

# Correspondence

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## Conjunctival intraepithelial neoplasia in association with HIV infection

Conjunctival intraepithelial neoplasia (CIN) is a rare tumour of the ocular surface, traditionally affecting elderly men. It has recently been reported in young adults of African extraction in association with HIV infection. We report the case of a young African woman recently found to be HIV positive with a long-standing conjunctival lesion. The tumour was biopsied and identified as CIN. HIV testing in young patients presenting with atypical conjunctival lesions is recommended.

### Case report

A 38-year-old Zambian woman was referred for counselling for HIV testing after her husband of 22 years presented with an AIDS-defining illness. She has three children delivered by caesarian section. She received blood transfusions after each operation. She had noted a conjunctival lesion in her left eye that had been slowly increasing in size over the preceding 5 years. This had been reviewed by several physicians in Zambia and was thought to be benign. She was otherwise asymptomatic.

On examination, Snellen visual acuities were 6/6 bilaterally. There was an elevated pigmented conjunctival lesion on the medial aspect of the left eye (Fig. 1). The anterior segments were otherwise normal. Dilated fundal examination revealed no evidence of intraocular infection or inflammation. Apart from oral candida, the systemic examination was unremarkable.

An enzyme-linked immunosorbent assay HIV test was positive. The CD4 cell count was 143 cells/mm<sup>3</sup> and the viral load was 13 400 copies/ml. She was commenced on



Fig. 1. Conjunctival lesion medial aspect left eye.

triple highly active retroviral therapy and fluconazole for oral candida.

The conjunctival lesion was excised and sent to pathology for analysis. Microscopy showed stratified squamous keratinized epithelium within which dysplastic and dyskeratotic cells were seen. There were occasional mitotic figures. A number of melanocytes were noted within the epithelium. These did not show cytological atypia. The appearances were consistent with CIN. This was noted to extend to the resection margins on histology. In view of this, the patient was commenced on a course of topical chemotherapy. This treatment consisted of two 3-week cycles of mitomycin C (0.04%) four times a day, betnesol four times a day and viscotears four times a day 3 weeks apart. She tolerated this therapy well, with no evidence of corneal epithelial toxicity. Her CD4 cell count has increased to 369 cells/mm<sup>3</sup> and the viral load is undetectable (< 50 copies/ml). She remains under regular review.

CIN (previously known as Bowen's disease) is the most common tumour of the ocular surface [1]. The incidence of this neoplasm is between one and 2.8 per 100 000 individuals per year, varying geographically [2]. CIN is generally a grey-white, gelatinous lesion found at the limbus, although less commonly it may be seen in the fornices or palpebral conjunctiva [3]. Intraepithelial squamous carcinoma may progress to invasive squamous cell carcinoma. This is characterized by cellular invasion through the basement membrane and into the substantia propria [4].

Risk factors implicated in the development of CIN include solar ultraviolet light, petroleum products, heavy cigarette smoking, ocular pigmentation and oncogenic viruses such as human papilloma virus (HPV), mainly types 11, 16 and 18 [5]. CIN traditionally affects elderly men. More recently, however, it has been diagnosed with increasing frequency in younger patients of African origin in association with HIV infection. This trend is now well documented in many African countries [6,7], and with increasing migration this trend may be echoed in developed countries.

The exact pathogenesis of CIN remains unclear. Waddell *et al.* [7] postulated that this is a complex carcinogenic process involving, among other agents, ultraviolet light, HIV infection and HPV. Furthermore, Karp *et al.* [5] suggested that HIV may predispose to CIN, by creating a 'permissive environment for HPV, acting as a cofactor in the development of neoplasia, or altering the host's immune response to neoplastic cells'. Unfortunately,

facilities for isolating HPV from histological sections of tissue were not available within our centre.

The treatment of CIN normally comprises complete excision with supplementary cryotherapy [2]. Adjunctive therapy in the form of topical mitomycin C is recommended [8]. 5-Fluorouracil or IFN- $\alpha$  2b have been described as a suitable treatment for those cases refractory to mitomycin C [9,10]. Cytological changes in the ocular surface induced by mitomycin C have been documented by Dogru *et al.* [11], and persist long after the completion of treatment. In an attempt to preserve the integrity of the conjunctival and corneal epithelium we prescribed topical steroid and ocular lubricants in addition to mitomycin C for the duration of treatment.

The conjunctival pathology in our patient predated the diagnosis of HIV infection by 5 years, and was thought, clinically, to be a benign lesion. This case report adds to the growing body of literature suggesting an association between HIV infection and CIN. Given the importance of the early detection of HIV infection, we would urge clinicians to consider HIV infection in young patients presenting with atypical conjunctival lesions.

