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Rates of cardiovascular disease following smoking cessation in patients with HIV infection: results from the D:A:D Study

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Abstract

Objective—To estimate the rates of cardiovascular disease (CVD) events after stopping smoking in patients with HIV-infection.

Design—Patients who reported smoking status, and no previous CVD prior to enrolment into D:A:D were included. Smoking status is collected at each visit as current smoker (yes/no) and ever smoker (yes/no). Duration since stopping smoking was calculated for persons who had reported current smoking during follow-up and no current smoking subsequently. Endpoints were: myocardial infarction (MI); coronary heart disease (CHD – MI plus invasive coronary artery procedure or death from other CHD); CVD (CVD – CHD plus carotid artery endarterectomy or stroke); and all-cause mortality.

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Methods—Event rates were calculated for never, previous and current smokers, and smokers who stopped during follow-up. Incidence rate ratios (IRR) were determined using Poisson regression adjusted for age, sex, cohort, calendar year, family history of CVD, diabetes, lipids, blood pressure and antiretroviral treatment.

Results—27,136 patients had smoking status reported, with a total of 432, 600, 746 and 1902 MI, CHD, CVD and mortality events respectively. The adjusted IRR of CVD in patients who stopped smoking during follow-up decreased from 2.32 within the first year of stopping to 1.49 after 3+ years compared to those who never smoked. Similar trends were observed for the MI and CHD endpoints. Reductions in risk were less pronounced for all cause mortality.

Conclusion—The risk of CVD events in HIV-positive patients decreased with increasing time since stopping smoking. Smoking cessation efforts should be a priority in the management of HIV positive patients.

Keywords

HIV-infection; smoking cessation; myocardial infarction; cardiovascular disease; cohort study

Introduction

Rates of cigarette smoking are high across most HIV populations in developed countries. Studies have reported at least a 2 to 3 fold increased rate compared to the general population, with 40 to 70% of HIV positive patients reporting current smoking [1–6]. Smoking has been independently associated with morbidity and mortality of HIV positive patients [7–11]; comorbid conditions include bacterial pneumonia [8,10,12], pulmonary disease [8,13], lung cancer [14,15] and cardiovascular disease (CVD) [7,16]. The contribution of smoking on the risk of MIs has also been shown to be considerably greater than other CVD risk factors. The Data collection on Adverse Events of Anti-HIV Drugs (D:A:D) study demonstrated a 2 fold increase risk of MIs among current and previous smokers compared to non-smokers. While other cardiovascular risk factors increased the risk of MIs by 16% per doubling in triglycerides, 20% per unit increase in total cholesterol, and 25% for patients with hypertension and diabetes [17].

In the era of effective combination antiretroviral treatment (cART), the effect of smoking on morbidity in HIV positive patients remains a concern, as HIV positive patients are living longer and at increased risk for many smoking associated non-AIDS defining illnesses including CVD, pulmonary disease and non-AIDS malignancies [7,15,18–20]. Despite this, HIV positive patients continue to smoke. Several reasons have been suggested, including social conditions, polysubstance abuse, psychiatric comorbities, physical and mental distress, access to smoking cessation interventions and adherence with such treatments, as well as the negative perception of long-term survival among HIV positive patients [3,5,21].

The health benefits of quitting cigarette smoking in the general population are substantial and widely documented. The risk of coronary heart disease and mortality is considerably reduced within the first two years of stopping smoking [22–27], and in some studies has been shown to return to levels observed in non-smokers within five years [22,23,25]. Whether HIV positive patients also benefit from quitting smoking in terms of cardiovascular and mortality risk has not previously been investigated; although recent data have demonstrated reduced risk of bacterial pneumonia after at least one year of having ceased smoking [28]. If similar evidence observed in the general HIV negative population could be demonstrated in HIV positive populations then this may provide additional incentive to quit smoking. The D:A:D study is a large international prospective cohort study with detailed follow-up information on incident CVD and smoking status. Our objective was to estimate

the rates of CVD events and mortality after smoking cessation in HIV positive patients participating in the D:A:D study.

Methods

The D:A:D study is a prospective, multi-cohort observational collaborative study, including 11 previously established cohorts following 33,308 patients at 212 clinics from Europe, Argentina, Australia and the US. The primary objective of the study is to investigate the possible association between cART and the risk of myocardial infarction (MI). At the time of enrolment into the D:A:D study, patients were under active follow-up at the individual cohorts, and were included in D:A:D irrespective of whether or how long they were receiving antiretroviral treatment (ART). Data were collected as part of their routine clinical care and include demographic and other prospectively collected data such as age, sex, body mass index (BMI), hepatitis B and C status, history of CVD, diabetes mellitus (DM), family history of CVD, cigarette smoking, blood pressure therapy, DM therapy, lipid lowering and antihypertensive therapy, and serum lipid levels. HIV related core clinical data collected include mode of HIV (transmission) risk group, ART medication received, CD4 and viral load and all clinical AIDS diagnoses. A detailed description of the study methodology has been described previously [17]. Ethics approval is sought by the individual D:A:D collaborating cohorts from their local Institutional Review Boards as required. Written informed patient consent is obtained for each cohort subject to local IRB requirements. All D:A:D and individual cohort procedures are developed in accordance with the revised 1975 Helsinki Declaration.

