THE LANCET Infectious Diseases

Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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Supplement – Technical details of the model

This supplementary material provides technical details of the model structure, including parameter values, variable fits and model validation checks. Briefly, the model is an individual-based model simulating an ageing HIV-infected population in the Netherlands (Figure 2). The model follows HIV-patients from the start of combination antiretroviral therapy (cART), as they age (Figure 2A Part II), develop non-communicable diseases (NCDs), namely diabetes, hypertension, hypercholesterolemia, osteoporosis and chronic kidney disease (CKD) or experience a stroke, myocardial infraction (MI) or malignancy, and start co-medication for these NCDs (Figure 2A Part I). Risk factors for these events are listed in the corresponding boxes in Figure 2B, with the probability of events occurring evaluated at one monthly time steps in the model. The individual-based model works by determining patient-level characteristics, generating cohorts, and aggregating patients against calendar time. The particulars of the model structure are outlined in detail below.

Demographic factors

Demographic factors (age and sex) are assigned probabilistically to individuals, according to the distribution in Table 1. In most simulations, the model assumes that mean age at treatment initiation will continue in a linear trend, described by the following equation, where *i* stands for sex and *t* stands for the year:

$$\overline{Age}_{i,t} = a_i * t_t - b_i$$

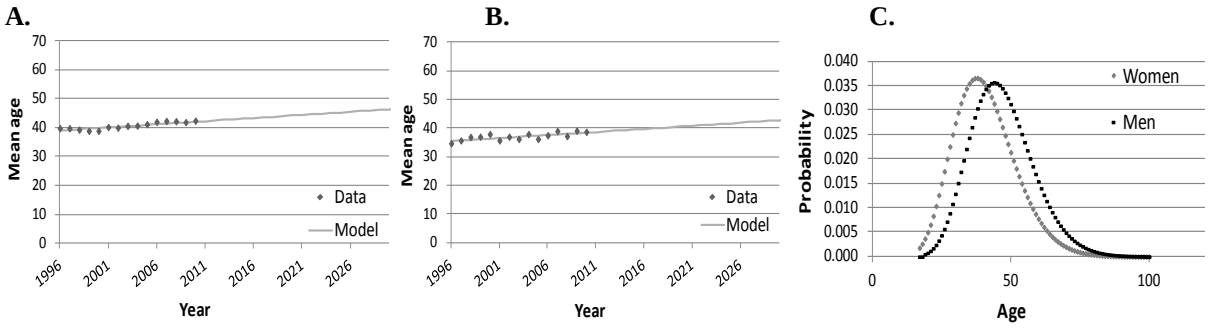
This is a direct extrapolation from the data (Figure 1A and B) and is considered reasonable because as incidence drops, mean age at infection will increase. In certain analysis this is modified (see main article). The distribution of age at ART initiation around this mean is constant and described by a Gamma distribution (Figure 1C):

$$Scale_i = \frac{\overline{Age}_{i,t}}{Shape_i}$$

Table 1. Demographic parameter. A. Proportion of male and female patients at entry into follow-up. B. Parameters for the gamma distribution for age at start of model, gamma(scale, shape) and C. Parameters for linear equation defining increase in mean age per year, $\overline{Age}_{i,t} = a_i * year_t - b_i$.

A. Sex Ratio			Data source
Male	0.84		ATHENA data
Female	0.16		ATHENA data
B. Age distribution			
Sex	**Shape**	**Scale**	
Men	2.50541	16.7205	ATHENA data
Women	2.88265	13.1475	ATHENA data
C. Increase in mean age per year			
Sex	a_i	b_i	
Men (*i*=1)	0.2157	391.54	ATHENA data
Women (*i=2)*	0.2137	391.07	ATHENA data

Figure 1. A and B. annual mean age at start of treatment of the observational ATHENA data and linear model fit for A. men and B. women. C. Age distribution at ART initiation in 2010, using a gamma distribution fitted to observed age distribution in the ATHENA cohort.



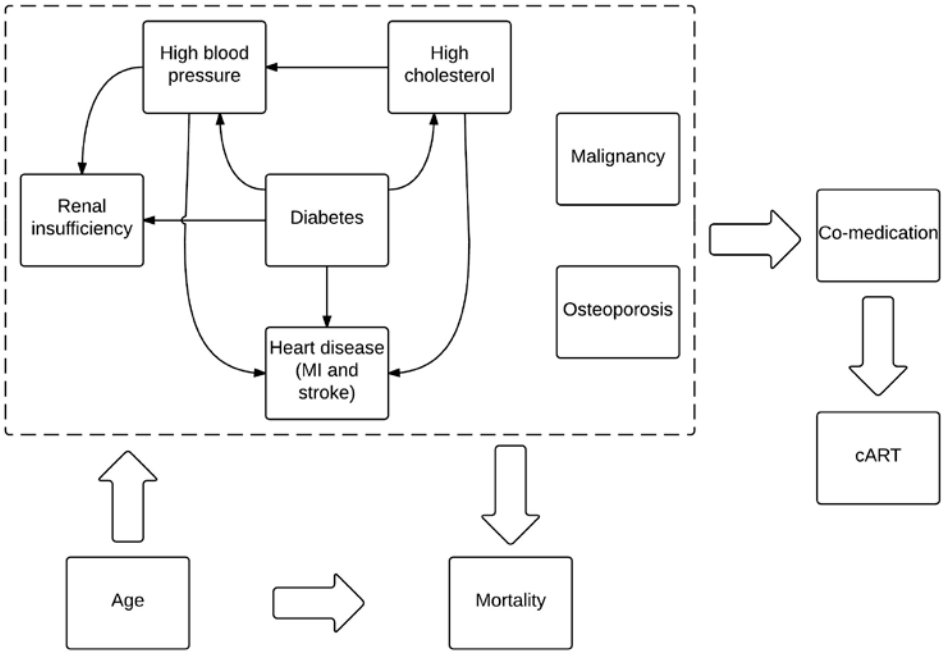


Figure 2. Schematic of the model of an ageing HIV-infected population. The model follows HIV-infected patients from the start of treatment until death or closing year of model (2030). The model simulates how HIV-infected patients age over time, develop co-morbidities over time, start co-medication for these conditions, and how these co-medications affect HIV-treatment. The dashed lined square shows the co-morbidities and interactions included in the model. Patients develop co-morbidities as a function of age and sex. Co-medication is prescribed according to the co-morbidities a patient has, which in turn impacts on drug-interactions with HIV-treatment (cART). Mortality risk is influenced by both age and the number and type of co-morbidity.

Mortality

Parameters defining death rates were taken from a large multi-cohort study by the Data Collection on Adverse Events of Anti-HIV drugs (D:A:D) Study Group.[1] The background death rate consisted of the sum of death rates – from causes other than the NCD. Patients with specific NCDs had an additive cause specific death rate. Age and sex contributed as factors to the overall death rate. Mortality can be expressed with the following equation, where *i* stands for sex, *a* stands for age, $\mu_i(a)$ stands for background mortality, α_j stands for additional mortality associated with conditions *j*, and I_j stands for the indicator variable for having condition *j* (1 if patient has condition, 0 otherwise):

$$Mortality_i = \mu_i(a) + \sum_j I_j \alpha_j$$

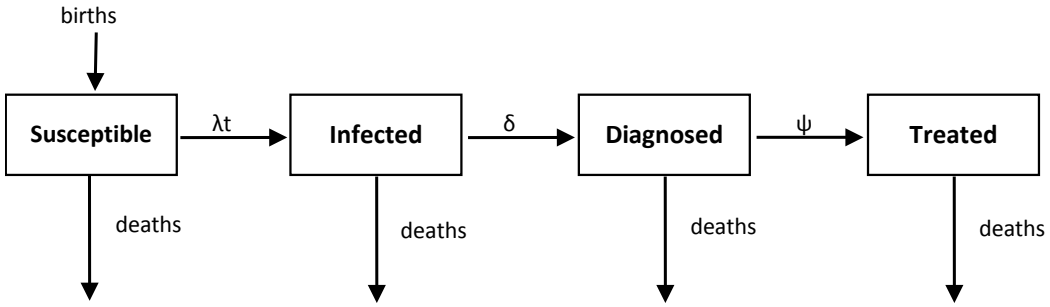
Incidence of starting treatment

In order to construct reasonable projections of future number of HIV-infected patients starting cART, a compartmental model of the HIV cascade was constructed to explore the different trajectories incidence could take in the future. A compartmental model of the HIV cascade, including incidence, disease progression and ART initiation, is used to predict the number of HIV-patients starting treatment each year. Figure 3 illustrates the flow diagram of this compartmental model, which consists of four compartments, susceptible, infected, diagnosed and treated and where λt is the incidence rate, δ is the rate of HIV-diagnosis and ψ is the rate of treatment initiation. The rates of diagnosis and treatment initiation were obtained from the ATHENA data, and were assumed to be time-dependent. Birth rates were taken from Dutch national birth statistics, with death rates assumed to equal birth rates to maintain constant population size. It is assumed that the age at infection is independent of the age at the start of treatment and of the incidence rate. This estimation model simulated infection and diagnosis from 1980, and ART initiation from 1996 onwards. The incidence rate is calculated using a non-parametric approach, with the following equation, where A stands for the starting year of the epidemic (1980), B and C are scaling parameter and α, β and γ are parameters defining the incidence rate:

$$\lambda t = \frac{\alpha * \exp\left(-\left((year_i - A) - B * \gamma)^2\right)\right)}{(\beta * C)^2} * S_t$$

