :266:12:1664-67) transmission of HIV.

1987 - 97 female partners of 93 infected males (23% infected), no association with oral intercourse.
1991 - 379 couples - 72 male partners of infected female (1%)
- 307 female partners infected male (20%)
No mention of oral sex risk in 1991 follow-up.

A10 **Darrow W.W. et al** - Risk factors for HIV infections in homosexual men. Am J. Public Health; April, 1987:77:4:479-483

Cohort of homosexual men (used in Hep B studies) re-contacted for HIV seroconversion study to compare risk factors seroconvertors vs sero-negative of 785 randomly selected - 492 located and enrolled - 240 HIV +ve + 119 sero-negative. No cases of only oral intercourse, oral intercourse not a significant factor in multivariate analysis. Four cases who did not have RAI but did have IAI, ROI and IOI

A11 **Kingsley L.A. et al** - Risk factors for seroconversion to HIV among male homosexuals. Lancet;Feb.14,1987:345-8

(MACS Cohort) 2507 homosexual men, sero-negative for HIV at enrolment were followed for 6 months.
95 seroconverted - 9 did not have RAI in last six months
- 3 of whom did not have RAI in preceding year but all 3 practised IAI
No HIV seroconversions occurred in the 220 men who did not practice RAI or IAI in 6 months preceding and during study (147 of these practised IOI or ROI only and none seroconverted).

A12 **Schechter M.T. et al** - Can HTLV-III be transmitted orally? Lancet;Feb.15,1986:379

Cohort of 700 homosexual men attending GPs in Vancouver - 6 monthly questionnaire, bloods including HIV, and physical examination, 21 individuals selected who had no RAI or Receptive fisting in year before or after enrolment and were HIV-ve at enrolment.
→20 IOI + 21 ROI (5 swallowed semen)
→10 IOA + 16 ROA (oroanal contact)
→16 IAI + 2 insertive fisting
One man seroconverted, he did have IAI, he rarely had ROI or ROA + did not swallow semen .i.e. 36 our of 99 initially sero-negative, who seroconverted all had RAI.

Schechter M.T. et al - The Vancouver lymphadenopathy - AIDS study: 6. HIV seroconversion in a cohort of homosexual men. Can. Med Assoc J;1986;135:1355-60.

(82 - 85) (same study cohort as above - Vancouver cohort) - 345 HIV-ve at enrolment Nov'82; 66 seroconverted by Oct'85. Neither oral sexual activity nor oral ingestion of semen related to seroconversion..

Soskolne et al /Schechter et al - Correspondence following cohort study A12 above. CMAJ;1987:137:474-80. Criticised power of the study to show oral sex as a risk. Recalculation shows that Relative Risk needed to be at least 1.85 to be significant. Soskolne says that even a small RR with a highly prevalent sexual practice such as oral sex could result in a substantial population attributable risk. Authors in reply state the consistency of other studies in showing lack of risk of oral sex for HIV seroconversion.

A13 **Winkelstein W. et al** - Sexual practices and risk of infection by HIV. JAMA;Jan.16,1987:257:3:321-5.

San Francisco Men's Health Study 25-54 yr. - prospective cohort 1034 single men (multistage probability sampling) at entry June'84 - Jan'85, 48.5% HIV +ve. Orogenital contact evaluated in those (215) who either report no ano-genital contact or IAI only in last 2 years, no increased risk of orogenital contact on HIV seropositivity,71 of 215 surveyed (data obtained on 64) 14 HIV +ve and 50 HIV -ve all fourteen HIV +ve gave a history of receptive ano-genital contact prior to two years previously.

Lyman D. et al - Minimal risk of transmission of AIDS associated retrovirus infection by oral-genital contact. JAMA;1986:255:13:1703.

Same study as above, at this stage 821 - of whom 48.4% +ve, 56 only orogenital contact in last 2 years and only 11 of these HIV+ve but likelihood of all 11 being infected prior to entry to the study.

A14 **Van Griensven G.J.P. et al** - Risk factors and prevalence of HIV antibodies in homosexual men in the Netherlands. Am J Epi;1987:125;1048-57.

Prospective study of AIDS in Amsterdam blood from 741 healthy homosexual men with multiple partners between Oct'84 + May'85, 233 (31%) HIV +ve. In this study orogenital sex not found to be significant.

A15 **Dean L. & Meyer I.** - HIV sero-prevalence and sexual behaviour in a cohort of New York City gay men (aged 18-24). J AIDS & Human Retrovirology;1995:8:208-211.

Cohort of New York City gay men aged 18-24 without a diagnosis of AIDS.
At start - 8/87 HIV positive
At 1 year - 1/57 HIV positive
HIV positive and unprotected anal intercourse: Odds ratio 2.56 (1-6)
Prevalence 40% in blacks, 30% Latinos and 2% white and other ethnic groups (not explained by other risk factors). No mention of oral sex risk.
Sexual behaviour - 91% unprotected receptive oral intercourse (almost all engaging in unprotected oral intercourse - 37% unprotected receptive anal intercourse.

A16 **Goedert J.J. et al** - Determinants of retrovirus (HTLV-III) antibody and immunodeficiency conditions in homosexual men. Lancet 1984; 29:711-6.

A cohort of homosexual men at high risk of AIDS. All patients entering a private clinic in Manhattan during 4 days of 1982. 67 were followed up. Seroconversion was 1.2% per month. In sero-positives, AIDS developed at 6.9% per year. Risk factors found were large numbers of homosexual partners and receptive anal intercourse.

Direct association with seropositivity	activity	p-value
↓	ROI	0.5
↓	IOI	0.1
↑	receptive oroanal	0.1
↓	insertive oroanal	0.2

A17 **Dillon B et al** – Primary HIV infection associated with oral transmission – The Options Project UCSF.

102 recent MSM seroconvertors recruited. Interviewed and risk assessed for the 6 month period prior to patient seroconversion.

Risk – unprotected RAI 69
" IAI 14
possible oral sex 19 – further interviews:
8 probably not oral
3 insufficient follow-up
8 oral sex

8 probable oral - further details
1 oral sex only - partner corroboration
1 oral sex only - no partner corroboration
4 protected anal - no partner corroboration
2 unprotected anal with documented negative partner

Poster presentation at Seventh Conference on Retroviruses & Opportunistic Infections, Chicago. Jan 2000 San Francisco.

Appendix B - Case Control and Cross-sectional Studies

B1 **Samuel M.C. et al** - Factors associated with HIV seroconversion in homosexual men in three San Francisco cohort studies. J AIDS;1993:6:303-312

Nested case control study:

- confirm RA1 is major risk factor and use of an enema/douche was the only other variable independently associated with infection.
- brought together 3 San Francisco cohorts which have followed a total of 1393 initially sero-negative homosexual men from 1/1/84 to 31/12/89.
- looked at the 83 seroconversions in these 6 years and took 3 continuing negative controls for each sero-converter.

