Enhanced risk of HIV sexual transmission during structured treatment interruption

We report a case of HIV transmission through sexual intercourse while the sexual partner underwent antiretroviral structured treatment interruption. We would like to underline that giving proper information about a higher contamination risk during structured treatment interruption is a critical issue. Moreover, we consider that it is the responsibility of a medical investigator and physician to deliver a clear message in order to reinforce prophylaxis indications for sexual intercourse during this period.

A patient was infected with HIV for 9 years when he started HAART. At this time, his CD4 count was 280 × 10^3/μl and plasma viral load was 5.1 log_{10}/ml. A first structured treatment interruption (2 months’ duration) was proposed after 2 years, while plasma viral load was undetectable. He was asked to use preservatives strictly at this time. A peak of HIV replication was observed (4.3 log_{10}/ml). A71V, and V77I) in both patients without any mutation on reverse transcriptase, which is another point to suggest the virus transmission by our patient.

Our HIV infected patient told us that he practised safe sex systematically during the first years of HIV infection, but that it was less systematic when viral load became undetectable (around 20% of unprotected sexual intercourse during the past 2 years with this partner). He practised safe sex during the first structured treatment interruption, but not during the second one. Both of them denied any record of sexually transmitted infection except HIV. They were found to be negative for hepatitis B and C and syphilis.

Structured treatment interruption is an attractive strategy currently in evaluation in HIV-1 infected patients after long term viral suppression. As far as we know, antiretroviral interruption does not reduce therapy efficacy once reinitiated, delaying the reduction of viral load.1 During the phase of drug interruption, plasma HIV RNA rebounds to detectable levels within days of stopping HAART (mean increase 0.2 log/day).2 HAART treatment decreases HIV RNA concentration in blood and is generally associated with a decrease of seminal HIV RNA.3 Moreover, an increase of HIV RNA in plasma is known to enhance the risk of transmission.4 Finally, we may assume that a sudden increase in HIV RNA in blood during structured treatment interruption may induce a viral rebound in semen.

Some key messages have to be taken into account. Firstly, the impact of sexual transmission during clinical trials assessing the benefit/risk ratio of structured treatment interruption has to be evaluated prospectively as a side effect of the strategy. Secondly, patients have to be informed that they are particularly at risk of HIV transmission during this period and that sexual relations during this period and that sexual relations with other sexual partners during this period, as well as any other risk factor for HIV transmission. Moreover, genetic sequencing of the viruses, which was performed in both patients at the same date, revealed minor mutations on the protease gene (L63P, A71V, and V71I) in both patients without any
Cytokine profiles in HIV seropositive patients with tuberculous meningitis

The immunological response in pulmonary and pleural tuberculosis has been extensively studied. However, the response in tuberculous meningitis has not been well documented. In pulmonary disease, exposure to tuberculous antigens results in a T cell and natural killer cellular response, elaborating various cytokines, mainly of T helper type 1 (Th1) origin. Stimulated macrophages elaborate tumour necrosis factor (TNF) α, interleukin (IL) 12, and IL 1, promoting further recruitment and activation of macrophages and lymphocytes. TNF α correlates with disease severity and may contribute to tissue necrosis; however, TNFα has also contributed to survival in mouse studies. Transforming growth factor β (Th3 cytokine) suppresses macrophage activation. IL 2 may be beneficial in promoting an immune response in HIV seropositive patients. Th1 and Th2 cytokine responses have been observed in cerebrospinal fluid (CSF) of HIV seronegative patients with tuberculous meningitis. Whether the response is similar in HIV seropositive patients with tuberculous meningitis is unknown.

We studied the cytokine response and its correlation with disease severity in HIV seropositive and HIV seronegative patients with tuberculous meningitis.

Tuberculous meningitis was diagnosed on clinical and CSF examination after exclusion of viral, acute bacterial, and other causes of aseptic meningitis. Disease severity was assessed according to the Medical Research Council stages 1 to 3. HIV ELISA was done on all patients. CSF samples were subjected to microscopy, culture, protein and glucose analysis, Venereal Disease Research Laboratory test, fluorescent treponemal antibody analysis, cryptococcal antigen analysis, viral studies, cysitercirus ELISA, CD4 counts, and determination of concentrations of adenosine deaminase (ADA), CSF IgG, and albumin. For cytokine assays, CSF was centrifuged at 3000 g, and supernatant was aliquoted and stored at −70°C. TNF α, interferon (IFN) γ, and IL 10 concentrations were measured by ELISA kits (Genzyme Diagnostics, Cambridge, Massachusetts, USA) with detection limits of 3 pg/ml, 3 pg/ml, and 5 pg/ml, respectively. Data were summarised as medians and ranges. Non-parametric Wilcoxon rank sum tests were used to compare HIV seropositive groups with HIV seronegative groups, tuberculous meningitis severity groups, and groups derived according to the blood brain barrier index for cytokine concentrations. Spearman’s rank correlation was used to derive correlations of cytokine concentration, ADA concentrations, and CD4 counts in CSF.

