Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix

METHODS: ADDITIONAL INFORMATION

Model Overview

Antiretroviral Treatment

In the model, all individuals are eligible for immediate antiretroviral therapy (ART) with dolutegravir/abacavir/lamivudine, a regimen recommended for initial treatment of HIV. The efficacy of ART (the likelihood of viral suppression) is positively correlated with an individual's adherence. People whose virus is initially suppressed are subject to a regimen-specific monthly probability of treatment failure after 48 weeks, which is inversely correlated with adherence. Treatment failure is detected through quarterly HIV RNA monitoring. Those who fail treatment are eligible to receive a subsequent ART regimen. Individuals can be switched to an alternative ART regimen if drug toxicity is noted. We assumed complete adherence to ART in the base case but accounted for incomplete adherence in sensitivity analysis.

Loss to Follow-up

In the base case, we assumed that all individuals are retained in HIV care (i.e., none are lost to follow-up). In sensitivity analysis, we accounted for loss to follow-up from HIV care, wherein individuals discontinue ART. The probability of loss to follow-up is inversely correlated with adherence. Following loss to follow-up, individuals have a monthly probability of returning to care.

AIDS-Related Causes of Death

In the model, AIDS-related causes of death are those from opportunistic infections or chronic AIDS-related disease. Opportunistic infections include *Pneumocystis jiroveci* pneumonia, *Mycobacterium avium* complex infection, toxoplasmosis, cytomegalovirus infection, severe fungal infection, and severe bacterial infection. Chronic AIDS-related mortality is that related to classic HIV syndromes and disorders, such as chronic wasting, that are not directly caused by an opportunistic infection. Input parameters for incidence and mortality from these diseases are derived from the literature and are described elsewhere (http://www.massgeneral.org/mpec/cepac/).

Model Validation

Our first validation strategy was done against case-control studies in Western European general populations. These reported cumulative lung cancer mortality by age 75, stratified by smoking exposure, without competing causes of death.[1,2] We used our model to predict cumulative lung cancer mortality by age 75, stratified by sex and smoking exposure, among 40 year-old HIV-uninfected people. Consistent with the Western European studies, we did not account for competing causes of death.

Our second validation strategy was done against a North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) study, which reported a modeled cumulative lung cancer incidence by age 75 for 20 year-old people living with HIV (PLWH) for different calendar periods, the most recent being 2005-2009.[3] The NA-ACCORD results were not stratified by sex or by smoking exposure (smoking prevalence was not reported). We used our model to predict cumulative lung cancer mortality among 20 year-old PLWH in care in the US, initially stratified by sex and smoking status. Because we did not have smoking intensity (cigarettes per day) data specific to 20 year-old PLWH, we assumed that all smokers consumed a moderate ("average") number of cigarettes per day. We accounted for reported rates of non-adherence to ART and loss to follow-up from HIV care, as described in a sensitivity analysis in this manuscript. Individuals could die from lung cancer, other non-AIDS-related causes, or AIDS-related causes. To facilitate comparison with the NA-ACCORD result, we weighted our model-generated results by the prevalence of men and women among PLWH in care in the US – approximately 75% and 25%, according to the Centers for Disease Control and Prevention (CDC)[4] – and the prevalence of current, former, and never smokers among 20 year-old PLWH in care in the US – 37.6%, 7.3%, and 55.1%, according to the CDC.[5] We assumed equal smoking prevalence among men and women with HIV.[5] We assumed no change in smoking status over time.

Input Parameters

Cohort Stratifications by Smoking Exposure

We stratified smokers by intensity: heavy, moderate, or light, based on the number of cigarettes consumed per day. We assumed that current smokers remained in one of these categories until the end of follow-up (e.g., they did not change from heavy smoking to light smoking). Former smokers were categorized based on smoking intensity prior to quitting. Rosenberg et al. previously derived the number of cigarettes consumed per day, stratified by sex, age, and five-year birth cohort, based on smoking data for people in the US followed through 2000.[6] Data sources for their derivations included the National Health Interview Survey, Substance Abuse and Mental Health Services Administration, American Cancer Society Cancer Prevention Studies, and the Berkeley Mortality Database. Within each stratum (e.g., 40 year-old women born in 1960-1964), they divided smokers into five quintiles based on the number of cigarettes smoked per day. We took the fifth, third, and first quintiles to represent heavy, moderate, and light smokers. The third quintile (moderate smokers) approximated the overall median cigarettes per day for each sex/age/five-year birth cohort stratum. The number of cigarettes smoked per day changed with age (in accordance with the data in Rosenberg et al.[6]), such that the number consumed by a moderate smoker at age 30 was different from the number consumed by a moderate smoker at age 50. We applied ages based on age in the year 2000, the last year of follow-up. For example, we applied cigarettes per day quantities for 20 year-olds based on data for 20 year-olds born in 1980; 21 year-olds were those born in 1979, and so on until reaching 80 year-olds who were those born in 1920.