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### **Increasing prevalence of male homosexual partnerships and practices in Britain 1990–2000: but why?**

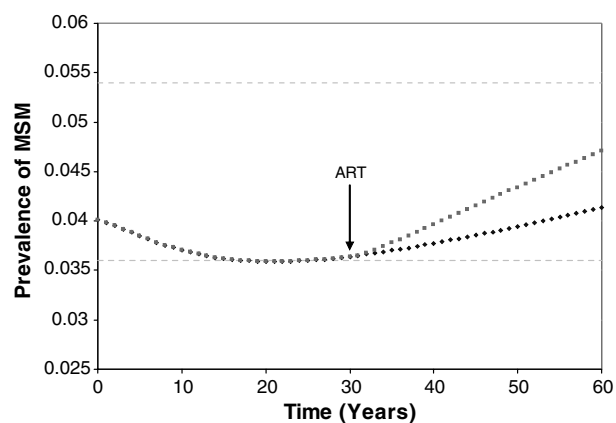
A recent study by Mercer *et al.* [1] reported an increase in the prevalence of men who have sex with men (MSM) from national probability samples of the British population. The authors found that the overall proportion of men reporting homosexual intercourse in their lifetime increased from 3.6% in 1990 to 5.4% in 2000. The authors note that although these increases may be explained by changes in the willingness to report same-sex behaviour, part of the increase is likely to be genuine. To support this assertion, the authors note that these results are consistent with recent increases in sexually transmitted infections (STI), and that similar increases in MSM prevalence were reported between 1988 and 2000 from the US General Social Surveys [1,2]. In terms of STI and HIV prevention, it is important to understand the likely causes of these increases and if they are likely to continue.

We agree with the Mercer *et al.* [1] that at least part of the increase in MSM prevalence and practice is genuine. However, we believe that recent increases in MSM prevalence and STI should be interpreted by taking into

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account the impact of the HIV/AIDS epidemic and antiretroviral therapy (ART) on the MSM population. Empirical and theoretical studies suggest that part of the decline in risk behaviour and STI among MSM early in the HIV epidemic may have been caused by AIDS differential morbidity/mortality of higher risk individuals [3–5]. A recent study [5] further suggested that by reducing disease progression, mortality and the HIV infectiousness of treated individuals, the wide-scale use of ART may have favoured the differential renewal of the high-risk MSM population, thus contributing to the reversal of these trends since the mid-1990s. These results have implications for the interpretation of recent increases in MSM prevalence reported by Mercer *et al.* [1]. In an open and sexually heterogeneous population, the size of the MSM population is expected to increase over time after the introduction of ART at a late epidemic stage (such as in the US or UK), even if the population size appeared to be grossly stable before ART (Fig. 1). The wide-scale use of ART and the slower spread of HIV considerably reduced morbidity/mortality, allowing the population to replenish, thus accelerating the population



**Fig. 1. Temporal changes in prevalence of men who have sex with men before and after the introduction of antiretroviral therapy when HIV is near HIV prevalence equilibrium.** The scenario presented is for an HIV epidemic of 19 and 13% peak and equilibrium HIV prevalence, respectively, without antiretroviral therapy (ART). Results are based on a dynamic model of HIV/AIDS and sexually transmitted infection (STI) transmission [6]. In this simulation: HIV-positive and AIDS cases are treated at a per capita rate of 1 year<sup>-1</sup>, ART reduces HIV infectiousness, disease progression and mortality rates by 90, 65 and 65%, respectively, withdrawal rates from treatment are 0.1 year<sup>-1</sup>. Full details can be found in Boily *et al.* [6]. The annual renewal rate of the population is 3%, the duration of sexual active life is 40 years, specific AIDS mortality is 1 year<sup>-1</sup>. Therefore in the absence of HIV/AIDS the annual population growth rate would be 0.5%. The two horizontal lines illustrate the prevalence of men who have sex with men (MSM) observed by Mercer *et al.* [1] in 1990 and 2000. ◆ No ART; ■ after ART; as observed in 1990; as observed in 2000.

growth rate, especially in higher risk groups (differential renewal), which benefit most from the reduction in morbidity/mortality. The accelerated population growth rate in higher risk groups is supported by two of the findings of Mercer *et al.* [1]. First, there was a much larger increase, although not significant, in the fraction of MSM reporting more than 10 partners than in overall MSM prevalence [1]. Second, increases in receptive anal intercourse (the most risky of the reported sexual practices in terms of acquiring HIV) were more pronounced and more significant than the increases in other, less risky sexual practices [1].

We have suggested that the introduction of ART would be expected to cause an increase in MSM prevalence over time. We note, however, that such changes in MSM prevalence as a result of ART are relatively slow (Fig. 1), and only explain a small fraction (< 10%) of the reported increase in MSM prevalence over the short time period reported by Mercer *et al.* [1]. The bulk of the increase in MSM prevalence must therefore be explained by genuine increases in MSM prevalence not explained by the

population-level effects of ART, or by a decrease in the under-reporting of MSM prevalence, or both. Based on our model that takes the impact of ART and HIV/AIDS into account, we estimated that to attribute the totality of the reported increase in MSM prevalence (50% over 10 years) to a genuine increase in MSM activity would require an annual 6.5% renewal rate of the MSM population (Fig. 1). In other words, this means that each year 15 or 1.6% of men aged 15 or 15–24 years would need to start having sex with other men, respectively. If empirical estimates of the renewal rate of the MSM population (such as the percentage of men aged 15–24 years who enter the MSM population) were available to compare with model prediction, it would give us an insight into the potential decrease in underreporting of MSM prevalence over the time period examined by Mercer *et al.* [1].