There were 27 patients: 18 (67%) women and 9 (33%) men. Seventeen were HIV seropositive and 10 HIV seronegative. The average interval between onset of symptoms and the first clinical assessment was 17 days (range 5–90 days) in 18 patients where this was recorded. The mean (SD) age was 26.8 (11.6) years. There was one patient aged 10 and one aged 60, and the rest were between 25 and 40. The cytokine concentrations were not analysed according to age, as this would make the categories too small and of little value. The IgG index was calculated for 23 patients. There was no significant difference between the HIV seropositive and HIV seronegative groups for ADA (p = 0.4) and CD4 counts (p = 0.19) in CSF and cytokine concentrations (table 1).

Ten patients (37%) were classified as having grade 1 tuberculous meningitis. Sixteen (59%) had grade 2 and one (4%) grade 3, which for analysis was considered to be grade 2. Table 1 summarises the cytokine concentrations for patients in stages 1 and 2.

Patients with stage 2 disease had significantly stronger Th1 responses. There was no difference in the IL 10 concentrations. The two patients with stage 2 disease who died had very high IFN γ concentrations, both greater than 2048 pg/ml.

IL 10 concentrations were moderately positively correlated with IFN γ concentrations (r = 0.53). The correlation coefficients were −0.18 for IFN γ, −0.33 for TNF α, and −0.34 for IL 10. Correlation coefficients between ADA and cytokine concentrations were 0.34 for IFN γ, 0.47 for TNF α, and 0.22 for IL 10. Cytokine concentrations correlated poorly with CD4 counts in CSF.

It is postulated that in HIV infection a predominant Th2 response accounts for extra-pulmonary disease. This study does not favour a predominance of either Th1 or Th2 in the CSF. It is possible that a Th0 response, which is a non-differentiated response seen early on in immune activation, was seen in our patients, as they were examined untreated and relatively early in the disease. Other investigators have also documented this phenomenon. The positive correlation between IFN γ and IL 10 suggests that these were produced concurrently. This may reflect a control mechanism regulating Th1 and Th2 responses.

There was no difference in cytokine and ADA concentrations and CD4 counts between HIV seropositive and HIV seronegative patients. It is known that the clinical response to antituberculous treatment in both groups is similar. Perhaps this similarity correlates with similar immune responses in both groups. The size of each group is small, and a type 1 statistical error has to be considered. Further studies to confirm our findings would be of value.

The significantly greater TNF α and IFN γ concentrations in the severe group of tuberculous meningitis is confirmed by other studies and suggests that disease severity results mainly from the immune response rather than the organism itself.

The lack of correlation between CD4 and cytokine concentrations may be explained by the fact that there are other sources of cytokines in the CSF, namely macrophages and natural killer cells. Concentrations of ADA, which are derived from lymphocytes, are consistent with other reports, where they were correlated with cytokine concentrations.

There was no correlation between the IgG index and cytokine concentrations, suggesting that the blood brain barrier did not
significantly influence concentrations. Unfortunately, corresponding serum concentrations were not available. This would have been valuable. This is the first study correlating CSF cytokine responses to severity of tuberculous meningitis and comparing HIV positive with HIV negative groups. Further studies should be done to confirm these findings, perhaps to define their relevance to complications and to explore the possibility of IL2 treatment in HIV positive patients.

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References

Hepatitis C testing in HIV infected patients

Numerous seroprevalence studies have shown a high rate of co-infection with hepatitis C among HIV-1 infected patients, ranging from 98% in haemophiliacs, 80% among injecting drug users, to 3–15% in homosexual/bisexual men. Although it is estimated that there are 200 000–400 000 people infected with hepatitis C (HCV) in the United Kingdom, the number of coinfected individuals is unknown. Data have shown that HCV increases the rate of HCV progression, and there is also some evidence suggesting that HCV worsens HIV progression, although this is more controversial.

