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# Smoking and Projected Cardiovascular Risk in an HIV-Positive Asian Regional Cohort

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## Summary

**Objective—**To assess the prevalence of and characteristics associated with current smoking in an Asian HIV-positive cohort, calculate the predictive risks of cardiovascular disease (CVD), coronary heart disease (CHD), and myocardial infarction (MI), and identify the impact that simulated interventions may have.

**Methods—**Logistic regression analysis distinguished associated characteristics. Five-year predictive risks of CVD, CHD, MIs and the impact of simulated interventions were calculated utilizing the Data Collection on Adverse Effects of Anti-HIV Drugs Study (D:A:D) algorithm.

**Results—**Smoking status data were collected from 4,274 participants and 1,496 of these had sufficient data for simulated intervention calculations. Current smoking prevalence in these two groups was similar (23.2% vs. 19.9%). Characteristics associated with current smoking included

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being ≥50 years compared to 30–39 years (OR, 0.65; 95% confidence interval [CI], 0.51–0.83), HIV exposure through injection drug use compared to heterosexual exposure (OR, 3.03; CI, 2.25–4.07), and receiving ART at study sites in Singapore, South Korea, Malaysia, Japan, and Vietnamese sites in comparison to Thailand (all odds ratios >2). Alternatively, females were less likely to smoke than males (OR, 0.11; CI, 0.08–0.14). In simulated interventions smoking cessation demonstrated the greatest impact in reducing CVD and CHD risk and closely approximated the impact of switching from abacavir to an alternate antiretroviral in the reduction of five-year MI risk.

**Conclusion—**Multiple interventions could reduce CVD, CHD, and MI risk in Asian HIV-positive patients, with smoking cessation potentially being the most influential.

### Keywords

smoking prevalence; Asia; cardiovascular risk; HIV

## Introduction

Individually, tobacco use, cardiovascular disease (CVD), and HIV all contribute to morbidity and mortality in Asia. However, limited studies have focused on how these epidemics are intertwined within resource limited settings (1–5). As antiretroviral therapy (ART) access expands, there is a greater need to better understand long-term treatment outcomes and the emergence of non-communicable diseases in the complex context of HIV infection (6–14). Within Asia, smoking is considered the third leading cause of death (10, 15, 16). When comparing the number of CVD-related deaths in resource-limited to resource-rich settings, the ratio is more than four to one (5, 17, 18). This has significant implications for people living with HIV (PLWH) on ART who carry a higher risk of CVD than the general population (19).

We sought to assess smoking prevalence in a regional cohort of Asian PLWH on ART, predictors of current smoking and associated demographic factors. Simulated interventions utilizing The Data Collection on Adverse Effects of Anti-HIV Drugs Study (D:A:D) risk algorithm were applied as a predictive tool to demonstrate how smoking may influence future CVD, coronary heart disease (CHD), and myocardial infarction (MI) risk outcomes and how simulated interventions may mitigate risk.

## Methods

The study population consisted of participants enrolled in the TREAT Asia HIV Observational Database (TAHOD). The cohort has previously been described (20, 21). Briefly, TAHOD is an observational study of PLWH involving 21 adult treatment sites in 12 countries and territories in Asia with recruitment that began in September 2003. The primary objective of the cohort study is to monitor and evaluate HIV disease and treatment outcomes. Each site contributes data from 100–450 participants that are biannually transferred to the data management and biostatical analysis center at the Kirby Institute, Sydney, Australia. At the September 2013 data transfer the entire cohort was comprised of 8,694 participants, 5691 (70.4%) were male, median age was 40.8 years (interquartile range

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[IQR], 34.7–47.8), and 5,220 (64.6%) were exposed to HIV via heterosexual contact. Of the total cohort 8,079 (93%) were on ART. Institution Review Board approval was obtained at the participating sites, the analysis center, and the coordinating center (TREAT Asia/amfAR, Bangkok). Informed consent was waived in this study unless locally required by a site's institutional review board.