<u>Lung Cancer Mortality</u>

In the model, we applied a monthly probability of dying from lung cancer based on sex, age, and smoking exposure. First, we derived annual lung cancer mortality rates in the US general population according to sex, five-year age group, and smoking exposure. The data we used in these derivations were: 1) overall lung cancer mortality rates stratified by sex and five-year age group (but not by smoking status) from the National Cancer Institute's Surveillance, Epidemiology, and End Results Program in 2000;[7] 2) the proportion of current, former, and never smokers in the US general population in 2000;[8] and 3) lung cancer mortality risk ratios for current and former smokers versus never smokers, further stratified for current smokers by current cigarettes per day (<10, 10-19, 20-39, or 40+) and for former smokers by cigarettes per day one year prior to smoking cessation and by age at smoking cessation (<40, 40-49, 50-59, or 60-69).[9,10] Because these derived rates were not specific to PLWH, in the base case we multiplied the derived rates by 1.7 to account for an independent risk of lung cancer conferred by HIV.[11] We converted the annual rates to monthly probabilities for use in our model, using the equation:

$$\text{MonthlyProbability} = 1 - \exp(-\text{AnnualRate}/12)$$

<u>Lung Cancer-Deleted, Non-AIDS-Related Mortality</u>

We applied mortality from non-AIDS-related causes other than lung cancer based on published lung cancer-deleted life tables, which were stratified by sex, age, birth year, and age at smoking initiation.[6] We assumed that all smokers started smoking at age 15. We again applied ages based on age in the year 2000 (e.g., we applied mortality rates for 40 year-olds based on data for 40 year-olds born in 1960). We assumed, like other studies, that there were no smoking-related differences in non-lung cancer mortality prior to age 40.[6,12,13] To account for smoking-related differences in mortality from age 40 onward, the data were stratified for never smokers and for the five quintiles of current smokers, who had been divided based on average number of cigarettes consumed per day. We again took the fifth, third, and first quintiles to represent heavy, moderate, and light smokers.

Mortality risks for former smokers, also stratified by sex, age, and birth year, were based on cigarettes per day consumed one year prior to quitting, age at quitting, and years since quitting. We applied the following "excess risk" multiplicative factor to the difference in mortality rates between current smokers (of the same smoking intensity as the former smoker) and never smokers, and the result was then added to the never smoker mortality rate:[6]

$$\text{Excess risk factor} = \exp\left[(-0.1711 + 0.00102 \cdot \text{CPD} + 0.00171 \cdot \text{QuitAge}) \cdot (\text{YearsQuit})^{1.08}\right]$$

$$M_{Former} = M_{Never} + (M_{Current} - M_{Never}) \cdot \text{Excess risk factor}$$

where CPD = cigarettes per day one year prior to quitting, QuitAge = age at smoking cessation, YearsQuit = years since smoking cessation, M_{Former} = mortality rate for former smokers, M_{Never} = mortality rate for never smokers, and $M_{Current}$ = mortality rate for current smokers . We converted all annual rates to monthly probabilities to be applied in our model.

Sensitivity Analysis

Incomplete Adherence to Antiretroviral Therapy and Loss to Follow-Up from HIV Care

In a sensitivity analysis, we accounted for reported rates of non-adherence to ART and loss to follow-up from HIV care. The distribution of ART adherence levels in the modeled cohorts reflects studies of medication possession ratios (MPRs) among PLWH in the US.[14,15] Based on these studies, we applied MPR distributions as follows: 3% of people had MPR <50%, 51% had MPR between 50% and 95%, and 46% had MPR >95%; these values translated to mean MPR 89% and standard deviation 14%.[16] We fit a logit-normal distribution to these data.[16] The model randomly draws a value from this distribution to generate an adherence level for an individual. As described elsewhere,[16] we used published data to derive the relationship between adherence and virologic suppression.[17] Overall, the suppression rate for the entire population matched clinical trial data, with no suppression if an individual's MPR was <5%, and virtually certain suppression if an individual's MPR was >91%.

