

Oral transmission of HIV

**Richard B. Rothenberg, Margaret Scarlett*, Carlos del Rio[†],
David Reznik[†] and Christine O'Daniels[†]**

AIDS 1998, **12**:2095–2105

Keywords: HIV, oral transmission, oral conditions

Introduction

Early in the AIDS epidemic, there was substantial concern over so-called 'casual' or non-sexual transmission of HIV, much of it centered on contact with saliva (sharing an eating utensil or toothbrush) [1,2]. Several epidemiologic studies and national AIDS case surveillance data demonstrated that the transmission of HIV depended on contact with infected body fluids, primarily blood and semen [3,4]. Studies of household transmission of HIV, involving family members who shared commonplace activities, could not demonstrate passage of the virus [5,6]. As the epidemic unfolded, concerns about casual contact abated and widespread major risk factors, such as needle-sharing, anal sexual contact, and transfusion, became the primary epidemiologic focus.

Another realignment of emphasis may now be taking place. After about 2 decades, the transmission of HIV in industrialized nations has showed some signs of amelioration. Recent surveillance data in the United States and Europe demonstrate a declining acceleration in the reporting of new incident cases of AIDS [7–9]. Over the past 2 years, there has been a substantial decline in AIDS deaths [7], attributed largely to new therapeutic developments, and continuing reports of declines in risk-taking [10,11]. A number of continuing concerns remain, however. Younger homosexual men may still be evidencing sexual behaviors that place them at risk [12], and the burden of HIV infection in women is growing [9].

Despite continuing concerns about the major risks, overall moderation of the epidemic pace offers an opportunity to reconsider several epidemiologic features whose importance may be modified by the changing epidemiologic picture. Although casual contact with saliva remains an insignificant factor, oral sexual contact may now be of increasing importance in the transmission of HIV. Oral sex may be less efficient than needle-sharing or anal intercourse for the transmission of HIV [13], but its increased use by men who have sex with men (MSM) [14,15] and its prominence in the sexual activity of crack smokers [16,17] may increase its contribution to HIV transmission. In this review, we assess the epidemiologic and anecdotal evidence for oral HIV transmission, review current laboratory investigations of the oral ecology of HIV, and suggest a classification scheme and an epidemiologic approach for further delineation of the role of oral sexual activity.

The epidemiologic evidence

The first major epidemiologic study of AIDS [18] appeared prior to the recognition of infectious virus in semen, blood, and saliva [19,20] or the availability of serologic testing. In that study, 98% of 50 cases and 99–100% of 120 controls reported receptive oral intercourse (ROI). The authors concluded that there was

From the Department of Family and Preventive Medicine, the *Division of Infectious Disease, Department of Medicine, Emory University School of Medicine, and the [†]National Center for HIV, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia, USA.

Requests for reprints to: Richard Rothenberg, Department of Family and Preventive Medicine, Emory University School of Medicine, 69 Butler Street SE, Atlanta, GA30303, USA.

Date of receipt: 14 May 1998; revised: 5 August 1998; accepted: 11 August 1998.

no difference in orogenital contact between cases and controls. Subsequently, a number of major epidemiologic studies (including the Centers for Disease Control and Prevention Hepatitis cohort, the Multicenter AIDS Cohort Studies, the San Francisco Men's Health Study) evaluated the risk of oral intercourse, both receptive and insertive, and calculated both adjusted and unadjusted relative risks (Table 1). Most studies calculated the relative risk as the odds ratio, either bivariate or using multiple logistic regression. A variety of study designs and specific risks (e.g., with or without swallowing semen) were used, but results were similar. Despite considerable variation in point estimates (31 out of 39 exceeded 1.0), the confidence intervals (CI) around the relative risk invariably included 1.0 until the mid 1990s (Fig. 1).

In 1993, Samuel *et al.* [21] studied 83 MSM who had seroconverted and 249 HIV-negative control MSM. The unadjusted relative risk for ROI was 5.3 (95% CI, 2.0–19.0) and for insertive oral intercourse was 3.6 (95% CI, 1.4–13.0). In addition, the relative risk for ROI in the absence of receptive anal intercourse was 3.0 (95% CI, 1.1–12.0). However, the relative risks for insertive oral intercourse in the absence of receptive anal intercourse and for all oral intercourse in adjusted computations were not significantly different from 1.0. These data, suggesting that insertive oral intercourse was not an independent risk factor, did give some credibility to the potential for transmission to those who practice ROI. In 1995, Ostrow and colleagues also found that oral exposure was not an independent risk factor, but noted situations in which it may have occurred, stated that their data were at the limits of detection, and felt uncomfortable with calling oral practices 'safe sex' [19–22]. In a large study of 2322 inner-city persons aged 18–29 years, Faruque *et al.* [16] noted a prevalence odds ratio for oral exposure of 1.5 (95% CI, 1.0–2.1) and an even stronger association with oral sores and ROI (adjusted prevalence odds ratio, 1.9; 95% CI, 1.0–3.6) [16]. Although Wallace and associates did not calculate relative risks, they noted in a study of 3073 female prostitutes that when ROI was the most prevalent sex act, 35.4% of prostitutes were HIV-positive, but when ROI was not most prevalent, 24.2% of prostitutes were HIV-positive (a

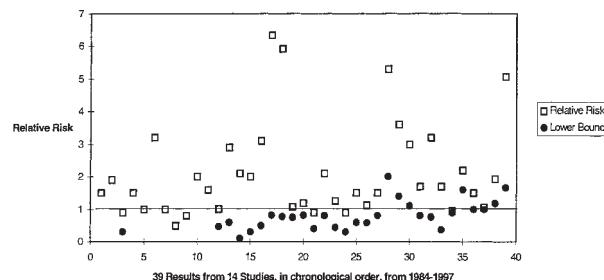


Fig. 1. Distribution of relative risks and lower bounds for oral transmission of HIV.

highly significant difference). Finally, Page-Shafer *et al.* [23], reporting the results of the Tricontinental Seroconversion Study, found a per partner relative risk for ROI of 1.05, a relative risk for ROI comparing those with 10 oral partners against all others of 1.93, and a relative risk for ROI comparing those with 10 oral partners against those with no receptive anal intercourse of 5.06. All of these results were statistically significant and their 95% CI excluded 1.0 (Table 1). Thus, although earlier studies tended to discount the risk associated with oral intercourse, these more recent investigations provide a substantial basis for reconsideration.

Case reports

Since 1987, there have been 21 case reports of 42 potential instances of oral transmission (Table 2). Given the thousands of cases of HIV infection that constitute the denominator, such a set of reports would appear to emphasize the rarity rather than the likelihood of the event. The infrequency of case reports may rest, in part, with the difficulty of providing credible validation of the absence of simultaneous risks. In fact, the common thread in these case reports is investigators' considerable efforts to document an exposure other than oral. The rarity of reported oral transmission may be, in part, the result of the rarity with which oral exposure occurs alone, and the hesitancy to assign transmission to oral activity in the presence of simultaneous risks. However, the fact that it appears to confer greater risk when it is the dominant (although not exclusive) behavior [24] gives impetus to the task of sorting out the contribution of oral intercourse to transmission.