This model is simultaneously fitted to the number of patients diagnosed and starting HIV-treatment per year between 1996 and 2010 from the ATHENA data, by varying the parameters defining the incidence rate. For the main results of the model a medium incidence scenario is assumed from 2010 onwards (Figure 4) , the graphs for the minimum and maximum incidence are presented below (see Results for additional incidence scenarios). Rate of diagnosis and of starting treatment were assumed to be constant from 2010 onwards. The fit of the model output to the data and future trends are illustrated in Figure 4. The number of people starting treatment between 2010 and 2030, as computed by the model, are presented in Table 3. In 2011, our estimates (of 897) fall in the middle between projections by the Institute for Health Metrics and Evaluation (estimates of 800) and European Centre for Disease Control (estimates of 1,019).[2,3]

Figure 3. Flow diagram of deterministic model to simulate predictions of the incidence of starting treatment. Parameter λt stands for the incidence rate, δ stands for the rate of diagnosis and ψ stands for rate of treatment.



NCDs

Each patient in the cohort is assigned whether or not they have any of the simulated NCDs at ART initiation. Prevalence of existing probabilities of NCDs prior to the start of ART is assigned probabilistically by age group using ATHENA data presented in Table 2. Development of newly diagnosed NCD is simulated as a function of age and sex, and other risk factors (such has having another NCD – see Figure 2A Part I), based on the observed incidence per 1,000 person-years of follow-up by age group and sex from the ATHENA cohort. Functions were fitted to these incidence data to allow continuous projection of developing NCDs by age. Functions fitted to the data are presented in Figure 5A and B, with their equations reported in Table 4.

In addition to age and sex specific risks, HIV-infected patients in the model can be at increased risk for certain NCDs if they have previously been diagnosed with another NCD (Figure 2A Part I). Common causal pathways of NCDs were incorporated into the model, with parameters defining these pathways based on both ATHENA data and an in-depth literature review (Table 5).

All NCDs were defined in the ATHENA data using clinical and laboratory guidelines for diagnosis where possible, according to the European AIDS Clinical Society.[4] Pathological reports were used where possible to confirm diagnosis of any non-AIDS malignancy.[5] Malignancies excluded the precancerous stages of anal and cervical cancer, basal-cell carcinoma, and squamous cell carcinoma of the skin. CKD is defined as an estimated glomerular filtration rate >60 ml/min, using the Cockcroft-Gault equation, confirmed after 3 months or later.[5]

Parameters comparing NCD burden in HIV-infected and HIV-uninfected individuals were taken from the AGE_hIV Cohort Study.[6] The AGE_hIV Cohort Study is a prospective cohort study in the Netherlands established in 2010, comparing the prevalence and incidence of a broad range of age-related NCDs and NCD risk factors in HIV-infected patients and non-HIV-infected controls.[6] The study found that HIV-infected patients were diagnosed with a significantly higher mean number of NCDs compared to HIV-uninfected controls.[6] In particular, HIV-infected patients are at increased risk of hypertension (45·4% vs. 30·5%, p<0·001), MIs (3·9% vs. 1·5%, p=0·018), CKD (4·3% vs 2·1%, p=0·044) and peripheral arterial vascular disease (2·6% vs. 0·6%, p=0·008).[6]

Table 2. Proportion of NCDs by age group amongst HIV-infected patients at ART initiation. **Source: Incidence data for all NCDs, except hypercholesterolemia and hypertension are from 2011 Monitoring Report Appendix.[5] The other NCDs are calculated from ATHENA data, using the same method.**

	Men		Women		Source
	Age category	**Prevalence (%)**	**Age category**	**Prevalence (%)**	
Diabetes	<30	0.0 (.-.)	<30	2.5 (0.5-4.5)	ATHENA
	30-40	0.7 (0.3-1.2)	30-40	1.3 (0.2-2.5)	data
	40-50	2.0 (1.4-2.7)	40-50	2.5 (0.3-4.6)	
	50-60	5.4 (3.8-7.0)	50-60	9.4 (3.4-15.3)	
	≥60	8.4 (4.9-11.8)	≥60	16.2 (3.8-28.7)	
Hypercholesterolemia	<30	0.3 (0.00-0.07)	<30	1.3 (0.0-2.7)	ATHENA
	30-40	0.6 (0.2-1.0)	30-40	0.8 (0.0-1.7)	data
	40-50	1.3 (0.8-1.8)	40-50	0.0 (.-.)	
	50-60	1.6 (0.7-2.5)	50-60	2.1 (0.0-5.0)	
	≥60	2.8 (0.7-4.8)	≥60	2.7 (0.0-8.2)	
Hypertension	<30	3.9 (2.4-5.4)	<30	2.1 (0.3-3.9)	ATHENA
	30-40	7.1 (5.9-8.4)	30-40	6.2 (3.7-8.7)	data
	40-50	11.2 (9.8-12.7)	40-50	11.8 (7.3-16.2)	
	50-60	15.0 (12.4-17.5)	50-60	12.5 (5.8-19.2)	
	≥60	14.0 (9.6-18.3)	≥60	16.2 (3.8-28.7)	
Malignancy	<30	0.6 (0.0-1.2)	<30	0.4 (0.0-1.2)	ATHENA
	30-40	0.4 (0.1-0.8)	30-40	0.0 (.-.)	data
	40-50	0.6 (0.2-0.9)	40-50	1.5 (0.0-3.1)	
	50-60	1.7 (0.8-2.6)	50-60	1.0 (0.0-3.1)	
	≥60	2.4 (0.5-4.3)	≥60	2.7 (0.0-8.2)	
Myocardial infarction	<30	0.0 (.-.)	<30	0.0 (.-.)	ATHENA
	30-40	0.1 (0.0-0.2)	30-40	0.0 (.-.)	data
	40-50	0.3 (0.0-0.5)	40-50	0.0 (.-.)	
	50-60	0.7 (0.1-1.2)	50-60	0.0 (.-.)	
	≥60	0.8 (0.0-1.9)	≥60	2.7 (0.0-8.2)	
Osteoporosis	<30	2.3 (1.2-3.5)	<30	0.8 (0.0-2.0)	ATHENA
	30-40	1.7 (1.0-2.3)	30-40	0.8 (0.0-1.7)	data
	40-50	1.7 (1.1-2.2)	40-50	1.0 (0.0-2.3)	
	50-60	1.6 (0.7-2.5)	50-60	3.1 (0.00-6.7)	
	≥60	2.0 (0.3-3.7)	≥60	0.0 (.-.)	
CKD	<30	0.2 (0.0-0.5)	<30	0.4 (0.0-1.2)	ATHENA
	30-40	0.3 (0.0-0.6)	30-40	0.3 (0.0-0.8)	data
	40-50	0.1 (0.0-0.2)	40-50	0.0 (.-.)	
	50-60	0.0 (.-.)	50-60	0.0 (.-.)	
	≥60	0.0 (.-.)	≥60	0.0 (.-.)	
Stroke	<30	0.0 (.-.)	<30	0.0 (.-.)	ATHENA
	30-40	0.0 (.-.)	30-40	0.3 (0.0-0.8)	data
	40-50	0.2 (0.0-0.4)	40-50	0.0 (.-.)	
	50-60	0.7 (0.1-1.2)	50-60	0.0 (.-.)	
	≥60	0.4 (0.0-1.2)	≥60	0.0 (.-.)	

Figure 4. Model projection of A. Incidence of HIV-infection at minimum, medium and maximum incidence rate, B. Number of people diagnosed with HIV, and C. Number of people starting ART which is fed into the ageing model, under a minimum, medium and maximum incidence rate scenario.

