Correspondence

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Human bites: a rare risk factor for HIV transmission

In a paper published in 1993, Richman and Rickman [1] had concluded that 'transmission of HIV through human bites is biologically possible but remains epidemiologically insignificant, and as yet, not well documented' [2].

We report a case of a child, who at the age of 3 years was bitten on the middle finger of her left hand by her father in September 2000, causing bleeding at the site. He had multiple sex partners in the past and had a history of dental caries and bleeding gums for years. He was known to have diabetes. He was first discovered to be HIV-antibody positive in June 2004, 3 years after the bite. His CD4 cell count was 4 cells/μl. No viral load assay was done. He died on 17 September 2004.

The child's mother was HIV-antibody negative when tested in June 2004. Sexual intercourse had been infrequent over the past 7 years because he was impotent as a result of his diabetes. Recalling the incident of the bite, the young child was brought by the mother to the clinic of the Medical Research Centre, Port of Spain, Trinidad, for testing. Her HIV antibody assay was positive by enzyme-linked immunosorbent assay and Western blot, her viral load was 20 909 copies/ml and her CD4 cell percentage was 23%. There was no history of sexual abuse or blood transfusion. The cause of the child's infection is believed to be a direct result of the bite from her father.

The first suggestion that the transmission of HIV by a human bite was biologically possible was in a paper by Wahn *et al.* [3] from Dusseldorf in 1986, who reported that a young child had died of AIDS at one year of age. There were no risk factors for the child's infection other than a bite on his forearm by his younger HIV-positive brother approximately 6 months before he died. It was suggested that the likely route of virus transmission was the bite from the seropositive younger brother.

In August 1987, there was a brief case report of a 26-year-old healthcare worker with no risk factors for HIV infection, who in early 1985 had a fight with her sister, an HIV-positive intravenous drugs abuser since 1980. During the fight, which caused bleeding in the mouth, she was bitten on the leg by her HIV-positive sister. Stored sera from the bitten sister was found to be HIV-antibody seronegative on 10 August 1983 (before the fight), but she was discovered to be seropositive on 12 January 1987. It was believed that the most likely route of her infection was the bite from her sister [4].

In 1996, Vidmar *et al.* [5] reported the case of a 47-year-old man, who, during late-stage HIV infection with a high HIV-RNA count, had a grand mal seizure in May 1995. A neighbour was bitten when placing his fingers in the man's mouth trying to prevent obstruction of his airway. The bite resulted in a small crack and a shallow wound on the left index fingernail. There was blood in the epileptic patient's saliva from a bite wound on his tongue as a result of the seizure. He died 13 days after the incident. Serum taken from the bitten man on the day of the incident was negative for HIV antibodies, p24 antigen and HIV RNA. However, he seroconverted 54 days after the incident.

Andreo *et al.* [6] in 2004 reported a case of an HIV-positive 31-year-old man who bit his mother on her hand during a seizure in November 1999. Blood was present in his mouth at the time of the bite, and the mother needed a suture in her hand. She was a 59-year-old widow who had had no sexual intercourse for the past 10 years. Forty days after the bite, she was found to be HIV positive by enzyme-linked immunosorbent assay and Western blot. A sensitive/less sensitive immunoassay of the blood sample confirmed a recent infection with HIV [7].

Apart from the brief case report of 1987 [4], which gave no indication of the stage of infection of the source patient, all the other transmissions of HIV from human bites were from patients in late-stage disease [8,9].

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Concerns regarding a randomized trial of two postexposure prophylaxis regimens

I would like to raise the following issues regarding your recent article by Gray *et al*. [1].

Perhaps as a result of the small sample size, exclusive and mixed breast-fed infants were combined into the same group. For some of the outcomes examined, keeping these groups separate is otherwise preferable.

Although the risk of mother-to-child transmission of HIV was twice as high in breast milk-exposed (BME) infants in multivariate analysis when the entire sample was included, the data for those receiving nevirapine, the option the authors clearly and with good reason suggest is preferred showed no statistically significant difference in the rates of mother-to-child transmission between BME infants and those not so exposed.

Among infants who received nevirapine, there was a 6.3% rate of transmission in the BME group at less than 10 days; the exclusively formula-fed group was 44% higher at 9.1%. This was not tested for significance but sample sizes were small.

There has previously been speculation that early breast milk may be protective against transmission, which otherwise can occur at or near labor [2]. Perhaps a meta-analysis should be performed to examine the possibility in a larger sample size.

Rates of transmission in the BME group treated with 6 weeks of zidovudine increased rapidly: from 5.1% at less than 10 days to 14.5% at 6 weeks to 20.6% at 12 weeks. Because this is more rapid than has been seen in untreated infants [3], the possibility that longer-term postnatal dosing with zidovudine actually increases breast milk transmission rates cannot be ruled out. This possibility urgently needs to receive further research, given the World Health Organization's recent decision to recommend the use of 4 weeks of zidovudine treatment to infants born to HIV-positive women who did not get prophylaxis during pregnancy [4].

