Is smoking tobacco an independent risk factor for HIV infection and progression to AIDS? A systemic review

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METHODS

Search strategy

In February 2005, we searched 13 bibliographic databases (Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, CINAHL, Database of Abstracts of Reviews of Effects (DARE), Embase, Health Management Information Consortium (HMIC), Medline, NHS HTA, PreMedline, PsychINFO, Science and Social Science Citation Indexes, the Current Controlled Trials database, and the UK National Research Register). We also conducted a search of abstract databases from three international AIDS conferences (2000, 2002, 2004), the World Health Organization website (www.who.int), and the Google search engine. Further unpublished reports were sought by contacting key experts and by a call for information through an email discussion group for tobacco control (Globalink). The reference lists from full papers were also checked. The searches were not limited by date.

Searches were performed using both free text and keywords. We used the following keywords and truncated free text terms: HIV, human immunodeficiency virus, human immune deficiency virus, HIV Infectio*, human immunodeficiency virus infection*, AIDS, acquired immunodeficiency syndrome, acquired immune deficiency syndrome, tobacco, smoke*, nicotin*, cigarette smoking, and cigar*.

Inclusion criteria are listed in table 1. Exclusion criteria were studies concerned with paediatric HIV (for example, mother to child transmission), study participants who already had AIDS, and non-English language publications.

Analysis

Data were extracted independently by two researchers (AF and RM) using a standard proforma covering year of publication, setting/country, sample size, population characteristics, study design, outcome measures, findings, and study limitations. We extracted both adjusted and crude results where available. Where no effect size had been estimated we reviewed the

Abbreviations: CI, confidence interval; DALYs, disability adjusted life years; HAART, highly active antiretroviral therapy; OR, odds ratio; PCP, Pneumocystis carinii pneumonia; RH, relative hazard; RR, relative risk
available data to see if this could be calculated. We assessed study quality using the Newcastle-Ottawa Scale as recommended by the Cochrane Collaborative Review Group on HIV Infection and AIDS. Meta-analysis was not undertaken as the studies identified used such a variety of approaches that it was considered that pooled results would be potentially misleading. As the study represents secondary research, we did not seek ethics committee approval.

RESULTS

Numbers of studies
We identified 3718 studies from the searches. After removing duplicates using Reference Manager software this number fell to 2808. The titles of these papers were reviewed to remove obviously irrelevant studies producing 121 references for which abstracts were read. From these, 49 papers were obtained and read in full; 15 papers met the inclusion criteria and are summarised in tables 2 and 3. Nine of these studies used progression to AIDS as an outcome measure, five used HIV seroconversion, and one used both.

Smoking tobacco as an independent risk factor for HIV infection
Six papers assessed whether smoking was associated with an increased risk of acquiring HIV infection (table 2). Of these five found that it was and one that it was not. The study that did not find an association produced an adjusted odds ratio of 1.22 in favour of an association but the 95% confidence interval (0.99 to 1.50) was consistent with no association. The other studies produced adjusted odds ratios ranging from 1.6 to 3.5. Crude odds ratios where provided were all larger than the adjusted ratios and ranged from 2.4 to 4.7. One paper did not provide an estimate of effect size and it was not possible to calculate one from the data provided.

Smoking tobacco as an independent risk factor for progression to AIDS
Ten papers assessed whether smoking was associated with more rapid progression to AIDS (table 3). Of these nine found no association. The study that did find an association was one of the poorer quality studies. Although not formally within the terms of this review, it is worth noting that two studies did not find an association between smoking and the development of bacterial pneumonia. One of these also noted an association between smoking and increased risk of developing AIDS related dementia but a protective effect against Kaposi's sarcoma.

DISCUSSION
The studies identified in this systematic review indicate that while smoking might be independently associated with acquiring HIV infection, it does not appear to be related to progression to AIDS. The consistency of the findings is striking and represents a major strength of this review. While the studies vary in quality, they include reports of high quality investigations using large sample sizes. However the methodology necessarily used (epidemiological, observational studies) is unable to demonstrate causal relations and is prone to confounding. Most of the studies assessing the association between smoking and HIV seroconversion were cross sectional. The only truly prospective study found no association. In contrast, all of the studies investigating the association between progression to AIDS and smoking were cohort studies and eight out of the 10 were prospective. Confounding is more likely to occur when exposure is measured at the same time as outcome (as in cross sectional studies) and this may well explain the paradoxical finding of an association between smoking and HIV seroconversion but not with progression to AIDS.