Given the data required for the D:A:D algorithm, predicted risks could only be generated for patients with an available baseline smoking assessment, cholesterol, HDL cholesterol, diabetes history, systolic blood pressure, and history of ART. Data analysis was limited to those with documented smoking data between March 2012 and September 2013. Self-reported smoking status included a yes/no response to current smoking, former smoking, or never smoking cigarettes. Comorbidities and their definitions included: being overweight as a body mass index >25 kg/m$^2$ and obesity as a body mass index of >30 kg/m$^2$ (22), hypertension being a systolic blood pressure >140 mmHg (22), diabetes when two consecutive fasting blood glucose values ≥7 mmol/L were observed (23), dyslipidemia when total cholesterol >6.2 mmol/L or HDL cholesterol <1 mmol/L or triglyceride >2.26 mmol/L were observed (24), and hepatitis B and C infection confirmed with a positive hepatitis B surface antigen test or positive hepatitis C antibody test, respectively.

Five-year predicted risks of CVD, CAD and MIs were based on the D:A:D risk algorithm, which delineates low (<1%), moderate (1–5%), high (5–10%) and very high (>10%) risk (25). The D:A:D algorithm more accurately ascertains cardiovascular risk in PLWH compared to the Framingham score and has been validated in PLWH in high-income countries as well as successfully applied in Thailand and Brazil (26, 27). Poisson regression models with prospective follow up of participants from baseline to time to event were calculated. Covariates were included in the model where the association with the outcome was significant at a p-value of <0.05.

Baseline was defined by the most recent smoking assessment date. CD4 cell count and viral load were within a window period of three months on either side of the smoking assessment and other laboratory and physical parameters were within six months. Patients with prior documented evidence of hepatitis B, hepatitis C, or diabetes were considered to have that condition at the time of their latest smoking assessment.

## Statistical analysis

Logistic regression evaluated baseline characteristics predictive of current smoking. Multivariate models selected variables based on a significance level of ≤0.10 in the univariate analyses. Predictors were retained in the multivariate model with a p-value of ≤0.05. Chi-squared test compared prevalence of comorbidities by prevalence of reported smoking status. The impact of different interventions on the predicted risk of CVD, CHD, and MI were investigated by creating the following hypothetical scenarios: 1) current smokers became former smokers; 2) patients with low HDL cholesterol increased their level to 1mmol/L; 3) patients with high cholesterol reduced their level to 5.2mmol/L; 4) patients with high systolic blood pressure reduced their level to 130mmHg; 5) patients using lopinavir switched to an alternate antiretroviral (ARV); 6) patients using abacavir switched

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to an alternate ARV. The target values defined for scenarios 2), 3) and 4) were based on recommendations from the U.S. National Heart, Blood, and Lung Institute (24).

Stata version 12 (College Station, TX, USA) was used for all statistical analysis.

## Results

### Smoking Prevalence

We identified 4,274 participants with a recorded smoking status. Of those, 2,278 patients were excluded from the prediction analysis due to missing data required for D:A:D calculations, leaving 1,496 patients. The prevalence rates of current, former, and never smoking between the total and the number of participants with sufficient data for analyses were similar (23.2 vs. 19.9, 20.3 vs. 22.5, and 56.5 vs. 57.6; Table 1).

### Demographic Variables

Table 1 outlines the demographic data of the 4,274 participants with documented smoking status. The median age was 40.7 years (IQR, 34.5–47.6) with the majority being male (70.7%) and exposed to HIV through heterosexual intercourse (65%). The age categories and percentages included >50 years (21.2 %), 40–49 years (36%), 30–39 years (34.6%) and <30 years (8.1%). Of the 1,496 participants with sufficient data for D:A:D calculations, the median age was older by 3.3 years (IQR, 38.5–50.4) and had a history of longer ART treatment by 2.3 years (IQR, 3.2–9.9). However, differences between the median age and duration of ART treatment were not statistically significant.

Table 2 outlines the percentage exposed to ART that may contribute to CVD, CAD and MI risk as identified under the D:A:D algorithm. In the 1,496 participants, 1.2% were exposed to indinavir, 12.7% to lopinavir, and 14.2% to abacavir. The median CD4 cell count was 460 cells/$mm^3$ (IQR 336–616 cells/$mm^3$) and 66.7% of participants had a viral load <400 copies/ml.