There is a growing recognition of the significant impact of co-infection on the management of HIV disease. Hepatitis morbidity and mortality among coinfected patients has increased fivefold in recent years. Furthermore the presence of HCV increases the frequency of hepatotoxicity with antiretroviral therapy, and may also impact on the choice of antiretroviral drug, with avoidance of drugs that are potentially hepatotoxic such as ritonavir and nevirapine. Most importantly, there is now effective treatment available for the management of HCV infection, and recent preliminary data suggest in HIV-HCV co-infected patients superior virological response in those receiving PEG-interferon with ribavirin compared to standard interferon with ribavirin. Finally, management of the HIV-HCV co-infected patients involves other interventions such as vaccination for other viral hepatitis A and B, and reducing alcohol intake.

These findings all highlight the importance of identifying those HIV infected patients who are co-infected with HCV. However, a recent survey at Kings’ College Hospital in March 2002 revealed that only 63% of a cohort of 850 current HIV infected attendees had been tested for HCV. The majority of those not yet tested for HCV were patients who had presented before the routine introduction of HCV testing in 1999. Similar findings have been reported from other European centres. In a French cohort of 4017 HIV infected patients only 2589 (64%) were tested for HCV. Although a substantial number of these patients have stored samples available on which retrospective HCV testing could be performed, the current guidance from Royal College of Physicians of London is that consent must be obtained before testing.

Current guidelines from the United States now recommends HCV testing for all HIV infected patients. Antibody based screening assays for HCV infection have evolved over the past decade and currently the most widely are third generation ELISA assays (Ortho). Confirmation of positive results by recombinant immunoblot assays (Chiron RIBA, others) is still recommended as a proportion of positive tests may represent false positive results. Qualitative and quantitative PCR (polymerase chain reaction) tests that detect the presence of HCV RNA and have sensitivity in the range of 50–1000 equivalents per ml are now also available. We undertook a recent informal survey of 10 UK teaching hospitals, which showed differences in HCV testing policies. Seven clinical sites use serological testing for screening and confirm all initially positive results with a second serological assay, and then confirm positive results with a qualitative PCR test. Three sites use qualitative PCR testing for those with an initial positive serological test. For those with a negative PCR further confirmatory antibody assay are done at two sites and one site requests repeat PCR testing at 6 and 12 months.

What is the role of PCR testing in coinfection? At least 4–7% of HIV-HCV co-infected patients have no detectable antibodies in the presence of HCV viraemia as they fail to produce antibodies or have low titres can’t be detected or give equivocal or indeterminate) or loss of detectable antibodies from serum despite persisting viraemia in immunosuppressed patients. Therefore, addition testing with PCR is often indicated. The guidelines recommend that all patients with positive HCV antibody tests and those patients thought to be at risk of HCV infection despite negative or indeterminate serological tests should undergo qualitative PCR testing of serum. A positive result confirms current viraemia whereas a negative test suggests non-viremic infection. Patients with a positive ELISA but negative PCR should be tested with recombinant immunoblot assay to confirm antibody status.

In conclusion, we recommend that centres caring for HIV infected patients should develop clear policies and strategies for ensuring all their new and existing HIV infected patients have undergone testing for HCV.

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First, do not harm: also an issue in NAA assay diagnostics for chlamydial infection

In his update on Chlamydia trachomatis diagnostics, Chernesy emphasizes that nucleic acid amplification (NAA) assays can be useful for screening purposes, because of their increased sensitivity and the possibility of non-invasive sample collection. Since the introduction of these assays, many screening interventions have been undertaken and evaluated mostly in an optimal research context. However, a number of problems can be expected if these diagnostics are implemented in large scale routine practice or in community screening programmes.

Firstly, multiple testing sites may be needed for accurate results, but cannot be realised for reasons of cost and inconvenience. Secondly, there is the problem of the predictive value of a test is low in low prevalence populations. To avoid false positive diagnoses in these situations repeat testing of the sample, preferably by a different technique, is highly recommended. However, in clinical practice a single
positive result is often considered to indicate that a patient is infected. Thirdly, reproducibility problems do occur and are varying in time, and confirmatory testing is required when test results are intermediate or near the cut-off value. A low positive test result that is not caused by the presence of amplification inhibitors points to a low number of target organisms in the sample. Repeat testing is then a matter of statistical chance of the second portion of the sample containing detectable numbers of target organisms. Such results should be transmitted to the clinician accompanied by interpretative comments.

Fourthly, diagnostic accuracy may be affected by contamination of the specimen during laboratory processing.

Fifthly, it is not clear whether detection of a very small amount of chlamydial DNA always results in subsequent infection. These assays might identify residual DNA from a cleared or treated infection, DNA of non-viable organisms, or DNA of levels of pathogens which are too low to be infectious. For this reason it is likely that in routine practice a number of results will be interpreted as positive in patients who are not truly infected.