Transmission estimates

Perhaps because of the perceived inefficiency of transmission, little attention has focused on the probability of transmission through oral intercourse, and it is not specifically addressed by several recent reviews [13,25]. The European study of heterosexual partners identified 50 couples who practiced unprotected orogenital sex, but protected penile–vaginal and penile–anal sex, and detected no HIV transmission after a median of 24 months of observations [26]. The authors noted, however, that with the small number of observations, the 95% CI around the estimate of transmission was 0.0–4.3 per 100 person-years. In addition, the long-term stability of these relationships suggests that the infected partner may have been in a stable stage of HIV progression, during which infectivity may be low. In an innovative approach, Samuel *et al.* [21] used the San Francisco Men's Health Study to provide data-based estimates of HIV prevalence, sexual intercourse

Table 1. Epidemiologic studies measuring oral risk for HIV transmission.

| First author [reference] | Year | Cohort | Findings | Risk assessment |
|--------------------------|------|---|---|---|
| Jaffe [76] | 1983 | 50 cases, 120 controls (MSM) | ROI: 98% (cases) versus 99–100% (controls) | No difference in orogenital contact for cases and controls |
| Marmor [77] | 1984 | 20 cases, 40 controls (MSM) | ROI (univariate): RR, 1.5 ($P = 0.01$) RR, 1.9 ($P = 0.003$) with swallowing semen; ROI (adjusted): NS | Oral exposure not an independent risk factor |
| Goedert [78] | 1984 | Cohort of 66 men (MSM) | Adjusted results: ROI: $\chi^2 = 0.42$ ($P = 0.5$) OI: $\chi^2 = 2.36$ ($P = 0.1$) | Oral exposure not an independent risk factor |
| Newell [79] | 1985 | 31 cases, 29 controls (MSM) | no difference in ROI or OI (data not provided) | Oral exposure not an independent risk factor |
| Lyman [80] | 1986 | Cohort of 1035 men | Prevalence of HIV infection: no partners in past 2 years: 3/15 (20%); OI only in past 2 years: 11/56 (19.6%) | No difference in infection in those with only OI suggests it is not an important mode of transmission |
| Moss [81] | 1987 | 187 MSM HIV-positive, 135 community controls, and 137 clinic controls | RR for OI (adjusted for no. partners): 0.5, cases versus community controls, NS; 0.8, cases versus clinic controls, NS; 2.0, HIV-positive versus community controls, NS; 1.6, HIV-positive versus clinic controls, NS; RR for ROI (adjusted for no. partners): 1.5, cases versus community controls, NS; 1.0, cases versus clinic controls, NS; 3.2, HIV-positive versus community controls, NS; 1.0, HIV-positive versus clinic controls, NS; similar results for RR by no. partners | Oral exposure not an independent risk factor |
| Winkelstein [82] | 1987 | 171 MSM with or without OI | OI: adjusted RR, 1.01 (95% CI, 0.47–2.18) | Oral exposure not an independent risk factor |
| van Griensven [83] | 1987 | 741 MSM | Increase in probability of being seropositive 0.28 to 0.40, with no. partners 0–20; NS in regression analysis | Oral exposure not an independent risk factor |
| Fischl [84] | 1987 | 26 positive and 19 negative spouses to HTLV-III-positive | ROI (females) 11 positive, 1 negative; no multivariate assessment | Oral exposure may be important in transmission; role of oral sex alone could not be determined |
| Darrow [85] | 1987 | Cohort of 492 MSM | Univariate RR (steady partners) OI: 2.9 (95% CI, 0.6–13.0); ROI: 2.1 (95% CI, 0.1–33.9); univariate RR (non-steady partners) OI: 2.0 (95% CI, 0.3–14.7); ROI: 3.1 (95% CI, 0.5–18.7) 95 conversions; 147 MSM, ROI 1 partner, no RAI or ROI, 0 seroconversions | Oral exposure not an independent risk factor |
| Kingsley [86] | 1987 | 2507 MSM cohort | Univariate RR (1/month) ROI: 6.33 (95% CI, 0.82–48.88); OI: 5.92 (95% CI, 0.77–45.81); adjusted RR ROI: 1.07 (95% CI, 0.75–1.53); OI: 1.19 (95% CI, 0.82–1.73) | Oral exposure is not a risk factor |
| McCusker [87] | 1988 | Cohort of 290 men (MSM) | Frequency of ROI and OI greater in negative spouses ROI with case: adjusted RR, 0.9 (95% CI, 0.4–2.4); ROI with partners: adjusted RR, 2.1 (95% CI, 0.8–5.6) ROI: 1.26 (95% CI, 0.44–3.60) | Oral exposure not an independent risk factor |
| Peterman [88] | 1988 | 80 spouses of HIV-positives | | Oral exposure not an independent risk factor |
| Osmond [89] | 1988 | 117 MSM contacts to AIDS cases | ROI with case: adjusted RR, 0.9 (95% CI, 0.4–2.4); ROI with partners: adjusted RR, 2.1 (95% CI, 0.8–5.6) ROI: 1.26 (95% CI, 0.44–3.60) | Oral exposure not an independent risk factor; possible seroconversion by oral contact in 2 instances |
| Coates [90] | 1988 | Cases: 246 MSM seroconverters | | No association could be made with orogenital contact |
| Burcham [91] | 1989 | Cases: 55 MSM seroconverters, controls: 588 non-seroconverters | ROI: unadjusted RR, 0.9 (95% CI, 0.3–2.4); OI: unadjusted RR, 1.5 (95% CI, 0.6–3.7) | Oral exposure not an independent risk factor |
| Evans [92] | 1989 | Cases: 272 MSM HIV-positive, controls: 778 MSM HIV-negative | Data collected on OI, NS, not reported | Oral exposure not an independent risk factor |
| Kuiken [93] | 1990 | Cases: 84 MSM seroconverters, controls: 168 MSM HIV-negative | ROI: unadjusted RR, 1.12 (95% CI, 0.59–2.12); OI: unadjusted RR, 1.50 (95% CI, 0.81–2.78) | Oral exposure not an independent risk factor |
| Samuel [21] | 1993 | Cases: 83 MSM seroconverters, controls: 249 MSM HIV-negative | ROI: unadjusted RR, 5.3 (95% CI, 2.0–19); OI: unadjusted RR, 3.6 (95% CI, 1.4–13); ROI (no RAI): RR, 3.0 (95% CI, 1.1–12); OI (no RAI): RR, 1.7 (95% CI, 0.8–4.1); ROI: adjusted RR, 3.2 (95% CI, 0.76–14); OI: adjusted RR, 1.7 (95% CI, 0.37–7.4) | Oral exposure not an independent risk factor |

Table 1. *Continued*

| First author [reference] | Year | Cohort | Findings | Risk assessment |
|--------------------------|------|---|---|---|
| Raiteri [94] | 1994 | 18 discordant lesbian couples practicing high-risk behavior observed for 3 months | No seroconversions | Non-existent risk of transmission in this setting |
| Ostrow [22] | 1995 | Cases: 76 MSM seroconverters, controls: 389 MSM HIV-negative | ROI: adjusted RR, 0.95 (95% CI, 0.89–1.01) | Oral exposure not an independent risk factor, but data at the limits of detection |
| Faruque [16] | 1996 | 2323 persons, innercity, 18–29 years | ROI: unadjusted POR, 2.2 (95% CI, 1.6–3.0); adjusted POR, 1.5 (95% CI, 1.0–2.1); oral sores and ROI: adjusted POR, 1.9 (95% CI, 1.0–3.6) | Oral exposure associated independently with HIV, especially among those with oral sores |
| Wallace [24] | 1996 | 3073 prostitutes | ROI: most prevalent act, 35.4% positive; not most prevalent, 24.2% positive ($P < 0.0001$; unadjusted) | Oral exposure associated with HIV-positive, especially with crack use |
| Page-Shafer [23] | 1997 | 345 MSM HIV-positive, 345 MSM HIV-negative | In MSM with no or little RAI: ROI (per partner): adjusted RR, 1.05 (95% CI, 1.00–1.11); ROI (≥ 10 partners versus all): adjusted RR, 1.93 (95% CI, 1.18–3.14); ROI (≥ 10 partners versus no RAI): adjusted RR, 5.06 (95% CI, 1.66–15.4) | Oral exposure significantly associated with HIV seroconversion |

A number of major epidemiologic studies of AIDS transmission did not report information about oral transmission, or provide even non-significant odds ratios [95–100]. OI, Oral intercourse; ROI, receptive oral intercourse; IOI, insertive oral intercourse; RAI, receptive anal intercourse; RR, relative risk; OR, odds ratio; CI, confidence interval; NS, not significant; POR, prevalence odds ratio.