The median time since ART initiation was 6.0 years (IQR, 3.2–9.9). The duration of ART treatment categories included >8 years (38.6%), 4–8 years (24.5%), 2–4 years (27.6%), <2 years (9.4%

### Predictors of Current Smoking

Predictive factors of smoking in the multivariate analysis were: age, sex, HIV exposure category, and location of treatment site. Participants aged ≥50 years were less likely to smoke than those aged 30–39 years (OR 0.65; 95% confidence interval [CI], 0.51–0.83), females were less likely to smoke than males (OR 0.11; CI, 0.08–0.14), MSM were less likely to smoke than heterosexuals (0.51; CI 0.38–0.67), and HIV exposure via injection drug use were more likely to currently smoke compared to heterosexual sex exposure (3.03; CI, 2.25 – 4.07). In comparison to sites in Thailand, participants in Singapore (OR 5.37; CI, 3.16–9.11), South Korea (OR 3.94; 2.43–6.39), Malaysia (OR 3.32; 2.39–4.63), Japan (OR 3.09; 2.06–4.65), and Vietnam (OR 2.35; 1.77–3.12; Table 3) were more likely to smoke.

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### Five-year Predicted Risk Using the D:A:D Risk Algorithm

Figure 1 illustrates percentages of participants with high or very high five-year predicted risk of CVD (15.5%), CHD (11.1%), and MI (5.6%). In the hypothetical intervention scenarios smoking cessation demonstrated the greatest impact followed by switching from abacavir to an alternate antiretroviral (ARV). This equated to a reduction of 4.15% and 2.54% in CVD, and 3.15% and 2.41% in CHD. With regards to MI, switching from abacavir to an alternate ARV demonstrated the greatest reduction at 2.13% followed by smoking cessation at 1.73%. These interventions were followed by normalizing dyslipidemia values, normalizing blood pressure values, switching from lopinavir to an alternate ARV, and increasing HDL.

## Discussion

To our knowledge, this is the first study to address predictors associated with current smoking in an Asian HIV-positive regional cohort. Resource-rich countries have reported current smoking prevalence in PLWH approximately doubles that in HIV-negative populations (18, 28–31). However, our findings suggest a lower smoking prevalence than that of resource-rich countries and the general male Asian population (34.7–61.1%) (32, 33). Furthermore, the prevalence of ever smoking in our cohort (43.5%) is lower than that found in a pooled Asian cohort (65.1% in men and 7.1% in women) (34). This discrepancy may be due to the lower percentage of women and relatively higher percentage of MSM in our cohort, who we identified as less likely to have ever smoked. Another explanation may be an overrepresentation of participants residing in settings with a smoking prevalence rate of <40% (i.e., India and Hong Kong SAR) and an underrepresentation in settings with a prevalence rate of >40% (i.e., China, South Korea, Japan, and Malaysia) (35).

Our analyses suggest that HIV exposure through injection drug use is a predictor of current smoking and being female and >50 years of age are negatively associated with current smoking. This corresponds with some studies in resource-rich settings (27, 31).

In simulated interventions, smoking cessation demonstrated the greatest potential impact on reducing five-year predicted risks of CVD and CHD, and closely approximated the impact of switching from abacavir to an alternate ARV in the reduction of five-year MI risk. This is consistent with Helleberg et al., who concluded that conditions attributed to smoking doubled the risk of mortality in PLWH vs. the general population (36) and Petoumenos et al., who concluded CVD, CHD and MI incidence rate ratios deceased with an increase in time since smoking cessation (37).