We derived adherence-specific rates of loss to follow-up to match retention-in-care data from the HIV Research Network.[16,18] Loss to follow-up rates ranged from 0.1 to 84.5/100 person-years, depending on adherence. We assumed that PLWH in the US returned to care at approximately half the rate of those in the Danish HIV Cohort Study.[19] Beginning six months after loss to follow-up, individuals had a 1.5% monthly probability of returning to care which increased to 50% in the month of an acute opportunistic infection.[16]

Varying the HIV-Associated Risk Ratio for Lung Cancer

In the base case, we applied an HIV-associated independent risk of lung cancer (versus HIV-uninfected persons) of 1.7, based on the result reported in the largest study to examine the relationship between HIV and lung cancer.[11] In a sensitivity analysis, we varied the HIV-associated risk, examining risk ratios of 1.5 and 1.9 (the lower and upper bounds of the 95% confidence interval reported in the aforementioned study), as well as a risk ratio of 1.0 (i.e., no independent risk of lung cancer conferred by HIV).

Varying the Initial CD4 Cell Count at Entry to HIV Care

In the base case, we applied an initial distribution of CD4 count based on NA-ACCORD data, where mean (standard deviation) CD4 count at entry to care was 360/μL (280/μL).[20] In a sensitivity analysis, we changed the initial CD4 count to either 200/μL for all or 500/μL for all (standard deviation of zero). Regardless of initial CD4 count, all subjects were eligible to immediately initiate ART, and we assumed complete adherence to ART.

Varying When Former Smokers Quit

In the base case, we assumed that former smokers quit smoking upon entering HIV care. In a sensitivity analysis, we assumed instead that they quit 10 or 20 years after entering HIV care. In these scenarios, they had the same mortality risks as current smokers until they quit, at which point their mortality risks decreased to those of former smokers.

Population-Level Impact

We estimated the total number of expected lung cancer deaths by age 80 among PLWH aged 20-64 in care in the US, and the number of lung cancer deaths that could be averted if a proportion of current smokers were to quit smoking. We have previously described the methodology of determining the number of current, former, and never smokers by sex and age group.[21] In brief, first, we obtained data on the number of new and established diagnoses of HIV infection in the US, stratified by five-year age increment.[4] Next, we multiplied these numbers by the linkage to care rate (77.5%) among those diagnosed with HIV.[22] We then multiplied the number of people linked to care within each five-year age group by the age-specific prevalence of current, former, and never smokers among PLWH, as reported by the CDC,[5] to obtain the number of current, former, and never smokers in each five-year age group. We used the published sex breakdown from the CDC (approximately 75% men and 25% women)[4] and assumed equal smoking prevalence among men and women with HIV. The smoking prevalence data we used for this HIV population-level analysis had been stratified by smoking status but not by intensity, so we assumed that all smokers were moderate ("average") smokers, reflecting the middle quintile of daily cigarette consumption.[5,6] Finally, we multiplied these counts by our model-generated results regarding the cumulative lung cancer mortality by age 80, depending on sex, age, and smoking status , to derive the total expected number of lung cancer deaths if smoking status did not change. We then converted a proportion (20%) of current smokers in each five-year age group to former smokers, to derive the number of lung cancer deaths that could be prevented if this proportion were to stop smoking now.

RESULTS: ADDITIONAL INFORMATION

Model Validation

Our model-generated cumulative lung cancer mortalities for HIV-uninfected people were similar to those reported in Western European studies, all without competing causes of death (eTables 1 and 2). For comparison purposes, we preferentially chose those published data that included 95% confidence intervals.