activity, and seroconversion status and used them to model the remaining unknowns (infectivity parameters). Based on several different models, the per-partner infectivity of ROI was about 1% (range, 0.85–2.3%), where 'per-partner' refers to the risk with a given partner, uncontrolled for activity level, and should be distinguished from the risk of a single sex act ('per-contact' risk). In comparison, the per-partner infectivity of anal receptive intercourse was about 10% (range, 4.2–12%). In a modeling study that incorporated the stage of infection, it was estimated that oral sex acts imposed a transmission risk that was one-sixth that of anal sex acts [27]. In an assessment of per-contact risk for transmission associated with four types of homosexual contact, Vittinghoff *et al.* [28] estimated that the risk for unprotected receptive anal sex (0.24%; 95% CI, 0.05–0.43) was eight times the risk for unprotected receptive oral sex (0.03%; 95% CI, 0.01–0.18). Other modeling endeavors have selected arbitrary parameters for transmission and focused on the subsequent dynamics. For example, Koopman *et al.* [29] modeled the number of new AIDS cases that would occur in a simulated epidemic involving oral and anal preference groups, and used an estimate of transmission per oral sex act of between 0.0005 and 0.01, setting these at one-quarter the corresponding estimates for transmission per anal sex act.

Biologic plausibility

The biologic risk for transmission or acquisition of HIV from oral sexual contact is not known, but the risk is likely to be related to a number of factors. These

include the presence or absence of virus at sexual sites (oral, vaginal, anal and penile), the titer of virus (if present), the integrity and mechanical properties of the sexual mucosa, mucosal immunity, local inhibitory factors, and the presence or absence of cofactors that may facilitate transmission. Finally, the frequency and nature of exposures (e.g., the relative effect of a large number of lower risk events compared with a small number of higher risk events) and the underlying epidemiologic features of HIV dynamics in the community may have an impact on the frequency of HIV transmission from oral intercourse. Assessment of many of these factors has only recently been undertaken.

Evidence from animal experiments

There is recent animal experimental evidence for and against ROI as a route for transmission. Stahl-Hennig and colleagues applied small amounts of simian immunodeficiency virus (SIV) to tonsils of rhesus monkeys and demonstrated that the tonsils may be a portal for non-traumatic entry of SIV [30]. Similarly, Baba *et al.* [31] were able to infect adult macaques in the absence of oral lesions with doses considerably below those required for infection through rectal exposure. In contrast, Bosch *et al.* [32] exposed 11 *Macaque nemestrina* neonates to HIV-1 infection via the oral, intravenous and rectal routes. Three out of five exposed rectally, two out of two exposed intravenously, and none out of four exposed orally became infected. The authors pointed to potential differences between SIV and HIV, and stated that the latter was not efficiently transmitted in macaques. Nonetheless, the possibility of atraumatic oral infection heightens the urgency of determining the mechanisms of action of inhibitors, and their role *in vivo*.

Table 2. Case reports and observations on oral transmission.

| First author [reference] | Year | Finding |
|--------------------------|------|---|
| Sabatini [101] | 1984 | Possible transmission by female to female sexual contact |
| Marmor [102] | 1986 | Two female patients, one of whom appeared to transmit HIV to the other throughogenital contact |
| Mayer [103] | 1987 | One out of eight seroconversions among 290 seronegative men attributable to oral contact (no anal sex since 1982; three negative tests before conversion) |
| Monzon [104] | 1987 | One woman with exclusive female-to-female orogenital contact and no other risk factors |
| Rozenbaum [105] | 1988 | Five men seroconverted with oral sex as the only risk factor for 3 months or more before seroconversion |
| Goldberg [106] | 1988 | One man with exclusive orogenital sexual contact; exposure to HIV-positive man 2 years prior to documentation of seroconversion |
| Perry [107] | 1989 | Male partial transsexual who became infected in a monogamous relationship with an HIV-positive women having only orogenital contact |
| Detels [108] | 1989 | One possible seroconversion related to orogenital contact among 232 (8%) converters out of 2915 men followed for 9330 person-intervals |
| Spitzer [109] | 1989 | One man (with subcortical dementia at age 60 years) with history of oral sex with one extramarital female partner (a prostitute) |
| Quarto [110] | 1990 | One man (age 25 years) with steady female partner and one other insertive orogenital contact with a female 1 month prior to probable acute AIDS syndrome |
| Lifson [111] | 1990 | Two men who seroconverted after receptive oral sex with ejaculation |
| Murray [112] | 1991 | One man acquired both gonorrhea and HIV from receptive oral sex |
| Lane [113] | 1991 | One man acquired HIV after deep kissing, receptive oral sex without ejaculation, and receptive anal intercourse with a condom |
| Keet [114] | 1992 | Nine men among 102 seroconverters (out of 757 followed) had only orogenital exposure confirmed by re-interview |
| Rich [115] | 1993 | One women with orogenital contact to an HIV-positive women and no other risk factors. |
| Vidmar [116] | 1996 | One older man exposed to bite from terminal AIDS patient whom he was assisting during a grand mal seizure |
| Schacker [117] | 1996 | Four patients (out of 46 seroconverted) reported only unprotected orogenital contact prior to critical exposure leading to HIV infection; confirmed by partners of two out of the four |
| Berry [118] | 1997 | One man with receptive orogenital contact with 20 partners, two of whom were known to the patient to be HIV-positive |
| Padian [119] | 1997 | Discordant couple; female partner became infected in association with oral exposure with good epidemiologic and virologic data for the likelihood of contact with contaminated salivary secretions as the route of transmission |
| Bratt [120] | 1997 | Two patients; one pair had concordant histories and an HIV strain genetically similar to that of the infected partner was passed via orogenital contact to the uninfected partner; in the second case, transmission may have been facilitated by penile skin damage |
| Senterfitt [121] | 1998 | Four persons; among 30 newly infected persons, these four had a risk context that suggested transmission from receptive oral sex |

Infectious HIV at sexual sites

It is now well established that infectious HIV can be found in semen, as well as in cervical and vaginal secretions. The potential for HIV transmission from these sites to oral mucosa has not been well studied, although inhibitory substances in saliva (see below) suggest that such transmission is not facile. More recently, information has emerged about the presence of infectious HIV in pre-ejaculatory fluid. Pudney and colleagues reported the presence of HIV-1-positive cells in three sperm-free samples from four donors [33]. They also noted a variable number of positive pre-ejaculate specimens from persons who were symptom-free (five out of six), symptomatic (one out of three), on zidovudine (two out of five), and not on therapy (four out of four). The presence of virus in these situations highlights the possibility of penile-oral transmission of HIV even in the absence of ejaculation. Similar possibilities would

exist from the transfer of vaginal/cervical secretions, and would similarly be dependent on a variety of as yet incompletely explored factors that affect the degree of shedding and the receptivity of the oral cavity to infection.

Virus in saliva

As noted above, the first report of virus in saliva [19] was followed quickly by a more extensive evaluation that found virus in only one out of 83 specimens [34]. Subsequently, investigators have reported a frequency of detection from 0 to 83%, depending on the type of specimen and the type of laboratory method (Table 3), but most of this work occurred before current staging methods were available. Culture attempts have generally placed the isolation proportion at under 5%, with the exception of a 21% positivity for low levels of virus found by Yeung *et al.* [35]. Results with PCR testing

have been more variable. For example, in an extensive study, 218 simultaneous blood and saliva specimens from 75 HIV-positive persons were tested for viral p24 antigen and infectious virus; 38% of blood specimens and 1% of saliva specimens were positive for cell-free infectious virus [36]. Goto *et al.* [37] used PCR testing to study 20 patients for long terminal repeat (LTR), *gag*, and *env* proviral sequences. With LTR probes, 10 out of 20 specimens were positive, but only 25% were positive with probes for *gag* and *env*. Repeated testing confirmed the higher positivity for LTR. With PCR testing, Quereshi and colleagues detected virus in 83% of specimens [38]. In an extensive review of the mechanisms of infectivity for salivary secretions, Shine *et al.* [39] concluded that the precise balance between infectious secretions and inhibitory effects *in vivo* remains to be elucidated. They stated that, 'it is important to establish the correlations among the amount of HIV, its infectivity in salivary secretions, and the level of anti-HIV factors present in these secretions' [39].