Endpoints

We assessed the following individual endpoints in these analyses: *myocardial infarction* (MI) - including fatal and non-fatal cases; c*oronary heart disease (CHD)* - MI plus invasive coronary artery procedure (including coronary artery by-pass or angioplasty), or death from other coronary heart disease; *cardiovascular disease (CVD)* - CHD plus carotid artery endarterectomy, or stroke; and *all cause mortality*. All endpoints are protocol defined, audited for completeness and centrally validated.

Smoking status

In the D:A:D study, smoking status is reported as Current Smoker (Yes/No) and Ever Smoker (Yes/No) at each visit. Dates of stopping or starting smoking are not recorded. Patients were therefore categorised as never smokers, previous smokers, current smokers or smokers who had stopped smoking during D:A:D follow up. Without dates of stopping or starting cigarette smoking, reasonably accurate durations of stopping smoking could only be calculated for those subjects who stopped smoking during the D:A:D study follow-up period. We calculated duration of stopping smoking from the mid-point between the last visit where a subject reported being a current smoker to the first visit a subject reported being a current non-smoker. Similarly, subjects who reported that they started smoking again were taken to do so at the mid-point of the respective visits. Where smoking status was reported to be missing, previous smoking status was carried forward. A sensitivity analysis was also performed omitting all periods of follow-up where smoking status was missing.

Statistical methods

These analyses were limited to D:A:D patients who ever report smoking status at enrolment (cohort entry) or during D:A:D follow-up, and had not reported a previous CVD event. Follow-up started at the later of D:A:D cohort entry (enrolment into D:A:D commenced December 1999) and first reported smoking status, and finished at the earlier of date of

death, 6 months after the patients last clinic visit, or 1 February 2008, whichever occurred first. Event rates for each endpoint were calculated for never, previous, current smokers, and smokers who stop during D:A:D follow-up. Event rates for smokers who stopped during D:A:D follow-up were calculated in annual increments (< 1 year, 1–2 years, 2–3 years and 3+ years). Smoking status for individual patients could change during D:A:D follow-up could. For example, never smokers may become current smokers and then stop smoking; while previous smokers may restart smoking during follow-up.

Crude unadjusted event rates for each smoking status group were calculated. We determined incidence rate ratios (IRR) using Poisson regression methods adjusted for age, sex, cohort, calendar year, family history of CVD, diabetes, time updated lipid (total cholesterol and high-density lipoprotein cholesterol [HDL-C], triglycerides) and systolic blood pressure assessments, and antiretroviral treatment (cumulative cART, cumulative indinavir, cumulative lopinavir, and current exposure to abacavir). IRRs are ratios of the incidence rates and can be interpreted as relative risks. These covariates were selected for adjustment based on factors identified in the D:A:D CVD prediction equation [29], and previous publications from this dataset [30,31]. For all-cause mortality we further adjusted for hepatitis B and C coinfection, mode of HIV transmission, ethnicity and incidence of CVD during follow-up. Testing for hepatitis B (HBV) and C (HCV) varies both between and within cohorts. It is unknown why patients are tested, and those who are positive probably would have been positive for some time prior to testing. HBV and HCV are therefore treated as fixed covariates categorised as ever versus never.

Results

Patient characteristics

Of the 33,308 participants in D:A:D as of February 2008, 27136 (82%) had reported smoking status at least once during prospective D:A:D follow-up. At the time of first report of smoking status, 8920 (33%) had never smoked, 6265 (23%) were previous-smokers, and 11,951 (44%) were current smokers. During 151,717 person years of follow-up, 8197 (30%) participants reported stopping smoking at least once (69% of those who reported current smoking). Characteristics of patients included in these analyses are shown in Table 1. A smaller proportion of current and previous-smokers were female, compared to those who never smoked (23% and 21% versus 35%). Current smokers were mostly of white ethnicity (70%) compared to previous (46%) and never (48%) smokers respectively, and were more likely to have reported mode of HIV transmission as injecting drug use (32% vs. 18% and 5%, respectively). In terms of HIV-related factors, never, previous and current smokers had similar median CD4 cell counts at baseline (IQR) (406 (255–591), 410 (250–603) and 440 (278–642) respectively, and all three groups had a median of at least 1.5 years of cART exposure. Total cholesterol, HDL-C, triglycerides and BMI were also similar across current, previous and never smokers (Table 1). Patient characteristics of the 20% (n=5623) patients excluded from these analyses were broadly similar to the included population for most demographic factors. Key differences were a smaller proportion of the excluded population reported mode of exposure as heterosexual (17% compared to 33%), were HBV and HCV positive (9% and 10% respectively compared to 16% and 22% in the included population), and less cART exposure (data not shown).

Cardiovascular disease rates

In these analyses there were 432 MI, 600 CHD and 746 CVD events reported during 15,1717 person years of follow up, yielding overall crude rates (and 95% CI) per 1000 person years of 2.85 (2.59, 3.13), 3.95 (3.64, 4.28) and 4.92 (4.57,5.28) for MI, CHD and CVD events respectively. Adjusted incidence rate ratios (IRR) for all cardiovascular events