Twenty-one of the seroconversions reported no RAI in the two time periods before seroconversion and six reported neither RAI nor IAI (two time periods need to be included since RAI or IAI just before the last negative test could have resulted in seroconversion and hence the sexual practice before the last negative needs to be taken into account). Multivariate logistic regression was difficult and could not be applied in a straightforward manner. In addition the small numbers made testing for statistical interaction not possible in the conventional way. The modelling therefore is open to debate. After RAI, ROI was shown to be the next most significant risk factor but did not reach statistical significance (p=0.5). If IAI and IOI are excluded from the model and only RAI and ROI included then ROI does become significant if only one time period is included. If two time periods are used the ROI does not reach statistical significance in the model, (p=0.07) when IAI and IOI are excluded.

Conclusion
Well constructed study, high powered analysis, but suffers from relatively small numbers of sero-converters in this prospective study and even smaller numbers where RAI was not undertaken.
Suggestion that ROI may be significant but by no means conclusively shown by this study.

B2 **Ostrow D.G. et al** - A case-control study of HIV type 1 seroconversion and risk-related behaviours in the Chicago MACS/CCS cohort, 1984-1992. Am J of Epi;1995:142:8: 875-883.

76 seroconvertors in the Chicago Illinois component of the MACS (Multi-centre AIDS Cohort Study)/CCS (Coping and Change Study) of homo/bi-sexual men between 1984-92. Five controls for each case comparing 84-88 and 89-92.

Univariate analysis
Seroconversion - strong association with RAI getting weaker over time, due to lower levels of RAI.
Seroconversion - stronger later period association with ROI and IAI but this disappears on multivariate analysis.

Multivariate analysis
Neither ROI nor IAI have replaced unprotected RAI as an important risk behaviour in HIV transmission. Non condom use and recreational drug use (poppers and cocaine) remained risk factors, but after multivariate analysis there was no increased risk of ROI.

B3 **Page-Shafer K. et al** - Sexual risk behaviour and risk factors for HIV-1 seroconversion in homosexual men participating in the tricontinental sero-converters study, 1982-1994. Am J of Epi: 1997:146:7:531-542.

5 cohort studies at 4 sites Amsterdam, San Francisco, Vancouver, Sydney.
3 time periods looked at 82-84, 85-87, 88-94. 345 sero-converters matched with 345 controls. Cases were significantly associated with multiple RA1 partners, and also with number of ROI partners. The analysis using number of partners collapsed into 0, 1, 2-9, $\geq$10 also showed that risk increased for both RAI and ROI. Risk was also increased with having had any STD and amphetamine use. In the uninvariate model risk associated ROI was compared with men who reported no RAI (113 cases) or only one RAI partner (72 cases). The odds ratio for ROI (per partner) was 1.05 and did not alter when controlling for number of RAI partners (none or one) but these values did not quite reach conventional levels of statistical significance (p=0.06). The section covering ROI in the multivariate conditional logistic model is short and not at all comprehensive and it is not clear if the risks of ROI disappeared in the multiple logistic model. The authors accept that the risk associated with ROI may be over estimated if RAI is under reported but give various reasons why they feel this is unlikely. This is probably one of the most important papers showing ROI risk but it is a great pity that the multivariate logistic analysis is so poorly done and written up within the paper.

B4 **Moss A.R. et al** - Risk factors for AIDS and HIV seropositivity in homosexual men. Am J Epi;1987:125:6:1035-47

cases - AIDS diagnosed between 1983-84 in SF 138 of 294 incident cases.
(remainder too ill, died, refused, not located; selection bias may have resulted from this)

(homosexual men aged 18 or more).

Controls - randomly selected homosexual man as neighbourhood control
- homosexual man as a STD clinic control.

No evidence for oral-genital, or oral anal transmission therefore suggest this transmission is low.

B5 **Messiah A. et al** - Factors correlated with homosexually acquired human immunodeficiency virus infection in the era of 'safer sex': was the prevention message clear and well understood? Sexually Transmitted Diseases 1993; 20 (1): 51-8.

Cross-sectional survey of 246 homo/ bisexual men attending GPs or dermato-venereologists involved in HIV prevention. (Excluding those with known HIV.) Self-administered questionnaire with emphasis on the frequency of those practices (in the preceding year) corresponding to safer sex recommendations, and HIV testing. After adjusting for the no. of partners and no. of unprotected RAI, neither genito-oral nor oro-anal practices were significantly (5% threshold) correlated with HIV sero-positivity in univariate analyses.

B6 **Evans B.A. et al** - Sexual lifestyle and clinical findings related to HTLV-III/LAV status in homosexual men. Genitourinary Medicine 1986; 62: 384-9.

Cross-sectional questionnaire survey of 304 homosexual men who attended a GUM clinic in West London during 6 months from Nov 1984 to May 1985. Also included physical examination and serology. There was no evidence that sero-positivity was associated with oro-genital or oro-anal contact.

B7 **Jaffe H.W. et al** - National case-control study of Kaposi's sarcoma and Pneumocystis carinii pneumonia in homosexual men: part 1, epidemiologic results. Ann. Int. Med. 1983; 99: 145-51.

As part of CDC surveillance - a case file of KS and PCP was established in June 1981. By Oct 1981, 70 cases had been recorded from New York, Atlanta, Los Angeles and San Francisco. 50 men were available to participate in this study. Controls were recruited from clinics (private and other) and friend of cases, and then matched for age race and metropolitan area of residence. Cases were more likely to have reported insertive rimming than controls during the year before the onset of illness. The differences were small between cases and controls in the frequency of having receptive oral intercourse.

	cases (50)	other clinic controls (79)	private clinic controls (42)
insertive anal intercourse	78%	64%	62%
receptive oral intercourse	98%	99%	100%

B8 **Marmor M. et al** - Kaposi's sarcoma in homosexual men - a sero-epidemiologic case-control study. Ann. Int. Med. 1984; 100: 809-815.

Cases were 20 of the first 21 patients diagnosed with KS in homosexual men aged 52 or less between March 1979 and August 1981 at a New York City Medical Centre. Two controls were identified for each case, age and race matched, randomly selected from the medical records of an internist with a homosexual population. Face to face interviews and blood tests were undertaken.

		RR		p-value
Receptive oral intercourse (ROI)		1.5		0.01
ROI plus swallowing semen	1.9		0.003	
insertive oral intercourse		1.3		0.05

None of the above remained significant in a stepwise linear multiple regression model.

B9 **Newell G.R. et al** - Risk factor analysis among men referred for possible acquired immune deficiency syndrome. Preventative Medicine 1985; 14: 81-91.