Inhibition by saliva

Coincident with early reports suggesting low level of HIV in saliva, early reports also determined that there were components in saliva that may inactivate HIV [40]. Subsequent research has clearly established the presence of such substances [39,41,42]. A number of mechanisms have been postulated for this inhibitory activity, including cell disruption, soluble antibody, high molecular weight proteins, and soluble anti-HIV components.

Baron and Cloyd [43] proposed that HIV transmission is inhibited by saliva-induced disruption of infected cells and neutralization of maturing HIV in cells made permeable by saliva. They demonstrated 30–45% cell disruption by saliva. Sanneman *et al.* [44] suggested that immune factors in whole saliva of HIV-1-infected persons, such as HIV-1-specific IgG from serum, may produce inhibition.

As reviewed by Shine *et al.* [39], submandibular, submaxillary and parotid secretions, as well as whole saliva,

reduce HIV infectivity *in vitro* and several modes of inhibition are discussed. High molecular weight salivary proteins such as mucins may entrap HIV-1 [45,46], although this mechanism has not been fully explained because anti-HIV-1 activity is retained in human parotid saliva, which does not contain mucin. Second, there may be a role for soluble anti-HIV components. Although a host of soluble proteins has been identified, and several (cystatin, lysozyme and lactoferrin) have anti-HIV-1 activity at concentrations above those found physiologically, the protein of greatest interest is recombinant secretory leukocyte protease inhibitor (SLPI). The mechanism for inhibition is under intense investigation. McNeeley and coworkers [47] observed that *in vitro* infection of monocytes by HIV-1, even after only 1 h of exposure to saliva, as measured by viral reverse transcriptase activity, is suppressed for 3 weeks after infection. They found that SLPI was inhibitory at physiologic concentrations and that the anti-HIV-1 antibody activity was dose-dependent. SLPI was shown to target a cell-associated molecule, but its inhibitory activity did not involve direct interaction with CD4 antigen. It has been suggested that SLPI's mode of action may be to inhibit the virus-cell fusion or uncoating step in the HIV infection cycle [48]. However, Shine *et al.* [39] present evidence that SLPI may inhibit virus-cell fusion but does not inhibit cell-cell fusion. A potential critical observation was made by Wahl and colleagues [49], who noted that SLPI accumulated in acinar cells or ductal epithelium, and that HIV-1 transcripts did not. The latter were found only in mononuclear cells within salivary gland stroma (in 19 out of 55 specimens tested), and there was no evidence of productive HIV-1 infection in salivary gland epithelium. This lack of colocalization suggests that SLPI may function to prevent transmission and infection, rather than influence established infection. From an epidemiologic point of view, it may operate to prevent acquisition by someone performing ROI, but may not play a role in preventing transmission from an infected person to a partner who practices oral insertion.

Antibody in saliva

The presence of anti-HIV antibody in saliva has been well recognized for over 10 years. As summarized by Malamud and Friedman [41], 15 studies demonstrated a concordance of 564 (97%) out of 582 paired specimens of saliva and serum. This correlation holds for whole saliva as well as for parotid saliva, and there is a virtual absence of false positives [50,51]. These initial observations have formed the basis for oral testing for HIV. Evaluation of available oral tests (14 studies) reveal a sensitivity of 97.2–100% and a specificity of 97.7–100% [52,53] as well as improved safety, ease of collection, and patient acceptability. Similar results were achieved under field conditions in a study of MSM in Mexico City [54]. The sensitivity, calculated from 369 paired

Table 3. Frequency of detection of HIV-1 in saliva.

| First author [reference] | Year | No. positive/ tested (%) | Type of sample |
|--------------------------|------|--------------------------|-----------------------|
| Groopman [19] | 1984 | 7/18 (39) | Culture |
| Ho [34] | 1985 | 1/83 (1) | Culture |
| Levy [122] | 1988 | 3/55 (5) | Culture |
| Schioldt [123] | 1989 | 0/21 (0) | Culture |
| O'Shea [124] | 1990 | 0/18 (0) | Culture |
| Goto [37] | 1991 | 10/20 (50) | PCR |
| Barr [36] | 1992 | 2/218 (1) | p24; infectious virus |
| Lucht [125] | 1993 | 9/59 (12) | PCR |
| Moore [126] | 1993 | 0/21 (0) | PBMC/PHA/IL-2 |
| Yeung [35] | 1993 | 6/28 (21) | Culture |
| Bergey [45] | 1994 | 1/21 (5) | Culture |
| Quereshi [37] | 1995 | 29/35 (83) | PCR |

PBMC, Peripheral blood mononuclear cells; PHA, phytohemagglutinin; IL-2, interleukin-2.

saliva–serum samples from a low prevalence population and 134 paired specimens from HIV-positive persons, was 98.5%, and the specificity was 100%. Although anti-HIV antibodies are an invaluable diagnostic aid, their role in the oral transmission of HIV is not yet clarified [39].

The role of oral pathology

The numerous ulcerative and non-ulcerative conditions that affect the oral cavity [55–60] may alter the biologic activity of infectious HIV and of inhibitors. In a review of periodontal complications, Mealey [55] noted that linear gingival erythema, a condition characterized by unresponsiveness to local debridement and mechanical plaque control, and necrotizing ulcerative periodontitis (NUP), characterized by rapid destruction of alveolar bone, play an important role in revealing to the clinician the overall clinical pace of HIV infection. NUP, for example, is a good predictor of CD4+ cell counts of below $200 \times 10^6/l$, and in one study was a strong predictor of rapid mortality [61]. The true prevalence of these conditions is difficult to assess because of the bias of ascertainment when clinic populations are used. In Mealey's review of existing studies, the prevalence for NUP was generally below 10%, although several studies report much higher values [55].

When considering the pathology of the entire oral cavity, a variety of neoplastic (Kaposi's sarcoma, non-Hodgkin's lymphoma), viral [herpes, human papillomavirus, Epstein–Barr virus (hairy leukoplakia)], bacterial (anaerobes, facultative anaerobes, *Mycobacterium avium* complex), and fungal (candidiasis, histoplasmosis) conditions are well described [58] as well as a variety of other conditions [epithelioid angiomyomatosis (*Rochalimea* spp.), aphous-like ulcers] in which infection plays a role [58]. Shibuski and colleagues [62] conducted a prospective study of oral lesions and HIV conditions on 176 HIV-infected women and 117 HIV-negative women who were at risk for infection. The prevalence of oral lesions was significantly higher amongst infected women (22%) than uninfected women (3%), and there was a substantial association between the presence of oral lesion and a CD4+ cell count of below $200 \times 10^6/l$ (OR, 8.9; 95% CI, 2.6–30.0) [62]. The authors noted that amongst those with CD4+ cell counts below $200 \times 10^6/l$, hairy leukoplakia was 5.5 times more common in those infected heterosexually than amongst injecting drug users.

Maternal–infant transmission through breastfeeding

Transmission of HIV by breastfeeding is well established, but the precise mechanism for transmission by this route is not known. Unlike saliva, levels of HIV are high in breastmilk. Although SLPI levels are high in both colostrum and breastmilk, as well as the saliva of the newborn immediately postpartum, only breastmilk

shows a dramatic decrease in SLPI levels over the few weeks postpartum. The potential relationship of this decline to HIV transmission via breastmilk requires further elucidation, particularly in relation to other potential risk factors such as breast abscess, nipple trauma, and oral lesions in the infant.