The measurement of the relevant risk factors including sexual behaviour and smoking status is difficult: these were mostly assessed from self reported data. Current smoking status is possible to verify biochemically but none of the studies did this. While the fundamental potential risk factor is past rather than current smoking status, validation of current smoking status might have gone some way to confirming self reported data. The studies included in this review classified ex-smokers as non-smokers in their analysis. This could cause possible misclassification bias. The effect of this would be to reduce any association between smoking and HIV seroconversion and progression to AIDS. Although attempts were made to identify unpublished studies, publication bias cannot be ruled out. Investigators who did not find an association between smoking and HIV seroconversion may not have tried or have been able to publish their findings. However publication bias is unlikely to be a factor for progression to AIDS, given the lack of association with smoking in published studies.

However, the consistent finding of an association between smoking and increased risk of becoming HIV seropositive could be a real effect. There is a theoretical basis for smoking being related to an increased risk of infection generally and an observed association in other infections, including sexually transmitted infections. The size of the effect observed (adjusted odds ratios ranging from 1.6 to 3.5) in the studies would indicate a magnitude of public health importance. Likewise, the consistent finding of no association between smoking and progression to AIDS could represent the true picture. Most of the studies were done before the widespread use of antiretroviral therapy and were conducted over a relatively short period of time in industrialised countries. In these circumstances it may be the case that smoking contributes little to the risk of developing AIDS. This may be because the immune mechanisms that smoking affects are less relevant in progression to AIDS than in acquiring the infection in the first place.

Further research is also needed to investigate whether the association between smoking and HIV seroconversion is related to residual confounding. Such research would need to prospectively record more accurately HIV risk behaviours including sexual intercourse and injecting drug use. Given the sensitivity of these issues and the difficulty of getting accurate self reported information, it may be preferable to “piggyback” studies on smoking and HIV onto ongoing cohort studies in high prevalence countries. The fact that all the studies that examined progression to AIDS were set in developed countries is an important limitation. Given that highly active antiretroviral therapy (HAART) has dramatically increased life expectancy for people with HIV, it may now be the case that smoking causes intercurrent illness, which could contribute to general debilitation and progression to AIDS. In particular, in developing countries where bacterial pneumonia might be less well treated and tuberculosis is more prevalent, smoking might be an important risk factor. Data from the United States suggest that smokers taking HAART had more inter-current, non-AIDS defining illnesses than non-smokers. The relation between long term treatment, dyslipidaemia, and the development of cardiovascular disease will also be of importance when considering the effects of smoking.

Although most studies identified in this review were set in developed countries, future research must examine the effect of smoking of people living with HIV in developing countries where the AIDS epidemic has the greatest impact. Although we already know tobacco control and smoking cessation are important public health measures, such research might add
### Table 2  Papers using HIV seroconversion as the outcome measure ranked by study quality (best quality study first)