Our model-generated cumulative lung cancer mortalities by age 75 for 20 year-old male current, former, and never smokers were 12.5%, 1.5%, and 0.7%. The corresponding model-generated cumulative lung cancer mortalities for female current, former, and never smokers were 10.9%, 1.0%, and 0.6%. Weighting these by the prevalence of men and women and of current, former, and never smokers among 20 year-old PLWH in care in the US, we derived a cumulative lung cancer mortality of 5.0% by age 75. In an NA-ACCORD study, the reported modeled cumulative lung cancer incidence by age 75 in 2005-2009 was 3.7%.[3]

Our projected cumulative lung cancer mortality was slightly higher than that reported in the NA-ACCORD study. The prevalence of current and former smokers was not reported in that study, but another NA-ACCORD study reported lower smoking prevalence compared with the CDC data we used, which may explain the difference in results.[5,23] Both our validation result and the NA-ACCORD result for 20 year-old PLWH are lower than our population-level projection (9.3% by age 80) because the latter included people entering HIV care between ages 20 and 64; the older people had survived long enough to face higher lung cancer risks, which increase with age.

Sensitivity Analysis

Incomplete Adherence to Antiretroviral Therapy and Loss to Follow-Up from HIV Care

Model-generated results when accounting for incomplete adherence to ART and loss to follow-up from HIV care are in the text and Figure 2 (Panels C-D) of the main manuscript, with additional detail in eTable 5 and eFigure 2 (Panel B) of this Supplement.

Varying the HIV-Associated Risk Ratio for Lung Cancer

eTable 6 shows the impact on model-projected cumulative lung cancer mortality of varying the HIV-associated independent risk factor for lung cancer (these analyses assumed no independent risk of HIV on other non-AIDS-related mortality). For example, our base case result, with a risk ratio of 1.7, for 40 year-old male/female current moderate smokers was 23.0%/20.9%. The results for men varied from 14.6% to 25.2%, and for women from 13.0% to 22.9%, when we varied the risk ratio from 1.0 to 1.9.

Varying the Initial CD4 Count at Entry to Care

There was little difference in the cumulative mortality from lung cancer, other non-AIDS-related causes, and AIDS-related causes when varying the initial CD4 count (eTable 7). These analyses assumed immediate ART initiation, complete adherence to ART, and no loss to follow-up from HIV care.

Varying When Former Smokers Quit

Smoking cessation 10 or 20 years after entering HIV care reduced lung cancer mortality by a lesser degree than cessation immediately upon entering care. Among male and female smokers entering care at age 40, relative reductions in lung cancer mortality by age 80 compared with those who continued to smoke were: for those who quit at age 40, 72.7-77.7%; quit at age 50, 53.9-62.7%; and quit at age 60, 24.9-36.7% (eTable 8).

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eTable 1. Validation of Model-Generated Cumulative Lung Cancer Mortality by Age 75 for HIV-Uninfected Current Smokers: Comparison with Case-Control Studies from Western Europe

	Model-Generated Results, Men/Women, %	Peto et al.,[1] UK, Men/Women, % (95% CI)	Crispo et al.,[2] UK, % (95% CI)	Crispo et al.,[2] Germany, % (95% CI)	Crispo et al.,[2] Italy, % (95% CI)
Current smokers, heavy	24.5/19.5	24.4 (17.1-31.2)/ 18.5 (9.4-26.7)	23.6 (17.5-29.3)	25.7 (24.3-27.0)	20.1 (18.6-21.5)
Current smokers, moderate	17.9/13.6	16.7 (13.4-19.9)/ 10.4 (7.7-13.0)	16.5 (13.7-19.2)	17.4 (16.6-18.2)	15.4 (14.4-16.4)
Current smokers, light	12.4/9.6	12.8 (10.2-15.4)/ 7.7 (5.4-9.9)	13.1 (11.2-16.0)	9.5 (9.0-10.1)	8.3 (7.6-9.0)

CI: confidence interval. Model-generated results were for 40 year-old, HIV-uninfected people in the US without competing causes of death, to match the analyses performed by Peto et al. and Crispo et al. for people in Western Europe.[1,2] Model-based lung cancer risks by cigarettes per day were based on stratifications from Thun et al.; we considered heavy, moderate, and light smokers to be those who consumed 20-39, 10-19, and <10 cigarettes per day.[9] The cigarettes per day stratifications in Peto et al. and Crispo et al. were slightly different; we present their data for heavy, moderate, and light smokers based on their stratifications of 25+, 15-24, and 5-14 cigarettes per day. The data reported by Crispo et al. were not stratified by sex.

eTable 2. Validation of Model-Generated Cumulative Lung Cancer Mortality by Age 75 for HIV-Uninfected Former and Never Smokers: Comparison with a Case-Control Study from Western Europe