Genuine increases in STI and MSM prevalence over time, especially of the higher risk groups, should be expected to occur in years to come over time because of the population-level impact of ART, even if the demographic and sexual behaviour profile of new recruits remains unchanged. These population-level changes may help to explain the upward trends in STI infection [6] and MSM prevalence (to a lesser extent) that have been observed since the time that ART became available. Although numerous other factors may have influenced these trends in sexual behaviour, MSM prevalence, and STI incidence, any interpretation of these trends or public health responses to these trends should take into account the sexual and demographic changes of the population induced by the dynamics of the HIV/AIDS epidemic and the wide-scale use of ART.

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### **Possible explanations for the increase in the prevalence of male homosexual partnerships and practices in Britain 1990–2000. A response to Boily *et al.***

We recently reported increases in the prevalence of male homosexual partnerships and practices in the British general population between 1990 and 2000 based on the two waves of the National Survey of Sexual Attitudes and Lifestyles ('Natsal') [1]. The paper did not focus on the underlying reasons for this, but acknowledged the possibility of an increase in the willingness to disclose such sensitive behaviours, and that the observed change partly reflects a genuine change in population behaviour, as Boily *et al.* [2] agree. Boily *et al.* [2] also suggest that the increased prevalence may be partly due to improved survival among HIV-positive men who have sex with men (MSM), who are also behaviourally higher-risk men. We agree that this is a plausible and interesting insight, but wonder whether the authors may have overestimated the impact of HIV survival on the numbers of MSM in the population. The magnitude of this effect depends on the proportion of MSM who are HIV positive. The London Gay Men's Sexual Health Survey (LGMSHS), an annual community survey of approximately 2000 MSM frequenting London gay bars and clubs, estimated that approximately one in 10 gay men in London in 2000 were HIV positive [3]. Given that there are now more MSM living with HIV as a result of antiretroviral therapy (ART), also that the LGMSHS estimate is based on a sample of MSM at higher behavioural risk of HIV infection, relative to the MSM identified through the Natsal 2000 survey of the British general population (J.P. Dodds, personal communication, November 2004), the HIV prevalence estimates used in the model of Boily *et al.* [2] seem rather high. However, even using their prevalence estimates, the authors demonstrate that it is unlikely that their hypothesized effect of ART accounts for more than 10% of the change in prevalence.

Boily *et al.* [2] also explore whether and how genuine increases in MSM activity might account for the increase in prevalence. Their model seems to assume that the replacement of MSM only occurs in those under the age of 25 years. However, because men can commence having sex with men at any age, a large increase in the proportion of young people joining the MSM population is not needed to account for the observed change. Indeed the median age at first homosexual intercourse was estimated from Natsal 2000 as 17 years, with an upper quartile of 23 years. In contrast, the median age at first heterosexual sex was estimated as 17 years, with an upper quartile of 18 years [4]. Furthermore, men interviewed in Natsal 1990 may have 'postponed' commencing sex with

men until a later date because of concern about the risk of acquiring HIV/AIDS in the late 1980s/early 1990s. These men may have then been 'prompted' to commence sex with men after the introduction of ART in 1996, when fears of the consequences of acquiring HIV may have diminished. Such a scenario could, of course, be viewed as another effect of ART on the prevalence of MSM. Furthermore, as we have already reported [1], changing social attitudes towards homosexuality, both in the general population and among MSM, may also have prompted these men to commence and/or report same-sex partnerships. Data from the LGMSHS show that the average age at first homosexual anal intercourse has significantly increased over the past decade (J.P. Dodds, personal communication, November 2004). In addition, Natsal data show a highly significant change in the prevalence of reporting homosexual intercourse among men aged 30–44 years [4.6%, 95% confidence interval (CI) 3.8–5.5% in 1990; 7.1%, 95% CI 6.1–8.2% in 2000,  $P = 0.0004$ ], but no significant change in the prevalence for men aged 16–29 years (2.7%, 95% CI 2.1–3.4% in 1990; 3.4%, 95% CI 2.6–4.3% in 2000,  $P = 0.1982$ ). Whereas the corresponding odds ratio (OR) for the interaction term between survey and age-group was not statistically significant (OR 1.25, 95% CI 0.81–1.93,  $P = 0.321$ ), surveillance data show that the greatest increases in the incidence of sexually transmitted infections in recent years have been among older MSM [5].

We thank Boily *et al.* [2] for their exposition of the hypothesis regarding HIV/AIDS morbidity and mortality and the introduction of ART, and we agree that this should be considered in understanding the change in prevalence of reporting male homosexual intercourse between 1990 and 2000, together with the evidence regarding changes in reporting biases [6]. However, we regard a true increase in the proportion of men ever having homosexual sex highly likely, and our findings of an increased prevalence of HIV risk behaviours [1] continue to be of concern given evidence of continuing HIV transmission among MSM and the growing HIV disease burden in the population [7].

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