A lifestyle questionnaire was administered to 13 KS and 18 opportunistic infection patients. Controls were symptom free referrals. (Some controls would become cases in the future.) No association was found with oral sex. Associations were found for:

cigarette use	OR 3.4
marijuana	OR 3.7
nitrite use	OR 5.5
bathhouse use	OR 7.6
prior syphilis	OR 3.4
fist-rectal	OR 3.5

B10 **McCusker J. et al** - Behavioural risk factors of HIV infection among homosexual men, Boston community health centre. Am J. Public Health 1988; 78: 68-71.

Cross-sectional study - 290 men recruited from Jan 1985 to April 1986 from men who visited the health centre in Boston during the previous 6 months. Inclusion criteria: recent homosexual activity and no diagnosis of AIDS or similar syndrome. Self-administered questionnaire, physical examination, full blood count and HIV antibody test.

			OR
Univariate - not significant	ROI	< 1 month ago	4.57

		>= 1 month ago	6.33	
	IOI	< 1 month ago		3.75
		>= 1 month ago	5.92	
	oro-anal (insertive) ever			1.53
Multivariate - not significant	ROI	OR 1.07 (0.75-1.53)		
	IOI	OR 1.19 (0.82-1.73)		
	IOA	OR 0.88 (0.71-1.09)		

B11 **Osmond D. et al** - Time of exposure and risk of HIV infection in homosexual partners of men with AIDS. Am J. Public Health 1988; 78: 944-8.

117 partners of cases of AIDS (at least 10 sexual contacts with AIDS cases within 24 months of the cases diagnosis). Interviewed and serology.
ROI with some or all partners OR 2.1 (0.8-5.6) (after controlling in multivariate analysis for the number of RAI partners and RAI with the case up to the date of diagnosis). The authors suggest an independent association after multivariate analysis but do not present the statistical findings.

B12 **Burcham J.L. et al** - Incidence and risk factors for human immunodeficiency virus sero-conversion in a cohort of Sydney homosexual men. Med. J. Aust. 1989; 150: 634-9.

Nested case-control within Sydney AIDS Project - prospective cohort of homosexual men recruited through general practice and hospital out-patient departments. Reassessed every 6 months with questionnaire, physical examination and blood tests. 643 were initially sero-negative and 415 sero-positive. 588 remained sero-negative (including those lost to follow up) and 55 sero-converted. Of the men that sero-converted, 7 denied RAI in the previous 6 months - 3 admitted IAI, and 1 RAI within 8 months, 1 fisting, 1 recent NSU and ano-genital herpes, and 1 none.

	RR	p-value
IOI	0.8	0.74
ROI	0.9	0.9
IOA	1.2	0.76
ROA	2.1	0.07

B13 **Peterman T.A. et al** - Risk of human immunodeficiency virus transmission from heterosexual adults with transfusion associated infections. JAMA 1988; 259: 55-8.

Adults patients reported to CDC with only blood product receipt as a risk factor. 80 spouses (with sexual contact) and 63 family members (without sexual contact) were interviewed and had blood test. For those with sexual contact: fellatio cunnilingus

husbands	HIV +ve	1		0	
	HIV -ve		6		4
wives	HIV +ve	2		2	
	HIV -ve		11		12

Described similar frequencies of oral sex among positive and negative partners. No statistical information given.

B14 **Senterfitt J.W. et al** - Study of acute and early infections yields surprising risk profile. Fifth Conference on Retroviruses and Opportunistic Infections. Chicago, February 1998 [abstract 141]

Interviews on risk behaviour following HIV diagnosis. Aim to characterise the risk contacts associated with cases of acute primary or early stages of HIV-1 infection. 30 subjects were recruited, of whom 4 probably acquired their infection through ROI (all homosexual/bisexual men).

Appendix C - Case Reports

C1 **Goldberg D.J. et al** - HIV and orogenital transmission. Lancet 1988; (ii):1363.
U.K./Canada case: Male-to-male. Only orogenital sex practised. Sex with Canadian who after oral sex told partner of HIV seropositivity.

C2 **Spitzer P.G. et al** - Transmission of HIV infection from a woman to a man by oral sex. N Eng J. Med 1989; 320:251.
United States case: Female-to-male. 60 year old male. Single contact with prostitute -oral sex only. HIV status of prostitute not known but was seen to inject drugs. Wife negative. Prostitute contact was only other sexual contact. (No corroboration of fact that prostitute was HIV positive and no previous negative test.)

C3 **Quarto M. et al** - HIV transmission by fellatio. Europ J. Epi 1990;339-340.
Italian case: female-to-male following single oral exposure. Clinical seroconversion illness one month after fellatio with occasional sexual partner -(this woman's sero-status not known). Regular female sexual partner HIV sero-negative.

C4 **Murray A.B. et al** - Coincident acquisition of Neisseria gonorrhoea and HIV from fellatio. Lancet 1991; 338:830.'
U.K. case (St. Bartholomew's): Male-to-male. Documented (by bloods) seroconversion three to six weeks following contact. No ano-penetrative sex for 8 years. Not an injecting drug user. Gonorrhoea and HIV infection acquired.

C5 **Clifford-Lane H et al** - HIV seroconversion and oral intercourse. Am J. Public Health 1991; 81:658.
Case report: male-to-male. Seroconversion illness and documented seroconversion four weeks after sexual contact. Deep kissing; receptive orogenital contact (unprotected) without ejaculation also receptive anal intercourse with condom use (no evidence of leakage or condom breakage).

C6 **Chen W. et al** - Allergy, oral sex and HIV. Lancet 1992; 339:627-8.
UK Two cases: Male to male. Both had negative tests in 1987, positive in 1989 and 1990. No unprotected anal sex, no recognised condom breakage. Both had history of atopy (hay fever and allergic pharyngitis) regular fellatio with multiple partners including swallowing semen.

C7 **Puro V et al**. - Male to Female transmission of HIV by oro genital sex. Euro J of Clinical Microbial Infectious Diseases 1991; 10: 47.
Italy : Two case reports: male-to-female
15 year old female fellatio with ejaculation with a positive partner. Stopped the relationship and tested negative in February 1989. In May 1989 acute adenopathy and August 1989 tested HIV positive. No other risk factors on questioning.
24 year old female. No negative test but only admitted to fellatio without receiving sperm. Known HIV positive partner.

C8 **Edwards S.K. et al** - HIV seroconversion illness after orogenital contact with successful contact tracing. Int J STD and AIDS 1995;6:50-51.
UK male to male transmission. In preceding 7 months 3 receptive orogenital contacts. Previous to that regular partner. Possible seroconversion illness. Of three contacts, one tested and was positive and felt they were sero-converting at time of contact. The patient was having chemotherapy for Hodgkins Lymphoma at the time of orogenital contact.

