Correspondence

AIDS 2006, **20**:1463–1470

Risk factors for active tuberculosis in adults on highly active antiretroviral therapy in Africa

In a recent limited article, we reported that a past history of tuberculosis (TB) at HAART initiation was significantly associated with the risk of active TB in adults on HAART in Côte d'Ivoire [1]. In another recent excellent study, Lawn and colleagues did not find such an association in South African adults [2]. This striking difference deserves further discussion.

In our study, 25% of patients had a past history of TB at HAART initiation, and 50% of the previous TB episodes were diagnosed more than 3 years prior to enrolment [1]. In the study by Lawn and colleagues, only 14% of patients had a TB history at baseline, and 50% of the previous TB episodes were diagnosed within the 13 months prior to enrolment [2]. Thus, we wonder if some previous episodes of TB could have been missed, particularly among the remotest ones. In sub-Saharan Africa, under-report of previous episodes is a well-known cause of TB recurrence underestimation [3]. As TB recurrence may vary over time [4], under-documenting the oldest past-episodes compared with the most recent ones could introduce a major bias in the analyses looking at the association between TB history and TB occurrence during HAART.

There is another consequence of this unusual distribution of the time since last episode in the study by Lawn and colleagues. Most of their patients with TB history received anti-TB drugs within the few months preceding HAART initiation. Thus, their trend toward an association between the variable 'TB history' and a lower risk of active TB during HAART is hard to distinguish from a trend toward a time-limited reduction in TB risk due to recent anti-TB treatment. This trend could even be interpreted as a strong argument for the necessity to assess the benefits of a time-limited TB prophylactic treatment during the first months of HAART.

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Risk factors for active tuberculosis among adults on highly active antiretroviral therapy in Africa: a reply

We thank Seyler and colleagues for their insightful thoughts concerning risk factors for the development of tuberculosis during HAART. Three studies addressing this question have been published and have differing findings [1–3]. The persistence of high rates of tuber- culosis during HAART is an important issue, and an accurate identification of risk factors is key to the development of appropriate strategies to reduce this burden of disease.

Studies from Cape Town, South Africa [1] and Europe/north America [3] found that more advanced pretreatment immunodeficiency and lack of response to HAART were the principal factors associated with the risk of tuberculosis during HAART. In contrast, Seyler and colleagues [2] found in a west African cohort in Abidjan that the only risk factor was a previous history of tuberculosis. We have previously suggested that the lack of an association between the risk of tuberculosis and pretreatment immunodeficiency in the Abidjan study may relate to the restricted composition of the cohort [4,5]. The inclusion of few patients with stage 1 or 2 disease or CD4 cell counts greater than 200 cells/μl will have diminished the power to assess CD4 cell count and clinical stage as risk factors.

Explaining the discrepancy in findings concerning a history of previous tuberculosis as a risk factor is probably more complex. HIV-associated immunodeficiency is an important risk factor for the recurrence of tuberculosis, whether caused by relapse (resulting from incomplete sterilization of tuberculous lesions) or exogenous re-infection [6]. Evidence suggests that the restoration of *Mycobacterium tuberculosis*-specific immunity is incomplete during at least the first year of HAART [7], and it is therefore certainly plausible that a previous history of tuberculosis would persist as a significant risk factor for incident tuberculosis after the initiation of HAART. However, whether such an association is demonstrable in a given cohort is likely to be determined by the proportion of patients who have a past history of tuberculosis, the relative strength of association of other variables such as baseline CD4 cell count and their risk of re-exposure to tuberculosis.

Whereas the underrecording of a previous history of tuberculosis may be a significant problem in community-based tuberculosis clinics [8], which are frequently overburdened in much of sub-Saharan Africa, we doubt that this is likely to be a significant factor among carefully documented patients in a study cohort, many of whom were in long-term medical care before antiretroviral therapy. Although the proportion of patients in the Cape Town cohort who had a previous history of tuberculosis was comparatively low (14%), this probably reflects the sociodemographic composition and immune profile of the cohort rather than reflecting underreporting. In marked contrast, approximately 50% of patients accessing a community-based antiretroviral treatment programme based within in a poor urban township in Cape Town (previously described in Lawn *et al.* [9]) have a history of previous tuberculosis. It may prove that study populations with markedly differing baseline characteristics and levels of community exposure to tuberculosis may have different risk factors associated with incident tuberculosis during HAART.