and smoking status groups are shown in table 2 and figure 1. For MI events, the IRR (95% CI) compared to never smokers decreased from 3.73 (2.46, 5.64) within the first year to 3.00 (1.84, 4.88) within one and two years, to 2.62 (1.42, 4.83) between two and three years, and to 2.07 (1.19, 3.63) after more than three years of having stopped smoking. Similarly, the IRR for CHD events decreased from 2.93 (95%CI: 2.07, 4.14) in the first year of having quit smoking, to 2.48 (1.65, 3.73) in the subsequent year, and 1.90 (1.09, 3.29) within the second and third year, to 1.83 (1.16, 2.89) after more than three years having stopped smoking. The IRRs (95% CI) also decreased for CVD events from 2.32 (1.69, 3.18) within less than one year, to 1.84 (1.25, 2.70) between the first and second year, and 1.60 (0.99, 2.61) and 1.49 (0.99, 2.24) for those who have stopped smoking between two and three years and more than three years respectively (Table 2 and Figure 1). Compared to current smokers, the risk of MI, CHD and CVD among patients who stopped smoking for more than 3 years was reduced by approximately 30% (IRR (95% CI): 0.61 (0.36, 1.04) for MI, 0.74 (0.48, 1.15) for CVD, and 0.68 (0.46, 1.01) for CHD) (Table 2).

Mortality rates

There were 1902 deaths reported during follow-up, yielding a crude rate of 12.54 (95% CI: 11.98–13.11) per 1000 person-years. Table 3 provides crude death rates per 1000 person years for specific smoking status groups and IRRs for previous, current and stopped smoking groups compared to the never smoked groups. Unlike the cardiovascular disease events, these IRRs did not decrease linearly with increased time since smoking cessation. In a post-hoc mortality analysis which aimed at demonstrating a clearer mortality signal in a subgroup at higher risk of mortality, we restricted the analysis to patients aged greater than 50 years during follow-up. In this group, a total 634 deaths were recorded (crude rate of 19.64 per 1000 person years). Again, there was no decreasing trend IRR for each additional year of having stopped smoking (Table 3 and Figure 1). The risk of death overall and for those aged greater than 50 were similar for patients who stopped smoking for more than 3 years compared to current smokers (Table 3).

Specific causes of death—One explanation for the lack of reduction in mortality following smoking cessation is that patients stopped smoking following diagnosis of a serious illness. To investigate this hypothesis further, we summarized causes of death by smoking status. Overall, HIV/AIDS was recorded as the underlying cause in 27% of deaths, 10% were cardiovascular disease, 13% chronic viral hepatitis, 12% non-AIDS malignances, 6% invasive bacterial, and 24% other. A larger proportion of never smokers died from HIV/AIDS (35%) compared to previous smokers (27%), current smokers (23%), and those who stopped smoking (29%). A greater proportion of previous-smokers and those who had stopped smoking during D:A:D follow-up who died had non-AIDs malignancies as the reported underlying cause of death (17% for both groups). This compared to 10% non-AIDS malignancy deaths in both the never smoked and current smokers. A larger proportion of current smokers died due to chronic viral hepatitis (17%) compared to 10%, 13% and 9% among those who never smoked, previous-smokers and those who stopped smoking during follow-up (Table 4). We also assessed rates of CVD related deaths by smoking status. There were 192 CVD deaths in total. The adjusted IRR for current smokers compared with never smokers was 1.33 (951% CI: 0.84, 2.10). The IRRs (95CI) for having stopped smoking for up to 1 year, 1 to 2 years, 2 to 3 years and more than 3 years were 0.90 (0.47,1.76), 0.59 (0.25,1.38), 1.20 (0.53,2.76) and 1.00 (0.47, 2.13) respectively.

Among the 20% of patients who smoking status was not ever known, and therefore excluded from these analyses, the crude rates for CVD, CHD, MI and deaths were 4.1, 3.7, 2.6 and 18.8 per 1000 person-years respectively. Of patients who reported current smoking status during follow-up, approximately 17% had some smoking data missing during follow-up. In

a sensitivity analysis for both the CVD endpoints and mortality omitting all periods of follow-up where smoking status was missing yielded similar results (data not shown).

Changes in lipids, blood pressure and medication use after stopping smoking —We assessed if lipid, blood pressure and BMI levels changed in those patients who stopped smoking, and also whether there were changes in lipid and blood pressure lowering therapy. The median changes in cholesterol, HDL, cholesterol:HDL ratio, triglycerides, systolic and diastolic blood pressure and BMI were all 0 up to two years following smoking cessation. There were, however, small mean decreases in cholesterol (mean (SD)−0.12 (1.16)), cholesterol:HDL ratio (−0.32(2.00)), triglycerides (−0.16(2.03)) and BMI (−0.20 (1.55)), and small mean increases in HDL (0.04 (0.35)) and blood pressure (diastolic: 0.40 (9.51); systolic:1.48 (13.72)) at 2 years. Use of lipid and blood pressure lowering medications both increased, from 12% and 9% respectively of patients at the time of stopping smoking, to 19% and 13% respectively two-years post-smoking cessation.

Discussion

This is the first study to assess the impact of smoking cessation on coronary heart disease and mortality in a HIV positive population. We found that the risk of MI, CVD and CHD decreased with each increasing year of having quit smoking, and after three years, the risk almost halved compared to the first year of stopping smoking. Rates of MI decreased from an almost 4 fold increased relative risk compared to never smokers among patients who were in the first year after having stopped smoking to just over 2 fold greater relative risk among those who had stopped smoking more than 3 years previously. Although less pronounced, the relative risk for CHD decreased from 2.5 fold to 1.8-fold, and from 2.3-fold to 1.5 fold for CVD. In the general population there is also an immediate benefit of quitting smoking, and in some studies the risk of events at about 5 years after stopping smoking is close to that in individuals who never smoked was noted [22,23,25]. Although we were not able to assess event rates beyond 3 years of having ceased smoking, our results show that the clinical benefits observed in the general HIV negative population are also seen in HIV positive patients.