C9 **Bratt G.A. et al** - Two cases of oral-to-genital HIV-1 transmission. Int J of STD and AIDS 1997;8:522-525. Sweden - two cases in homosexual men.
a) insertive oral sex only in recent years (no kissing) last negative March'93 (annual test as part of cohort) possible seroconversion in July'93 in June and July only one partner. First +ve in Sept. '93. Partner HIV+ve after contact tracing in Nov'93 and shown to have previous -ve in 1989.

b) in cohort - annual testing last -ve March'93 after oral insertive sex in Oct'94 (which involved biting and drawing blood) attended GUM clinic Dec'94 with friable secreting erosion on glans penis. HIV testing was positive, regular partner negative; few anonymous casual contacts.

C10 **Berrey M.M. et al**- Oral sex and HIV transmission. J AIDS and Human Retrovirology;1997:14:475-477.
Homosexual man HIV-ve June '96 (biannual HIV testing). Later in June uvulopalatoplasty and tonsillectomy for chronic sleep apnoea complicated by two episodes of pharyngeal bleeding in 3 weeks after both requiring cauterisation. After surgery he resumed sexual activity. Early Sept. HIV seroconversion illness.
20 anonymous unprotected ROI partners but not to ejaculation (2 of whom were HIV positive)
One anonymous RAI partner with a condom

Appendix D - Related Papers

D1 **Koopman J.S.** - HIV transmission probabilities for oral and anal sex by stage of infection. Amsterdam - International Conference on AIDS [abstract PoC 4101].
Mathematical modelling which shows only high potential risk of transmission during the seroconversion phase - this is estimated to be much greater than at any other stage of infection. Estimate that ROI has less then one sixth of the risk of RAI. They conclude that primary infection is a more important determinant of transmission risk than is type of sex. (Data on which calculations are based are from the M.A.C.S. study.)

D2 **Vittinghoff E. et al** - Per-contact risk for transmission of HIV associated with 4 types of homosexual contact. Fifth Conference on Retroviruses and Opportunistic Infections. Chicago, 1998 [abstract 140].
Using a modified Bernolli model per contact risk was estimated. The data used for the models was high-risk HIV uninfected gay men in the CDC collaborating HIV sero-incidence study.

unprotected RAI	0.24%
protected RAI	0.10%
unprotected IAI	0.03%
unprotected ROI	0.03%

D3 **Samuel M. et al** - Infectivity of HIV by anal and oral intercourse among gay men: estimates from a prospective study in San Francisco. VIII Int Conf on AIDS 1992; 2: c262 (PoC4104)
Estimations of per partner infectivity of anal and oral receptive intercourse among gay men. Based on the San Francisco Men's Health Study. Per partner infectivity for ROI was about 1 %, and RAI was about 10%. The data suggested that oral intercourse had become a more important risk factor in recent time periods.

D4 **Piazza M. et al** - Passionate kissing and lesions of oral mucosa in anti-HIV positive subjects: possible implication in AIDS transmission. VII Int Conf on AIDS 1991.
Testing for haemoglobin in saliva of HIV+ves after brushing teeth. Anti HIV+ve IDU highest tendency to bleeding and this increased with the severity of HIV related disease.

D5 **Salahuddin S.Z. et al** - HTLV-III in symptom-free sero-negative persons. Lancet 1984:1418-1420.
One woman (partner of transfusion assoc. AIDS) has not had sex for three years since husband was impotent as a result of aneurysm repair. Only had exchange of saliva through kissing but very early case report and no detail of any other sexual practice or other sexual partners.

D6 **Padian N et al** - Transmission of HIV possibly associated with exposure of mucous membranes to contaminated blood. MMWR 1997; 46 (27): 102-5.
Mucous membrane transmission - heterosexual couple (male HIV positive) - deep kissing often after brushing teeth causing bleeding gums, oral sex, protected vaginal intercourse, shared razor and toothbrush on one occasion each (not sure when in relation to seroconversion dates). Woman also had gingivitis. Last negative July 1994. First positive July 1995.

D7 **Landor M. et al** - What is safe sex? Am J Med;1988:84:175
Discussion of possible risk of HIV transmission associated with orthodontic braces not actual case - cut on penis caused by dental brace with possibility of BBV transmission.

D8 **Fischl M.A. et al** - Evaluation of heterosexual partners, children, and household contacts of adults with AIDS. JAMA; 1987:257:640-4.
45 adult AIDS patients, their spouses (who did not have risk factors for HIV), 109 children and 29 household contacts. 4-6 monthly follow-up for 1-3 years. At enrolment 13 spouses HIV +ve, 13 seroconverted during study.
26 - 14 vaginal intercourse only
- 12 vaginal and oral intercourse (of whom 3 had anal intercourse)
Seropositivity related to repeated oral sex, especially in females for receptive oral sex. (Repeated oral sex - twice per month or less than 50% of total sexual activity.) No couples had oral sex only so confounded by vaginal sex. Only three couples used condoms regularly and all were sero-negative.

D9 **Wallace J. et al** - Fellatio is a significant risk activity for acquiring AIDS in New York City street walking sex workers. XI Int Conf on AIDS. Vancouver, July 1996 [abstract TuC2673].
Questionnaire, testing and counselling of street walking sex workers. 31.3% of the sample were HIV positive. 69% smoked crack (which causes gum fissures and ulcerations).

Most prevalent sex act	HIV prevalence
fellatio	34.4% (CF 24.2% of others)

P<0.0001

vaginal intercourse	22.9% (CF 32.7% of others)
never use condoms for:	
vaginal intercourse	24%
fellatio	35%

D10 **Faruque S. et al** - Crack cocaine smoking and oral sores in three inner city neighbourhoods. J. AIDS & Human Retrovirology 1996; 13: 87-92.
Participants were recruited from the streets in inner city neighbourhoods in New York, Miami and San Francisco. They were aged 18-29 years and grouped into current regular crack smokers, and non-smokers. Each participant was interviewed and tested for HIV and syphilis antibodies. 2,323 participants were recruited, of whom 1404 were crack smokers. Of 429 who reported oral sex, those who reported oral sores were more likely to have HIV infection than those who did not, after controlling for other risk factors (adjusted prevalence OR 1.9, CI 1.0-3.6).

D11 **Alcorn K. et al** - Oral sex and HIV transmission. A briefing for HIV workers. (1997)
The Terrence Higgins Trust and National AIDS Manual booklet, briefing for HIV workers on oral sex and HIV transmission. Sums up the current risks well and debates the implications of the health promotion approaches. References used detailed in the AIDS Reference Manual.