	Model-Generated Results, Men/Women, %	Crispo et al.,[2] UK, % (95% CI)	Crispo et al.,[2] Germany, % (95% CI)	Crispo et al.,[2] Italy, % (95% CI)
Former smokers	3.5/2.7	2.6 (1.3-3.9)	1.8 (1.4-2.1)	3.3 (2.1-4.4)
Never smokers	0.8/0.6	0.2 (0.01-0.4)	0.6 (0.4-0.7)	0.6 (0.3-0.9)

CI: confidence interval. Model-generated results were for 40 year-old HIV-uninfected people in the US without competing causes of death, to match the analysis performed by Crispo et al.[2] Model-generated results assumed moderate ("average") smoking intensity for former smokers prior to quitting at age 40; we used the risk ratio reported by Thun et al., for those who consumed 10-19 cigarettes per day.[9] The cumulative lung cancer mortality for former smokers reported by Crispo et al. were for those who quit at age 40. Their results were not further stratified by sex or cigarettes per day.

eTable 3. Cumulative Mortality by Age 80 from Various Causes for People Entering HIV Care at Age 40, by Smoking Exposure, Assuming Complete Antiretroviral Therapy Adherence and No Loss to Follow-up from HIV Care

	Lung Cancer, Men/Women, %	Other Non-AIDS-Related, Men/Women, %	AIDS-Related, Men/Women, %	Ratio of Lung Cancer vs AIDS-Related Mortality, Men/Women	Combined Ratio of Lung Cancer or Other Non-AIDS-Related vs AIDS-Related Mortality, Men/Women
Current smokers, heavy	28.9/27.8	55.4/47.1	2.2/2.4	13.1/11.6	38.3/31.2
Current smokers, moderate	23.0/20.9	56.9/45.7	2.3/2.5	10.0/8.4	34.7/26.6
Current smokers, light	18.8/16.6	49.0/37.2	2.5/2.6	7.5/6.4	27.1/20.7
Former smokers, heavy	7.9/7.5	46.9/32.9	2.5/2.8	3.2/2.7	21.9/14.4
Former smokers, moderate	6.1/5.2	44.5/32.0	2.7/2.8	2.3/1.9	18.7/13.3
Former smokers, light	4.3/3.7	43.2/31.2	2.7/2.8	1.6/1.3	17.6/12.5
Never smokers	1.6/1.2	42.5/30.8	2.7/2.8	0.6/0.4	16.3/11.4

These analyses assumed complete adherence to antiretroviral therapy and no loss to follow-up from HIV care. Smokers are stratified by smoking intensity, based on cigarettes per day. Current smokers continued smoking until the end of follow-up. Former smokers quit at age 40 and remained abstinent.

eTable 4. Cumulative Mortality by Age 80 from Various Causes, by Age at Entry to HIV Care and Smoking Exposure

	Lung Cancer, Men/Women, %	Other Non-AIDS-Related, Men/Women, %	AIDS-Related, Men/Women, %
Enter HIV Care at Age 30			
Current smokers, heavy	28.2/27.1	56.0/47.9	2.8/3.0
Current smokers, moderate	22.4/20.3	57.5/46.6	2.9/3.1
Current smokers, light	18.4/16.2	49.7/38.3	3.1/3.3
Former smokers, heavy	4.2/2.9	44.4/32.6	3.3/3.5
Former smokers, moderate	3.2/2.0	43.8/32.4	3.4/3.5
Former smokers, light	2.1/1.4	43.6/32.2	3.4/3.5
Never smokers	1.5/1.2	43.6/32.1	3.4/3.5
Enter HIV Care at Age 50			
Current smokers, heavy	30.9/28.3	52.5/46.1	1.6/1.8
Current smokers, moderate	24.0/21.0	55.1/44.8	1.7/1.9
Current smokers, light	19.4/16.8	47.4/36.1	1.8/2.0
Former smokers, heavy	13.5/11.6	49.1/37.0	1.8/2.0
Former smokers, moderate	10.6/8.2	46.3/34.2	1.9/2.0
Former smokers, light	7.7/6.0	42.6/31.0	2.0/2.1
Never smokers	1.6/1.2	41.5/30.0	2.1/2.2