Unlike the CVD endpoints, we did not observe a decrease in the mortality rates for patients who quit smoking during follow-up. Even when we restricted our analysis to the over 50 year age group, a population at increased risk of the detrimental effects of smoking, mortality rates did not decrease with increasing years of having stopped smoking. These findings are in contrast to what has been reported in the literature for the general population both for all cause-mortality as well as for specific causes of death [24,26,27]. One possible explanation for our findings is that some patients who stopped smoking following diagnosis of a serious illness such as lung cancer may have quit smoking too late to benefit from stopping smoking. We do not collect reasons for quitting smoking, and also have only just begun collecting information on other serious non-AIDS endpoints such as non-AIDS malignancies, and so were not able to attempt to adjust for this bias. We were, however, able to summarise data on causes of death to assess this. We found a larger proportion of previous smokers and those who stopped smoking during follow-up died from non-AIDS malignancies, while a larger proportion of non-smokers died from HIV/AIDS compared to all the smoking status groups. This lends some support to the notion that some patients who died most likely stopped smoking at too late a stage of their illness to benefit from quitting. It is also notable that most reported causes of death are not directly associated with smoking, suggesting that we might have missed a reduction in smoking related mortality due to competing risks. We did assess reductions in CVD mortality only, but did not see any clear reduction, perhaps due to the relatively small numbers of CVD deaths. It may be that this

issue will become clearer with further follow-up in D:A:D, and the recent inclusion of data on serious non-AIDS endpoints.

Whether the rates of CVD in HIV positive patients return to levels observed in non-smokers after five or more years, as observed in the general population, remains unanswered. Indeed, although we observed a decrease in CVD on stopping smoking that is qualitatively similar to the trends seen in HIV-negative populations, making exact quantitative comparisons is not possible.

There are a number of limitations to our analyses. First, we do not collect start or stop dates for smoking, and also do not collect data on smoking exposure such as pack-years. We were therefore only able to determine duration of stopping smoking with any accuracy for patients who reported stopping smoking during follow-up. While these data limitations may have resulted in some inaccuracy in our estimates of duration of stopping smoking, it is difficult to imagine how such inaccuracies might have created an association. It seems more likely that this bias is akin to misclassification in epidemiological studies, and hence would lead to underestimates of associations. Furthermore, a sensitivity analysis excluding patient follow-up where smoking data was missing gave similar results. Therefore we believe that the decreases in risk of CVD following smoking cessation that we have seen can be interpreted robustly. Second, in our analyses we adjusted for time-updated lipids and blood pressure measurements. These are variables which might be expected to improve on stopping smoking, leading to issues around time-varying confounding. We did not perform more complex statistical models that attempt to account for such confounding such as marginal structural models given the very small mean changes in such variables that we observed. By including changes in lipids and blood pressure post stopping smoking, if these variables improved as a result of stopping smoking the risk predicted by the model would decrease, and yet we still observed a decrease in the adjusted risk of CVD after stopping. Hence, the analyses we performed that did adjust for time-updated changes in these variables would be expected to lead to underestimates in reduction of CVD disease, again suggesting that our observed decrease in CVD can be interpreted robustly. Third, we do not collect reasons for stopping smoking or any other health behaviour data, and it is possible that quitting smoking may have been accompanied by other beneficial lifestyle changes such as improved diet, increased exercise and reduced recreation drug use, that may also explain the observed lower rates among patients who stopped smoking. Hence we cannot exclude that some of the observed decrease in CVD may be due to other improved lifestyle behaviours and not entirely due to stopping smoking. Finally, we did not have any historical smoking data (prior to entry into D:A:D), and therefore we were unable to accurately determine number of attempts at quitting smoking in this population. However other studies have reported that at least 70% of HIV positive patients who were regular smokers had tried quitting at least once before [2,5], 42% after their HIV diagnosis [2] which is consistent with what we observed during D:A:D follow-up.

In conclusion, we found that rates of CVD decreased in HIV positive patients who stopped smoking. Successfully quitting smoking can overall reduce the disease burden of HIV positive patients and improve quality of life, and smoking cessation efforts should be made a priority in the clinical management of HIV positive patients. This will require research into identifying the most effective smoking cessation approaches in HIV-positive patients. Our results provide further incentive to quit smoking among a population where smoking is highly prevalent