The relative contribution of relapse versus re-infection as a cause of recurrent tuberculosis is also likely to differ between settings. Inadequate antituberculosis treatment increases the risk of tuberculosis relapse; in contrast, a higher incidence of tuberculosis in a community is associated with an increased likelihood of exogenous re-infection [6,10]. As patients with tuberculosis in Cape Town receive a 6-month rifampicin-containing regimen and the tuberculosis incidence rates in some communities are among the highest in the world [11], we suspect that a large proportion of recurrent tuberculosis is caused by exogenous re-infection. In this context, one would expect that antituberculosis treatment would be followed by a time-dependent reduction in tuberculosis incidence, and that the rate would gradually increase with time after the completion of antituberculosis treatment as the opportunity for re-exposure increases. Seyler and colleagues rightly point out that among patients with a history of previous tuberculosis, a greater proportion of those in the Cape Town cohort compared with the Abidjan cohort completed antituberculosis treatment in the year before the initiation of HAART. This may have conferred a time-dependent protective effect against tuberculosis during the first 1–2 years of HAART in the Cape Town cohort when the majority of cases of incident tuberculosis occurred. This may be an important factor contributing to the differing findings between the Abidjan and Cape Town studies. The potential benefit from the co-administration of isoniazid prophylaxis concurrently when initiating HAART may thus be diminished if a high proportion of enrolling patients have recently completed antituberculosis treatment.

In conclusion, risk factors for tuberculosis during HAART may differ between study populations of differing composition and in different settings. Data from many different sites are needed to clarify the overall picture.

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Prevention of mother-to-child transmission of multi-drug resistant HIV-1 using maternal therapy with both enfuvirtide and tipranavir

The management of multi-drug resistant HIV is a complex challenge in daily practice. Of particular concern is the presence of these strains in pregnant females as drug resistance does not only limit therapeutic options for the mother but may also reduce the effectiveness of perinatal prophylaxis. In order to avoid mother-to-child transmission clinicians may feel compelled to prescribe recently approved drugs for which there is none or only limited experience in pregnancy.

We present a case of a pregnant female with drug-resistant HIV who received a mega-HAART regimen including the recently approved drugs enfuvirtide and tipranavir. Only limited information is available on perinatal prescription of enfuvirtide and the use of tipranavir in pregnancy has not yet been reported [1,2].

The patient was a 33-year-old gravida 1 para 0 woman who presented at 27 weeks' gestation at the HIV-treatment center. She had been on HAART since 1996. She irregularly attended the out-patient clinic and received various antiretroviral regimens without ever achieving sustained virological suppression and with a fluctuating immunological response. At time of presentation she was taking stavudine, tenofovir and lopinavir/ritonavir with wavering compliance. The viral load and CD4 cell count were $> 200\,000$ copies/ml and 380 cells/μl. The plasma level of lopinavir was 6.0 mg/l, which is 84% of the expected value according to population pharmacokinetics. Genotypic analysis revealed an extensive drug-resistance pattern although some previously identified mutations were currently not detected (Fig. 1).