These analyses assumed complete adherence to antiretroviral therapy and no loss to follow-up from HIV care. Current smokers continued smoking until the end of follow-up. Former smokers quit at entry to HIV care and remained abstinent.

eTable 5. Cumulative Mortality by Age 80 from Various Causes for People Entering HIV Care at Age 40, by Smoking Exposure, Accounting for Incomplete Antiretroviral Therapy Adherence and Loss to Follow-up from HIV Care

	Lung Cancer, Men/Women, %	Other Non-AIDS-Related, Men/Women, %	AIDS-Related, Men/Women, %	Ratio of Lung Cancer vs AIDS-Related Mortality, Men/Women	Combined Ratio of Lung Cancer or Other Non-AIDS-Related vs AIDS-Related Mortality, Men/Women
Current smokers, heavy	22.7/21.6	44.8/36.9	23.0/25.5	1.0/0.8	2.9/2.3
Current smokers, moderate	17.8/16.1	45.4/35.7	24.3/26.4	0.7/0.6	2.6/2.0
Current smokers, light	14.5/12.8	38.7/29.1	25.9/27.6	0.6/0.5	2.1/1.5
Former smokers, heavy	6.1/5.8	37.3/25.6	26.6/28.6	0.2/0.2	1.6/1.1
Former smokers, moderate	4.6/4.0	35.0/24.8	27.4/28.9	0.2/0.1	1.4/1.0
Former smokers, light	3.3/2.8	33.5/24.1	28.0/29.2	0.1/0.1	1.3/0.9
Never smokers	1.2/0.9	32.8/23.6	28.7/29.5	0.04/0.03	1.2/0.8

These analyses assumed that all individuals entered HIV care (i.e., entered model) at age 40 and accounted for reported rates of non-adherence to antiretroviral therapy and loss to follow-up from HIV care. Current smokers continued smoking until the end of follow-up. Former smokers quit at age 40 and remained abstinent.

eTable 6. Cumulative Lung Cancer Mortality by Age 80, by Smoking Exposure: Varying the HIV-Associated Independent Risk of Lung Cancer

	HIV-Associated Independent Risk Ratio for Lung Cancer			
	1.0 Men/Women, %	**1.5 Men/Women, %**	**1.7 (Base Case) Men/Women, %**	**1.9 Men/Women, %**
Current smokers, heavy	18.9/17.9	26.2/25.2	**28.9/27.8**	31.4/30.3
Current smokers, moderate	14.6/13.0	20.8/18.8	**23.0/20.9**	25.2/22.9
Current smokers, light	11.7/10.2	16.9/14.8	**18.8/16.6**	20.7/18.4
Former smokers, heavy	4.8/4.5	7.0/6.6	**7.9/7.5**	8.8/8.3
Former smokers, moderate	3.6/3.1	5.4/4.6	**6.1/5.2**	6.8/5.7
Former smokers, light	2.6/2.1	3.8/3.2	**4.3/3.7**	4.8/4.1
Never smokers	0.9/0.7	1.5/1.2	**1.6/1.2**	1.8/1.3

These analyses assumed that all individuals entered HIV care (i.e., entered the model) at age 40 and assumed complete adherence to antiretroviral therapy and no loss to follow-up from HIV care. Current smokers continued smoking until the end of follow-up. Former smokers quit at age 40 and remained abstinent. Base case results are shown in bold type.

eTable 7. Effect of Varying the Initial CD4 Cell Count on Model-Projected Cumulative Mortality by Age 80 from Various Causes, by Smoking Status

Initial CD4 Cell Count of Cohort, Mean (sd)	Lung Cancer, Men/Women, %	Other Non-AIDS-Related, Men/Women, %	AIDS-Related, Men/Women, %
CD4 200/μL (0)			
Current smokers	23.0/20.9	56.9/45.7	2.2/2.5
Former smokers	6.1/5.2	44.6/32.1	2.6/2.7
Never smokers	1.6/1.2	42.6/30.8	2.7/2.8
CD4 360/μL (280/μL), Base Case			
Current smokers	**23.0/20.9**	**56.9/45.7**	**2.3/2.5**
Former smokers	**6.1/5.2**	**44.5/32.0**	**2.7/2.8**
Never smokers	**1.6/1.2**	**42.5/30.8**	**2.7/2.8**
CD4 500/μL (0)			
Current smokers	23.0/21.0	57.4/46.2	1.7/2.0
Former smokers	6.2/5.2	45.0/32.6	2.1/2.2
Never smokers	1.6/1.2	43.2/31.3	2.2/2.3

sd: standard deviation. These analyses assumed that all individuals entered HIV care (i.e., entered the model) at age 40 and assumed complete adherence to antiretroviral therapy and no loss to follow-up from HIV care. Current smokers continued smoking until the end of follow-up. Former smokers quit at age 40 and remained abstinent. The intensity of smoking was moderate ("average"). Base case results are shown in bold type.