<table>
<thead>
<tr>
<th>Ranking</th>
<th>Reference (date of publication)</th>
<th>Setting/country</th>
<th>Design, population, and sample size</th>
<th>Relevant outcome measures</th>
<th>Findings</th>
<th>Quality assessment: study strengths</th>
<th>Quality assessment: study weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Halsey et al (1992)</td>
<td>Primary healthcare clinic in Cite Soleil, Haiti</td>
<td>Nested-case-control study of 41 HIV positive women and 373 HIV negative women who had all participated while 6–7 months pregnant in a survey assessing HIV risk factors</td>
<td>HIV-1 serostatus</td>
<td>After adjustment for factors associated with HIV-1 infection and smoking in regression analysis, smoking was independently associated with HIV-1 infection (adjusted OR = 3.4, 95% CI = 1.6 to 7.5, crude OR = 4.7, 95% CI = 2.0 to 10.9)</td>
<td>Investigators blinded and important confounders taken into account (marital status, number of non-marital unions, visits to folk healers, religion, age at first intercourse, number of lifetime sexual partners, socio-economic status as indicated by floor type in home)</td>
<td>Smoking status not biochemically validated</td>
</tr>
<tr>
<td>2</td>
<td>Chao et al (1994)</td>
<td>Antenatal clinic serving a semi-rural population in Butare region, Rwanda</td>
<td>Cross sectional survey of 5690 pregnant women attending an antenatal clinic</td>
<td>HIV-1 antibody serology</td>
<td>OR for HIV-1 seropositivity in smokers against non-smokers after adjusting for factors listed in next cell OR = 1.6 (95% CI = 1.1 to 2.4). The unadjusted OR = 2.4 (95% CI = 1.7 to 3.2)</td>
<td>Interviewer blinded, important confounders taken into account (history of sexually transmitted disease, number of sexual partners, maternal age, education, marital status, income, age at first pregnancy, parity, oral contraceptive use, partner circumcision, had sex to support herself)</td>
<td>Recruitment method unclear (may not have been consecutive patients)</td>
</tr>
<tr>
<td>2</td>
<td>Boulos et al (1990)</td>
<td>Outpatient clinics operated by a philanthropic organisation in a periurban slum in Port-au-Prince, Haiti</td>
<td>Cross sectional survey of 4485 pregnant women (6–7 months gestation) attending a well child clinic and also participating in a measles vaccine study</td>
<td>HIV-1 antibody serology</td>
<td>Adjusted OR for HIV-1 seropositivity in smokers against non-smokers = 1.6 (95% CI 1.1 to 2.4). Dose-response effect noted between number of cigarettes smoked and risk of HIV-1 seropositivity. Crude OR not provided</td>
<td>Accounted for important confounders (marital status, age, previous pregnancy, number of sexual partners, positive VDRL [test for syphilis])</td>
<td>Recruitment method not adequately described, no biochemical validation of smoking status, assessors not blinded</td>
</tr>
<tr>
<td>2</td>
<td>Penkower et al (1991)</td>
<td>Baltimore, Chicago, Los Angeles, and Pittsburgh, United States</td>
<td>A nested case-control study of 644 bisexual and homosexual men practising receptive anal intercourse drawn from a prospective cohort study (Multicentre AIDS Cohort Study). Seroincident men were matched with men who remained HIV negative throughout the study period (1984–7)</td>
<td>HIV-1 seroconversion</td>
<td>Smoking was not associated with HIV-1 seroconversion (adjusted OR = 1.22, 95% CI = 0.99 to 1.50, crude OR not provided)</td>
<td>Accounted for appropriate confounders (number of sexual partners, number of anonymous partners, condom use, CD4+ lymphocyte count, age, education, ethnic origin, alcohol use, and recreational drug use)</td>
<td>No biochemical validation of smoking status, assessors not blinded</td>
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<tr>
<td>5</td>
<td>Burns et al (1991)</td>
<td>Primary care setting in Washington DC and New York, United States</td>
<td>Prospective cohort study of 202 homosexual men consecutively enrolled with three primary care physicians. Analysis included those found to be HIV-1 antibody positive during enrolment (n = 84) and those who seroconverted (n = 47) during the observation period (1982–8). Control group were those who remained HIV-1 antibody negative at the end of the study period (n = 71)</td>
<td>HIV-1 antibody seroconversion, diagnosis of AIDS by CDC definition (1987)</td>
<td>Participants who were initially HIV-1 seronegative were more likely to become seropositive if they smoked (p = 0.03). No difference between smokers and non-smokers in progression to AIDS (p = 0.31) or development of PCP. Insufficient data provided to calculate OR</td>
<td>Appropriate selection and comparability of exposed and non-exposed cohorts, good assessment of key confounders (number of partners, frequency of receptive anal intercourse, percentage of CD4+ and CD8+ lymphocytes)</td>
<td>Smoking status self reported and not biochemically validated. Assessors not reported as being blind to study hypothesis or outcomes. Unclear how key confounders were used in the analysis</td>
</tr>
<tr>
<td>6</td>
<td>Siriprapasiri et al (1996)</td>
<td>Sexually transmitted diseases clinic in Chiang Mai, Thailand</td>
<td>Cross sectional study of men attending the clinic. 124 men who were HIV negative and 26 who were HIV positive at recruitment were included</td>
<td>HIV serostatus</td>
<td>In multivariate analysis, smoking was associated with HIV seropositivity (adjusted OR = 3.5, 95% CI = 1.2 to 10.5, crude OR = 3.7, 95% CI = 1.3 to 11.0)</td>
<td>Accounted for appropriate confounders (age, educational attainment, marital status, frequency of sex with a commercial sex worker, history of sexually transmitted infection)</td>
<td>Recruitment methods unclear, no biochemical validation of smoking status, assessors not blinded</td>
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</tbody>
</table>