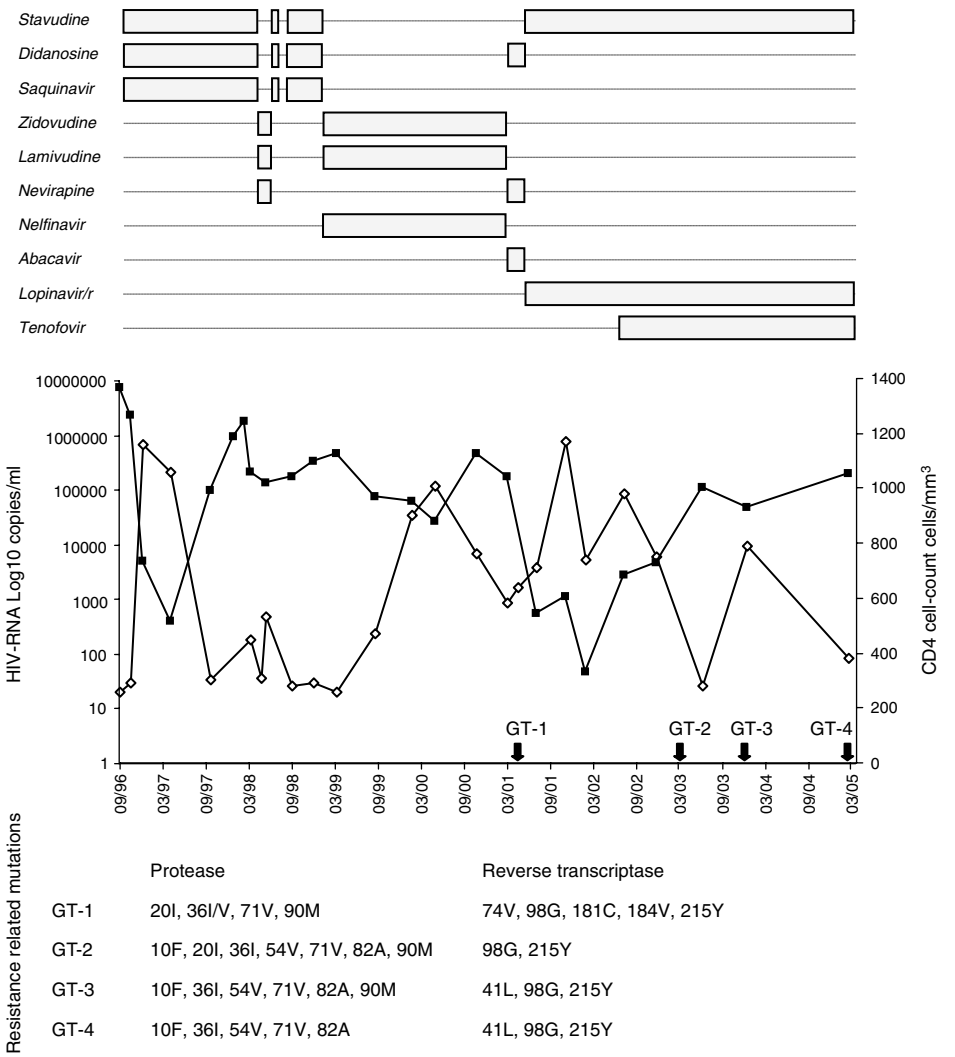
Based on the history of antiretroviral drug use, the associated HIV RNA response and current and archived resistance mutations the following regimen was selected: zidovudine, lamivudine, abacavir, tenofovir, enfuvirtide and boosted tripranavir. The non-nucleoside inhibitors to which currently no extensive resistance was detected in the plasma but to which resistance was likely to be present in the proviral DNA were preserved for neonatal prophylaxis.

The patient was admitted to the ward to enable directly observed therapy and close monitoring of potential adverse events. Initially, she suffered from severe nausea and experienced a weight loss of 8 kg. After a short period of drip-feeding the nausea disappeared and a normal diet was continued. At 34 weeks' gestation a Cesarean section was performed after breaking of the waters. During the procedure high-dose zidovudine was given. At time of delivery the maternal viral load was reduced to 73 copies/ml. A premature healthy neonate was born. Immediately after birth prophylaxis with boosted lopinavir, nevirapine and lamivudine was started and continued for 4 weeks. This medication was clinically well tolerated. A low hemoglobin (5.6 mmol/l) was observed during and just after the prophylaxis which is in the lower range for premature children and probably consistent with the frequent blood sampling. HIV RNA analysis of plasma was < 50 copies/ml at day of birth and remained undetectable at 6 and 26 weeks of age.