This study has multiple limitations that affect generalizability. Data analyses were restricted to those with a recorded smoking status, which is subject to reporting bias. As our criteria for comorbidities were based on cross-sectional data, our prevalence may be overestimated due to selective testing of patients most at risk of those comorbidities. In addition, missing data prevented the application of the D:A:D algorithm uniformly with simulations primarily completed in Thai, Hong Kong SAR, and Indian participants. Variability in the number of cohort sites located within each country may also impact generalizability due to over or under representation. Thai participants were chosen as the reference group for analysis due to the larger number of participants with the full complement of data and a smoking history

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(43.5%) that approximated the regional mean of male smokers (47.9%) (36). Consequently, results would differ had another country been chosen. Moving forward, longitudinal studies that quantify smoking exposure would better characterize the degree of risk and associated health outcomes in Asian PLWH, allowing for epidemiological tracking of emerging trends. Primary and secondary intervention studies focused on CVD would guide future care as non-communicable diseases become more common among aging Asian PLWH.

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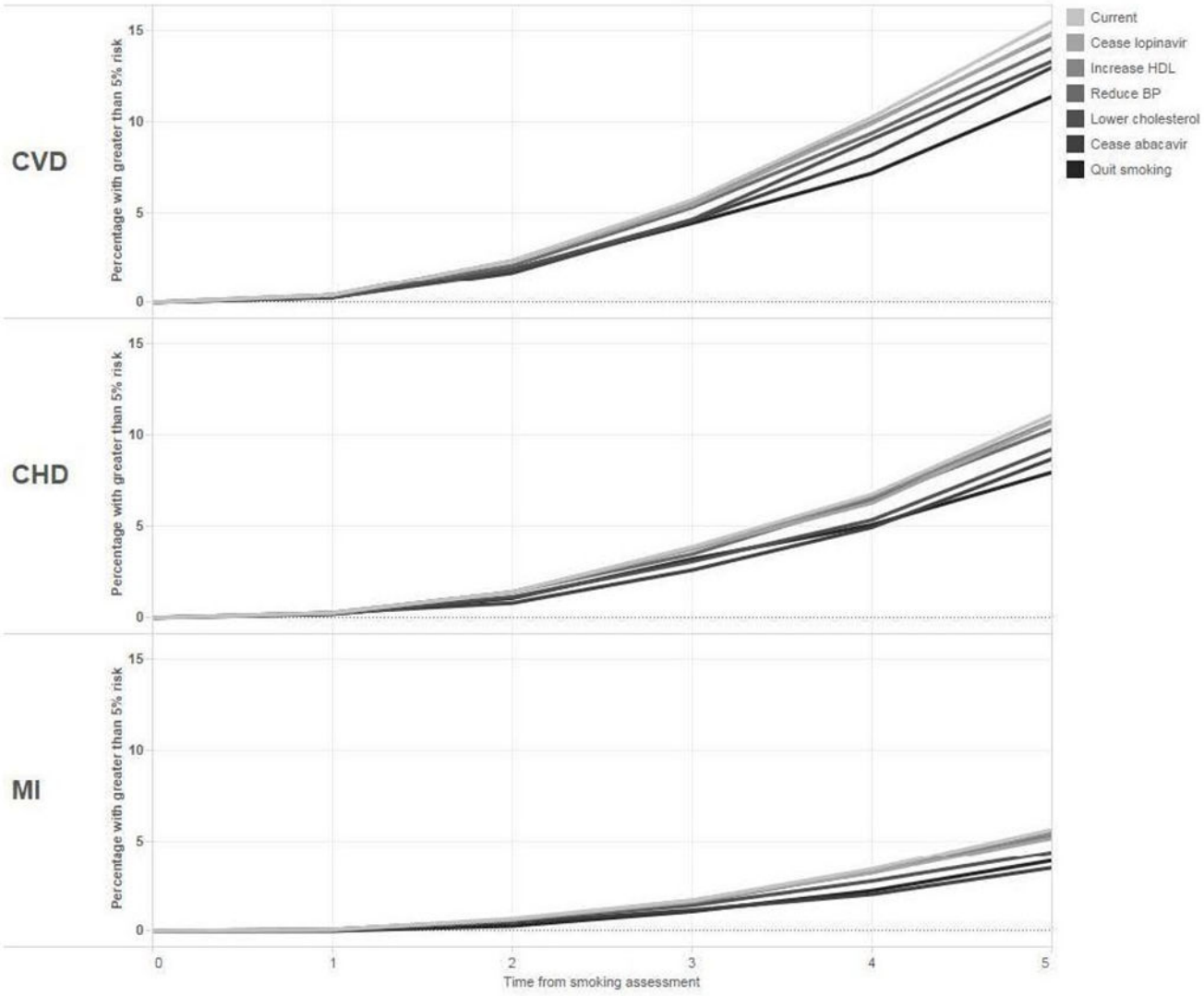