Several investigators have tried to understand the role of saliva, SLPI, and oral factors in maternal–infant transmission. Southern and Southern [63] observed that productively infected milk monocytes and macrophages can be detected by *in situ* RNA hybridization and immunocytochemistry in the breastmilk of HIV-1-infected mothers. Adhesion molecules in infant saliva may be important in transporting infected cells into tonsillar and intestinal crypts, and may facilitate HIV transmission during breastfeeding. Janoff *et al.* [64] found that levels of SLPI were well below the HIV-1 inhibitory level in breastmilk from nursing mothers from Rwanda and the United States. There was, however, an elevation of SLPI in colostrum. These observations support their epidemiologic counterparts that oral transmission may be low, but maternal–child transmission by breastmilk is appreciable [49].

Discussion

The epidemiologic and biologic features of HIV transmission undergo continuing reevaluation. In the case of oral transmission, dismissal in the early years of the epidemic [65] was replaced by anecdotal recognition of its possibility (Table 2), and more recently by studies which suggest that oral sex, especially ROI, is an independent risk factor for transmission (Table 1). There are several potential reasons for the discrepancy between early findings and more recent ones. First, earlier studies dealt almost exclusively with MSM, whose frequency and intensity of receptive anal intercourse may well have obscured any small effect of oral intercourse. Second, the recent studies of MSM [22,23] carefully delineated the time of seroconversion, and were thus dealing with sexual behavior that may have been more directly related to the actual transfer of virus. Third, these later studies have taken place at a time of changing sexual practices as well as increased HIV prevalence. As noted, the decline in unprotected receptive anal intercourse and the possibility that MSM are favoring ROI gives the latter's potential for transmission more prominence, whatever its actual magnitude [14,15]. Finally, the other studies that indicate the potential for oral transmission [16,24] were conducted in environments in which transmission by MSM does not predominate. Rather, young, inner-city, minority persons and prostitutes, whose risks are more linked to drug use and heterosexual activity, were the primary focus. In such circumstances, receptive anal intercourse,

although present, is less intense, oral intercourse may play a larger role, and its role may be more amenable to discovery.

Thus, the reevaluation of the role of oral transmission rests on a confluence of events that includes a decline in the risks that appear to be most effective in propagating the virus (e.g., infected blood products, anal sexual activity, needle-sharing), an increase in oral sexual activity, both among MSM and among persons who smoke crack cocaine, oral pathology that is associated with HIV infection, and oral lesions that may result directly from smoking crack cocaine. To these can be added the poor state of oral health of inner-city persons who use drugs, work as prostitutes, and are involved in the oral sexual activity that is a concomitant of crack cocaine use (unpublished observations). This confluence raises several issues of public health importance.

The presence of chronic conditions, the occurrence of chronic ulcerating lesions (candidiasis, herpes simplex virus infection, aphous ulceration, ulcers secondary to crack cocaine use), and the presence of many oral pathogens may provide an opportunity for facilitation of HIV transmission similar to that which occurs with sexually transmitted diseases [66] (J. Wasserheit, personal communication, 1998). In the genital tract, these conditions and pathogens create an environment of increased HIV shedding, and elevate the relative risk for HIV transmission by three- to fivefold. If such an analogy exists for the oral cavity, it is possible that such increased shedding could overwhelm the natural inhibitory activity of saliva and other oral secretions, and would contribute to the circumstances that heighten the importance of oral transmission. Just as treatment of sexually transmitted diseases in persons with and at risk for HIV may have an ameliorative effect on transmission, the aggressive treatment of oral lesions and conditions may reduce the potential for oral sexual transmission of HIV.

The need for more definitive epidemiologic and biologic evaluation is heightened by the problems of providing authoritative counseling to persons about the risks of HIV and oral sex. Currently, there is considerable ambiguity about what can be said, based on evidence, with regard to what is 'safe' and what is 'safer' [67]. Counseling guidelines are hotly debated, not only because of differing interpretations of the available data, but because of different approaches to how counseling should be conducted [68–71]. The recent introduction of antiviral therapy and viral load therapy has further complicated people's perception of risk and the tailoring of messages [72].

Some of the confusion may relate to a failure to clarify exactly what is meant by oral sex, a failure to distinguish between transmission and acquisition, and a neglect of the setting in which the sex act takes place.

In theory, oral sex could encompass insertive and receptive combinations of the oral cavity with four potential sexual sites: oral cavity, vagina, rectum, and penis. All eight combinations permit the exchange of saliva but only one, receptive penile–oral intercourse, may expose the receptor to semen. Current evidence would suggest that the risk of HIV transmission from exposure to saliva is considerably smaller than the risk from exposure to semen [13,25]. Thus, exposure to semen during the sex act probably imparts a heightened risk, and other oral sex acts may also differ with regard to the probability of HIV transmission. A rational approach to counseling would require better information on the nature of these risks, how they are affected by the oral milieu, and by local epidemiologic circumstances, and, by analogy with vaginal shedding of HIV [73], with plasma viral titer. Similarly, the proportional importance of oral sex to HIV transmission will be a complex result of the relative frequency of oral sex compared with other activities, infectivity of oral secretions and its modification by oral pathology, resistance to infection by inhibitory substances in saliva, the HIV prevalence in the community in which such activity takes place, the maturity of the epidemic in the community (given recent observations on differential infectivity by stage of infection [74,75]), the role of high activity antiretroviral therapy, and the extent to which personal prophylaxis is adopted.

A research agenda that clarifies the risk from oral sexual contact is certainly important for rational counseling and prevention, but even a firm estimate for transmission may not be adequate. The evidence from this review supports the notion that unprotected ROI is of low but non-trivial infectivity and widespread occurrence. It may be misleading to couch future recommendations in terms such as 'safe' and 'safer', which are ambiguous and subjective at best, since risk is a function of both the estimate for transmission and the frequency of the event. Perhaps recommendations and counseling that incorporate the importance of persons' awareness of their own risk orientation in personal decision-making can lead to a better appreciation of the spectrum of 'safety'.

References

1. Centers for Disease Control: **Acquired immunodeficiency syndrome (AIDS): precautions for health care workers and allied professionals.** MMWR 1983, 32:450–452.
2. Centers for Disease Control: **Recommendations for preventing transmission of infection with human T-lymphotrophic virus III/lymphadenopathy-associated virus in the workplace.** MMWR 1985, 34:681–696.
3. Centers for Disease Control: **Update: acquired immunodeficiency syndrome – United States.** MMWR 1985, 34:245–248.
4. Sande MA: **Transmission of AIDS. The case against casual contagion.** N Engl J Med 1986, 314:380–382.