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Appendix

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References

1. Grierson, J.; Thorpe, R.; Saunders, M.; Pitts, M. HIV Futures4: state of the [positive] nation, monograph series number 48. Melbourne Australia: The Australian Research Centre in Sex, Health and Society, Latrobe University; 2004.
2. Benard A, Bonnet F, Tessier JF, Fossoux H, Dupon M, Mercie P, et al. Tobacco addiction and HIV infection: toward the implementation of cessation programs. ANRS CO3 Aquitaine Cohort. AIDS Patient Care STDS. 2007; 21:458–468. [PubMed: 17651027]
3. Duval X, Baron G, Garelik D, Villes V, Dupre T, Leport C, et al. Living with HIV, antiretroviral treatment experience and tobacco smoking: results from a multisite cross-sectional study. Antivir Ther. 2008; 13:389–397. [PubMed: 18572752]
4. Tesoriero JM, Gieryic SM, Carrascal A, Lavigne HE. Smoking Among HIV Positive New Yorkers: Prevalence, Frequency, and Opportunities for Cessation. AIDS Behav. 2008
5. Mamary EM, Bahrs D, Martinez S. Cigarette smoking and the desire to quit among individuals living with HIV. AIDS Patient Care STDS. 2002; 16:39–42. [PubMed: 11839217]
6. Crothers K, Goulet JL, Rodriguez-Barradas MC, Gibert CL, Butt AA, Braithwaite RS, et al. Decreased awareness of current smoking among health care providers of HIV-positive compared to HIV-negative veterans. J Gen Intern Med. 2007; 22:749–754. [PubMed: 17503106]
7. Friis-Moller N, Weber R, Reiss P, Thiebaut R, Kirk O, d'Arminio Monforte A, et al. Cardiovascular disease risk factors in HIV patients--association with antiretroviral therapy. Results from the DAD study. Aids. 2003; 17:1179–1193. [PubMed: 12819520]
8. Crothers K, Griffith TA, McGinnis KA, Rodriguez-Barradas MC, Leaf DA, Weissman S, et al. The impact of cigarette smoking on mortality, quality of life, and comorbid illness among HIV-positive veterans. J Gen Intern Med. 2005; 20:1142–1145. [PubMed: 16423106]
9. Clifford GM, Polesel J, Rickenbach M, Dal Maso L, Keiser O, Kofler A, et al. Cancer risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy. J Natl Cancer Inst. 2005; 97:425–432. [PubMed: 15770006]
10. Burns DN, Hillman D, Neaton JD, Sherer R, Mitchell T, Capps L, et al. Cigarette smoking, bacterial pneumonia, and other clinical outcomes in HIV-1 infection. Terry Beirn Community Programs for Clinical Research on AIDS. J Acquir Immune Defic Syndr Hum Retrovirol. 1996; 13:374–383. [PubMed: 8948377]
11. Conley LJ, Bush TJ, Buchbinder SP, Penley KA, Judson FN, Holmberg SD. The association between cigarette smoking and selected HIV-related medical conditions. AIDS. 1996; 10:1121–1126. [PubMed: 8874629]
12. Caiaffa WT, Vlahov D, Graham NM, Astemborski J, Solomon L, Nelson KE, Munoz A. Drug smoking, Pneumocystis carinii pneumonia, and immunosuppression increase risk of bacterial pneumonia in human immunodeficiency virus-seropositive injection drug users. Am J Respir Crit Care Med. 1994; 150:1493–1498. [PubMed: 7952605]
13. Crothers K, Butt AA, Gibert CL, Rodriguez-Barradas MC, Crystal S, Justice AC. Increased COPD among HIV-positive compared to HIV-negative veterans. Chest. 2006; 130:1326–1333. [PubMed: 17099007]
14. Kirk GD, Merlo C, P OD, Mehta SH, Galai N, Vlahov D, et al. HIV infection is associated with an increased risk for lung cancer, independent of smoking. Clin Infect Dis. 2007; 45:103–110. [PubMed: 17554710]
15. Bonnet F, Lewden C, May T, Heripret L, Jougla E, Bevilacqua S, et al. Malignancy-related causes of death in human immunodeficiency virus-infected patients in the era of highly active antiretroviral therapy. Cancer. 2004; 101:317–324. [PubMed: 15241829]
16. Mercie P, Thiebaut R, Lavignolle V, Pellegrin JL, Yvorra-Vives MC, Morlat P, et al. Evaluation of cardiovascular risk factors in HIV-1 infected patients using carotid intima-media thickness measurement. Ann Med. 2002; 34:55–63. [PubMed: 12014436]

17. Friis-Moller N, Sabin CA, Weber R, d'Arminio Monforte A, El-Sadr WM, Reiss P, et al. Combination antiretroviral therapy and the risk of myocardial infarction. N Engl J Med. 2003; 349:1993–2003. [PubMed: 14627784]

18. Monforte A, Abrams D, Pradier C, Weber R, Reiss P, Bonnet F, et al. HIV-induced immunodeficiency and mortality from AIDS-defining and non-AIDS-defining malignancies. AIDS. 2008; 22:2143–2153. [PubMed: 18832878]

19. Palella FJ Jr, Baker RK, Moorman AC, Chmiel JS, Wood KC, Brooks JT, Holmberg SD. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. J Acquir Immune Defic Syndr. 2006; 43:27–34. [PubMed: 16878047]

20. Lewden C, Salmon D, Morlat P, Bevilacqua S, Jougla E, Bonnet F, et al. Causes of death among human immunodeficiency virus (HIV)-infected adults in the era of potent antiretroviral therapy: emerging role of hepatitis and cancers, persistent role of AIDS. Int J Epidemiol. 2005; 34:121–130. [PubMed: 15561752]

21. Lloyd-Richardson EE, Stanton CA, Papandonatos GD, Shadel WG, Stein M, Tashima K, et al. Motivation and patch treatment for HIV+ smokers: a randomized controlled trial. Addiction. 2009; 104:1891–1900. [PubMed: 19719796]

22. Wolf PA, D'Agostino RB, Kannel WB, Bonita R, Belanger AJ. Cigarette smoking as a risk factor for stroke. The Framingham Study. JAMA. 1988; 259:1025–1029. [PubMed: 3339799]

23. Wannamethee SG, Shaper AG, Whincup PH, Walker M. Smoking cessation and the risk of stroke in middle-aged men. JAMA. 1995; 274:155–160. [PubMed: 7596004]