**Figure 1.**

Percentage of patients with ≥5% predicted risk of cardiovascular disease (CVD), coronary heart disease (CHD), and myocardial infarction (MI) over time by simulated interventions

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## Table 1

Demographic Variables and Smoking Status

| | All patients on ART with smoking status available (n=4274) | Patients on ART with all cardiovascular disease risk data available (n=1496) |
|---|---|---|
| **Median (IQR) age, years** | 40.7 (34.5 – 47.6) | 44.0 (38.5 – 50.4) |
| **Age, years** | | |
| <30 | 348 (8.1%) | 40 (2.7%) |
| 30 – 39 | 1480 (34.6%) | 370 (24.7%) |
| 40 – 49 | 1540 (36.0%) | 646 (43.2%) |
| ≥50 | 906 (21.2%) | 440 (29.4%) |
| **Sex** | | |
| Female | 1253 (29.3%) | 482 (32.2%) |
| Male | 3021 (70.7%) | 1014 (67.8%) |
| **HIV exposure** | | |
| Heterosexual | 2776 (65.0%) | 1178 (78.7%) |
| Homosexual | 900 (21.1%) | 223 (14.9%) |
| Injecting drug use | 348 (8.1%) | 32 (2.1%) |
| Other/unknown | 250 (5.8%) | 63 (4.2%) |
| **Family history of MI or stroke** | | |
| Yes | 165 (3.9%) | 56 (3.7%) |
| No | 2296 (53.7%) | 888 (59.4%) |
| Unknown | 1813 (42.4%) | 552 (36.9%) |
| **Location of TAHOD site(s)** | | |
| Thailand | 1291 (30.2%) | 695 (46.5%) |
| Vietnam | 536 (12.5%) | 3 (0.2%) |
| Indonesia | 454 (10.6%) | 47 (3.1%) |
| India | 406 (9.5%) | 197 (13.2%) |
| Hong Kong SAR | 357 (8.4%) | 350 (23.4%) |
| Philippines | 339 (7.9%) | 5 (0.3%) |
| Taiwan | 301 (7.0%) | 6 (0.4%) |
| Malaysia | 224 (5.2%) | 91 (6.1%) |
| Japan | 190 (4.4%) | 32 (2.1%) |
| South Korea | 92 (2.2%) | 22 (1.5%) |
| Singapore | 69 (1.6%) | 48 (3.2%) |
| China | 15 (0.4%) | 0 (0.0%) |
| **Smoking status** | | |
| Current | 992 (23.2%) | 298 (19.9%) |
| Former | 867 (20.3%) | 337 (22.5%) |
| Never | 2415 (56.5%) | 861 (57.6%) |

ART, antiretroviral therapy; IQR, interquartile range; MI, myocardial infarction; TAHOD, TREAT Asia HIV Observational Database; SAR, special administrative regions of China