5. Fischl MA, Dickinson GM, Scott GB, et al.: **Evaluation of heterosexual partners, children, and household contacts of adults with AIDS.** *JAMA* 1987, **257**:640-644.
6. Rogers MF, White CR, Sanders R: **Lack of transmission of HIV from infected children to their household contacts.** *Pediatrics* 1990, **85**:210-214.
7. Ward JW, Duxin JS: **The epidemiology of HIV and AIDS in the United States.** *AIDS Clin Rev* 1997-1998;1-45.
8. Hamers FF, Batter V, Downs AM, et al.: **The HIV epidemic associated with injecting drug use in Europe: geographic and time trends.** *AIDS* 1997, **11**:1365-1374.
9. Centers for Disease Control and Prevention: **Update: trends in AIDS incidence - United States, 1996.** *MMWR* 1997, **46**:861-867.
10. Stempel R, Gorman M, Shibuski S, et al.: **Changes in sexual practices and drug use among gay men in San Francisco.** *VIII International Conference on AIDS.* Amsterdam, July 1992 [abstract PoC4095].
11. Wiebel WW, Jimenez A, Johnson W, et al.: **Risk behavior and HIV seroincidence among out-of-treatment injection drug users: a four-year prospective study.** *J Acquir Immune Defic Syndr* 1996, **12**:282-289.
12. Osmond DH, Page K, Wiley J, et al.: **HIV infection in homosexual and bisexual men 18 to 29 years of age: the San Francisco Young Men's Health Study.** *Am J Public Health* 1994, **84**:1933-1937.
13. Mastro TD, de Vincenzi I: **Probabilities of sexual HIV-1 transmission.** *AIDS* 1996, **10**(suppl A):S75-S82.
14. Schwarcz SK, Kellogg TA, Kohn RP, et al.: **Temporal trends in human immunodeficiency virus seroprevalence and sexual behavior at the San Francisco municipal sexually transmitted disease clinic, 1989-1992.** *Am J Epidemiol* 1995, **142**:314-322.
15. Ostrow DG, DiFrancesco W: **Why some gay men choose condoms and others switch to 'safer' sex.** *XI International Conference on AIDS.* Vancouver, July 1996 [abstract Tu.D.365].
16. Faruque S, Edlin B, McCoy CB, et al.: **Crack cocaine smoking and oral sores in three inner-city neighborhoods.** *J Acquir Immune Defic Syndr* 1996, **13**:87-92.
17. Hoffman JA, Klein H, Clark DC: **HIV risk behavior among crack-using women.** *Latin American Congress on Sexually Transmitted Disease and Pan-American Conference on AIDS.* Lima, Peru, December 1997 [abstract PCV267].
18. Jaffe HW, Choi K, Thomas PA, et al.: **National case-control study of Kaposi's sarcoma and Pneumocystis carinii pneumonia in homosexual men: Part I, epidemiologic results.** *Ann Intern Med* 1983, **99**:145-158.
19. Groopman JE, Salahuddin SZ, Sarngadharan MG, et al.: **HTLV-III in saliva of people with AIDS-related complex and healthy homosexual men at risk for AIDS.** *Science* 1984, **226**:447-449.
20. Ho DD, Schooley RT, Rota TR, et al.: **HTLV-III in the semen and blood of a healthy homosexual man.** *Science* 1984, **226**:451-453.
21. Samuel MC, Hessol NA, Shibuski S: **Factors associated with human immunodeficiency virus seroconversions in homosexual men in three San Francisco cohort studies.** *JAIDS* 1993, **6**:303-312.
22. Ostrow DG, DiFrancesco WJ, Chmiel JS: **A case-control study of human immunodeficiency virus type 1 seroconversion and risk-related behaviors in the Chicago MACS/CCS cohort, 1984-1992.** *Am J Epidemiol* 1995, **142**:875-883.
23. Page-Shafer K, Veugelers PJ, Moss AR, et al.: **Sexual risk behavior and risk factors for HIV-1 seroconversion in homosexual men participating in the Tricontinental Seroconverter Study, 1982-1994.** *Am J Epidemiol* 1997, **146**:531-542.
24. Wallace JI, Bloch D, Whitmore R, et al.: **Fellatio is a significant risk activity for acquiring AIDS in New York City (NYC) street-walking sex workers.** *XI International Conference on AIDS.* Vancouver, July 1996 [abstract Tu.C.2673].
25. Royce RA, Sena A, Cates W, et al.: **Sexual transmission of HIV.** *N Engl J Med* 1997, **336**:1072-1078.
26. de Vincenzi I: **A longitudinal study of human immunodeficiency virus transmission by heterosexual partners.** *European Study Group on Heterosexual Transmission of HIV.* *N Engl J Med* 1994, **331**:341-346.
27. Koopman JS, Simon CP, Jacquez JA, et al.: **HIV transmission probabilities for oral and anal sex by stage of infection.** *XIII International Conference on AIDS.* Amsterdam, July 1992 [abstract PoC4101].
28. Vittinghoff E, Bucbinder SP, Judson F, Douglas J, McKirnan D, MacQueen K: **Per contact risk for transmission of HIV associated with four types of homosexual contact.** *Fifth Conference on Retrovirus and Opportunistic Infections.* Chicago, February 1998 [abstract 140].
29. Koopman JS, Simon CP, Jacquez JA, et al.: **Selective contact within structured mixing with an application to HIV transmission risk from oral and anal sex.** In *Mathematical and Statistical Approaches to AIDS Epidemiology.* Edited by Castillo-Chavez. Berlin: Springer-Verlag; 1989.
30. Stahl-Hennig C, Tenner-Racz C, Stolte N, et al.: **The tonsil as a portal of entry for simian immunodeficiency virus (SIV).** *15th Annual Symposium on Nonhuman Primate Models for AIDS.* Seattle, Washington, September 1997 [abstract 17].
31. Baba TW, Trichell AM, An L, et al.: **Infection and AIDS in adult macaques after nontraumatic oral exposure to cell-free SIV.** *Science* 1996, **272**:1486-1489.
32. Bosch ML, Schmidt A, Agy MB, Kimball LE, Morton WR: **Rectal but not oral administration of HIV-1 leads to productive infection in pigtailed macaques.** *HIV-1 Infection, Mucosal Immunity and Pathogenesis.* Natcher Conference Center, NIH. October 1997 [abstract p.52].
33. Pudney J, Oneta M, Mayer K, et al.: **Pre-ejaculatory fluid as potential vector for sexual transmission of HIV-1 [letter].** *Lancet* 1992, **340**:1470.
34. Ho DD, Byington RE, Schooley RT, et al.: **Infrequency of isolation of HTLV-III virus from saliva in AIDS.** *N Engl J Med* 1985, **313**:1606-1606.
35. Yeung SC, Kazazi F, Randle CG, et al.: **Patients infected with HIV-1 have low levels of virus in saliva even in the presence of periodontal diseases.** *J Infect Dis* 1993, **167**:803-809.
36. Barr CE, Miller LK, Lopez MR, et al.: **Recovery of infectious HIV-1 from whole saliva.** *J Am Dent Assoc* 1992, **123**:37-48.
37. Goto Y, Yen CK, Notkins AL, et al.: **Detection of proviral sequences in saliva of patients infected with HIV-1.** *AIDS Res Hum Retroviruses* 1991, **7**:343-347.
38. Queresi MN, Barr CE, Seshamma T, et al.: **Infection of oral mucosal cells by HIV type 2 in seropositive persons.** *J Infect Dis* 1995, **171**:190-193.
39. Shine N, Konopka K, Duzgunes N: **The anti-HIV-1 activity associated with saliva.** *J Dent Res* 1996, **76**:634-640.
40. Fultz P: **Components of saliva inactivate human immunodeficiency virus [letter].** *Lancet* 1986, **ii**:1215.
41. Malamud D, Friedman HM: **HIV in the oral cavity: virus, viral inhibitory activity, and antiviral antibodies.** *Crit Rev Oral Biol Med* 1993, **4**:461-466.
42. Archibald DW, Cole GA: **In vitro inhibition of HIV-1 infectivity by human salivas.** *AIDS Res Hum Retroviruses* 1990, **6**:1425-1432.
43. Baron S, Cloyd MW: **Why is HIV only rarely transmitted normally via the oral cavity?** *HIV-1 Infection, Mucosal Immunity and Pathogenesis.* Natcher Conference Center, NIH. October 1997 [abstract p.50].
44. Sanneman TC, Wahl SM, Youssef R, Janoff EN: **Specific and innate immune factors in saliva: concerted systemic and mucosal activity limiting HIV-1 infectivity.** *HIV-1 Infection, Mucosal Immunity and Pathogenesis.* Natcher Conference Center, NIH. October 1997 [abstract p.62].
45. Bergey EJ, Cho JE, Hammarskjold JL, et al.: **Aggregation of human immunodeficiency virus type 1 by human salivary secretions.** *Crit Rev Oral Biol Med* 1993, **4**:467-474.
46. Bergey EJ, Cho JE, Blumberg BM, et al.: **Interaction of HIV-1 and human salivary mucins.** *J Acquir Immune Defic Syndr* 1994, **7**:995-1002.
47. McNeely TB, Dealy M, Dripps DJ, et al.: **Secretory leukocyte protease inhibitor: a human saliva protein exhibiting anti-human immunodeficiency virus 1 activity in vitro.** *J Clin Invest* 1995, **96**:456-464.
48. Shugars DC, McNeely TB, Eisenberg S, et al.: **Secretory leukocyte protease inhibitor targets an early event in HIV infection [letter].** *J Dent Res* 1996, **75**:114.
49. Wahl SM, Worley P, Jin W, et al.: **Anatomic dissociation between HIV-1 and its endogenous inhibitor in mucosal tissues.** *Am J Pathol* 1997, **150**:1275-1283.
50. Parry JV, Perry KR, Mortimer PP: **Sensitive assays for viral antibodies in saliva: an alternative to tests on serum.** *Lancet* 1987, **ii**:72-75.
51. Johnson AM, Parry JV, Best SJ, Smith AM, de Silva M, Mortimer PP: **HIV surveillance by testing saliva.** *AIDS* 1988, **2**:369-371.