Recently a case of perinatal transmission of multi-drug resistant HIV-1 despite viral suppression below 50 copies/ml on an enfuvirtide-based regimen was reported. This patient also experienced virological failure of a lopinavir-containing regimen during pregnancy. The resistance profile was comparable to the pattern detected in our patient during consecutive genotypic analyses. In this case no Cesarean section was performed nor tipranavir given. The authors hypothesized that ineffective concentrations of enfuvirtide in the genital tract might have resulted in failure to prevent HIV transmission. The outcome underlines the relevance of the conclusion of the European Collaborative Study that a Cesarean section reduces the likelihood of perinatal transmission independently of maternal antiretroviral therapy (also at viral load < 1000 copies/ml) [3,4].

Our patient had experienced therapy failure during treatment with almost all reverse transcriptase inhibitors and several protease inhibitors, including most recently a lopinavir-containing regimen. The fusion inhibitor enfuvirtide was the only approved drug available from which full activity could be expected. However resistance to enfuvirtide may develop quickly if only a suboptimal background regimen can be selected [5].

The new protease inhibitor tipranavir showed in clinical trials superior activity against strains that have developed substantial resistance to other protease inhibitors. A significant viral response was reported in 92% of protease



Resistance related mutations

	Protease	Reverse transcriptase
GT-1	20I, 36I/V, 71V, 90M	74V, 98G, 181C, 184V, 215Y
GT-2	10F, 20I, 36I, 54V, 71V, 82A, 90M	98G, 215Y
GT-3	10F, 36I, 54V, 71V, 82A, 90M	41L, 98G, 215Y
GT-4	10F, 36I, 54V, 71V, 82A	41L, 98G, 215Y

Fig. 1. History of antiretroviral drug use, HIV RNA and CD4 cell response and genotypic resistance patterns. ■ HIV-RNA; ◇ CD4 cell count; GT, genotype resistance analysis.

inhibitor experienced patients if the tipranavir score was less than three [6]. The current and previous viral populations within our patient displayed a tipranavir resistance score of two (I13V, I54V) resulting in a high probability of response. However, teratogenicity studies have shown foetal toxicity (decreased ossification and body weight) in rats at approximately 0.8-fold human exposure of the recommended dose [7]. We carefully considered the risk of toxicity but included tipranavir in the maternal therapy because of the considerable likelihood of perinatal transmission of a multi-drug resistant strain that would have left very limited neonatal therapeutic options.

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Young men's HIV risks in South Africa: the importance of multiple risk behaviors

In a recent research letter, Lane *et al.* [1] presented findings regarding heterosexual anal intercourse as a risk factor for HIV infection among young South African men. This research, based on an analysis of data from a nationally representative household survey of youth aged 15–24 years [2], assesses the prevalence of heterosexual anal intercourse and its association with HIV infection. This research is welcome, because of the paucity of data on heterosexual anal intercourse as a risk factor for HIV transmission, particularly in African settings. As the authors note, anal intercourse is a potentially significant pathway for HIV transmission, and those who engage in this risk behavior may be less inclined to use condoms, partly because anal sex is erroneously viewed as safer than vaginal intercourse.

In their report, Lane *et al.* found that young men who engage in anal intercourse were significantly more likely than those experiencing vaginal intercourse only to be HIV infected (odds ratio 2.0, 95% confidence interval 1.3–3.6). Younger men aged 15–19 years were more than four times more likely to be HIV infected than those reporting only vaginal intercourse. Risk factors independently associated with this outcome included more than four lifetime partners, sexual intercourse under the influence of alcohol or drugs, and transactional sex [1]. The importance of this finding should not be minimized. However, the fact that anal intercourse may be one of a number of risk behaviors that enhance young men's risk of HIV infection should also be emphasized.

Research on youth HIV-related risk behaviors increasingly suggests that some young men experience a constellation of risk factors, including an early age at sexual debut, the pursuit of multiple and concurrent partnerships, and inconsistent condom use [2–4]. Our research in KwaZulu/Natal province suggests that early sexual debut for men, in particular, may be an important factor associated with various subsequent sexual risk behaviors. For example, in our studies of youth and HIV-related risk behaviors, a consistent minority of men, approximately 13–15%, report sexual initiation at the age of 14 years or younger [3] (Harrison *et al.*, 2006; in preparation). Often, men with early sexual debut have riskier first sexual experiences than men with an older age at first sex. Furthermore, our findings show that early sexual debut for young men is strongly associated with multiple sexual partnerships in the later teen and young adult years [3]. These data reveal patterns of sexual behavior broadly similar to the national youth survey. The prevalence of anal sex was higher (11.7%), but was not independently associated with other sexual risk outcomes (Harrison *et al.*, 2006; in preparation).