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**Table 2**

Comorbidities and HIV Care and Treatment Variables

| | **Patients on ART with all cardiovascular disease risk data available (n=1496)** |
|---|---|
| **Median (IQR) body mass index** | 22.3 (20.3 – 24.6) |
| **Body mass index** | |
| <18.5 | 139 (9.3%) |
| 18.5 – 25 | 952 (63.6%) |
| 25 – 30 | 266 (17.8%) |
| >30 | 48 (3.2%) |
| Unknown | 91 (6.1%) |
| **Median (IQR) blood pressure, mmHg** | 128 (116 – 139) / 79 (70 – 85) |
| **Hypertension (systolic >140 mmHg)** | 304 (20.3%) |
| **Diabetes mellitus (fasting** ≥7mmol/L) | 124 (8.3%) |
| **Median (IQR) total cholesterol, mmol/L** | 5.1 (4.4 – 5.8) |
| **Total cholesterol (>6.2 mmol/L)** | 686 (45.9%) |
| **Median (IQR) HDL cholesterol, mmol/L** | 1.2 (1.0 – 1.5) |
| **HDL cholesterol (<1 mmol/L)** | 322 (21.5%) |
| **Median (IQR) triglycerides, mmol/L** | 1.7 (1.1 – 2.6) |
| **Triglycerides (>2.26 mmol/L)** | 584 (39.0%) |
| **HBV co-infection** | |
| Positive | 130 (8.7%) |
| Negative | 1168 (78.1%) |
| Not tested | 198 (13.2%) |
| **HCV co-infection** | |
| Positive | 83 (5.5%) |
| Negative | 1178 (78.7%) |
| Not tested | 235 (15.7%) |
| **Median (IQR) CD4 cell count, cells/mm$^3$** | 460 (336 – 616) |
| **CD4 count, cells/mm$^3$** | |
| <200 | 85 (5.7%) |
| ≥200 | 1149 (76.8%) |
| Unknown | 262 (17.5%) |
| **Viral load, copies/mL** | |
| ≥400 | 46 (3.1%) |
| <400 | 998 (66.7%) |
| Unknown | 452 (30.2%) |
| **Prior AIDS diagnosis** | |
| Yes | 721 (48.2%) |
| None known | 775 (51.8%) |
| **Current indinavir use** | |
| Yes | 18 (1.2%) |

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| | Patients on ART with all cardiovascular disease risk data available (n=1496) |
|---|---|
| No | 1478 (98.8%) |
| **Current lopinavir use** | |
| Yes | 190 (12.7%) |
| No | 1306 (87.3%) |
| **Current abacavir use** | |
| Yes | 213 (14.2%) |
| No | 1283 (85.8%) |
| **Median (IQR) time since ART initiation, years** | 6.0 (3.2 – 9.9) |
| **Time since ART initiation, years** | |
| <2 | 140 (9.4%) |
| 2 – 4 | 413 (27.6%) |
| 4 – 8 | 366 (24.5%) |
| >8 | 577 (38.6%) |
| **Year of smoking assessment** | |
| Before 2011 | 43 (2.9%) |
| 2011 | 165 (11.0%) |
| 2012 | 690 (46.1%) |
| 2013 | 598 (40.0%) |
| **Smoking status** | |
| Current | 298 (19.9%) |
| Former | 337 (22.5%) |
| Never | 861 (57.6%) |

ART, antiretroviral therapy; IQR, interquartile range; MI, myocardial infarction; TAHOD, TREAT Asia HIV Observational Database