52. Emmons W: **Accuracy of oral specimen testing for human immunodeficiency virus.** *Am J Med* 1997, **102**:15-20.

53. Malamud D: **Oral diagnostic testing for detecting human immunodeficiency virus-1 antibodies: a technology whose time has come.** *Am J Med* 1997, **102**:9-14.

54. del Rio C, Guarner J, Izazola-Licea JA: **The use of oral fluid to determine HIV-1 prevalence rates among men in Mexico City [letter].** *AIDS* 1996, **10**:233-235.

55. Mealey BL: **Periodontal implications: medically compromised patients [review].** *Annu Periodontol* 1996, **1**:256-321.

56. Coates E, Slade GD, Goss AN, et al.: **Oral conditions and their social impact among HIV dental patients.** *Aust Dent J* 1996, **41**:33-36.

57. Cruz GD, Lamster IB, Begg MD, et al.: **The accurate diagnosis of oral lesions in human immunodeficiency virus infection. Impact on medical staging.** *Arch Otolaryngol Head Neck Surg* 1996, **122**:68-73.

58. Itin PH, Lautenschlager S, Fluckiger R, et al.: **Oral manifestations in HIV-infected patients: diagnosis and management.** *J Am Acad Dermatol* 1993, **29**:749-760.

59. Aldous JA, Aldous SG: **Management of oral health for the HIV-infected patient.** *J Dent Hyg* 1991, **65**:143-145.

60. Gandolfo AM, De Luca P, Modugno G, Mangione R: **The oral status of HIV+ patients. The clinico-statistical results with reference to 2 examination check-ups [in Italian].** *Minerva Stomatol* 1991, **40**:651-656.

61. Glick M, Muzyka BC, Salkin LM, et al.: **Necrotizing ulcerative periodontitis: a marker for immune deterioration and a predictor for the diagnosis of AIDS.** *J Periodontol* 1994, **65**:393-397.

62. Shibuski CH, Hilton JF, Greenspan D, et al.: **HIV-related oral manifestations in two cohorts of women in San Francisco.** *J Acquir Immune Defic Syndr* 1994, **7**:964-971.

63. Southern S, Southern PJ: **Oral transmission of HIV-1 during long-term breastfeeding.** *HIV-1 Infection, Mucosal Immunity and Pathogenesis.* Natcher Conference Center, NIH. October 1997 [abstract p.57].

64. Janoff EN, Eidman K, McNeely TB, et al.: **Secretory leukocyte protease inhibitor (SLPI), an HIV-1-inhibitory protein, and rates of HIV-1 transmission by mucosal fluids.** *HIV-1 Infection, Mucosal Immunity and Pathogenesis.* Natcher Conference Center, NIH. October 1997 [abstract p.51].

65. Lifson AR: **Do alternate modes for transmission of human immunodeficiency virus exist? A review.** *JAMA* 1988, **259**:1353-1356.

66. Dickerson MC, Johnston J, Delea TE, et al.: **The causal role for genital ulcer disease as a risk factor for transmission of human immunodeficiency virus. An application of the Bradford Hill criteria.** *Sex Transm Dis* 1996, **23**:429-440.

67. Ostrow DG, DiFrancesco WJ, Chmiel JS, et al.: **A case-control study of human immunodeficiency virus type 1 seroconversion and risk-related behaviors in the Chicago MACS/CCS cohort, 1984-1992.** *Am J Epidemiol* 1995, **142**:875-883.

68. Anonymous: **What to tell your clients about oral-sex risk.** *AIDS Alert* 1995, **10** (suppl 2):1-2.

69. Anonymous: **Is oral sex safer sex? An AIDS education dilemma.** *AIDS Alert* 1995, **10**:112,117-112,118.

70. Anonymous: **Researchers warn oral sex riskier than expected.** *AIDS Alert* 1996, **11**:109-111.

71. Anonymous: **Oral sex.** *AIDS Policy Law* 1996, **11**:12.

72. Kravcik S, Victor G, Houston S, et al.: **The effect of protease inhibitor therapy and 'undetectable' viral load on perceived risk of HIV transmission and the need for safer practices.** *Fifth Conference on Retrovirus and Opportunistic Infections.* Chicago, February 1998 [abstract 187].

73. Hart C, Palmore M, Wright T, et al.: **Correlation of cell-free and cell-associated HIV RNA levels in plasma and vaginal secretions.** *Fourth Conference on Retroviruses and Opportunistic Infections.* Washington, DC, January 1997 [abstract 25].

74. Jacquez JA, Koopman JS, Simon CP, et al.: **Role of the primary infection in epidemics of HIV infection in gay cohorts.** *J Acquir Immune Defic Syndr* 1994, **7**:1169-1184.

75. Koopman JS, Jacquez JA, Welch GW, et al.: **The role of early HIV infection in the spread of HIV through populations.** *J Acquir Immune Defic Syndr* 1997, **14**:249-258.

76. Jaffe HW, Choi K, Thomas PA, et al.: **National case-control study of Kaposi's sarcoma and *Pneumocystis carinii* pneumonia in homosexual men: Part 1. Epidemiologic results.** *Ann Intern Med* 1983, **99**:145-158.

77. Marmor M, Friedman-Kien AE, Zolla-Pazner S, et al.: **Kaposi's sarcoma in homosexual men: a seroepidemiologic case-control study.** *Ann Intern Med* 1984, **100**:809-815.

78. Goedert JJ, Sarngadharan MG, Biggar RJ, et al.: **Determinants of retrovirus (HTLV-III) antibody and immunodeficiency conditions in homosexual men.** *Lancet* 1984, **ii**:711-716.

79. Newell GR, Mansell PWA, Wilson MB, et al.: **Risk factor analysis among men referred for possible acquired immune deficiency syndrome.** *Prev Med* 1985, **14**:81-91.

80. Lyman DM, Winkelstein W, Ascher M, Levy JA: **Minimal risk of transmission of AIDS-associated retrovirus infection by oral-genital contact [letter].** *JAMA* 1986, **255**:1703.

81. Moss AR, Osmond D, Bacchetti P: **Risk factors for AIDS and HIV seropositivity in homosexual men.** *Am J Epidemiol* 198, **12**:1035-1047.

82. Winkelstein W, Lyman DM, Padian N: **Sexual practices and risk of infection by the human immunodeficiency virus: the San Francisco Men's Health Study.** *JAMA* 1987, **257**:321-325.

83. van Griensven GJP, Tielman RAP, Goudsmit J: **Risk factors and prevalence of HIV antibodies in homosexual men in the Netherlands.** *Am J Epidemiol* 1987, **125**:1048-1057.

84. Fischl MA, Dickinson GM, Scott GB, et al.: **Evaluation of heterosexual partners, children, and household contacts of adults with AIDS.** *JAMA* 1987, **257**:640-644.

85. Darrow WW, Echenberg DF, Jaffe HW, et al.: **Risk factors for human immunodeficiency virus (HIV) infections in homosexual men.** *Am J Public Health* 1987, **77**:479-483.