24. Tverdal A, Thelle D, Stensvold I, Leren P, Bjartveit K. Mortality in relation to smoking history: 13 years' follow-up of 68,000 Norwegian men and women 35–49 years. J Clin Epidemiol. 1993; 46:475–487. [PubMed: 8501474]

25. Rosenberg L, Kaufman DW, Helmrich SP, Shapiro S. The risk of myocardial infarction after quitting smoking in men under 55 years of age. N Engl J Med. 1985; 313:1511–1514. [PubMed: 4069159]

26. Godtfredsen NS, Holst C, Prescott E, Vestbo J, Osler M. Smoking reduction, smoking cessation, and mortality: a 16-year follow-up of 19,732 men and women from The Copenhagen Centre for Prospective Population Studies. Am J Epidemiol. 2002; 156:994–1001. [PubMed: 12446255]

27. Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. BMJ. 2004; 328:1519. [PubMed: 15213107]

28. Benard A, Mercie P, Alioum A, Bonnet F, Lazaro E, Dupon M, et al. Bacterial Pneumonia among HIV-infected patients: decreased risk after tobacco smoking cessation. ANRS CO3 Aquitaine Cohort, 2000–2007. PLoS One. 5:e8896. [PubMed: 20126646]

29. Friis-Moller NRT, Reiss P, Weber R, D'Arminio Monforte A, De Wit S, El-Sadr W, Fontas E, Worm S, Kirk O, Phillips A, Sabin CA, Lundgren JD, Law MG. Predicting the risk of cardivascular disease in HIV-infected patients; The Data-collection on Adverse Effects of Anti-HIV Drugs (D:A:D) Study. Eur J Cardiovasc Prev Rehabil. 2010

30. Sabin CA, Worm SW, Weber R, Reiss P, El-Sadr W, Dabis F, et al. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. Lancet. 2008; 371:1417–1426. [PubMed: 18387667]

31. Worm SW, Sabin C, Weber R, Reiss P, El-Sadr W, Dabis F, et al. Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the data collection on adverse events of anti-HIV drugs (D:A:D) study. J Infect Dis. 201:318–330. [PubMed: 20039804]

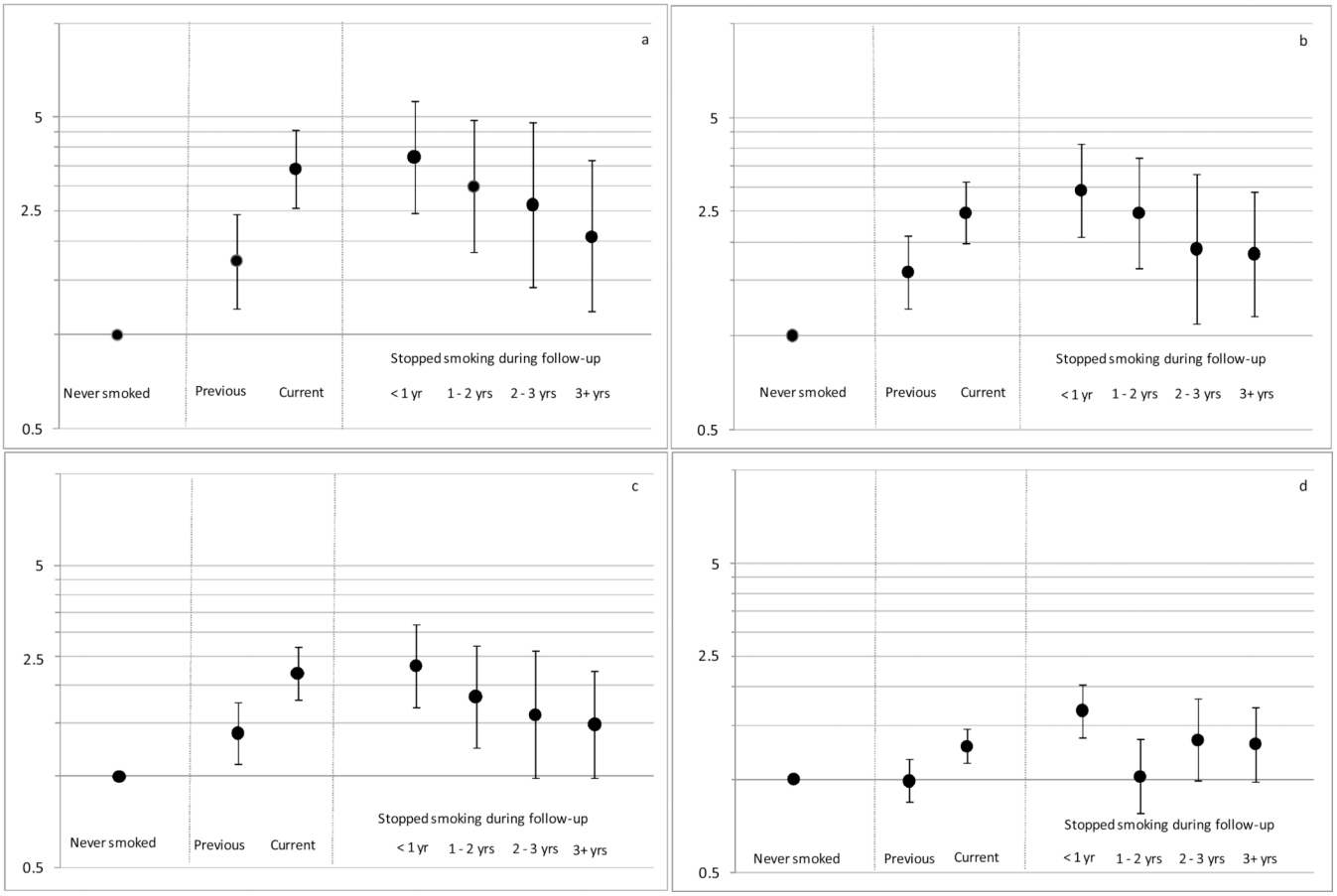

Figure 1.
Cardiovascular and mortality incidence rate ratios: (a) MI, (b) CVD, (d) CHD, (d) Mortality

