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 infarction (MI) or malignancy, and start co-medications 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:

\[
\text{Age}_{i,t} = a_i \times t - b_i
\]

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):

\[
\text{Scale}_{i,t} = \frac{\text{Age}_{i,t}}{\text{Shape}_{i}}
\]

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, \( \text{Age}_{i,t} = a_i \times \text{year}_t - b_i \).

| 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. 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, \( \alpha_j \) 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):

\[
Mortality = \mu_i(a) + \sum_j I_j \alpha_j
\]

**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 \( \lambda t \) is the incidence rate, \( \delta \) is the rate of HIV-diagnosis and \( \psi \) 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 \( \alpha, \beta \) and \( \gamma \) are parameters defining the incidence rate:
\[
\lambda_t = \frac{\alpha \cdot \exp \left( -\left( \text{year}_t - A - B \cdot \gamma \right)^2 \right)}{(\beta \cdot C)^2} \cdot S_t
\]

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 \( \lambda_t \) stands for the incidence rate, \( \delta \) stands for the rate of diagnosis and \( \psi \) 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 as 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 AGEhIV Cohort Study.6 The AGEhIV 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
| NCD                         | Age category | Men | Prevalence (%) | Age category | Women | Prevalence (%) | Source          |
|-----------------------------|--------------|-----|----------------|--------------|-------|----------------|----------------|
| Diabetes                    | <30          | 0.0 | (< -)         | <30          | 2.5   | (0.5-4.5)     | ATHENA data     |
|                             | 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 data     |
|                             | 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 data     |
|                             | 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 data     |
|                             | 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 data     |
|                             | 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 data     |
|                             | 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 data     |
|                             | 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 data     |
|                             | 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.

| 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.  

Myocardial infarction in men

Myocardial infarction in women

Osteoporosis in men

Osteoporosis in women

Renal insufficiency in men

Renal insufficiency in women

Stroke in men

Stroke in women
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 \( f(x) = \sum \beta_i x^{i-1} \) and exponential equations \( f(x) = A \times \exp(-Bt) \).

| NCD               | Function type | Parameters | Function type | Parameters |
|-------------------|---------------|------------|---------------|------------|
| Diabetes mellitus | Quadratic     | \( \beta_1 = 0.0016 \), \( \beta_2 = 0.0944 \), \( \beta_3 = -2.8117 \) | Quadratic     | \( \beta_1 = -0.0045 \), \( \beta_2 = 0.5470 \), \( \beta_3 = -0.2069 \) |
| Hypercholesterolemia | Quadratic     | \( \beta_1 = 0.0364 \), \( \beta_2 = 26.1037 \), \( \beta_3 = -0.9590 \) | Cubic         | \( \beta_1 = -0.0019 \), \( \beta_2 = 0.3638 \), \( \beta_3 = 26.703 \) |
| Hypertension      | Cubic         | \( \beta_1 = -0.0009 \), \( \beta_2 = -5.1142 \), \( \beta_3 = 0.1368 \), \( \beta_4 = 75.8735 \) | Cubic         | \( \beta_1 = -0.0330 \), \( \beta_2 = -114.245 \), \( \beta_3 = 4.9647 \), \( \beta_4 = 39.2327 \) |
| Malignancy        | Quadratic     | \( \beta_1 = 0.0069 \), \( \beta_2 = 3.9815 \), \( \beta_3 = -0.2808 \) | Quadratic     | \( \beta_1 = -0.0005 \), \( \beta_2 = -0.6260 \), \( \beta_3 = 0.2584 \) |
| MI                | Quadratic     | \( \beta_1 = 0.0019 \), \( \beta_2 = 0.5064 \), \( \beta_3 = 0.0118 \) | Exponential   | \( A = 4.6287 \times e^6 \), \( B = 0.2013 \) |
| Osteoporosis      | Quadratic     | \( \beta_1 = 0.0006 \), \( \beta_2 = -1.8368 \), \( \beta_3 = 0.0678 \) | Cubic         | \( \beta_1 = 0.0005 \), \( \beta_2 = -0.34167 \), \( \beta_3 = 0.0784 \), \( \beta_4 = 45.2435 \) |
| CKD               | Quadratic     | \( \beta_1 = 0.0085 \), \( \beta_2 = 10.0968 \), \( \beta_3 = -0.4979 \) | Quartic       | \( \beta_1 = 0.0050 \times e^{-5} \), \( \beta_2 = 1.23060 \), \( \beta_3 = 0.0027 \), \( \beta_4 = 5.17111 \), \( \beta_5 = -0.1089 \) |
| Stroke            | Quadratic     | \( \beta_1 = 0.0043 \), \( \beta_2 = 5.2414 \), \( \beta_3 = -0.2780 \) | Quadratic     | \( \beta_1 = 0.0038 \), \( \beta_2 = 3.9809 \), \( \beta_3 = -0.2205 \) |

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.

| Condition                   | HR (95% CI)               | Data source       |
|-----------------------------|---------------------------|-------------------|
| MI or stroke given diabetes | 2.31 (1.83-2.92)          | Worm et al 2009¹  |
| MI or stroke given hypertension | 1.26 (0.98-1.62)        | Worm et al 2009²  |
| MI or stroke given hypercholesterolemia | 1.41 (1.12-1.76) | Worm et al 2009²  |
| CKD given diabetes*         | 1.50 (1.05-2.16)         | Mocroft et al 2010³ |
| CKD given hypertension      | 1.69 (1.26-2.27)         | Mocroft et al 2010³ |
| Hypertension given diabetes | 1.39 (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 contraindicated 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-therapy⁵, 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.