D12 **Spencer B.** - Orogenital sex and risk of transmission of HIV. Lancet;1993:341:441.
As a point for debate highlights the fact that just because HIV is found in pre-ejaculatory fluid it does not mean it is a risk in oral sex; and he raises the question whether unprotected anal intercourse will increase, by education that advocates no oral sex.

D13 **Edwards S. et al** - Oral sex and transmission of viral STIs. Sex Transm Inf 1998; 74: 6-10.
Summary of current evidence: biological plausibility; homosexual - male-to-male: in early studies oral sex was obscured by other riskier behaviours e.g. RAI, however behaviour is changing, and cases are being picked up within cohorts; female-to-female: refer to one case report; heterosexual - male-to-female: happens but vaginal sex usually also occurring; female-to-male: refers to 2 case reports.

D14 **Wadsworth J et al** - Sexual Attitudes and Lifestyle. Blackwell 1994.
The National Sexual Attitudes and Lifestyle Survey asked questions relating to the frequency of oral sex within the general population. The table below highlights the results as presented in the above publication.

Sexuality	**Frequency**	**Men**	**Women**
Heterosexual	never	24.8%	30.8%
	in the last week	24.5%	19.9%
	ever	75.2%	69.2%

Homosexual	**Age group (years)**	**Frequency**	**Receptive**	**Insertive**
Males	16-24	ever	68.0%	63.6%
		in last year	34.1%	37.7%
	25-34	ever	71.9%	65.8%
		in last year	35.0%	35.4%
	35-44	ever	44.9%	39.0%
		in last year	9.5%	12.4%
	45-59	ever	49.0%	44.6%
		in last year	16.6%	15.1%
Females			**Passive**	**Active**
	16-24	ever	80.1%	67.8%
		in last year	42.3%	30.0%
	25-34	ever	60.0%	57.7%
		in last year	20.3%	23.4%
	35-44	ever	51.8%	53.7%
		in last year	9.0%	9.0%
	45-59	ever	37.3%	34.7%
		in last year	3.0%	3.0%

D15 **Gruer L.D. et al** - Sexual behaviour and use of condom by men attending gay bars and clubs in Glasgow and Edinburgh. Int J STDs and AIDS;1993:4:95-98.
Sexual behaviour questionnaire of gay men in bars and clubs in Edinburgh and Glasgow. 84% of all respondents had orogenital contact without a condom i.e. very prevalent practice.

D16 **De Vroome E, et al** - Over-estimating the risk of a low risk sexual technique increases or decreases behavioural risk, depending on mediating factors. VIII Int Conf on AIDS (Amsterdam) 1992 Abstract PoD 5125.
Cohort of homosexual men (1989) who had had oro-genital sex and perceived ano-genital sex to be of high risk. 53% perceived oro-genital sex as low risk, and 47% perceived oro-genital sex as high risk. Among those who had sex with a positive partner, over-estimating the risk of oro-genital sex, increased high risk behaviour. Whilst for those in steady relationships, over-estimating the risk, decreased high risk behaviour.

D17 **Hunt A.J. et al** - Changes in condom use by gay men. AIDS Care;1993:5:4:439-448.
Part of Project SIGMA 6 year five phase longitudinal cohort 930 men face to face interviews.

Condom use fellatio:		regulars	casuals
active	- never	90.9	88.1
	- sometimes	8.3	11.3
	- always	0.8	0.6
passive	- never	93.1	89.9
	- sometimes	6.3	9.5
	- always	0.6	0.6

i.e. condom use rare in all fellatio contacts

D18 **Meris RS et al** – Patterns of oral sex among men who have affective and sexual relations with other men in Montreal. 12th Int Conf on AIDS (Geneva 1998) Abstract 23117.
Men who have affective and sexual relationships. Unprotected oral sex with sero-negative partners 93.9% (196); with partners of unknown status 90.9% (186); and with sero-positive partners 87.5% (32)

D19 **Silva S et al** – Unprotected oral sex among men who have sex with men. 12th Int Conf on AIDS (1998 Geneva) Abstract 23142.
Reported condom use for oral sex in men who have sex with men in Brazil: 7% with a regular partner and 11% with a casual partner

D20 **Wahn V. et al** - Horizontal transmission of HIV infection between two siblings. Lancet 1986; 2: 694.
Transmission between siblings. Index case acquired HIV through blood transfusion. Only risk identified between children was a possible bite from the index case, where there was no bleeding or haematoma at the time.

D21 **Anon** - Transmission of HIV by human bite. Lancet 1987; 2: 522.
26 year old health care worker (HCW). Last negative in 1983. Since then 3 partners - 2 HIV negative and 1 one-night stand. Sister - HIV positive IVDU. In 1985 involved in fight with sister where some of sister's teeth were knocked out and resulted in bleeding. Then sister bit HCW on the leg. HCW became positive. Probable route of transmission through bite.

D22 **Vidmar L. et al** - Transmission of HIV-1 by human bite. Lancet 1996; 347: 1762-3.
Index case homosexual man with AIDS. Sought help from neighbour whilst fitting (grand mal seizure). Neighbour was bitten whilst trying to maintain an airway. Neighbour seroconverted (documented) and had no other risk factors.

Appendix E - Female to Female Transmission

E1 **Marmor et al** - Possible female to female transmission of HIV. Ann Int Med 1986;105: 969
Case report. Oral and digital vaginal contact and oroanal contact during menses plus traumatic bleeding.
Oct. '82 - unwell 4-6 weeks after initiation of relationship with parenteral drug abuser.
Aug. '84 - one night protected intercourse with bisexual man
Dec. '84 - HIV +ve
Other sexual contacts from'77 - 85': one woman not IDU; two hetero men without AIDS risk factor - one -ve.

E2 **Monzon et al** – Female to female transmission of HIV. Lancet 1987:ii;40-41
Case report. Philippine dancer. Tested for HIV on entering Mediterranean country Nov.'86.
Feb.'87 unwell - TB plus entamoeba coli cysts in stool.
Before '81 regular female partner; 81-83 many women of different nationalities - orogenital contact; 83 re-established relationship with previous partner.
No heterosexual/IDU/blood transfusion admitted.

E3 **Sabatini MT et al** – KS and T cell Lymphoma in an immunodeficient woman: a case report. AIDS Res:1984; 1 (2): 135-7
AIDS death in homosexual female 37 year old with no risk factors for AIDS: not an IVDU, no male partners with AIDS or IDU or Haitian in origin. She did have a blood transfusion but had some symptoms prior to the transfusion. She died of lymphoma and KS.

E4 **Perry S et al** - Orogenital transmission of HIV. Ann Int Med 1989; III:951-2.
HIV positive woman, since 1980 only orogenital contact with other women (one of whom was an IDU) no sero-negative test. Presumed female to female transmission.