CI, confidence interval; OR, odds ratio; PCP, Pneumocystis carinii pneumonia; RH, relative hazard; RR, relative risk.
### Table 3 Papers using progression to AIDS as the outcome measure ranked by study quality (best quality study first)

<table>
<thead>
<tr>
<th>Rank</th>
<th>Quality assessment</th>
<th>Reference (date of publication)</th>
<th>Setting/country</th>
<th>Design, population and sample size</th>
<th>Relevant outcome measures</th>
<th>Findings</th>
<th>Quality assessment: study strengths</th>
<th>Quality assessment: study weaknesses</th>
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</thead>
<tbody>
<tr>
<td>2</td>
<td>= 1</td>
<td>Webber et al. (1996)††</td>
<td>Hospital affiliated methadone maintenance programme with on-site primary care in New York City, United States</td>
<td>Prospective cohort study of 524 HIV positive people who attended the methadone programme</td>
<td>Time to AIDS defining condition (by CDC 1993 definition) but excluding CD4+ cell count &lt;200 x 10^6/l and death</td>
<td>Cigarette smoking did not add information to a model controlling for CD4+ cell counts, constitutional symptoms, crack cocaine use, after adjustment for zidovudine use and age (hazard ratios not provided and data insufficient to calculate) In multivariate analysis, rate of progression to AIDS and mortality were not affected by smoking status. Adjusted hazard ratio for smokers versus non-smokers for progression to AIDS was 1.36 (95% CI 0.75 to 2.45) Crude hazard ratio not provide and data insufficient to calculate.</td>
<td>Wide range of confounders taken into account (age, sex, CD4+ cell counts, constitutional symptoms, crack cocaine use, zidovudine use, type and route of drug use, sexual risk factors, and sociodemographic variables)</td>
<td>Investigators not blinded and smoking status not biochemically validated</td>
</tr>
<tr>
<td>3</td>
<td>= 1</td>
<td>Stephenson et al. (1999)††</td>
<td>15 genitourinary medicine clinics in Britain and Ireland</td>
<td>Prospective observational cohort study of 385 women aged over 18 years with a positive HIV antibody test who progressed to AIDS</td>
<td>Incidence of AIDS (criteria for AIDS or AIDS defining condition not stated)</td>
<td>Wide range of confounders taken into account (CD4+ lymphocyte count, antiretroviral drug use, Pneumocystis carinii prophylaxis, age, ethnic origin, number of sexual partners, occupational status, marital status, alcohol use, and use of oral contraception). Adequate assessment of baseline characteristics including date of seroconversion</td>
<td>Date of HIV seroconversion was unknown but CD4+ lymphocyte count was fitted as a fixed variable to adjust for illness on entry to study. Investigators not blinded and no biochemical validation of smoking status</td>
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<td>5</td>
<td>= 1</td>
<td>Conley et al. (1996)††</td>
<td>San Francisco, Denver, and Chicago, United States</td>
<td>Prospective and retrospective cohort study of 232 HIV infected homosexual and bisexual men previously enrolled for a hepatitis B study. Participants classified as either smokers (n = 106) or non-smokers (n = 126)</td>
<td>Included diagnosis of AIDS by CDC definition (1987)††</td>
<td>Neither univariate analysis nor Kaplan-Meier survival analysis found any association between cigarette smoking and the development of AIDS (univariate RR = 1.0, 95% CI = 0.8 to 1.3), PCP (univariate RR = 0.9, 95% CI = 0.5 to 1.6), or Kaposi’s sarcoma (univariate RR = 0.6, 95% CI = 0.3 to 1.1). Cox regression models showed no relation between smoking status and progression to AIDS (hazard ratio not provided or raw data to calculate)</td>
<td>Interviewer administered questionnaire of exposure (smoking status) and complete follow up of eligible participants. Confounders taken into account were age, alcohol consumption, recreational drug use, sexually transmitted infections, and intestinal parasites. Selection criteria clear and appropriate with important confounders taken into account (age, gender, race/ethnicity, HIV-1 risk behaviour, previous disease progression, baseline CD4+ lymphocyte count, Karnofsky score, use of antiretroviral therapy, use of Pneumocystis carinii prophylaxis, alcohol use, and “street” drug use)</td>
<td>Assessors not blinded, smoking status not biochemically assessed</td>