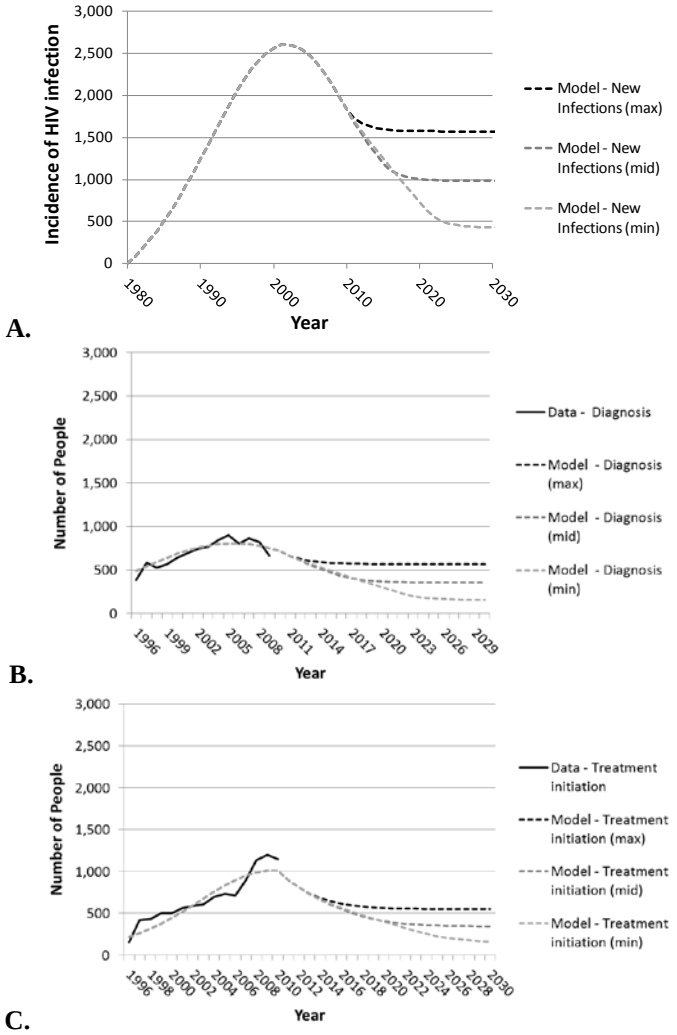


Table 3. Projected number of people starting treatment as predicted by the deterministic model of HIV-infection using three scenarios for the epidemic; minimum, medium and maximum.

Number of new treatment initiations			
Year	Min scenario	Mid scenario	Max scenario
2010	1009	1009	1009
2011	897	897	897
2012	805	805	805
2013	730	730	734
2014	667	667	681
2015	612	612	642
2016	563	563	614
2017	518	518	594
2018	476	476	580
2019	436	441	570
2020	397	414	564
2021	359	394	559
2022	322	379	556
2023	285	369	554
2024	252	361	552
2025	225	356	551
2026	204	352	550
2027	189	349	550
2028	177	348	550
2029	169	346	549
2030	163	345	549

Figure 5. The incidence per 1,000 person years of follow-up of newly diagnosed NCD from the data and model fit for men and women on ART by age group. The graphs of hypercholesterolemia and hypertension have different scales than the other NCDs.

Source: all figures created based on ATHENA data. All NCDs (except hypercholesterolemia and hypertension) are from Monitoring report 2011, Appendix.[5]

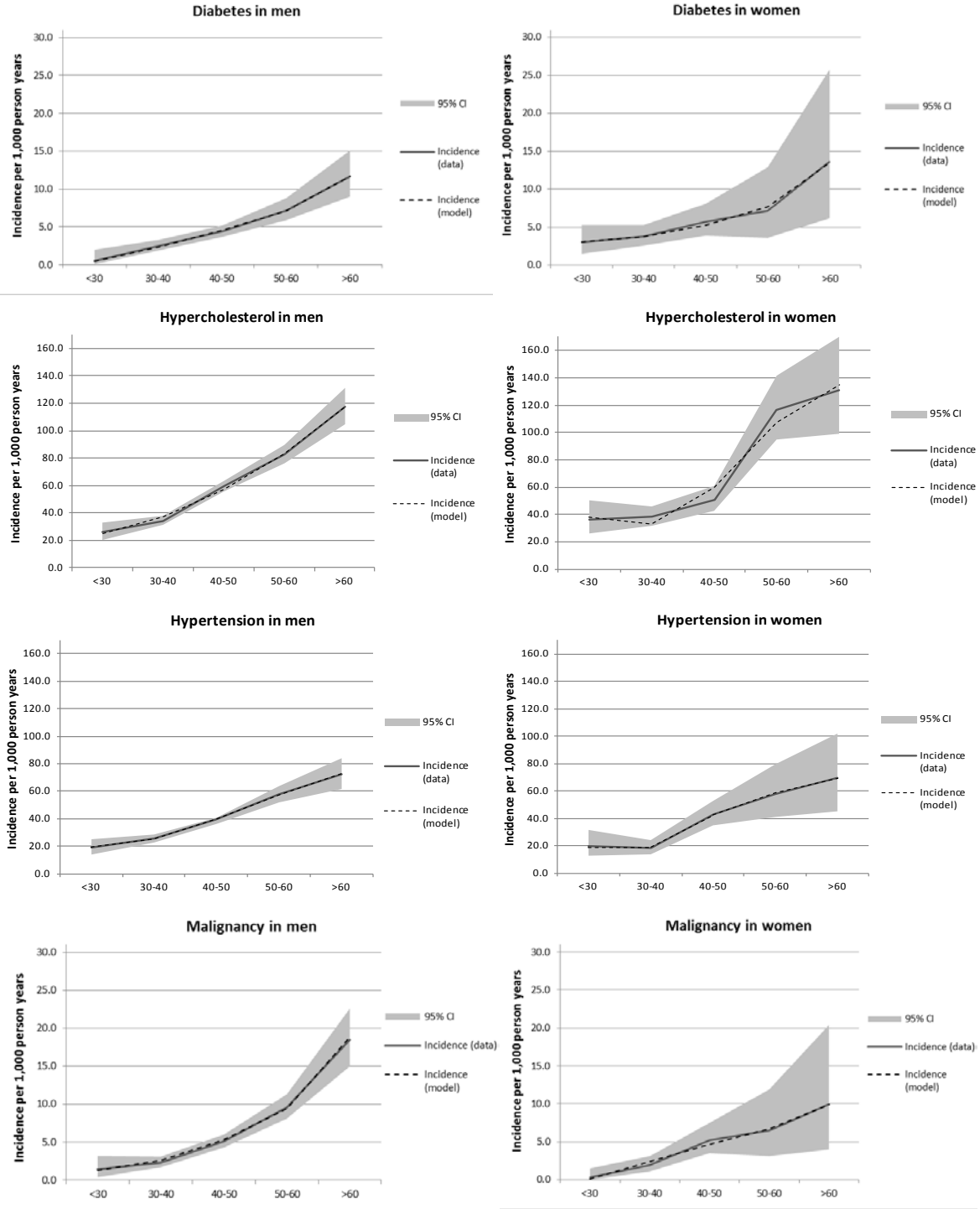


Figure 5[continued]. The incidence per 1,000 person years of follow-up of newly diagnosed NCD from the data and model fit for men and women on ART by age group. Note: the graphs of hypercholesterolemia and hypertension have different scales than the other NCDs.

Source: all figures created based on ATHENA data. All NCDs (except hypercholesterolemia and hypertension) are from Monitoring report 2011, Appendix.[5]