Table 1

Patient characteristics at date of first reported smoking status

	Smoking status at baseline			Reported stopping smoking during D:A:D follow-up[1]
	Never smoked (n=8920)	Previous-smoker (n=6265)	Current smoker (n=11951)	(n=8197)
Age (years)	38 (33, 46)	39 (34, 46)	38 (33, 43)	41 (37, 47)
Female	35%	21%	23%	21.5%
Transmission group				
Heterosexual	45%	28%	26%	28%
Homosexual	42%	48%	38%	47%
Injecting drug use	5%	18%	32%	20%
Ethnicity				
White	48%	46%	70%	54%
Non-white	19%	4%	5%	5%
Unknown	34%	50%	25%	41%
HCV Positive	8%	19%	34%	24%
Not tested/Unknown	27%	22%	22%	15%
HBV Positive	14%	15%	17%	17%
Not tested/Unknown	21%	17%	20%	12%
CD4 count (cells/μl)	406 (255, 591)	410 (250, 603)	440 (278, 642)	480 (320, 680)
Viral load >50 copies/ml	62.9%	65.6%	63.7%	47.7%
cART exposure (years)	1.5 (0, 3.0)	1.5 (0, 3.1)	1.8 (0, 3.1)	4.1 (1.8, 6.1)
PI exposure (years)	1.0 (0, 2.7)	0.7 (0, 2.7)	1.3 (0, 2.8)	2.5 (0, 4.7)
Systolic BP (mmHG)	120 (115, 130)	120 (110, 130)	120 (110, 130)	120 (110, 130)
Diastolic BP (mmHG)	80 (70, 84)	80 (70, 82)	80 (70, 80)	80 (70, 80)
Total cholesterol (mmol/L)	5.0 (4.2, 6.0)	5.0 (4.2, 6.0)	4.9 (4.0, 5.8)	5.0 (4.2, 5.8)
HDL-C (mmol/L)	1.2 (0.9, 1.4)	1.1 (0.9, 1.4)	1.1 (0.9, 1.4)	1.2 (0.9, 1.4)
Cholesterol:HDL-C ratio	4.4 (3.4, 5.7)	4.6 (3.4, 6.0)	4.4 (3.4, 5.7)	4.3 (3.3, 5.6)
Triglycerides (mmol/L)	1.5 (1.0, 2.6)	1.6 (1.1, 2.7)	1.6, (1.1, 2.6)	1.7 (1.1, 2.7)
BMI (kg/m^2)	23.5 (21.5, 25.8)	23.0 (21.1, 25.2)	22.5 (20.7, 24.6)	22.8 (20.9, 25.0)
Lipid medication	4%	6%	4%	12%
BP medication	5%	5%	4%	9%
Family history of CVD	6%	8%	10%	10%
Diabetes	3%	3%	2%	5%

[1] Characteristics at first attempt to stop smoking. Figures are medians (inter quartile ranges) unless otherwise specified

Table 2

Cardiovascular event rates by smoking status

	Number of events	Person years	Crude rate (/1,000 years)	Poisson regression[1] IRR	(95% CI)	p-value	Poisson regression[1,2] IRR	(95% CI)	p-value
Myocardial infarction									
Never smoked	65	46 601.3	1.39	Ref			0.29	(0.22, 0.39)	<0.001
Previous smoker at baseline	66	23 972.8	2.75	1.73	(1.22, 2.44)	0.002	0.51	(0.38, 0.68)	<0.001
Current smoker	212	60 302.7	3.52	3.40	(2.56, 4.53)	<0.001	Ref		
Stopped smoking during follow-up									
<1 year	36	7 571.6	4.75	3.73	(2.46, 5.64)	<0.001	1.10	(0.76, 1.58)	0.624
1–2 years	23	5 288.2	4.35	3.00	(1.84, 4.88)	<0.001	0.88	(0.56, 1.38)	0.578
2–3 years	13	3 232.6	4.02	2.62	(1.42, 4.83)	0.002	0.77	(0.43, 1.38)	0.381
3+ years	17	4 747.4	3.58	2.07	(1.19, 3.63)	0.011	0.61	(0.36, 1.04)	0.068
Coronary heart disease									
Never smoked	113	46 502.8	2.43	Ref			0.40	(0.32, 0.51)	<0.001
Previous smoker at baseline	102	23 898.9	4.27	1.60	(1.22, 2.09)	0.001	0.64	(0.51, 0.82)	<0.001
Current smoker	267	60 224.2	4.43	2.48	(1.98, 3.12)	<0.001	Ref		
Stopped smoking during follow-up									
<1 year	47	7 546.0	6.23	2.93	(2.07, 4.14)	<0.001	1.18	(0.86, 1.62)	0.308
1–2 years	31	5 266.9	5.89	2.48	(1.65, 3.73)	<0.001	1.00	(0.68, 1.47)	0.999
2–3 years	15	3 222.2	4.66	1.90	(1.09, 3.29)	0.023	0.76	(0.45, 1.30)	0.324
3+ years	25	4 730.1	5.29	1.83	(1.16, 2.89)	0.009	0.74	(0.48, 1.15)	0.176
Cardiovascular disease									
Never smoked	160	46 364.4	3.45	Ref			0.46	(0.37, 0.55)	<0.001
Previous smoker at baseline	130	23 824.2	5.46	1.39	(1.10, 1.76)	0.006	0.63	(0.51, 0.79)	<0.001
Current smoker	321	60 115.9	5.34	2.19	(1.80, 2.67)	<0.001	Ref		
Stopped smoking during follow-up									
<1 year	53	7 525.7	7.04	2.32	(1.69, 3.18)	<0.001	1.06	(0.78, 1.42)	0.717
1–2 years	33	5 253.0	6.28	1.84	(1.25, 2.70)	0.002	0.84	(0.58, 1.21)	0.349
2–3 years	19	3 211.6	5.92	1.60	(0.99, 2.61)	0.058	0.73	(0.45, 1.18)	0.197
3+ years	30	4 704.4	6.38	1.49	(0.99, 2.24)	0.057	0.68	(0.46, 1.01)	0.058