E5 **Chu SY et al** Update: epidemiology of reported AIDS cases in women who report sex only with other women United States 1980-91. AIDS 1992; 6:518-9.
Two women initially reported as having had sex with other women only. After follow up both reported as bisexual: one had sex with a male injecting drug user and one with a bisexual man.
At 30 June 1991, 164 women with AIDS who reported sexual contact only with other women:

Injecting drug users	152
Had received blood prior to 1985	12
Total	**164**

This was an update of an earlier assessment of AIDS in lesbians in United States (see below).

E6 **Chu SY et al** – Epidemiology of Reported Cases of AIDS in Lesbians, US 1980-89. Am J. Public Health 1990; 80,(11):1380-1
National surveillance data for reported cases 1980-9 of AIDS. 79 women reported sex only with other females. 95% IVDUs; 5% receipt of blood products.
Of bisexual women (103) only one female had no admitted risk.

E7 **Chu SY et al** Female to female sexual contact & HIV transmission. JAMA 1994; 272 (6): 433
Special surveillance project in 9 states and two health departments. 1122 women interviewed re: HIV/AIDS between 90-93; sexual behaviour and drug use.
→55 bisexual in last 5 years
→10 homosexual in last 5 years →8 IVDUs
→1 received blood
→1 unknown - sex with man in 1981 - four women in last 5 years; oral sex and sex toys; some IVDUs as female sexual partners; two female sexual partners with symptoms of AIDS.

E8 **Raiteri R** – Seroprevalence, risk factors and attitude to HIV-1 in a representative sample of lesbians in Turin. Genitourinary Med 1994;70:200-5
Sero-prevalent, behaviour and attitudes to HIV in lesbians. Snowball sample →181 lesbians. 11 HIV +ve (6.1%) →10 IVDUs. Multivariate analyses - HIV association with IVDU and bisexual behaviour.

E9 **McComb S** - Epidemiology of HIV infection in bisexual women. JAIDS 1992; 5,8: 850-2
Survey of risk behaviour in HIV testers at STD and women health clinics 89-91. Women who have had sex with women since 1978 = 511/15685 women (as above)
→470 bisexual →13 HIV+ve (- 1 IVDU; 7 IVDU + sex with HIV risk man; 4 sex with HIV risk man; 1 exchanged sex for drugs) → 41 lesbian → 0 HIV+ve

E10 **Peterson LR** - No evidence of female to female HIV transmission among 960,000 female blood donors. JAIDS 1992; 5: 853-55.
Among 960,000 female blood donors to 20 centres during 1990. 144 HIV sero-positive. 106 interviewed. None exclusively female to female since '78.

E11 **Raiteri R** – Lesbian Sex & Risk of HIV Transmission. AIDS 98;12:450-1
'92-'97 - 28 HIV discordant couples formed by multiple partnerships of 10 infected lesbians. Rel. >6 months; after diagnosis of infection; no other risk; f/u 6 months after end of relationship. Prospective 3 month daily record of sex, then monthly updates.
→434 partnership months
→6742 sexual exposures (14-67/month)
→ no transmission so risk estimation not possible.

E12 **Cohen H et al** – Risk Assessment of HIV transmission among lesbians. JAIDS 1993;6:1173-4
Two surveys - lesbian magazine readers. 165 (42% RR) postal questionnaires
76 tested for HIV - 4 HIV+ve (all IDUs + sex with male IDUs)
(3 out of 4 infected female partners).
- OP clinic in NYC. Face to face interview. 101/1014 had same sex contact. 13 HIV +ve (12 IVDUs; one sex with male and IVDU)

E13 **Raiteri R** - No HIV-1 infections through lesbian sex. Lancet 1994; 344: 270.
Referring to other two studies - Lesbians in Turin and discordant couples.

E14 **Reynolds G** – HIV & lesbian sex. Lancet 1994;344:544-5
Comment on Raiteri in 23 July '94. Querying definition of risk behaviours and claim of non-existent risk. Calculates a 40% probability of finding no transmission, given numbers involved and time periods.

E15 **Troncoso AR et al** - [Probable HIV transmission by female homosexual contact] Medicina 1995;55(4):334-6 (Spanish)
HIV positive lesbian without other risk factors.

E16 **Gille-Johnson P et al** - [A case report: sexually transmitted HIV between two women] Lakartidningen 1996;93,(39):3382 (Swedish)
A case report of sexually transmitted HIV between two women. Seroconversion illness (confirmed) in lesbian. Sex during menstruation probably increased the risk. Assistance at road traffic accident. Partner not contactable for testing but had considered to be possible HIV positive (but refused testing at that time).

E17 **Rich JD et al** - Transmission of HIV presumed to have occurred via female homosexual contacts. Clin Inf Dis 93;17:1003-5
Case report of female to female transmission. Two year monogamous relationship.
Oral and digital stimulation of genitalia plus use of shared vibrator. No sharing of tooth brushes or razors. Also refer to a total of five possible cases of female-to-female U.S. cases published in this paper. Five includes this case report, and three of the others had sexual contact with males.

NB There is no appendix F relating to table F.

Appendix G - Oral-Anal Sex

G1 **Gill S.K. et al -** Transmission of HIV-1 infection by oroanal intercourse. Genitourinary Med 1992; 68:254-7.
U.K. - One case oral anal contact (Rimming). Index case part of Middlesex cohort - seroconverted following passive unprotected anal intercourse - seroconversion confirmed May 1988. Sexual partner of index case counselled - last intercourse was in February 1988 (anal) no other sexual contacts. Seroconverted in January 1989 following oroanal intercourse. Careful history taking. Positive index case had persistent p 24 antigenaemia, low CD4 and gingivitis.

G2 **Beral V et al** – Risk of KS and sexual practices associated with faecal contact in homosexual or bisexual men with AIDS. Lancet 1992; 339: 632-5
65 men with AIDS. Sexual practices associated with KS increase risk with insertive 'rimming' and other sexual activities involving faeces (plus this group were more sexually active).

Conclusion - agent transmitted via oro-faecal route causing K.S.

G3 **Van Griensven GJP et al** – Ora-anal sex and the occurrence of KS. Genitourinary Med 1993; 69(1): 77-8
Letter commenting on Beral (above) analysed 1000 men from Amsterdam cohort.
KS + rimming - no association found.

G4 **Darrow WW et al** – KS and exposure to faeces. Lancet 1992; 339: 685-6
Comment on Beral also analysed 57 men with AIDS from Atlanta, New York City, Los Angeles and San Francisco. KS associated significantly with oro-anal contact when compared to pneumocystis pneumoniae.