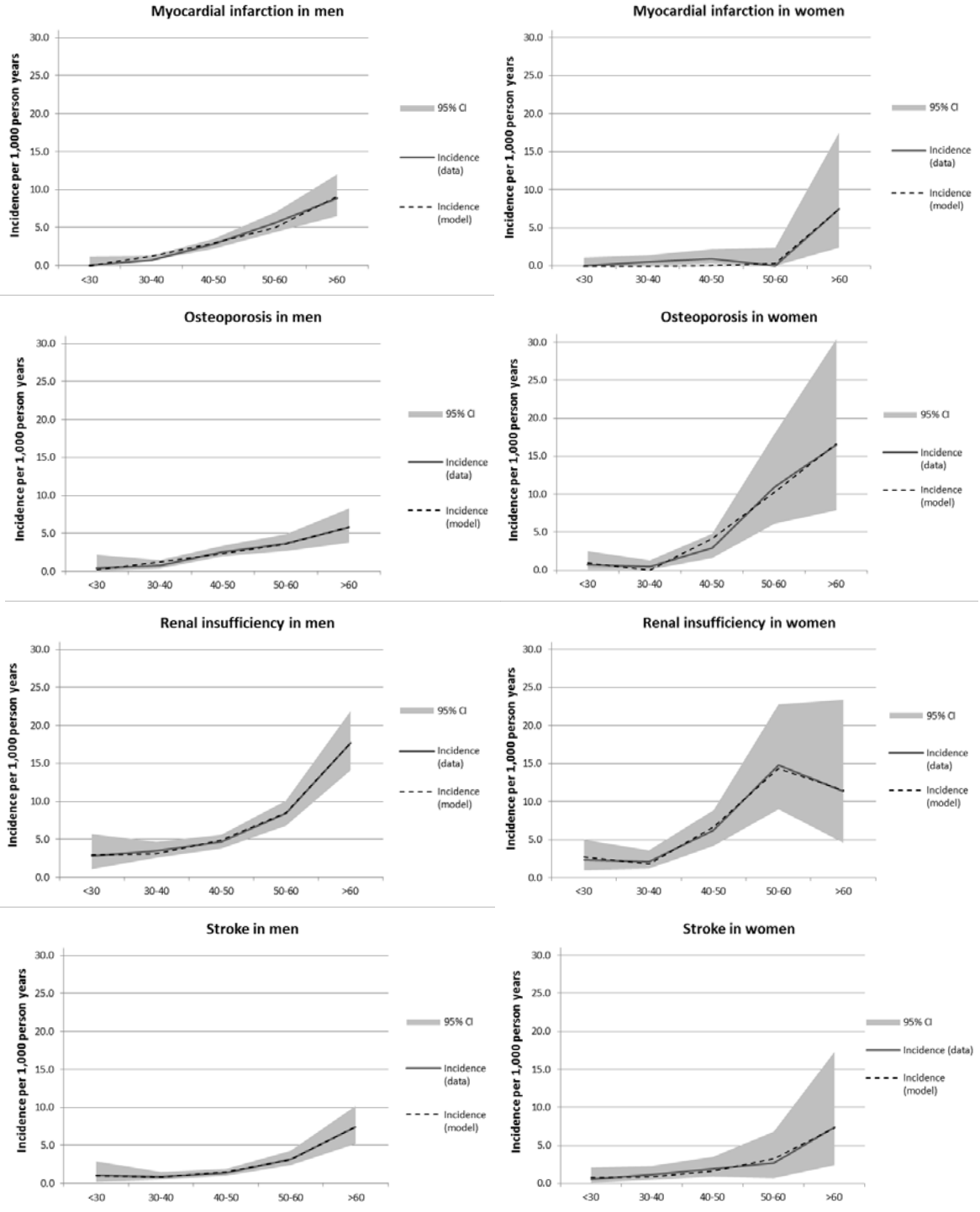


Table 4. Model parameter equations for incidence of new NCDs per 1,000 person-years of follow-up as a function of age for patients on cART. NB.
Polynomial equations $f(x) = \sum_i \beta_{i-x^{i-1}}$ and exponential equations $f(x) = A * exp(-Bt)$.

	Men		Women	
	Function type	**Parameters**	**Function type**	**Parameters**
Diabetes mellitus	Quadratic	β_1= 0.0016 β_3= -2.8117 β_2= 0.0944	Quadratic	β_1= 0.0045 β_3= 5.4700 β_2= -0.2069
Hypercholesterolemia	Quadratic	β_1= 0.0364 β_3= 26.1037 β_2= -0.9590	Cubic	β_1= -0.0019 β_3= -17.0424 β_2= 0.3638 β_4= 266.703
Hypertension	Cubic	β_1= -0.0009 β_3= -5.1142 β_2= 0.1368 β_4= 75.8735	Cubic	β_1= -0.0330 β_3= -114.245 β_2= 4.9647 β_4= 39.2327
Malignancy	Quadratic	β_1= 0.0069 β_3= 3.9815 β_2= -0.2808	Quadratic	β_1= -0.0005 β_3= -6.0260 β_2= 0.2584
MI	Quadratic	β_1= 0.0019 β_3= -1.5064 β_2= 0.0118	Exponential	A= 4.6287e^6 B= 0.2013
Osteoporosis	Quadratic	β_1= 0.0006 β_3= -1.8368 β_2= 0.0678	Cubic	β_1= -0.0005 β_3= -3.4167 β_2= 0.0784 β_4= 45.2435
CKD	Quadratic	β_1= 0.0085 β_3= 10.0968 β_2= -0.4979	Quartic	β_1= -2.0050e^5 β_4= 1.23060 β_2= 0.0027 β_5= 5.1711 β_3= -0.1089
Stroke	Quadratic	β_1= 0.0043 β_3= 5.2414 β_2= -0.2780	Quadratic	β_1= 0.0038 β_3= 3.9869 β_2= -0.2205

Table 5. Relationship between the risk of developing a new condition, given current conditions. HR gives ratio of risk for developing condition given another underlying condition compared to patients without another underlying condition.

	HR (95% CI)	**Data source**
MI or stroke given diabetes	2.31 (1.83-2.92)	Worm et al 2009[7]
MI or stroke given hypertension	1.26 (0.98-1.62)	Worm et al 2009[7]
MI or stroke given hypercholesterolemia	1.41 (1.12-1.76)	Worm et al 2009[7]
CKD given diabetes*	1.50 (1.05-2.16)	Mocroft et al 2010[8]
CKD given hypertension	1.69 (1.26-2.27)	Mocroft et al 2010[8]
Hypertension given diabetes	1.396 (1.19-1.64)	ATHENA data
Hypercholesterolemia given diabetes	1.12 (0.968-1.295)	ATHENA data
Hypertension given hypercholesterolemia	1.277 (1.16-1.397)	ATHENA data

Co-medication
The model simulates the treatment of NCDs. Co-medication in the model included diabetes medication (metformin, insulin and the sulfonylurea derivatives glibenclamide, gliclazide, glipizide, and tolbutamide), alendronic acid, Vitamin D and calcium supplements for osteoporosis, and ACE inhibitors (captopril, enalapril, and lisinopril), beta blockers (atenolol and metoprolol), calcium channel blockers (amlodipine, nifedipine, and verapamil), diuretics (bumetanide, furosemide, and hydrochlorothiazide) and statins (atorvastatin, pravastatin, and rosuvastatin) for CVD. The choice of co-medication in the model is limited to the most commonly prescribed co-medication amongst HIV-infected patients in the Netherlands, and any co-medication contra-indicated in HIV-infected patients on ART according to European guidelines are excluded.[4]

Only long-term treatment of NCDs is modeled in order to capture long-term burden of polypharmacy and drug interactions - consequently the treatment of malignancies is not included. The model reflected that current guidelines in the Netherlands do not recommend any specific CKD-therapy[4], and that not all HIV-patients with a given NCD receive treatment in the Netherlands. The point estimates for the proportion of HIV-patients prescribed co-medication for NCDs were obtained from ATHENA data and are presented in Table 6, Table 7,

and Table 8. They show, for example, that only 78% of HIV-infected patients on ART with diabetes are prescribed anti-diabetics.

The data further show that the prescription of cardiovascular co-medication is dependent on the number of CVDs as well as the presence or absence of diabetes, so that a patient with more than one CVD and diabetes is more likely to be prescribed CVD medication than a patient with only one CVD and no diabetes. The point estimates for CVD medication (Table 7) and a random number generator are used to assign co-medication, using the highest point estimate where a patient has more than two CVD or diabetes. For example, a patients with hypercholesterolemia alone (no other CVD and no diabetes) would have a 4·5% probability of being prescribed an ACE inhibitor, while a patient with hypercholesterolemia and an MI would have a 40·7% probability of being prescribed an ACE inhibitor (Table 7). The model assumes that future prescribing practices will remain the same, and that patients do not change co-medication.

Table 6. Proportion of HIV-infected patients on ART who start medicine for diabetes and osteoporosis.

	Proportion	Data source
Patients with diabetes		
Patients with diabetes on anti-diabetics	78.1%	ATHENA data
Patients with diabetes not on anti-diabetics	21.9%	ATHENA data
Total	**100%**	
Of patients on anti-diabetics		
Metformin alone	57.4%	ATHENA data
Metformin with sulfonylurea derivatives	13.4%	ATHENA data
Metformin with insulin	29.2%	ATHENA data
Total	**100%**	
Patients with Osteoporosis		
On alendronic acid, calcium supplement and Vitamin D	42.9%	ATHENA data
On no osteoporosis medication	57.1%	ATHENA data
Total	**100%**	

Table 7. Prevalence of patients on CVD-medication by number of CVDs and diabetes status.