However, the impact of a chlamydia diagnosis on people’s lives is considerable, and can include stigmatisation, anxiety about reproductive health, and potential partner discord. Pre-test and post-test counselling has been shown to be labour intensive for healthcare providers too, since most infections in asymptomatic patients will be unexpected.

To overcome these problems, rigid diagnostic protocols must be developed before introducing screening programmes. Not only should infected people be identified but false positive diagnoses should be avoided. Laboratories should participate in quality control programmes, and test runs should include multiple control samples. Healthcare providers should be offered agreed standards to which they can manage the different aspects of screening and counselling for chlamydial infection.

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References

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Geographical focusing: an intervention to address increased risk for sexually transmitted diseases during repatriation and resettlement in post-war Mozambique

Countries in the early post-war phase face population movements contributing to increased vulnerability for sexually transmitted diseases (STD) and HIV. Mozambique chose geographically focused interventions to control STD spread in the first post-war years.

Mozambique was one of the poorest countries in the world in 1993 with per capita GNP of US$63 and life expectancy of 48 years.

Seventeen years of civil war and economic crisis destabilised the country causing massive population movements towards urban areas and newly pregnant women. Between 1992 and 1995, an estimated 1.7 million refugees from Malawi, Zimbabwe, Tanzania, Zambia, and Swaziland returned, soldiers were demobilised, and internal displaced people resettled. The war destroyed the health infrastructure, especially in rural areas, precluding provision of STD services and effective primary health care (PHC).

Vulnerable groups and populations of the areas through which the refugees were returning, were considered particularly vulnerable to the risk of STD/HIV.

The National STD/AIDS Control Programme, supported by the European Commission, decided to focus STD/HIV interventions at the PHC level in the areas most affected by population movements.

Four studies carried out between 1987–92 showed HIV seroconversion rates of 3.2%–4.6% in displaced populations, higher than the 1.2% of the general population.

Very high STD prevalence rates (51%) were demonstrated in pregnant women attending PHC services for antenatal care.

Displaced populations showed lower awareness of condoms than the general population.

Fifteen districts in five provinces were selected on the basis of existing population health facilities and projected influx of people. PHC services were strengthened overcoming the existing shortages of staff, drugs, and materials. Clinical, laboratory, and health education skills of over 100 PHC workers in these priority districts were upgraded through training. Drugs for STD treatment, condoms, and educational materials were delivered. An existing popular health education initiative using theatre groups expanded, reaching over 100,000 people in local languages.

Difficulties encountered were mostly related to the destabilisation due to the war, such as transport problems, demobilisation and relocations of health staff, parallel drug and treatment markets, and poor condom availability. Nevertheless, significant progress was noted. One major achievement was the increase in STD patient attendance, quadrupling in one province and doubling or tripling in others. The number of contacts reached also increased significantly: in 1992, 4.5% of STD patients were contacts, in 1993 9%, and in 1994 20.8%. Another major achievement was increased condom distribution, from 2.5 million in 1993 to 5 million in 1994.

Geographical focusing of interventions in early post-war Mozambique showed significant impact on STD attendance, proving the feasibility of introducing STD care in difficult circumstances. Strengthening 15 districts provided the basis for improvement of the STD programme in other areas and enhanced general functioning of PHC centres in the initial priority districts. Improved supervision, in turn improving clinical, laboratory, and educational activities, was subsequently expanded to other districts. The use of syndromic management protocols contributed positively to STD management throughout the country.

Focusing interventions in areas with especially vulnerable populations, combined with an integrated approach to STD/HIV control, may have contributed to the decline in the spread of STD and HIV in early post-war Mozambique.

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www.sextransinf.com
A novel research approach in sex on premises venues (SOPV): objective measure of sexual behaviour and low level intrusion to patrons

Sex on premises venues (SOPV) are commercial venues where men who have sex with men (MSM) meet other MSM for casual, usually anonymous, sex. These venues are challenging environments for traditional methods of behavioural research—for example, interviews. An alternative research method adapted from a study with sex workers in Nicaragua may be used in SOPVs. This study counted the number of used condoms per client as a measure of “safe” sexual behaviour. A pilot study in two parts was conducted at a Melbourne SOPV to determine the feasibility of this approach. The merit of this method was dependent on the consistency of the ratio of used condoms per SOPV patron, and consequently the method’s sensitivity to detect behaviour change.