The authors stated that there was 'no increased mortality in the formula-fed group' based on the lack of statistical significance of that group's 72% higher death rate (3.8 versus 2.2%). This strikes me as a statement far beyond what the data support, given that the sample size was not adequate to measure mortality differences if they were indeed occurring.

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Cidofovir treatment of HIV-associated cytomegalovirus polyradiculopathy

Cytomegalovirus polyradiculopathy is an unusual complication of late-stage HIV infection, with a 100% mortality in the era before effective therapies [1–5]. We present the first report of the successful treatment of this condition with cidofovir with HAART, a previously unreported regimen.

In June 2004, a 34-year-old woman with long-standing HIV infection presented with faecal incontinence, urinary hesitancy and low backache. She was diagnosed with HIV in 1998 after presenting with cerebral toxoplasmosis, and since diagnosis had multiple HIV-related complications exacerbated by poor adherence to

antiretroviral therapy and multiple drug-resistant HIV. She had suffered severe cytomegalovirus retinitis and experienced ganciclovir-induced myelosuppression while undergoing treatment. At this presentation she had not taken any HIV treatment or cytomegalovirus prophylaxis for over one year. She had pre-existing peripheral neuropathy and vulval ulceration caused by herpes simplex virus infection. Examination revealed symmetrical flaccid weakness (power 3/5 all groups) of her lower limbs, sensory loss affecting all modalities from T11 to L3, and a loss of knee and ankle jerks with upgoing plantar reflexes. There was no evidence of active retinopathy.

Her CD4 cell count was 28×10^6 cells/μl on admission and had been consistently less than 70×10^6 cells/μl for the preceding year. The HIV viral load was 1 500 000 copies/ml. An enhanced magnetic resonance imaging scan of the entire spine did not reveal any compressive pathology, but did show meningeal enhancement from L1 to L4. A lumbar puncture revealed 2270 white cells/ml (97% polymorphs) and 415 red cells/ml. A Gram stain and auramine phenol stain of the cerebrospinal fluid (CSF), cryptococcal antigen, herpes simplex, varicella zoster virus, enteroviruses, parechoviruses, Epstein–Barr virus and JC virus polymerase chain reactions and pneumococcal antigen were all negative as were appropriate cultures of both blood and CSF. CSF biochemistry showed a protein level of 2.43 g/dl and glucose 1.5 mmol/l (30% of serum). In the CSF cytomegalovirus was present at the very high level of 2.0×10^7 genome copies/ml compared with the much lower level of cytomegalovirus in the plasma of 5450 genome copies/ml (measured concurrently).

Cytomegalovirus treatment was instigated in order to reduce cytomegalovirus viraemia until immune restoration with HAART. Effective therapeutic options for active cytomegalovirus disease were limited, and cidofovir was chosen as the agent least likely to cause complications. Ganciclovir was contraindicated because of previous severe myelosuppression, and foscarnet was avoided in view of her genital ulceration. Initial therapy was based on cidofovir regimens for cytomegalovirus retinitis, with 5 mg/kg intravenously fortnightly, with prehydration and probenicid modified for her reduced glomerular filtration rate. This was continued for 5 weeks, with no complications or deterioration in renal function, after which she received a monthly regimen.

From admission to the initiation of therapy on day 4, progression of the polyradiculopathy had resulted in a sensory level at T8 and global power reduction in both lower limbs varying from 0 to 1/5 by muscle group. By the end of the first week of therapy this progression appeared to have halted, with the sensory level remaining at T8 and by week 4 there was a drop in sensory level and an improvement in power in both lower limbs.

Despite clinical signs of recovery, the cytomegalovirus viraemia was slow to decrease. At week 4 a double-boosted protease inhibitor HAART regime based on resistance testing was started (lopinavir/ritonavir, atazanavir and zalcitabine), and it was only after starting HAART that cytomegalovirus was undetectable in the blood by polymerase chain reaction. Her sensory level continued to fall and muscle power increased. Rehabilitation was undertaken on our ward with intensive physiotherapy and occupational therapy input. Six months after admission, she was able to mobilize independently with a frame and transfer from bed to chair. She was discharged home, where she remains under follow-up one year after admission.

This appears to be the first report of cytomegalovirus polyradiculopathy being successfully treated with cidofovir followed by HAART.

Although neurological complications of cytomegalovirus occur in less than 1% of cytomegalovirus infections in HIV [6,7], the frequency of cytomegalovirus infection in HIV is such that clinicians need to be aware of its clinical spectrum, including cytomegalovirus polyradiculopathy. This patient had a classical presentation both clinically and in terms of her CSF and radiology findings, with no evidence of alternative pathology. Untreated cytomegalovirus polyradiculopathy carries 100% mortality from progressive cytomegalovirus disease, and still carries a 22% mortality rate [8] with anticytomegalovirus therapy.