	Patients with one CVD or diabetes	Patients with multiple CVDs and/or diabetes	Data source
ACE Inhibitors	4.5% (2.9-6.2) for hypercholesterolemia 10.9% (9.0-12.9) for hypertension 15.8% (0.0-33.8) for MI 6.3% (0.0-19.6) for stroke 11.5% (5.0-17.9) for diabetes	18.7% (14.8-22.5) for hypercholesterolemia 20.7% (16.8-24.5) for hypertension 40.7% (20.9-60.5) for MI 39.1% (17.6-60.7) for stroke 22.0% (14.8-29.1) for diabetes	ATHENA data
Beta Blockers	2.3% (1.2-3.5) for hypercholesterolemia 10.0% (8.1-11.8) for hypertension 73.7% (51.9-95.5) for MI 25.0% (1.2-48.8) for stroke 16.7% (9.1-24.3) for diabetes	16.7% (13.0-20.3) for hypercholesterolemia 15.9% (12.4-19.4) for hypertension 77.8% (61.0-94.5) for MI 21.7% (3.5-40.0) for stroke 19.7% (12.8-26.6) for diabetes	ATHENA data
Calcium Channel Blockers	0.2% (0.00-0.5) for hypercholesterolemia 4.3% (3.0-5.5) for hypertension 5.3% (0.00-16.3) for MI 6.3% (0.00-19.6) for stroke 2.1% (0.0-5.0) for diabetes	4.7% (2.6-6.8) for hypercholesterolemia 6.7% (4.3.9.0) for hypertension 3.7% (0.00-11.3) for MI 13.0% (0.00-27.9) for stroke 9.8% (4.7-15.0) for diabetes	ATHENA data
Diuretics	4.5% (2.9-6.2) for hypercholesterolemia 10.6% (8.7-12.5) for hypertension 31.6% (8.6-54.6) for MI 6.3% (0.00-19.6) for stroke 22.9% (14.4-31.5) for diabetes	16.7% (13.0-20.3) for hypercholesterolemia 19.2% (15.5-23.0) for hypertension 18.5% (2.9-3.4) for MI 34.8% (13.7-55.8) for stroke 28.0% (20.3-35.7) for diabetes	ATHENA data
Statins	16.9% (14.0-19.8) for hypercholesterolemia 4.9% (3.5-6.2) for hypertension 78.9% (58.8-99.1) for MI 18.8% (0.0-40.2) for stroke 18.8% (10.8-26.7) for diabetes	34.6% (30.0-39.2) for hypercholesterolemia 32.8% (28.3-37.3) for hypertension 70.4% (52.0-88.8) for MI 43.5% (21.6-65.4) for stroke 40.2% (31.7-48.6) for diabetes	ATHENA data

Table 8. Point estimates for individual cardiovascular drugs amongst patients on CVD-medication.

Drug Group	Individual drugs	Proportion	Data source
Ace Inhibitors	Captopril	5.4%	ATHENA data
	Enalapril	29.9%	
	Lisinopril	64.7%	
Beta Blockers	Atenolol	12.8%	ATHENA data
	Metoprolol	87.2%	
Calcium Channel Blockers	Amlodipine	0.0%	ATHENA data
	Nifedipine	92.1%	
	Verapamil	7.9%	
Diuretics	Bumetanide	7.3%	ATHENA data
	Furosemide	41.5%	
	Hydrochlorthiazide	51.3%	
Statins	Atorvastatine	31.1%	ATHENA data
	Pravastatine	44.9%	
	Rosuvastatin calcium	24.0%	

Drug-drug interactions

The model keeps track of all patients, their NCDs and the co-medication they are prescribed. This allows quantifying the burden of drug-interaction with HIV-medication as well the number of contra-indications between NCDs and ART regimens. The Liverpool Drug interaction webpage [9] (seeTable 9) provides a tool to explore the possible drug-interactions that exist between co-medication and HIV-medication. In addition European AIDS Clinical Society (EACS) guidelines outline which NCDs are contra-indicated for certain antiretrovirals, including that the use of tenofovir is contra-indicated in patients with CKD and patients at risk of CVD or with high cardiovascular risk (in this model defined as 'ever had' a stroke or MI) abacavir should be used with caution [4]. Together these provide the model with a means of quantifying the potential problem ageing HIV-infected patients will experience with HIV-therapy. Of particular interest are long-term restrictions to 2013 EACS recommended regimens. Current EACS recommended regimens (as of Oct 2013) consist of a backbone of tenofovir/ emtricitabine or abacavir/lamivudine combined with either efavirenz, rilpivirine, raltegravir or ritonavir-boosted atzanavir, darunavir or lopinavir.[4]

Table 9. Drug interaction chart. Adapted from http://www.hiv-druginteractions.org/.

	NRTIs							NNRTIs					PIs									Entry / Integrase Inhibitors			
	Abacavir	Didanosine	Emtricitabine	Lamivudine	Stavudine	Tenofovir	Zidovudine	Delavirdine	Efavirenz	Etravirine	Nevirapine	Rilpivirine	Atazanavir	Darunavir	Fosamprenavir	Indinavir	Lopinavir	Nelfinavir	Ritonavir	Saquinavir	Tipranavir	Dolutegravir	Elvitegravir/cobicistat	Maraviroc	Raltegravir
Anti-diabetics																									
Glibenclamide	○	○	○	○	○	○	○	◆	◆	◆	◆	○	◆	◆	◆	◆	◆	◆	◆	◆	◆	○	◆	○	○
Gliclazide	○	○	○	○	○	○	○	◆	◆	◆	○	○	◆	◆	◆	◆	◆	◆	◆	◆	◆	○	◆	○	○
Glipizide	○	○	○	○	○	○	○	◆	◆	◆	○	○	◆	◆	◆	◆	◆	◆	◆	◆	◆	○	◆	○	○
Insulin	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Metformin	○	○	○	○	○	○	○	○	○	○	○	◆	○	○	○	○	○	○	○	○	○	◆	◆	○	○
Tolbutamide	○	○	○	○	○	○	○	◆	◆	◆	○	○	◆	◆	◆	◆	◆	◆	◆	◆	◆	○	◆	○	○
Beta Blockers																									
Atenolol	○	○	○	○	○	○	○	○	○	○	○	○	◆	○	○	○	◆	○	◆	◆	○	○	○	○	○
Metoprolol	○	○	○	○	○	○	○	○	○	○	○	○	◆	◆	◆	◆	◆	○	◆	◆	▲	○	◆	○	○
Calcium Channel Blockers																									
Amlodipine	○	○	○	○	○	○	○	◆	◆	◆	◆	○	◆	◆	◆	◆	◆	◆	◆	◆	◆	○	◆	○	○
Nifedipine	○	○	○	○	○	○	○	◆	◆	◆	◆	○	◆	◆	◆	◆	◆	◆	◆	◆	◆	○	◆	○	○
Verapamil	○	○	○	○	○	○	○	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	○
Hypertension / Heart Failure Agents																									
Bumetanide	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧
Captopril	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧
Enalapril	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Furosemide	○	○	○	○	○	◆	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Hydrochlorthizide	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧
Lisinopril	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Lipid Lowering Agents																									
Atorvastatin	○	○	○	○	○	○	○	◆	◆	◆	◆	○	◆	◆	◆	◆	◆	◆	◆	◆	◆	○	◆	○	○
Pravastatin	○	○	○	○	○	○	○	○	○	◆	○	○	○	◆	○	◆	○	◆	○	◆	◆	○	○	○	○
Rosuvastatin	○	○	○	○	○	○	○	○	◆	◆	○	○	◆	◆	◆	◆	◆	◆	◆	◆	◆	○	○	○	○
Osteoporosis Agents																									
Alendronic Acid	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Colecalciferol (Vitamin D3)	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	◆	◆	○	◆
Caclium supplement	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧

Keys to symbols: ✧ There are no clear data ○ No clinical significant interaction expected ◆ Potential interaction – may require close monitoring, alteration of drug dosage or timing of administration

▲ These drugs should not be co-administered

Model validation checks
A number of checks were carried out to ensure that the model adequately captures clinical care in the Netherlands and could be used to reliably predict the future age-structure, burden of NCD and polypharmacy in the Netherlands. These checks include doing out-of-sample checks with 2011 to 2013 ATHENA data. The results of these model validation checks show that the model consistently generates output of the right order of magnitude, leading to the conclusion that the model provides projections of the right direction.

Age and incidence of treatment initiation check
Results of the model output for age and incidence of treatment initiation were compared to out-of-sample ATHENA data. Data from the ATHENA cohort from 2010 to 2012 were used to compute the mean and median age at start of treatment which were then compared to model output. Results of the model output and data are presented in Table 10. In addition, the number of people starting treatment and the total number of people in follow-up per year was compared between the model and data for 2010 and 2012, to check if the deterministic model of HIV incidence was reliable in predicting future trends of HIV-infection. Model output with medium incidence rate was compared to ATHENA cohort data. The results are presented in Table 11 and show that the incidence model used in the individual-based model is essentially adequate in projecting short-term trends in HIV-infection in the Netherlands.

Table 10. Mean and median age according to observation data from the ATHENA cohort and model output.

	Mean		Median	
	Data	**Model estimates**	**Data**	**Model estimates**
2010	45.0	44.7	44.5	43.9
2011	45.6	45.4	45.2	44.6
2012	46.25	46.0	46.0	45.0
2013	47.1	46.1	46.8	45.3

Table 11. Number of patients starting ART according to observed data from the ATHENA cohort and model output.

	Year	Data	Model
Number of people starting treatment	2010	1,250	1,009
	2011	1,158	897
	2012	899	805
	2013	800	728
Number of people on treatment	2010	9,777	10,012
	2011	10,851	10,814
	2012	11,924	11,502
	2013	12,922	12,091

Mortality check
Mortality was validated in three ways. One way was to compare the modelled standardized mortality ratio (SMR) between the HIV-infected population and general population to the SMR obtained in a study by the Collaboration of Observational HIV Epidemiological Research Europe (COHERE). COHERE calculated the overall SMRs of HIV-patients compared to the general population in a large European cohort as 4·2 (95% CI 3·5-5·2).[10] Background death rate ($\mu_i(a)$) was reduced to provide a match to this in the model of SMR=4·4.