eTable 8. Model-Generated Cumulative Lung Cancer Mortality and Relative Risk Reduction Based on Age at Smoking Cessation, for Those Entering HIV Care at Age 40

	Men		Women	
	Cumulative Lung Cancer Mortality	Relative Risk Reduction, vs Current Smokers	Cumulative Lung Cancer Mortality	Relative Risk Reduction, vs Current Smokers
Current smokers, heavy	28.9%	-	27.8%	-
Current smokers, moderate	23.0%	-	20.9%	-
Current smokers, light	18.8%	-	16.6%	-
Former smokers, quit at age 40				
Heavy	7.9%	-72.7%	7.5%	-73.0%
Moderate	6.1%	-73.5%	5.2%	-75.1%
Light	4.3%	-77.1%	3.7%	-77.7%
Former smokers, quit at age 50				
Heavy	13.3%	-54.0%	12.0%	-56.8%
Moderate	10.6%	-53.9%	8.5%	-59.3%
Light	7.8%	-58.5%	6.2%	-62.7%
Former smokers, quit at age 60				
Heavy	21.7%	-24.9%	18.9%	-32.0%
Moderate	16.8%	-27.0%	13.8%	-34.0%
Light	13.0%	-30.9%	10.5%	-36.7%

Individuals in the simulation model were assumed to enter HIV care at age 40 and to remain in the model until death or age 80. These model simulations assumed complete adherence to antiretroviral therapy and no loss to follow-up from HIV care. Current smokers continued smoking until the end of follow-up. Those who quit smoking remained abstinent.

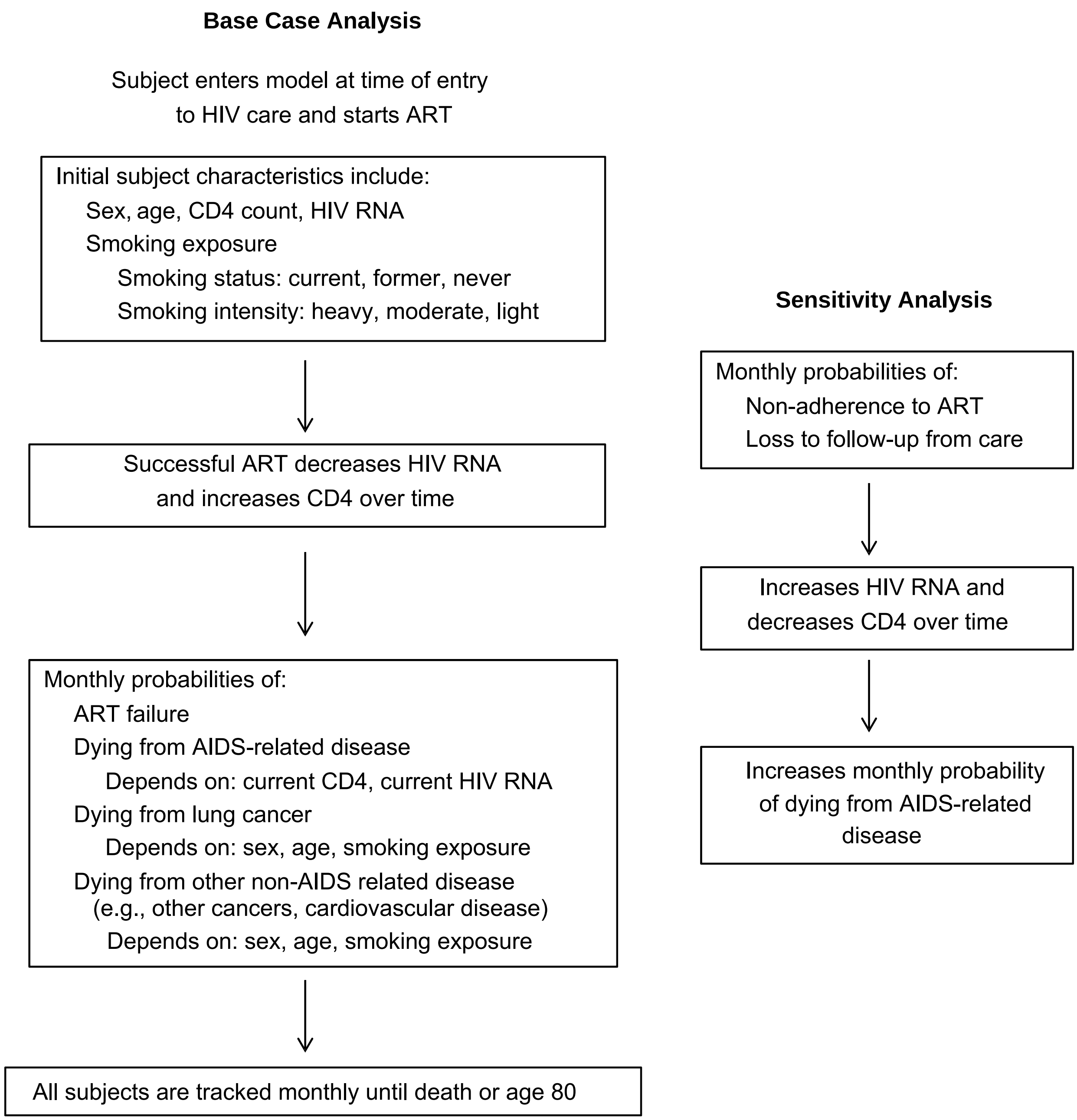
eFigure 1. Overview of Flow Through CEPAC Monte Carlo Microsimulation Model.