86. Kingsley LA, Kaslow RA, Rinaldo CR: **Risk factors for seroconversion to human immunodeficiency virus among male homosexuals.** *Lancet* 1987, **i**:346-349.

87. McCusker J, Stoddard AM, Mayer KH, et al.: **Behavioral risk factors for HIV infection among homosexual men at a Boston community health center.** *Am J Public Health* 1988, **78**:68-71.

88. Peterman TA, Stoneburner RL, Allen JR, et al.: **Risk of human immunodeficiency virus transmission from heterosexual adults with transfusion-associated infections.** *JAMA* 1988, **259**:55-58.

89. Osmond D, Bacchetti P, Chaisson RE, et al.: **Time of exposure and risk of HIV infection in homosexual partners of men with AIDS.** *Am J Public Health* 1988, **78**:944-948.

90. Coates RA, Calzavara LM, Read SE: **Risk factors for HIV infection in male sexual contacts of men with AIDS or an AIDS-related condition.** *Am J Epidemiol* 1988, **128**:729-739.

91. Burcham JL, Tindall B, Marmor M: **Incidence and risk factors for human immunodeficiency virus seroconversion in a cohort of Sydney homosexual men.** *Med J Aust* 1989, **150**:634-639.

92. Evans BA, McLean KA, Dawson SF: **Trends in sexual behavior and risk factors for HIV infection among homosexual men 1984-1987.** *BMJ* 1989, **298**:215-218.

93. Kuiken CL, Griensven GJP, de Vroome EMM: **Risk factors and changes in sexual behavior in male homosexuals who seroconverted for human immunodeficiency virus antibodies.** *Am J Epidemiol* 1990, **132**:523-530.

94. Raiteri R, Fora R, Sinicco A: **No HIV-1 transmission through lesbian sex [letter].** *Lancet* 1994, **344**:270.

95. Lifson AR, Darrow WW, Hessel NA, et al.: **Kaposi's sarcoma among homosexual and bisexual men enrolled in the San Francisco City Clinic Cohort Study.** *J Acquir Immune Defic Syndr* 1990, **3** (suppl 1):S32-S37.

96. Winkelstein W, Samuel MC, Padian NS: **The San Francisco Men's Health Study III: reduction in human immunodeficiency virus transmission among homosexual/bisexual men.** *Am J Public Health* 1987, **77**:685-689.

97. Winkelstein W Jr, Wiley JA, Padian NS, et al.: **The San Francisco Men's Health Study: continued decline in HIV seroconversion rates among homosexual/bisexual men.** *Am J Public Health* 1988, **78**:1472-1474.

98. van Griensven GJP, de Vroome EMM, Goudsmit J: **Changes in sexual behavior and the fall in incidence of HIV infection among homosexual men.** *BMJ* 1989, **298**:218-221.

99. Schechter MT, Craib KJP, Willoughby B: **Patterns of sexual behavior and condom use in homosexual men.** *Am J Public Health* 1998, **78**:1535-1538.

100. Chmiel JS, Detels R, Kaslow RA: **Factors associated with prevalent human immunodeficiency virus (HIV) infection in the Multicenter AIDS Cohort Study.** *Am J Epidemiol* 1987, **126**:568-577.

101. Sabatini MT, Patel K, Hirschman R: **Kaposi's sarcoma and T-cell lymphoma in an immunodeficient woman: a case report.** *AIDS Res* 1984, **1**:135-137.
102. Marmor M, Weiss LR, Lyden M, et al.: **Possible female-to-female transmission of human immunodeficiency virus [letter].** *Ann Intern Med* 1986, **105**:969.
103. Mayer KH, DeGruttola V: **Human immunodeficiency virus and oral intercourse.** *Ann Intern Med* 1987, **107**:428-429.
104. Monzon OT, Capellan JMB: **Female-to-female transmission of HIV.** *Lancet* 1987, **ii**:40-41.
105. Rozenbaum W, Gharakhanian S, Cardon B, et al.: **HIV transmission by oral sex [letter].** *Lancet* 1988, **i**:1395.
106. Goldberg DJ, Green ST, Kennedy DH, Emslie JA, Black JD: **HIV and orogenital transmission [letter].** *Lancet* 1988, **ii**:1363.
107. Perry S, Jacobsberg L, Fogel K: **Orogenital transmission of human immunodeficiency virus (HIV).** *Ann Intern Med* 1989, **111**:952-953.
108. Detels R, English P, Visscher BR, et al.: **Seroconversion, sexual activity, and condom use among 2915 HIV seronegative men followed for up to 2 years.** *J Acquir Immune Defic Syndr* 1989, **2**:77-83.
109. Spitzer PG, Weiner NJ: **Transmission of HIV infection from a woman to a man by oral sex [letter].** *N Engl J Med* 1989, **320**:251.
110. Quarto M, Germinario C, Troiano T, et al.: **HIV transmission by fellatio [letter].** *Eur J Epidemiol* 1990, **6**:339-340.
111. Lifson AR, O'Malley PM, Hessol NA, et al.: **HIV seroconversion in two homosexual men after receptive oral intercourse with ejaculation: implications for counseling concerning safe sexual practices.** *Am J Public Health* 1990, **80**:1509-1511.
112. Murray BA, Greenhouse PRDH, Nelson WLC, et al.: **Coincident acquisition of *Neisseria gonorrhoeae* and HIV from fellatio.** *Lancet* 1991, **338**:830-830.
113. Lane HC, Holmberg SD, Jaffe HW: **HIV seroconversion and oral intercourse.** *Am J Public Health* 1991, **81**:658-658.
114. Keet IPM, van Lent NA, Sandfort TGM, et al.: **Orogenital sex and the transmission of HIV among homosexual men.** *AIDS* 1992, **6**:223-226.
115. Rich JD, Buck A, Tuomata RE, et al.: **Transmission of human immunodeficiency virus infection presumed to have occurred via female homosexual contact.** *Clin Infect Dis* 1993, **17**:1003-1005.
116. Vidmar L, Poljak M, Tomazic J, Seme K, Klavs I: **Transmission of HIV-1 by human bite [letter].** *Lancet* 1996, **347**:1762.
117. Schacker T, Collier A, Shea T, et al.: **Oral/genital contact as an increasing means of HIV acquisition among men who have sex with men.** *XI International Conference on AIDS.* Vancouver, July 1996 [abstract TUC2694].
118. Berry MM, Shea T: **Oral sex and HIV transmission [letter].** *J Acquir Immune Defic Syndr* 1997, **14**:475-477.
119. Padian N, Glass S: **Transmission of HIV possibly associated with exposure of mucous membrane to contaminated blood.** *MMWR* 1997, **46**:620-623.
120. Bratt GA, Berglund T, Glantzberg BL, et al.: **Two cases of oral-to-genital HIV-1 transmission.** *Int J STD AIDS* 1997, **8**:522-525.
121. Senterfitt JW, Harawa NT, Whitefield C, Kerndt PR, Daar E: **Study of acute and early infections yields surprising risk profile.** *Fifth Conference on Retrovirus and Opportunistic Infections.* Chicago, February 1998 [abstract 141].
122. Levy JA, Greenspan D: **HIV in saliva [letter].** *Lancet* 1988, **ii**:1248.
123. Schioldt M, Greenspan D, Levy JA, et al.: **Does HIV cause salivary gland disease?** *AIDS* 1989, **3**:819-822.
124. O'Shea S, Cordery M, Barrett WY: **HIV excretion patterns and specific antibody response in body fluids.** *J Med Virol* 1990, **31**:291-296.
125. Lucht E, Albert J, Linde A: **Human immunodeficiency virus type 1 and cytomegalovirus in saliva.** *J Med Virol* 1993, **39**:156-162.
126. Moore BE, Flaitz CM, Coppenhaver DH, et al.: **HIV recovery from saliva before and after dental treatment: inhibitors may have a critical role in viral inactivation.** *J Am Dent Assoc* 1993, **124**:67-74.