The second check was to compare the age-specific death-rates amongst HIV-patients to those in the general Dutch population, to ensure mortality amongst HIV-patients was similar or greater than in the general population. Age-specific death-rates were taken from the WHO Global Health Observatory Data Repository for the Netherlands and used to model death rates in 2010, 2020, and 2030 amongst the general population [11]. Figure 7 shows the model outputs and confirms that model simulations generate death rates greater than the general Dutch population, as expected with the different greatest at older age.

Finally, the annual percentage of deaths amongst patients on ART was compared between the model and ATHENA between 2010 and 2012. The results are presented in Table 12 and show that the percentage deaths in the model are a good match to the data.

Figure 7. Age-specific modelled mortality rates for HIV-infected patients and the general population in the Netherlands in A. 2010, B. 2020, and C. 2030.

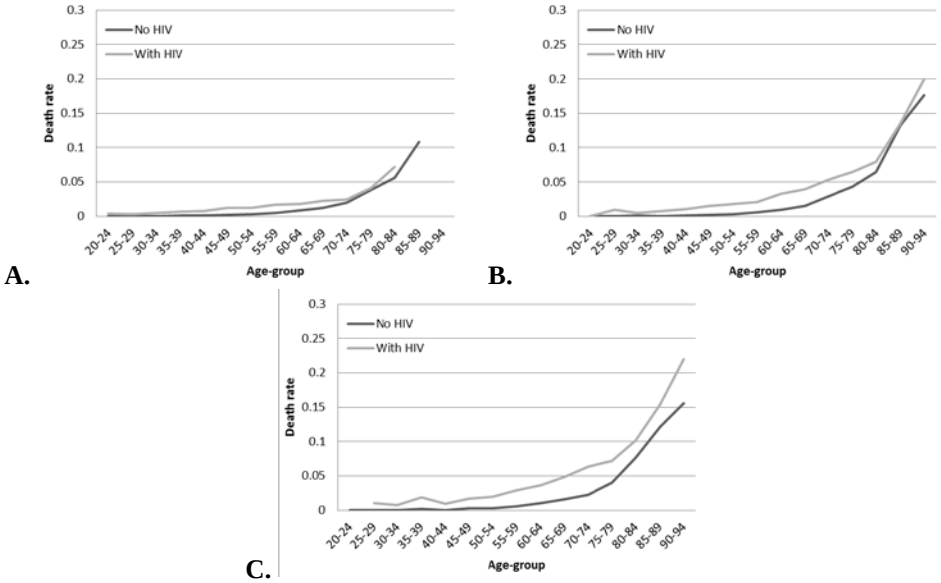


Table 12.. Annual percentage of HIV-infected patients on ART dying according to the observational data from the ATHENA cohort and the model output.

	Data	Model estimates
2010	0.8%	0.8%
2011	0.9%	1.2%
2012	0.9%	1.2%
2013	0.7%	1.0%

NCD and co-medication check

The model simulated the development of newly diagnosed NCD through a combination of demographic factors (age and sex) and medical factors, via a system of common causal pathway with parameter values coming from different sources.

In order to check the robustness of this approach, the number of people diagnosed with NCDs between 2010 and 2013 was compared between out-of-sample ATHENA data and the model output. The results are presented in Table 13 and show that the model consistently generates output of the right order of magnitude.

In addition, incidence of NCDs was compared between HIV-patients and the general Dutch population to ensure that the model captured the increased risk of NCDs in HIV-patients. The incidence of NCDs was obtained from the literature and the Dutch National Public Health Compass. Age-specific and sex-specific incidence data for the Netherlands was available for diabetes [12], CKD [13], malignancies [14], MI [15], osteoporosis [1] and stroke [17], with the remainders, namely hypertension and hypercholesterolemia not compared to the general population. Comparison of incidence in HIV-patients and the general population show that the incidence of NCDs is generally higher in HIV-infected individuals (not shown).

Model output on CVD medication was compared to observational data from the ATHENA cohort. Results of this comparison (Table 14) show that the model generates output of the right order of magnitude compared to out-of-sample data.

Table 13. The annual number of new NCDs developed by HIV-patients according to the observational data from the ATHENA cohort and the model output.

	2010		2011		2012		2013	
	Data	**Model estimates**	**Data**	**Model estimates**	**Data**	**Model estimates**	**Data**	**Model estimates**
Diabetes	72	67	68	64	75	68	61	70
Hypertension	445	416	441	453	430	506	380	519
Hypercholesterolemia	247	542	347	618	469	622	750	610
Malignancy	85	59	77	76	98	82	67	72
MI	21	36	22	43	30	38	19	40
Osteoporosis	152	87	242	82	151	94	94	83
CKD	101	65	99	65	117	87	65	87
Stroke	18	33	20	30	18	25	12	30

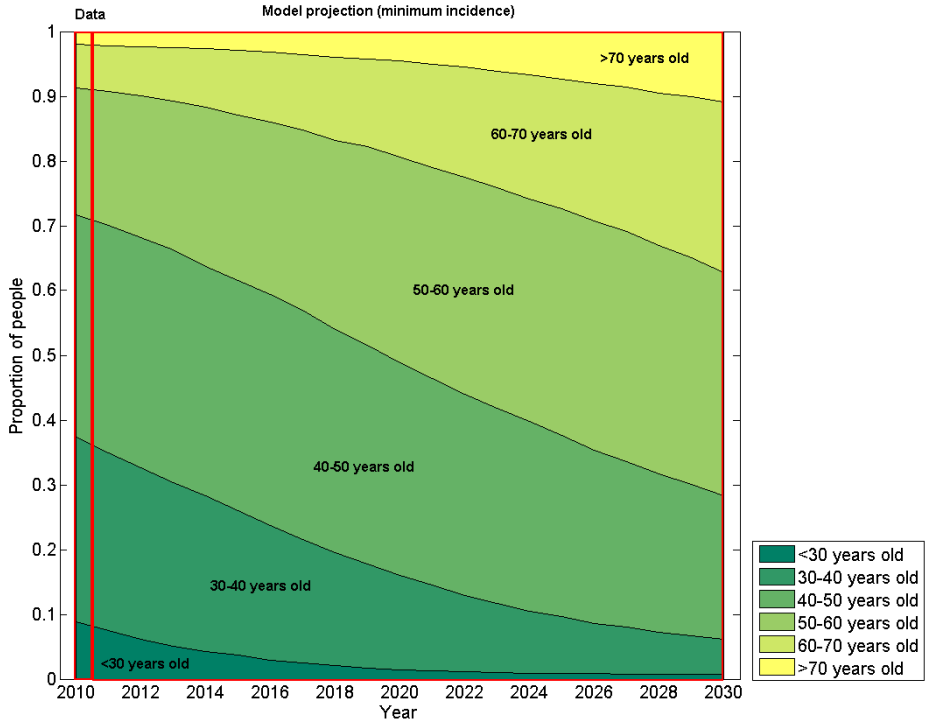
Table 14. The annual number of HIV-infected patients who start a co-medication according to the observational data from the ATHENA cohort and the model output.

	2010		2011		2012		2013	
			Data	Model	Data	Model		
ACE inhibitor	244	108	234	133	254	150	219	162
Beta blockers	220	119	187	138	194	144	157	162
Calcium blockers	78	25	69	52	81	46	64	34
Diuretics	277	123	313	137	277	146	266	146
Statins	368	184	370	230	388	255	326	238
Anti-diabetics	72	48	65	55	75	55	61	55
Osteoporosis	26	42	53	27	70	45	63	36

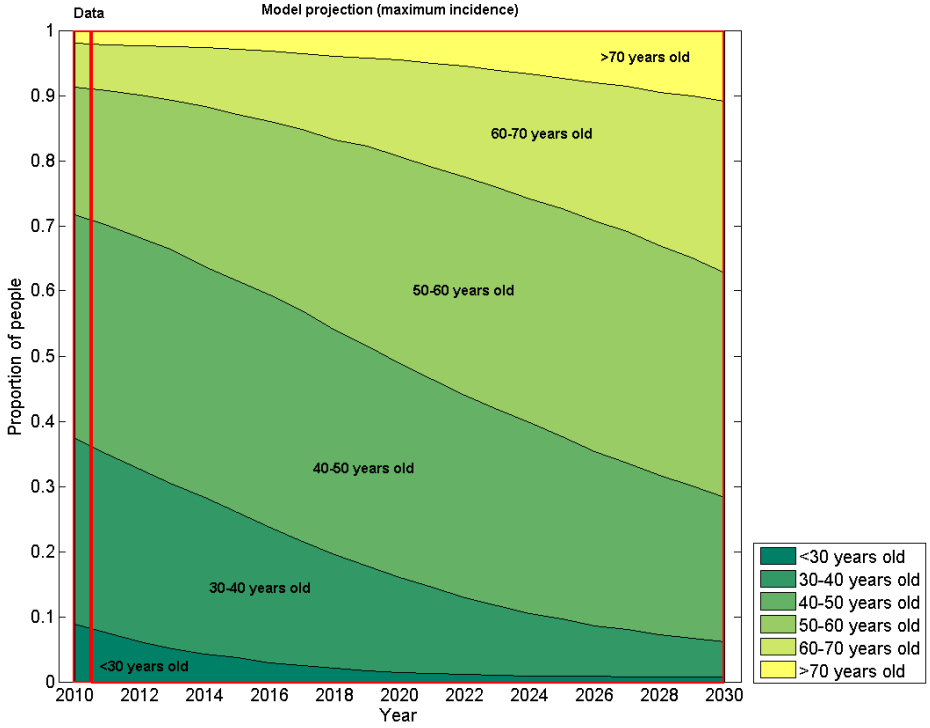
Results for additional incidence scenarios

The below show the results with the minimum and maximum HIV incidence scenarios.