Ganciclovir is considered first-line therapy for most cytomegalovirus-related diseases [9], but second-line agents are often needed as a result of frequent toxicity. When ganciclovir therapy is contraindicated or has failed, monotherapy for cytomegalovirus with foscarnet still has a mortality rate as high as 60–70% [8], and cidofovir may be an effective alternative.

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Pakistan/India open borders ... to HIV?

It finally seems that India and Pakistan have realized the eternal truth: 'War is not a solution'. Amicability between the two nations is peaking right now, compared with a few years ago when the two countries were on the brink of a nuclear debacle. Warmth in diplomatic relations is in vogue now; a bus service is being run in the disputed Kashmir region, and there is even talk of making Siachen, the world's highest battlefield, a Glacier of Peace. All of this may seem to be a call from heaven, but a silent killer also lurks in the shadows. India currently has an HIV burden of 5.1 million [1]. Pakistan's projection, on the other hand, lies under 0.1 million [2]. With the recent thaw in relations, India/Pakistan transborder movement is being encouraged by both the governments. Decades-old shut doors have now opened to a number of possibilities, good and bad. Among the latter is the risk of HIV transmission from India to Pakistan. A small epidemic in Pakistan, so far confined only to certain high-risk pockets of population, now faces the chance of getting out of control.

For the first time ever, encouraged by the establishment of the South Asia Free Trade Agreement (SAFTA), a great bustling of economic activity has started across the Indo-Pak border. This would practically translate into a greater mobility of goods over the border. This means that truck drivers, one of the recognized routes of spread of HIV, would be allowed to move more freely across border. Studies show that India's long-distance truck drivers average 200 sexual encounters per year. HIV seroprevalence among truckers with sexually transmitted diseases (STD) in Madras approaches an astounding 91% [3]. The story is equally grim in Pakistan. A survey at Mauripur, one of Asia's biggest truck terminals, through which some 20 000 truck drivers, their assistants and cleaners pass every day, revealed 56% of them as having extramarital relations [4]. Several research articles also link the outbreak of HIV in Pakistan to repatriates who got infected during their stay in the states of the Arabian Gulf [4]. Pakistanis, once out of their country, probably find themselves no longer obligated to their conservative religious and cultural codes. Free of the orthodox shackles, they are anxious to indulge in what they desire. Now that the Indian borders are open, all sorts of wonders await exploration from curious Pakistani tourists; the neighboring Kamathipura, Mumbai's oldest and Asia's largest red-light district, for example, housing over 70 000 prostitutes, a fair proportion of them HIV positive. The same argument works for Indian tourists in Pakistan. With the relaxing of the visa regimen by the Pakistani government, the Travel Agents Association of India (TAAI) estimates approximately half a million tourists from India every year. The transfusion of unscreened blood is yet another recognized source of HIV transmission. Blood donation in India as well as in Pakistan is low, because of low awareness; so at any time, a dire need for blood exists. It is estimated that 40% of the 1.5 million annual blood transfusions in Pakistan are not screened for HIV or hepatitis virus [5]. The condition in India is similarly apathetic. The rise of hepatitis C in this part of the world should serve as an eye-opener for the future; blood transfusions should help to bring a new life, not death. Finally, bearing in mine the appalling literacy rate (in 2001, the illiteracy rate for Pakistani women over 15 year old was 72%) [6], one of the weakest healthcare systems and a burgeoning population (growth rate of Pakistan lies at 2.5%) [6], the potentials for the spread of HIV are enormous. The social and religious stigma attached to contraception only helps to add fuel to the fire.

Peace is undoubtedly the New World Order. The recent clearing of the war clouds in South-Asia is indeed a very promising sign, but it also warrants caution. Indian and Pakistani governments, keen on promoting interregional friendliness, must also prepare for the risks that it entails. Both governments need to work together to modify their policies concerning immigration and travel across borders. Travellers should be required by law to get screened for HIV before crossing borders. In addition, public awareness programmes must be implemented to educate travellers about the risks of HIV, and to discourage careless sexual practices. Time is of the essence now because an HIV epidemic in Pakistan is already in the making. For the peace to survive and prosper between India and Pakistan, the war against HIV, sexual illiteracy, and complacent health policies must begin.

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HIV-discordant couples and parenthood: how are we dealing with the risk of transmission?

Parenthood is a strong, biologically motivated, instinctive desire. In the past, individuals infected with HIV struggled with the dilemma of a limited life expectancy and the strong wish to reproduce themselves. The risk of viral transmission to uninfected partners and offspring posed an additional barrier to conception. Many couples have practised unprotected intercourse to conceive, despite the risk of HIV transmission. The introduction of antiretroviral therapy with dramatically improved life expectancy has resulted in a resurgence of interest in parenting by HIV-affected couples.