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<tr>
<td>6</td>
<td>= 4</td>
<td>Coates et al. (1990)††</td>
<td>Toronto, Canada</td>
<td>Prospective cohort study of 159 apparently healthy homosexual or bisexual male contacts of other men known to have AIDS with follow up for 4.5 years</td>
<td>Diagnosis of AIDS by CDC definition (1985)††</td>
<td>After adjustment for confounders, there was no difference between current and never smokers for overall risk of opportunistic diseases (adjusted RH = 1.05, 95% CI = 0.9 to 1.23) or death (adjusted RH = 1.00, 95% CI = 0.86 to 1.18). However current smokers were at greater risk than non-smokers of developing bacterial pneumonia (adjusted RH = 1.57, 95% CI = 1.14 to 2.15) and AIDS dementia complex (adjusted RH = 1.80, 95% CI = 1.1 to 2.90). Current smokers were less likely than never smokers to develop Kaposi’s sarcoma (adjusted RH = 0.58, 95% CI = 0.39 to 0.88). Crude RH not provided and data insufficient to calculate</td>
<td>Smoking status not biochemically confirmed. Disease progression for 143 participants who were HIV seropositive on enrolment assessed by estimated length of HIV infection (rather than known dates or proxy measure such as CD4+ cell count). Assessors not blinded.</td>
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<td>6</td>
<td>= 4</td>
<td>Burns et al. (1996)††</td>
<td>17 community based clinical centres in 13 cities in the United States</td>
<td>Prospective cohort study of 3221 HIV-1 seropositive men and women with median follow up of 36 months for current smokers and never smokers and 37 months for former smokers</td>
<td>Participants classified as never (n = 760), former (n = 618), or current (n = 1843) smokers on the basis of an enrolment questionnaire (not biochemically validated). Outcome measures were HIV related diagnoses similar to CDC list of AIDS defining illnesses (1987)††</td>
<td>After adjustment for confounders, there was no difference between current and never smokers for overall risk of opportunistic diseases (adjusted RH = 1.05, 95% CI = 0.9 to 1.23) or death (adjusted RH = 1.00, 95% CI = 0.86 to 1.18). However current smokers were at greater risk than non-smokers of developing bacterial pneumonia (adjusted RH = 1.57, 95% CI = 1.14 to 2.15) and AIDS dementia complex (adjusted RH = 1.80, 95% CI = 1.1 to 2.90). Current smokers were less likely than never smokers to develop Kaposi’s sarcoma (adjusted RH = 0.58, 95% CI = 0.39 to 0.88). Crude RH not provided and data insufficient to calculate</td>
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<td>Ranking</td>
<td>Reference (date of publication)</td>
<td>Setting/country</td>
<td>Sample size</td>
<td>Design, population and sample size</td>
<td>Relevant outcome measures</td>
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<td>4</td>
<td>Eskild et al (1994)(^1) A clinic for homosexual and bisexual men in Oslo, Norway</td>
<td>Prospective cohort study of 78 HIV infected homosexual and bisexual clinic clients classified as either non-smokers (n=31), smoking 1–20 cigarettes a day (n=26) or more than 20 cigarettes daily (n=21)</td>
<td>Diagnosis of AIDS by CDC definition (1987)(^2)</td>
<td>No association found between cigarette smoking and progression to AIDS (adjusted relative risk of developing AIDS in smokers versus non-smokers for 1–20 cigarettes per day was 0.4 (95% CI 0.1 to 1.2) and for &gt;20 cigarettes per day was 1.1 (95% CI 0.4 to 2.7). Crude relative risks were 0.4 (95% CI = 0.2 to 1.2) and 1.1 (95% CI = 0.5 to 2.7), respectively.</td>
<td>Important confounders assessed by interview (age, year of HIV diagnosis, number of male lifetime partners, frequency of receptive anal intercourse, alcohol consumption). Small loss to follow up (2.5%).</td>
<td>Disease progression only accounted for reported year of HIV diagnosis. Smoking status not biochemically verified. Assessors not blinded. No statistically significant association found between known risk factors (number of male lifetime partners, frequency of receptive anal intercourse) and progression to AIDS suggesting study may have been underpowered</td>
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<td>4</td>
<td>Gobi et al (1997)(^3) Baltimore, Chicago, Los Angeles, and Pittsburgh, United States</td>
<td>Prospective cohort study (part of Multicentre AIDS Cohort Study) of 2420 men with HIV</td>