Figure 1. Projected age distribution of HIV-infected patients on ART in clinical care in the Netherlands. The red box represents the age distribution in 2010, which matches the data exactly and the model output from 2011-2030 for A. minimum and B. maximum incidence scenario.

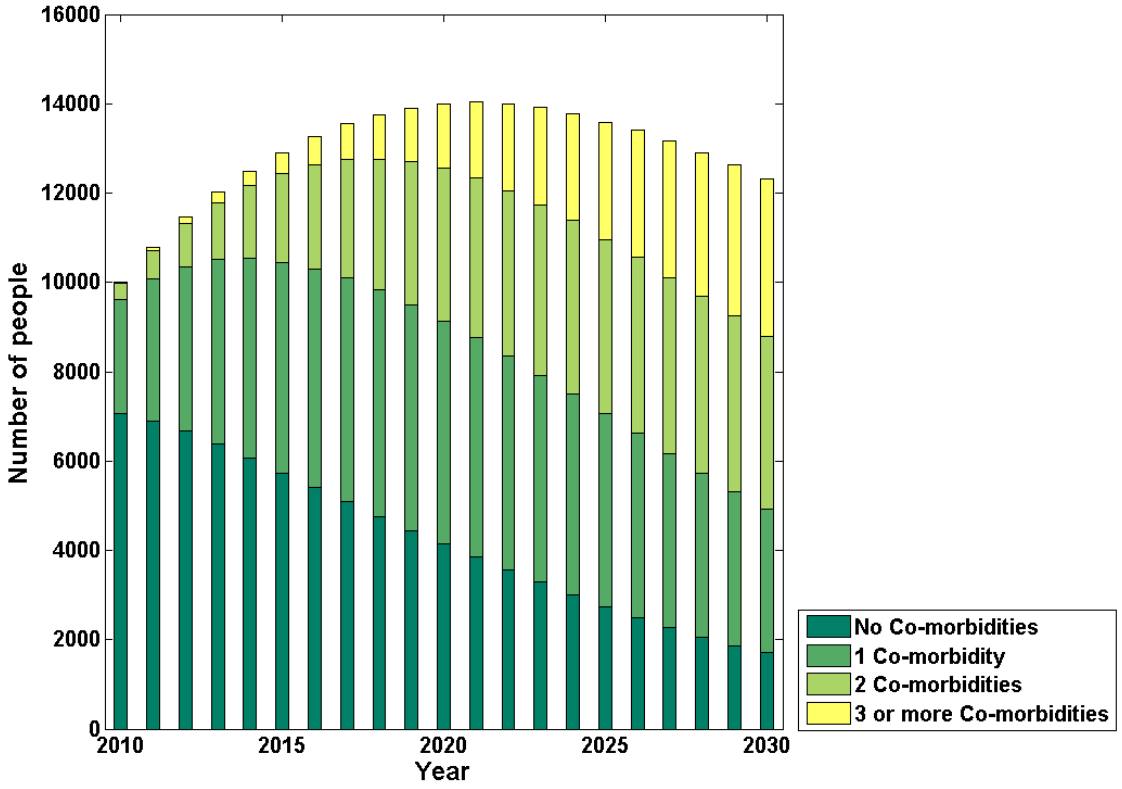


A.

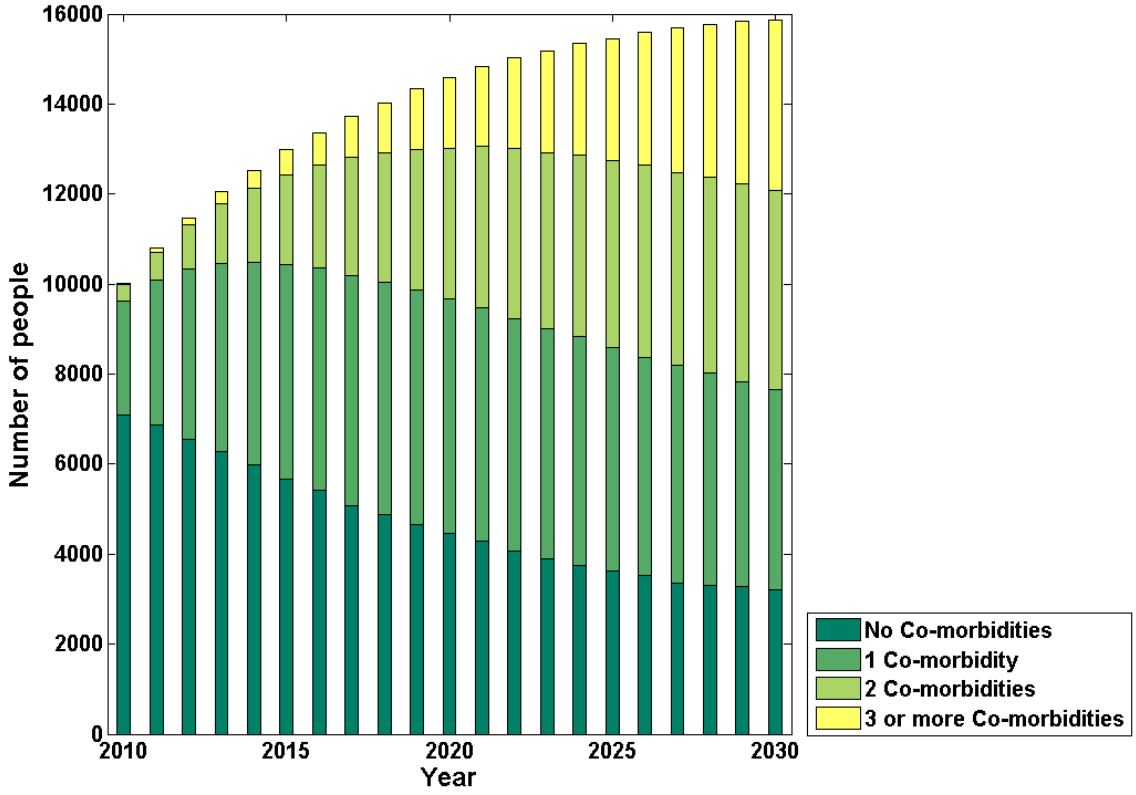


B.

Figure 2. Stacked bar graph of the projected burden of NCDs in HIV-infected patients between 2010 and 2030 as simulated by the mode for A. minimum and B. maximum incidence scenario.