Of note is the fact that age of sexual debut did not emerge as a behavioral risk associated with anal intercourse in the report by Lane *et al.* This may result from the way that the age of sexual debut was categorized. In their analysis, sexual debut was measured as being above or below 17 years of age, the approximate median age at first sex for young men and women in South Africa [2,3]. This measure of age at sexual debut thus compares roughly equivalent categories of young people on either side of the median, and does not adequately distinguish those with early debut who may represent a higher risk group. Data from the national youth survey indicate that 12% of young men report sexual debut at the age of 14 years or younger [2]. If the data of Lane *et al.* were re-analysed to examine the association between early sexual debut (i.e. sexual intercourse at 15 years of age or younger) and the practice of anal sex, it is possible that an association would be found.

We do not wish to minimize the importance of these findings, nor to engage in statistical nitpicking. Rather, our aim is to encourage a thorough understanding of

the factors that place young South African men at risk of HIV infection. Other research on men in Africa suggests that early sexual behaviors influence risk throughout the life course [5]. As Lane *et al*. note, a high prevalence of anal sex may represent an HIV risk reduction strategy among youth who are avoiding the known risks associated with vaginal intercourse. Equally, however, it may be one of a number of risk behaviors exhibited by a highly vulnerable group of young men. Too little is known about young men's sexual behaviors and their determinants, as well as the social factors that influence them. Prevention efforts should focus not only on increasing the safety of anal sex, or other HIV risk-related behaviors, but rather on comprehensive prevention interventions to promote sexual health while addressing young men's vulnerability and risk in the broader contexts of their lives.

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Response to Harrison *et al*. 'Young men's HIV risks in South Africa: the importance of multiple risk behaviors'

We are grateful to Harrison *et al*. for sharing the insights on early sexual debut and HIV risk among young men from their own work, and for their constructive engagement with our letter.

In the National Youth Survey, respondents were asked three separate questions about sexual debut: age of first vaginal sex (for men, mean 16 years), age of first oral sex, and age of first anal sex (both mean 18 years). After recategorizing the age of sexual debut for men as vaginal sex at less than 15 years of age or 15 years and older, early sexual debut was associated with a reduced, although not statistically significant, risk of ever engaging in anal intercourse in bivariate analyses (odds ratio 0.5, 95% confidence interval 0.2–1.0).

Our outcome of interest was HIV infection. Vaginal sexual debut at less than 15 years of age and HIV infection were not associated ($P = 0.11$), nor was the effect of vaginal sexual debut at less than 15 years of age significant when substituted for the early sexual debut variable (debut before age 17 years) that we explored in the multiple logistic regression model from our initial analysis. Early debut at less than 15 years of age was also not significantly associated with HIV infection among men or women, as reported in the main paper from this study [1]. When we combined all three forms of sexual debut before the age of 15 years into a single early sexual debut variable, this variable was also not associated with HIV infection ($P = 0.63$). However, we would not want anyone to conclude from this analysis that the youngest sexually active men are not at high risk of HIV infection. There are a number of possible reasons that might explain why in this study no association was found between early debut and prevalent infection. A smaller, more concentrated sample drawn from a vulnerable youth population may have shown the significant associations postulated by Harrison *et al*.

It is impossible to speculate whether an HIV-infected young man was infected through oral, vaginal, or anal intercourse from these data. We are naturally in agreement with Harrison *et al*. that a comprehensive approach to HIV prevention among young people must address the HIV transmission risks that early sexual debut in any form present, both at the time of sexual debut and later in life.