ART: antiretroviral therapy. This figure highlights key initial subject characteristics and events in the model. In the base case analysis, there is complete adherence to ART and no loss to follow-up from HIV care. In a sensitivity analysis, there is incomplete adherence to ART and loss to follow-up from HIV care, which ultimately increase the probability of dying from an AIDS-related disease.

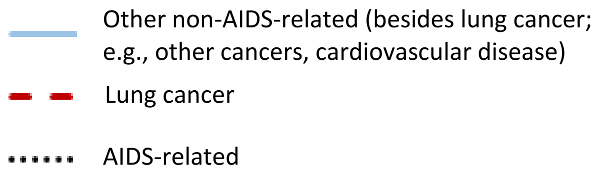
eFigure 2. Cumulative Mortality by Cause among Male Never Smokers Entering HIV Care at Age 40.

ART: antiretroviral therapy; LTFU: loss to follow-up. This is an extension of Figure 2 in the main manuscript. The panels here represent never smokers. Panel A reflects simulations of men who are completely adherent to ART and are never lost to follow-up from HIV care. Panel B reflects simulations incorporating reported rates of non-adherence to ART and loss to follow-up from HIV care. Deaths from non-AIDS-related causes besides lung cancer are depicted by the solid blue lines, deaths from lung cancer are depicted by the dashed red lines, and deaths from AIDS-related causes are depicted by the dotted black lines.

eFigure 1.


Base Case Analysis
Subject enters model at time of entry to HIV care and starts ART
Initial subject characteristics include:
Sex, age, CD4 count, HIV RNA
Smoking exposure
Smoking status: current, former, never
Smoking intensity: heavy, moderate, light
Successful ART decreases HIV RNA and increases CD4 over time
Monthly probabilities of:
ART failure
Dying from AIDS-related disease
Depends on: current CD4, current HIV RNA
Dying from lung cancer
Depends on: sex, age, smoking exposure
Dying from other non-AIDS related disease (e.g., other cancers, cardiovascular disease)
Depends on: sex, age, smoking exposure
All subjects are tracked monthly until death or age 80
Sensitivity Analysis
Monthly probabilities of:
Non-adherence to ART
Loss to follow-up from care
Increases HIV RNA and decreases CD4 over time
Increases monthly probability of dying from AIDS-related disease

eFigure 2.



<u>Completely Adherent to ART, no LTFU</u> **<u>Incompletely Adherent to ART, with LTFU</u>**