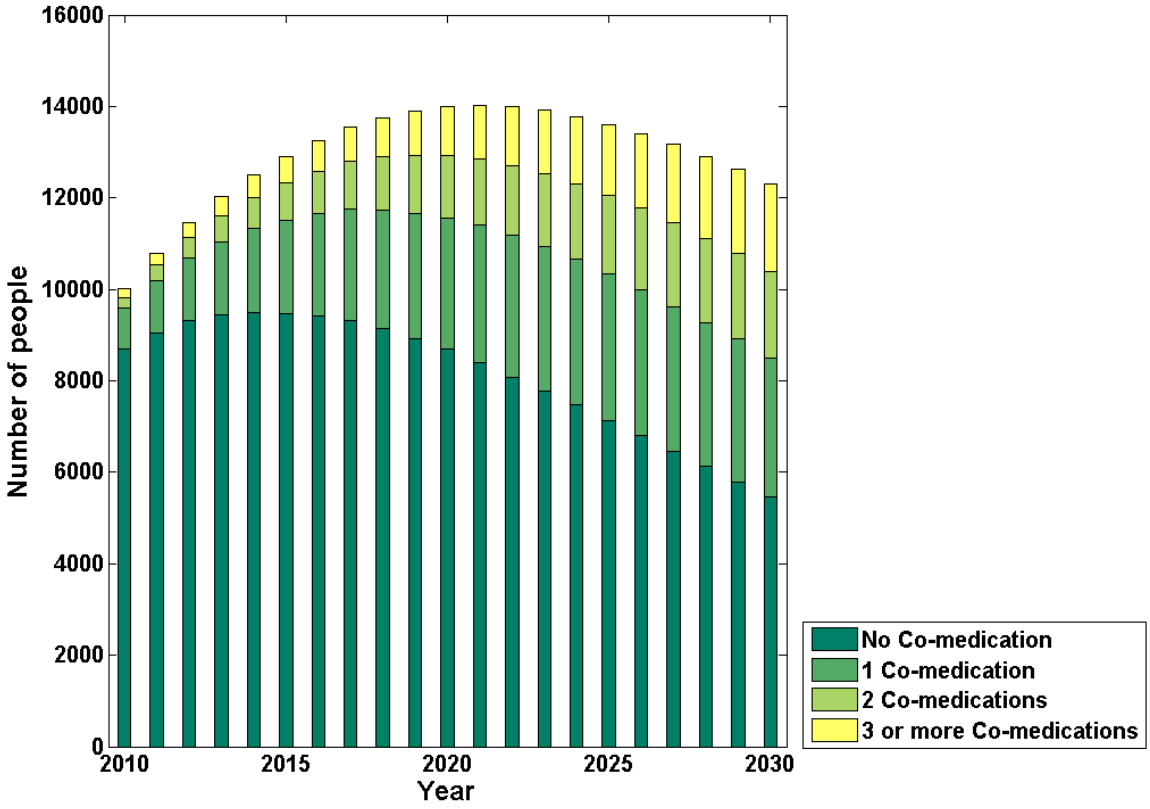


A.

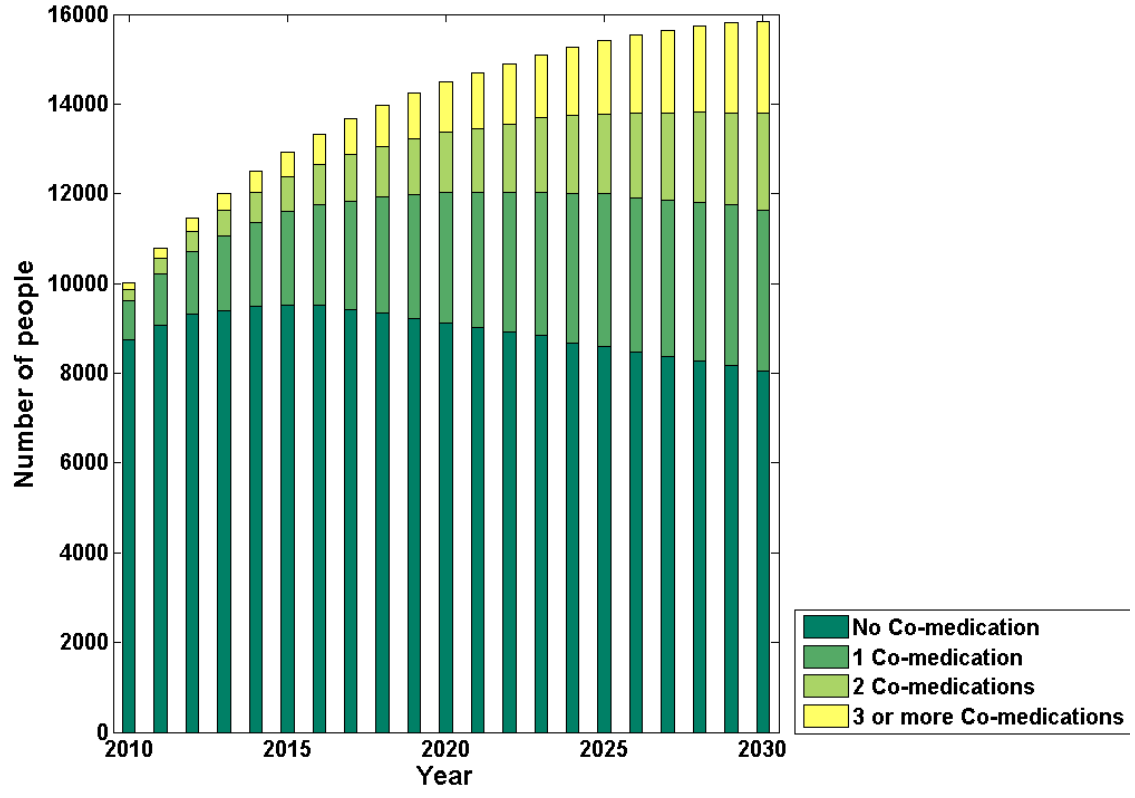


B.

Figure 3. Stacked bar graph of the projected burden of NCDs in HIV-infected patients between 2010 and 2030 for A. minimum and B. maximum incidence scenario.

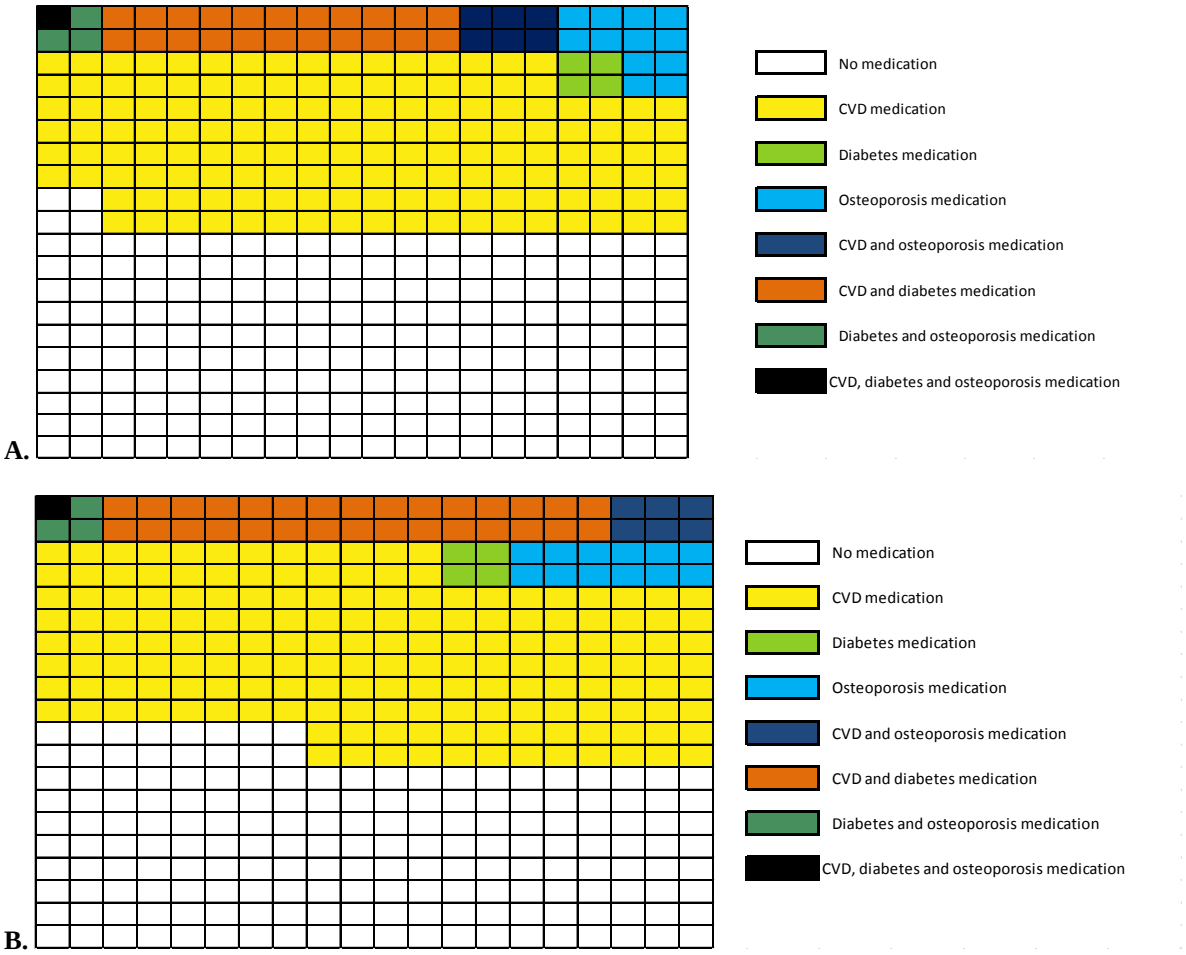


A.



B.

Figure 4. Prevalence of co-medication in 2030 as projected by the model. Figure represents cross-sectional number of patients on the different types of co-medications based on a representative 400 patients (each square is a patient) for A. minimum and B. maximum incidence scenario.



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