We focused our analysis on heterosexual anal intercourse because the few prevention messages in South Africa that do address the risk associated with it tend to be judgmental, 'just say no' approaches; such messages stifle frank discussions about risky sexual behavior that are important to effecting behavior change. Furthermore, we believe such approaches stigmatize individuals who have engaged in anal intercourse, and further place these individuals at risk of infection by alienating them from the reach of existing comprehensive HIV prevention messages. Our aim was not to argue that one single risk behavior was more worthy of attention than others. Rather, we sought to present data that show that we can no longer afford to overlook heterosexual anal intercourse in current and future comprehensive approaches to HIV prevention.

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Can India abolish the anachronistic homosexuality law to battle HIV/AIDS?

Despite the fact that the journal *AIDS* has covered various articles related to HIV in Asia, the thorny issue of the colonial era homosexuality law of India has seldom been discussed. We are concerned about the recent increase in the reported cases of HIV among homosexual men in India. We believe that it is time for India to repeal the colonial era homosexuality law so that intervention measures can be enforced to help the often ignored gay community, one of the vulnerable groups for HIV infection.

The first report of HIV infection in India was in 1986, and within just two decades this immune-stripping disease has infected over 5 million people [1]. According to reports, the HIV prevalence among men who have sex with men was 23.6% in Maharashtra State and 2.4% in Tamilnadu State, respectively [2,3]. Detailed statistics on India's current homosexual practice and its implications on the spread of HIV, however, are not known clearly because homosexuality is illegal in India and is punishable by imprisonment for up to 10 years. This unfortunate legal stumbling block prevents gay men from coming forward for HIV screening; it also frustrates health workers in providing information regarding treatment, monitoring and counseling.

The major provisions of the criminalization of same-sex acts are found in Section 377 of the Indian Penal Code of 1860. According to Section 377, gay sex is bracketed with sex with animals and paedophilia and is classed as an 'unnatural' offence, punishable by imprisonment. Even though only a few individuals have been prosecuted under the law, its continued existence on the statute books has meant that homosexual men and organizations promoting AIDS awareness across India remain vulnerable to police aggravation and legal prosecution.

For example, the police force in Lucknow city has been bizarrely upbeat in its attempts to enforce this outdated Section 377. In 2001, the police invaded two offices of the local AIDS prevention organizations to arrest staff members, condemning them for encouraging homosexuality in the city. Early this year, police arrested four men and accused them of operating an online gay 'racket' and engaging in unnatural sex. International human rights organizations condemned the arrests, and India's coordinator for UNAIDS stated that treating homosexuals as criminals in fact increases the stigma and discrimination they face, and therefore hinders the ongoing fight against AIDS.

Sexuality on the whole is somewhat a taboo in traditionalist India, and individuals often regard same-sex relationships as illegal or even profane. However, what people forget is that India has a long history of including homosexuals as part of society, and ancient Hindu texts such as the *Kama Sutra* describe homosexuality more accurately than any other religions in the world. As a matter of fact, the 145-year-old law originated during the British occupation of India, when there was no freedom of speech or democracy. The United Kingdom has indeed changed many laws over the past few decades as society has progressed towards freedom and democracy. Unfortunately, India has been struck with this outdated anomaly that deserves to be abolished if India is to be recognized globally as a true democratic nation that respects all people equally.

AIDS experts have already raised alarm bells over the spread of the disease in Asia and the Pacific region, and called for a united effort to control it [4]. The government of India is increasingly committed to HIV prevention and control efforts. But it regrettably continues to ignore the

implications of Section 377 on India's gay community, social workers and HIV prevention programmes. There is insufficient public awareness at present about India's homosexual community. Therefore it is crucial for health education professionals and social work experts to take a leading role to reach out to policy makers, politicians, community leaders, and the media to alert the public on the dire social and health consequences of the homosexuality law.

Press releases from international human rights groups condemning India's homosexuality law are not enough to make legal changes in India. Public pressure with the support of parliamentarians and local political parties is the key to changing the law, especially when there is a coalition government in New Delhi similar to the present one, which often needs the crucial support of small parties and independent members of parliament to stay in power. Finally, we urge people from all walks of life in India to play an active role in bringing public pressure to abolish Section 377, so that the neglected homosexual community in the world's largest democracy can be free at last!

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