<td>Included diagnosis of AIDS by CDC definition (1987),(^4) PCP</td>
<td>No association found in Kaplan-Meier or multivariate Cox regression analyses between smoking and AIDS (adjusted hazard ratio 0.96, p = 0.7, CI not provided or data available to calculate) or PCP. Participants who were initially HIV-1 seronegative were more likely to become seropositive if they smoked (p = 0.03). No difference between smokers and non-smokers in progression to AIDS (p = 0.31) or development of PCP. Insufficient data provided to calculate relative risk.</td>
<td>Large cohort with important confounders assessed (date of seroconversion, CD4+ lymphocyte count, antiretroviral and anti-PCP therapy)</td>
<td>Smoking status assessed only by participant completed questionnaire and not biochemically verified. Assessors not blinded</td>
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<td>8</td>
<td>Burns et al (1991)(^5) See table 2</td>
<td>See table 2</td>
<td>HIV-1 antibody seroconversion, diagnosis of AIDS by CDC definition (1987)(^6)</td>
<td>No effect of smoking on progression to AIDS (p = 0.829) or diagnosis of PCP (p = 0.894). Insufficient data provided to calculate relative risk.</td>
<td>See table 2</td>
<td>See table 2</td>
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<td>8</td>
<td>Craib et al (1992)(^7) Two general practices in Vancouver, Canada</td>
<td>Prospective cohort study of 122 seroincident homosexual men classified as either smokers (n=74) or non-smokers (n=48) followed up for 3 years</td>
<td>HIV-1 antibody seroconversion, diagnosis of AIDS by CDC definition (1987)(^8)</td>
<td>No effect of smoking on progression to AIDS (p = 0.829) or diagnosis of PCP (p = 0.894). Insufficient data provided to calculate relative risk.</td>
<td>Representative sample with adequate assessment of disease stage at diagnosis (measured by CD4+ and CD8+ lymphocyte counts and date of seroconversion). However use of log rank test meant analysis did not adjust for these confounders</td>
<td>Other potential confounders apart from age and disease progression not assessed. Assessors not blind to smoking status. Unclear why only 122 participants included in analysis</td>
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<tr>
<td>8</td>
<td>Nieman et al (1993)(^9) Genitourinary medicine outpatient department in London, UK</td>
<td>Retrospective cohort study of 84 clients (2 women and 82 men) with AIDS (CDC definition),(^10) of whom 43 were classified as smokers and 41 as non-smokers (never smoked or stopped more than 12 months ago)</td>
<td>Diagnosis of AIDS by CDC definition (1986)(^11)</td>
<td>Median time to AIDS (all diagnoses) was 8.17 months for smokers and 14.50 months for non-smokers (p = 0.003). Median time to PCP was 9.0 months for smokers and 16.0 months for non-smokers (p = 0.002). No difference was noted between smokers and non-smokers on the development of non-PCP AIDS</td>
<td>Complete follow up and adequate assessment of disease stage at enrollment (measured by CDC stages) were not significantly different between smokers and non-smokers at initial assessment</td>
<td>Other important confounders (eg, CD4+ cell counts and continued risk behaviours) not measured. Smoking status not biochemically verified. Assessors not blinded to smoking status</td>
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CI, confidence interval; OR, odds ratio; PCP, Pneumocystis carinii pneumonia; RH, relative hazard; RR, relative risk.
evidence to inform decisions at population and individual levels. The public health message on smoking remains clear—
tobacco is not good for health. Smoking prevalence is high among groups who are also vulnerable to HIV infection, 
including sex workers and men who have sex with men. In developing countries these groups are especially marginalised 
and providing any sort of support, let alone smoking cessation services, is difficult. Research is required into the best 
approaches for these groups.11

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CONTRIBUTORS

The study was conceived by AF and the protocol was developed by all the authors; CC developed and performed the literature searches; AF and RM extracted the data; AF wrote the first draft with all authors contributing to later drafts; AF is the guarantor.

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