[1] Adjusted for cohort, calendar year, age, sex, family history of CVD, time-updated diabetes and lipids (total cholesterol, HDL-C, systolic blood pressure), cumulative cART, cumulative indinavir, cumulative lopinavir, current exposure to abacavir;

[2] Reference group **current smoker**

Table 3

Mortality event rates by smoking status

	Number of events	Person years	Crude rate (/1,000 years)	Poisson regression[1]			Poisson regression[1,2]		
				IRR	(95% CI)	p-value	IRR	(95% CI)	p-value
Mortality									
Never smoked	417	46717.9	8.93	Ref			0.78	(0.68, 0.89)	<0.001
Previous smoker at baseline	251	24107.2	10.41	0.99	(0.85, 1.17)	0.931	0.77	(0.67, 0.90)	<0.001
Current smoker	911	60694.8	15.01	1.28	(1.13, 1.46)	<0.001	Ref		
Stopped smoking during follow-up									
<1 year	146	7675.4	19.02	1.67	(1.37, 2.03)	<0.001	1.30	(1.08, 1.56)	0.005
1–2 years	62	5379.5	11.53	1.02	(0.78, 1.35)	0.864	0.80	(0.61, 1.04)	0.095
2–3 years	48	3296.7	14.56	1.34	(0.99, 1.83)	0.062	1.05	(0.77, 1.41)	0.774
3+ years	67	4873.0	13.75	1.30	(0.98, 1.71)	0.065	1.01	(0.77, 1.32)	0.943
Mortality (over 50 year age group)									
Never smoked	186	11649.9	15.97	Ref			0.76	(0.62, 0.95)	0.014
Previous smoker at baseline	127	6736.9	18.85	1.21	(0.96, 1.53)	0.109	0.93	(0.73, 1.18)	0.524
Current smoker	198	8693.5	22.78	1.31	(1.06, 1.63)	0.014	Ref		
Stopped smoking during follow-up									
<1 year	50	1558.2	32.09	1.68	(1.21, 2.32)	0.002	1.28	(0.93, 1.76)	0.131
1–2 years	23	1240.5	18.54	1.02	(0.65, 1.59)	0.935	0.78	(0.50, 1.21)	0.268
2–3 years	21	847.8	24.77	1.43	(0.89, 2.80)	0.134	1.09	(0.68, 1.75)	0.707
3+ years	29	1558.0	18.61	1.16	(0.76, 1.77)	0.484	0.89	(0.58, 1.35)	0.579

[1] Adjusted for cohort, calendar year, age sex, HCV and HBV status, mode of HIV exposure, ethnicity, family history of CVD, and incident CVD during follow-up, time updated diabetes and lipid (total cholesterol, HDL-C, systolic blood pressure), cumulative cART, cumulative indinavir, cumulative lopinavir, current exposure to abacavir.

[2] Reference group **current smoker**

Table 4

Causes of death by smoking status reported at time of death

Cause of death	Never smoked		Previous smoker		Current smoker		Stopped smoking		Total
	N	%[1]	N	%	N	%	N	%	N
HIV/AIDS	154	*36.9*	69	*27.5*	214	*23.5*	94	*29.1*	531
Invasive bacterial infection	31	*8.4*	9	*12.4*	51	*10.0*	20	*12.4*	111
CVD	35	*9.8*	31	*12.7*	91	*16.7*	40	*9.3*	197
Chronic viral hepatitis	41	*9.8*	32	*17.1*	152	*9.7*	30	*16.7*	255
Non AIDS malignancies	41	*2.9*	43	*4.8*	88	*10.0*	54	*5.3*	226
Suicide and overdose	12	*7.4*	12	*3.6*	91	*5.6*	17	*6.2*	132
Other (inc. unknown)	82	*19.7*	44	*17.5*	179	*19.6*	46	*14.2*	351
Unknown	21	*5.0*	11	*4.4*	45	*4.9*	22	*6.8*	99
Total	*417*		*251*		*911*		*323*		*1902*

[1] Denominator is total number of deaths within the respective smoking status group