Since its introduction by Semprini *et al*. [1] in 1992, several European antiretroviral therapy clinics have adopted the approach of intrauterine insemination with processed semen and other risk-reduction measures to minimize the risk of HIV transmission in discordant couples with infected male partners. More than 4500 inseminations have been performed without the apparent transmission of HIV to the uninfected female partner (manuscript in preparation). Although semen washing is relatively simple and inexpensive, polymerase chain reaction (PCR) testing of the final sperm aliquot to ensure HIV removal, and intensive medical supervision, render the final costs above the financial means of most HIV-discordant couples. In addition, patients may often need to travel long distances to reach these specialized units.

In Milan and St Gallen, approximately 30% of couples did not start the insemination process after initial counseling. Another 30% subsequently withdrew after a number of failed cycles. A recent survey from the Milan centre involving 500 HIV-discordant couples who participated in the insemination programme found that almost half of the couples who did not conceive with artificial insemination attempted spontaneous conception through unprotected intercourse, and at least one infection occurred. The percentage of spontaneous conception attempts increased up to fivefold in couples residing a long distance from the centre. Finally, reproductive assistance for HIV-discordant couples is not widely available outside of Europe, including regions of the world with the highest HIV prevalence. The number of HIV-discordant couples worldwide practising unprotected sex for the purpose of conception could number in the millions.

The counseling provided to HIV-discordant couples seeking assisted reproduction at these centres includes a discussion of strategies aimed at maximizing protection from HIV transmission (such as adoption, intrauterine insemination or in-vitro fertilization and intracytoplasmic sperm injection with processed semen), but also includes important information on other risk-reduction measures that draw on recent advances in therapeutics and a scientific understanding of factors underlying HIV transmission. We propose that this information be provided to all HIV-discordant couples seeking reproductive advice. Ideally, counseling should include a discussion of what is known, and the effectiveness of each strategy. Unfortunately, at present, data on the efficacy of most of the risk-reduction strategies listed below are unavailable as there has been no systematic data collection on how often these measures are used and with what outcomes.

The possible HIV risk-reduction measures for HIV-infected men with HIV-uninfected partners can be divided into five categories: (i) Optimization of the chances of conception. Fertility should be confirmed in both partners; couples should be counseled to practise unprotected intercourse only during the fertile window of a woman's cycle, identified by luteinizing hormone peak measurement in the urine when possible. (ii) Suppression of viral load. HIV transmission risk is related to peripheral and seminal HIV viral load. Men with peripheral viral loads greater than 1000 should be treated with antiretroviral therapy to suppress the seminal viral load and transmission risk. Confirmation of undetectable HIV RNA in the seminal plasma is recommended, when possible. (If HIV viral load cannot be suppressed, sperm wash/intrauterine insemination should be recommended.) (iii) The exclusion and treatment of genital tract infections or inflammatory processes in both partners and the avoidance of products and practices that irritate the vaginal epithelium. Bacterial vaginosis and infections with herpes simplex virus 2, *Trichomonas vaginalis*, *Chlamydia trachomatis*, *Neisseria gonorrhoeae* and

Treponema pallidum can increase HIV transmission [2]. Vaginal products that contain nonoxynol-9 or other irritants [3], and the practice of dry sex [4], anal intercourse and other behaviours that lacerate genital mucosal surfaces are other risk factors for HIV transmission and should be avoided. (iv) Experimental approaches to reduce further the susceptibility of the uninfected woman should be discussed, with the proviso that data supporting their potential efficacy are preliminary: (a) Pre-exposure prophylaxis [5,6]. Tenofovir was recently recommended as pre-exposure prophylaxis because of the limited presence of tenofovir resistance, its rapid mode of action during the pre-integration phase of viral replication and its long intracellular half-life (> 60 h) [7]. Given the rapid uptake of tenofovir, we suggest one tablet of tenofovir taken orally 2 h before the unprotected sex act; (b) The vaginal application of estriol gel during the first 5 days of the menstrual cycle. This method has been shown to protect macaques from vaginal challenge with SIV by increasing the thickness of the vaginal epithelium [8]. The gel has been widely used by postmenopausal women and appears to be non-toxic and not irritating. (v) Immediately discontinue unprotected intercourse should pregnancy occur because seroconversion during pregnancy greatly increases the risk of fetal infection. Also, retest the partner for HIV during pregnancy as the use of antiretroviral drugs reduces the risk of transmission to the baby [9].

The purpose of this commentary is to start a discussion about the appropriateness of such counseling, and to call for a central registry that collects information from physicians worldwide about their individual experience with the reproductive counseling of HIV-discordant couples.

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