| Patients with diabetes | Proportion | Data source |
|------------------------|------------|-------------|
| 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 | Proportion | Data source |
|-------------------------------|------------|-------------|
| 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 | Proportion | Data source |
|----------------------------|------------|-------------|
| 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                    |                                               | ATHENA data |
| hypercholesterolemia              | 4.5% (2.9-6.2) for                          | 18.7% (14.8-22.5) for hypercholesterolemia |
| hypertension                      | 10.9% (9.0-12.9) for                         | 20.7% (16.8-24.5) for hypertension |
| MI                                | 15.8% (0.0-33.8) for                         | 40.7% (20.9-60.5) for MI |
| stroke                            | 6.3% (0.0-19.6) for                           | 39.1% (17.6-60.7) for stroke |
| 11.5% (5.0-17.9) for diabetes      | 18.7% (14.8-22.5) for                         | 18.7% (14.8-22.5) for hypercholesterolemia |
| Beta Blockers                     |                                               | ATHENA data |
| hypercholesterolemia              | 2.3% (1.2-3.5) for                           | 16.7% (13.0-20.3) for hypercholesterolemia |
| hypertension                      | 10.0% (8.1-11.8) for                         | 15.9% (12.4-19.4) for hypertension |
| MI                                | 73.7% (51.9-95.5) for                         | 77.8% (61.0-94.5) for MI |
| stroke                            | 25.0% (1.2-48.8) for                           | 21.7% (5.5-40.0) for stroke |
| 16.7% (9.1-24.3) for diabetes      | 19.7% (12.8-26.6) for                         | 19.7% (12.8-26.6) for hypercholesterolemia |
| Calcium Channel Blockers          |                                               | ATHENA data |
| hypercholesterolemia              | 0.2% (0.0-0.5) for                           | 4.7% (2.6-6.8) for hypercholesterolemia |
| hypertension                      | 4.3% (3.0-5.5) for                            | 6.7% (4.3-9.0) for hypertension |
| MI                                | 5.3% (0.00-16.3) for                          | 3.7% (0.00-11.3) for MI |
| stroke                            | 6.3% (0.00-19.6) for                           | 13.0% (0.00-27.9) for stroke |
| 2.1% (0.0-5.0) for diabetes        | 9.8% (4.7-15.0) for                           | 9.8% (4.7-15.0) for hypercholesterolemia |
| Diuretics                         |                                               | ATHENA data |
| hypercholesterolemia              | 4.5% (2.9-6.2) for                           | 16.7% (13.0-20.3) for hypercholesterolemia |
| hypertension                      | 10.6% (8.7-12.5) for                          | 19.2% (15.5-23.0) for hypertension |
| MI                                | 31.6% (8.6-54.6) for                          | 18.5% (2.9-34.3) for MI |
| stroke                            | 6.3% (0.00-19.6) for                           | 34.8% (13.7-55.8) for stroke |
| 22.9% (14.4-31.5) for diabetes     | 28.0% (20.3-35.7) for                         | 28.0% (20.3-35.7) for hypercholesterolemia |
| Statins                           |                                               | ATHENA data |
| hypercholesterolemia              | 16.9% (14.0-19.8) for                         | 34.8% (30.0-39.2) for hypercholesterolemia |
| hypertension                      | 4.9% (3.5-6.2) for                            | 32.8% (28.3-37.3) for hypertension |
| MI                                | 78.9% (58.8-99.1) for                          | 70.4% (52.0-88.8) for MI |
| stroke                            | 18.8% (0.0-40.2) for                           | 43.5% (21.6-65.4) for stroke |
| 18.8% (10.8-26.7) for diabetes     | 40.2% (31.7-48.6) for                         | 40.2% (31.7-48.6) for hypercholesterolemia |
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%      |               |
|                       | Hydrochlorothiazide | 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 webpage⁹ (see Table 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 caution⁴. 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 | Deferoxamine | Etanercept | Etavirine | Nevirapine | Rilpivirine | Atazanavir | Darunavir | Fosamprenavir | Indinavir | Lopinavir | Maraviroc | Nelfinavir | Ritonavir | Saquinavir | Tipranavir | Tipranavir/Ritonavir | Dolutegravir | Raltegravir |
|-------|--------|--------|----------------|--------------|----------|---------|---------|-------------|-------------|-----------|-----------|----------|-------------|---------|----------|---------|---------|----------|----------|----------|-----------|-------------|----------|-------------|
| Calcium Channel Blockers | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Amlodipine | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Nifedipine | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Verapamil | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hypertension / Heart Failure Agents | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bumetanide | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Captopril | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Enalapril | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Furosemide | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hydrochlorothiazide | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lisinopril | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lipid Lowering Agents | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Atorvastatin | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pravastatin | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Rosuvastatin | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Osteoporosis Agents | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Alendronic Acid | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Colecalciferol (Vitamin D3) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Calcium 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 Data | Model estimates | Median 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     | 2010 | 1,250     | 1,009     |
| starting treatment   | 2011 | 1,158     | 897       |
|                      | 2012 | 899       | 805       |
|                      | 2013 | 800       | 728       |
| Number of people     | 2010 | 9,777     | 10,012    |
| on treatment         | 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). 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. 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, CKD, malignancies, MI, osteoporosis and stroke, 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      | 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.
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.
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.
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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