G5 **Peterman TA et al** - KS and exposure to faeces. Lancet 1992; 339: 685
Also comment on Beral.
Case control study attempted but not succeeded.
Of cases (12) - 3 no anilingus, fisting or IAI; 5 insertive anilingus, 9 receptive anilingus, therefore is this entirely an infectious agent?

G6 **Elford J et al** KS & insertive rimming. Lancet 1992; 339: 938
Comment on Beral. Analysis of Sydney data (171 men) did not support oro-anal hypothesis with KS

G7 **Page-Bodkin K et al** – KS & faecal-oral exposure. Lancet 1992; 339: 1490

Comment on Beral. Analysis using SF MM study data. No association between rimming and KS but agree that appears to be sexually transmitted.

G8 **Russel JM et al** – Pharyngeal flora in a sexually active population. Int J STD & AIDS 1995; 6:211-5
Pharyngeal swab and questionnaire (on sexual behaviour) from 1141 GUM clinic attenders. Meningococcal carriage increased in homosexual men and in those with oroanal contact - Beta haemolytic streptococcal carriage was associated with meningococcal carriage.

G9 **Jacobson LP et al** - J. AIDS 1990'; 3(1): Suppl. 1
Increased rimming in KS AIDS compared with non KS AIDS; oral gonorrhoea associated with KS group – postulate cofactors in transmission.

G10 **A2** - one of two cases had oroanal contact; and orogenital contact ; in cohort.

G11 **A7** - cohort - no association of HIV with oroanal contact.

G12 **A16** - cohort - no significant association found

G13 **B4** - case control study - no association with HIV.

G14 **B5** - cross-sectional study - no association with seropositivity.

G15 **B6** - cross-sectional study - no association found

G16 **B7** - cross-sectional study - 78% of cases cf. 62-64% of controls had insertive oro-anal contact, this was not statistically significant.

G17 **B10** - cross-sectional study - no significant association found.

G18 **B12** - nested case-control - not statistically significant association, but ROA RR=2.1 (p=0.07).

Annex 2

HIV in genital tract secretions and saliva

Introduction

There are a number of published reports of the detection and/or quantification of HIV in semen, cervical/vaginal secretions and saliva. Although the presence of viral nucleic acid can be detected in all of these body fluids in the majority of individuals, the findings must be interpreted with caution as relatively few studies have included quantification on infectious virus. Many of the studies involve small numbers of individuals and none have presented data on variability in levels of production of infective virus over a period of months or years. The virus load in blood plasma has been shown to correlate with the viral infectivity titre and there is epidemiological evidence to link the risks of transmission of HIV to the blood plasma viral load. Application of quantitative, sensitive, molecular genetic techniques to other body fluids, while indicating the presence of viral nucleic acid may not, in the absence of infectivity titrations, indicate the presence of infectious viral particles. Seminal plasma and saliva have been shown to contain a number of substances which inactivate HIV and, in addition, there is experimental evidence to indicate that the likely sources of infection in male and female genital tract secretions are lymphocytes and monocyte-macrophages. Although the level of HIV RNA or proviral DNA in a body fluid may not be correlated directly with the level of infective virus, changes in the amount of viral nucleic acid may indicate enhanced viral production or a higher number of virus-infected cells. Some of the conditions associated with an increased rate of horizontal transmission of HIV, such as gonococcal urethritis, have been shown to increase the level of HIV RNA in seminal plasma. This has returned to the level seen in HIV-positive men without urethritis after antibiotic treatment.

Semen

There is evidence to show separate compartmentalisation of HIV in blood and semen such that the level of activity of the virus in one compartment may not reflect replication in the other. Thus, although the amount of HIV RNA in seminal plasma is strongly associated with the level of infectious virus in semen, there is only a weak correlation between the infectivity of semen and the viral load and/or CD4 lymphocyte count in peripheral blood. In general, HIV RNA levels are lower in seminal plasma than in blood. In some individuals the situation is reversed, however, and the amount of HIV RNA in seminal plasma has been up to tenfold higher than in blood.

The level of shedding of HIV in semen has been shown to be increased in the later stages of infection, in leukocytospermia and in gonorrhoea and other causes of urethritis. In one study, the level of HIV RNA in seminal plasma and blood plasma was found to be 3-4 times and 5-7 times higher, respectively, in African men when compared to US/Swiss controls. These groups were matched for CD4 levels and none of the individuals had urethritis or was on anti-retroviral drugs. There is, at present, no clear correlation between the response to anti-retroviral drugs, as indicated by suppression of plasma viraemia, and an effect on HIV in semen. Some studies have shown a reduction in HIV RNA in seminal plasma and/or infective virus, while others have not. This apparent absence of a parallel effect in the two body fluids is further evidence for compartmentalisation of the virus and raises the possibility that patterns of genotypic resistance may vary in the two compartments.

Cervical/vaginal secretions

Early reports of isolation of HIV from cervical and vaginal secretions indicated that infectious virus was present in the cell fraction and supernatant fluid at any stage of the menstrual cycle. Problems with bacterial and fungal contamination of cell cultures have resulted in the use of the polymerase chain reaction (PCR) to detect RNA or DNA in more recent studies. In a recent study of HIV-positive women in Denmark, many of whom were on anti-retroviral drugs, the detection rates for RNA and DNA in one or more genital swabs were 64% and 71% respectively. Using quantitative PCR it was noted that the higher the viral load in the cervical region the more widespread was the

distribution of the virus in the genital tract. In contrast to the situation with semen, a strong correlation between the level of HIV in the blood plasma and genital tract secretions was reported with the viral load in genital secretions recorded as 10-100% of the plasma level. There was less association between the detectability of HIV proviral DNA in the genital tract and positivity was only recorded in-patients who had a blood plasma HIV RNA level of over 50,000 copies/ml.

The level of shedding of HIV in the female genital tract is increased during pregnancy and in the presence of cervical ectopy of cervicitis. A report, from one study, of increased shedding in women using oral contraceptives may have been due to the presence of cervical ectopy. As with the male, the situation with regard to the effect of combination anti-retroviral therapy on viral shedding in the female genital tract requires further present, results of small studies, usually in-patients receiving one or two nucleoside analogues, are conflicting, and there is a need for large studies of patients on HAART study. At. Apparent failure to suppress HIV in genital secretions in women receiving drug combinations, which have reduced their blood plasma viral loads to very low or undetectable levels, emphasises the need for caution in assuming that anti-retroviral drugs will affect the infectivity of women (or men).