Part 1 of this pilot aimed to establish a system of SOPV waste collection and condom counting. SOPV staff collected venue waste and research staff counted the number of condoms in the waste that were free from condom packaging. Part 2 piloted SOPV staff handing out anonymous, self-complete questionnaires to patrons during the time periods when waste was being collected. The questionnaire only asked about anal sex and condom use during the participant’s visit at the SOPV.

Part 1 operated on 16 Saturdays and Sundays during the day. An overall ratio of 0.8 condoms per patron was calculated (95% CI: 0.7 to 1.1), and the ratio for each day ranged from 0.3 to 1.6. It was suspected that inconsistent collection of waste on Saturdays and Sundays contributed to the variability of the calculated condom to patron ratio each day. To have the same SOPV staff collecting waste each time and to avoid weekend functions at the SOPV, collection continued on the following nine Wednesday and Thursday evenings. For these evenings an overall ratio of 0.56 condoms per patron was calculated (95% CI: 0.4 to 0.7), and the ratio for each day ranged from 0.2 to 1.0.

Part 2 of this pilot operated on Wednesday and Thursday evenings of the following 8 weeks. Approximately 180 patrons were given a questionnaire by SOPV staff, of which 76 (~40%) completed and returned the questionnaire (mean 43.8 (SD 13.3 years). Forty four participants reported engaging in protected anal sex during their visit to the SOPV (58%, 95% CI: 47% to 69%), with a mode of one episode of protected anal sex per visit. Using this proportion of 58%, a ratio of 1.4 condoms per patron engaging in protected anal sex was recalculated for the Saturday and Sunday collections. For all Wednesday and Thursday collections (Part 1 and 2) the ratio was 0.9.

The findings of this pilot study are inconclusive with respect to the value of this research method for behavioural study. Controlling for measurement and selection bias was difficult and resulted in a variable ratio of used condoms to patrons for each collection day. Research projects with more resources should look for greater control of bias, including encouragement of good communication with SOPV staff. However, this pilot study has demonstrated the potential of counting discarded condoms as a measure of safe sex behaviour in SOPVs. Counting condoms is an objective measure that doesn’t rely on self reports of behaviour, and condom collection can be conducted with minimal intrusion to patrons visiting the SOPV.

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References

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NOTICES

International Herpes Alliance and International Herpes Management Forum
The International Herpes Alliance has introduced a website (www.herpessalliance.org) from which can be downloaded patient information leaflets. Its sister organisation the International Herpes Management Forum (website: www.IHMF.org) has launched new guidelines on the management of herpesvirus infections in pregnancy at the 9th International Congress on Infectious Disease (ICID) in Buenos Aires.

Pan-American Health Organization, regional office of the World Health Organization
A catalogue of publications is available online (www.paho.org). The monthly journal of PAHO, the Pan American Journal of Public Health, is also available (subscriptions: pubsvc@tsp.sheridan.com).

XIX International Congress of the Society of The Fetus as a Patient
1–4 May 2003, Gran Hotel Sitges, Barcelona-Sitges, Spain

Further details: (fax: +34 93 418 7832; email: bcn2003@iulicexus.ub.es).

Australasian Sexual Health Conference: Down South—2003!
4–7 June 2003, Christchurch Convention Centre, New Zealand
Further details: Dart Associates (tel: +02 9418 9396/97; email: dartconv@mpx.com.au; web site: http://www.acshp.org.au)

CORRECTION

We would like to apologise for an error that occurred in the paper by McCarrigle et al (Sex Transm Infect 2002;78:398–405). In table 2, under the heading “Name and custodian” the following affiliations should have appeared. Row one: London School of Hygiene and Tropical Medicine, National Centre for Social Research, and Royal Free & University College Medical School. Row six: City University and Department of Primary Care and Population Sciences and Royal Free Centre for HIV Medicine, Royal Free & University Medical College. Row seven: Study on HIV testing, Royal Free Hampstead NHS Trust Hospital and Department of Primary Care and Population Sciences and Royal Free Centre for HIV Medicine, Royal Free & University College Medical School.

EDITORS’ NOTICE

Inadvertent failure to disclose an interest
Podophyllin office therapy against condyloma should be abandoned. Von Krogh et al (Sex Transm Infect 2001;77:409–12). The author Dr G Von Krogh inadvertently failed to disclose that he had received consultancy fees or reimbursement of expenses to attend educational meetings relating to anogenital papilloma virus infection from the following companies: 3M, Perstorp, Stiefel, Ocllassen, and MSD. In addition clinical trials on anogenital HPV infection had been funded within his department by both 3M and MSD.