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**Table 3**

Predictors of Current Smoking Status

| Predictor | Number of current smokers | Number of current non-smokers | Univariate OR (95%CI) | p | p overall | Multivariate[¥] OR (95%CI) | p | p overall |
|---|---|---|---|---|---|---|---|---|
| **Age[¤], years** | | | | | | | | |
| <30 | 78 | 270 | 0.81 (0.61 – 1.07) | 0.130 | | 1.11 (0.80 – 1.53) | 0.528 | |
| 30 – 39 | 390 | 1090 | 1.00 | | | 1.00 | | |
| 40 – 49 | 351 | 1189 | 0.83 (0.70 – 0.97) | 0.023 | | 1.02 (0.83 – 1.25) | 0.862 | |
| ≥50 | 173 | 733 | 0.66 (0.54 – 0.81) | <0.001 | 0.002[†] | 0.65 (0.51 – 0.83) | **0.001** | **0.001**[†] |
| **Sex[¤]** | | | | | | | | |
| Male | 932 | 2089 | 1.00 | | | 1.00 | | |
| Female | 60 | 1193 | 0.11 (0.09 – 0.15) | <0.001 | | 0.11 (0.08 – 0.14) | **<0.001** | |
| **HIV exposure[¤]** | | | | | | | | |
| Heterosexual | 516 | 2260 | 1.00 | | | 1.00 | | |
| Homosexual | 200 | 700 | 1.25 (1.04 – 1.50) | 0.017 | | 0.51 (0.38 – 0.67) | **<0.001** | |
| Injecting drug use | 224 | 124 | 7.91 (6.23 – 10.05) | <0.001 | | 3.03 (2.25 – 4.07) | **<0.001** | |
| Other/unknown | 52 | 198 | 1.15 (0.84 – 1.58) | 0.391 | <0.001[‡] | 0.62 (0.42 – 0.89) | **0.011** | **<0.001**[‡] |
| **Location of TAHOD site(s)[¤]** | | | | | | | | |
| Thailand | 186 | 1105 | 1.00 | | | 1.00 | | |
| Vietnam | 209 | 327 | 3.80 (3.01 – 4.79) | <0.001 | | 2.35 (1.77 – 3.12) | **<0.001** | |
| Indonesia | 159 | 295 | 3.20 (2.50 – 4.10) | <0.001 | | 1.53 (1.12 – 2.08) | **0.007** | |
| India | 20 | 386 | 0.31 (0.19 – 0.50) | <0.001 | | 0.20 (0.12 – 0.33) | **<0.001** | |
| Hong Kong | 82 | 275 | 1.77 (1.32 – 2.37) | <0.001 | | 1.50 (1.09 – 2.06) | **0.012** | |
| Philippines | 25 | 314 | 0.47 (0.31 – 0.73) | 0.001 | | 0.40 (0.25 – 0.64) | **<0.001** | |
| Taiwan | 72 | 229 | 1.87 (1.37 – 2.54) | <0.001 | | 1.71 (1.16 – 2.51) | **0.006** | |
| Malaysia | 97 | 127 | 4.54 (3.34 – 6.17) | <0.001 | | 3.32 (2.39 – 4.63) | **<0.001** | |
| Japan | 64 | 126 | 3.02 (2.15 – 4.23) | <0.001 | | 3.09 (2.06 – 4.65) | **<0.001** | |
| South Korea | 40 | 52 | 4.57 (2.94 – 7.10) | <0.001 | | 3.94 (2.43 – 6.39) | **<0.001** | |
| Singapore | 37 | 32 | 6.87 (4.17 – 11.30) | <0.001 | | 5.37 (3.16 – 9.11) | **<0.001** | |

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| Predictor | Number of current smokers | Number of current non-smokers | Univariate OR (95%CI) | p | p overall | Multivariate[¥] OR (95%CI) | p | p overall |
|---|---|---|---|---|---|---|---|---|
| China | 1 | 14 | 0.42 (0.06 – 3.25) | 0.409 | <0.001[≠] | 0.41 (0.05 – 3.22) | 0.394 | **<0.001**[≠] |
| **Family history of MI or stroke** | | | | | | | | |
| No | 548 | 1748 | 1.00 | | | | | |
| Yes | 36 | 129 | 0.89 (0.61 – 1.30) | 0.550 | | | | |
| Unknown | 408 | 1405 | - | | | | | |
| **CD4 cell count, cells/mm$^3$** | | | | | | | | |
| ≥200 | 540 | 2146 | 1.00 | | | | | |
| <200 | 150 | 263 | 2.27 (1.82 – 2.83) | <0.001 | | | | |
| Unknown | 302 | 873 | - | | | | | |
| **Time since ART initiation, years** | | | | | | | | |
| <2 | 248 | 681 | 1.00 | | | | | |
| 2 – 4 | 285 | 958 | 0.82 (0.67 – 0.99) | 0.044 | | | | |
| 4 – 8 | 215 | 822 | 0.72 (0.58 – 0.89) | 0.002 | | | | |
| >8 | 244 | 821 | 0.82 (0.67 – 1.00) | 0.051 | 0.032[†] | | | |

ART, antiretroviral therapy; IQR, interquartile range; MI, myocardial infarction; TAHOD, TREAT Asia HIV Observational Database;

[¤] Included in final model;

[¥] Adjusted for predictors of any failure included in the final model;

[*] Time updated;

[†] p overall for linear trend;

[≠] p overall for heterogeneity