Saliva

It is generally acknowledged that saliva presents a low risk of transmission of HIV. On the basis of epidemiological studies, saliva (in the absence of contamination with blood) has been designated a low-risk body fluid in the context of transmission of all blood borne viruses. A number of workers have reported that isolation of HIV from saliva is rarely achieved and, if present, it is of low titre. This may be explained by the fact that saliva contains a number of constituents that will inactivate HIV or inhibit replication of the virus in cell culture. These include HIV-specific antibodies (IgA and IgG), high molecular weight mucins which aggregate the virus, and secretory leukocyte protease inhibitor (SLPI) which is found naturally in serous secretions. The apparent scarcity of HIV infectivity in saliva is mirrored by studies of HIV RNA. In one comparative study, the median RNA value for salivary HIV was 162 copies/ml (range 0-72,000) as compared to a median of 14,817 copies/ml (range 167-254,800) in blood plasma.

It appears, therefore, from epidemiological and virological data that the risks of acquiring HIV from exposure to saliva are low. As with any body fluid, however, the risk of infection is likely to be increased if blood contamination is present. Use of sensitive assays to detect blood in saliva have revealed the presence of blood in 50% of random samples from HIV-negative individuals and in 65% of those who were HIV-positive. Thus any condition, which increases the likelihood of oral bleeding, or which reduces the salivary flow, may increase the risk of HIV transmission.

Annex 3

Anatomy and Pathology of the Oropharyngeal Cavity

The HIV Negative Mouth

The oral cavity is designed in such a way that minimalises access of antigens or microbes through the tissues. The hard palate, gingiva and dorsum of the tongue are covered by cornified epithelium, through which antigens do not penetrate easily. The floor of the mouth, the cheeks, lip and ventral surface of the tongue are covered with much thinner non-cornified epithelium and are about 20 times more permeable than the palate. The likelihood of antigen penetration is still thought to be small because this non-cornified epithelium is covered in a layer of high molecular weight mucins derived from saliva. It is now known that saliva contains several very powerful anti-viral factors, which are active against HIV. Thus in the normal uninflamed situation, the mouth and pharynx are protected by mucus membrance lining and anti-viral secretions.

Any inflammation in the oral cavity and pharynx such as pharyngitis would increase the risk of access of viral particles across the mucosa. In-patients with loss of lubrication, abrasions are more likely, though squamous epithelium turns over at a rate of two layers per hour, thus constantly repairing damage.

Teeth

Teeth penetrate through the oral mucosa and are attached to bone via a periodontal ligament. The ligament and necks of the teeth are protected by a transudation from serum lying in the gingival crevice. Viral entry via the gingival crevice is possible, since bacteraemias have been observed even after chewing in-patients with relatively good gingival health. The risk of viral entry by this route would be increased in the presence of gingivitis or periodontal disease.

Gingiva (Gums)

Most of the population probably suffers from mild gingivitis at some time. However in most gingivitis the mucosa remains intact and covered with saliva, so that there is probably no serious increased risk of HIV transmission. About 10% of the population suffer from periodontal disease, in which the tissue around the necks of the teeth is irreversity damaged. Bacteraemias are more common and suggest that this is a potential route for entry of HIV.

Both gingivitis and periodontal disease increase the risk of blood in saliva, which can be detected by red cells or haemoglobin presence. The amount of haemoglobin is proportional to the amount of gingivitis. Tooth brushing causes mild trauma and where there is gingivitis and gums are fragile, this may lead to gingival bleeding. This bleeding probably only lasts for a few minutes (less than 10). (Common advice gay men is to avoid tooth brushing for two hours before oral sex).

Mouth Ulcers

Mouth ulcers by definition are a breach of the epithelium and allow two-way passage of microbes and antigens across the mucosa. There is evidence that food antigens for instance can pass across the oral mucosa in the presence of ulceration, and that bacteraemias are increased. Conversely, serum proteins can be detected in saliva in the presence of mouth ulcers. It is likely that such lesion would increase the risk of HIV transmission during oral sex. Aphthous ulceration affects about 10% of the population, although the actual mouth ulcers may only be present for between two and four weeks of the year. Younger people up to the age of 30 are more prone to oral ulceration.

Tonsils

Tonsils are large accumulations of organised lymphoid tissue and have a role in antigen sampling and are designed for antigen penetration. There is evidence of easy transfer of antigens such as prions and viruses into the tonsils so that they are a potential site of entry for HIV.

Presence of Other Infections

Other oral infections may act as co-factors in HIV transmission and there are reports of HIV infection acquired via orogenital intercourse when there was co-infection with gonorrhoea. Oropharyngeal gonorrhoea causes significant inflammation and so could increase vulnerability to HIV infection. Many patients with gonorrhoea have oropharyngeal involvement, of which they are unaware.

Dry Mouths

Saliva is a very powerful defence against HIV and other viral infections. Patients with xerostomia are likely to be more susceptible than normal. Dry mouths may be caused by many drugs including many of the cocktails of anti-viral therapies, but also many anti-depressants, tranquillisers, anxiolytics, anti-hypertensives and some non-steroidal anti-inflammatory drugs can all affect salivary flow.

Conclusion

In the normal healthy mouth, the mucosa and its secretions are an effective barrier to HIV. The tonsils present a possible route of entry for HIV, as do the gingival crevices around the teeth. There is not sufficient evidence to state with confidence that HIV could not penetrate the intact oropharyngeal mucosa.

The likelihood of virus entry through the mouth is increased in the presence of mouth ulcers, gingivitis, pharyngitis, tonsilitis and xerostomia.

The HIV-Positive Mouth

Over half of HIV-positive subjects and three-quarters of AIDS patients have some specific oral lesions as a result of HIV infection, including various opportunistic bacterial fungal and viral pathogens, including candida, HSV, EBV, HPV and CMV (though the prevalence may be reduced in patients on effective HAART therapy). In London HIV-positive patients, over 30% of HIV or AIDS patients have oral hairy leukoplakia and oral candidiasis.

There are a number of conditions affecting the gingival margin which are specific to HIV or increased in HIV-infected persons. These include linear gingival erythema, necrotising ulcerative gingivitis (ulceration of the gingival margin usually involving several teeth), necrotising periodontitis (a painful ulcerative condition which can lead to loss of teeth and localised osteomyelitis), chronic inflammatory periodontal disease, gingivitis and bleeding of the gums is more common in HIV-positive people. These gingival lesions are likely to increase the vulnerability of HIV-positive patients to acquiring through oral sex and other pathogens such as HSV, HPV, Hepatitis B or C. In addition saliva of these subjects is more likely to contain HIV because of bleeding from the gums. There is also some evidence of an association between HIV and epithelial cells, and since epithelial cells are shed into saliva, this offers another possibility for HIV in saliva.

Conclusions

Gingival inflammation is increased in patients with HIV infection, and this and a number of the oral manifestations of HIV, would be likely to increase oral shedding of HIV into saliva.

These lesions, as well as mucosal ulceration, would make the mouth more vulnerable to other pathogens, which could be transmitted through oral sex.