# Future challenges for clinical care of an ageing population infected with HIV: a modelling study

*Mikaela Smit, Kees Brinkman, Suzanne Geerlings, Colette Smit, Kalyani Thyagarajan, Ard van Sighem, Frank de Wolf, Timothy B Hallett, on behalf of the ATHENA observational cohort*

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See Comment page 753

**Department of Infectious Disease Epidemiology, Faculty of Medicine, Imperial College London, London, UK** (M Smit PhD, Prof F de Wolf MD, Prof T B Hallett PhD); **Department of Internal Medicine, Onze Lieve Vrouwe Gasthuis, Amsterdam, Netherlands** (K Brinkman MD); **Division of Infectious Diseases, Amsterdam Medical Centre, Amsterdam, Netherlands** (S Geerlings MD); **Stichting HIV Monitoring, Amsterdam, Netherlands** (C Smit PhD, A van Sighem PhD, Prof F de Wolf); **and independent consultant, London, UK** (K Thyagarajan PhD)

Correspondence to: Dr Mikaela Smit, Department of Infectious Disease Epidemiology, Faculty of Medicine at St Mary's Campus, Imperial College London, London W2 1PG, UK **mikaela.smit@imperial.ac.uk**

## Summary

**Background** The population infected with HIV is getting older and these people will increasingly develop age-related non-communicable diseases (NCDs). We aimed to quantify the scale of the change and the implications for HIV care in the Netherlands in the future.

**Methods** We constructed an individual-based model of the ageing HIV-infected population, which followed patients on HIV treatment as they age, develop NCDs—including cardiovascular disease (hypertension, hypercholesterolaemia, myocardial infarctions, and strokes), diabetes, chronic kidney disease, osteoporosis, and non-AIDS malignancies—and start co-medication for these diseases. The model was parameterised by use of data for 10 278 patients from the national Dutch ATHENA cohort between 1996 and 2010. We made projections up to 2030.

**Findings** Our model suggests that the median age of HIV-infected patients on combination antiretroviral therapy (ART) will increase from 43·9 years in 2010 to 56·6 in 2030, with the proportion of HIV-infected patients aged 50 years or older increasing from 28% in 2010 to 73% in 2030. In 2030, we predict that 84% of HIV-infected patients will have at least one NCD, up from 29% in 2010, with 28% of HIV-infected patients in 2030 having three or more NCDs. 54% of HIV-infected patients will be prescribed co-medications in 2030, compared with 13% in 2010, with 20% taking three or more co-medications. Most of this change will be driven by increasing prevalence of cardiovascular disease and associated drugs. Because of contraindications and drug–drug interactions, in 2030, 40% of patients could have complications with the currently recommended first-line HIV regimens.

**Interpretation** The profile of patients in the Netherlands infected with HIV is changing, with increasing numbers of older patients with multiple morbidities. These changes mean that, in the near future, HIV care will increasingly need to draw on a wide range of medical disciplines, in addition to evidence-based screening and monitoring protocols to ensure continued high-quality care. These findings are based on a large dataset of HIV-infected patients in the Netherlands, but we believe that the overall patterns will be repeated elsewhere in Europe and North America. The implications of such a trend for care of HIV-infected patients in high-burden countries in Africa could present a particular challenge.

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## Introduction

More than 30 years after HIV started to spread, and almost 20 years after combination antiretroviral therapy (ART) became available, the profile of the HIV epidemic in Europe is changing. HIV treatment has improved substantially since the introduction of ART.[1] Improved efficacy of ART to suppress HIV replication has reduced the mortality of HIV-infected patients on treatment.[2] This reduction in mortality has transformed HIV into a long-term chronic illness for many patients, characterised by an ageing HIV-infected population who are increasingly affected by age-related non-communicable diseases (NCDs).[3] The increasing prevalence of NCDs complicates treatment and care for HIV-infected patients.[3,4] Treatment for NCDs can cause problems related to polypharmacy—coadministration of multiple drugs in addition to HIV drugs—leading to increased pill burden,[3,4] potential drug–drug interactions and adverse effects, and loss of treatment efficacy and subsequent virological breakthrough. Results from several studies have shown that people infected with HIV might have a higher prevalence and earlier age of onset for many NCDs than do age-matched uninfected individuals.[5–7] This effect has been shown for several comorbidities, including cardiovascular disease,[8,9] non-AIDS malignancies,[10] liver and kidney disease,[11] and osteoporosis.[12,13]

A Dutch prospective cohort study[6] noted that prevalence of hypertension, cardiovascular and peripheral vascular disease, and impaired renal function (but not metabolic, pulmonary, bone, and malignant disease) was significantly increased in HIV-infected participants compared with uninfected controls, with no reported difference by sex. In 2014, a study of the Veterans Ageing Cohort reported that, although HIV-infected adults had increased risk of age-related NCDs, they occurred at similar ages in uninfected individuals.[7] Long-term use of

antiretroviral drugs, sustained HIV-associated immune activation, and chronic inflammation have all been reported to be associated with increased risk of comorbid disease.[5,6,13–15] Although concentrations of some biomarkers of inflammation and immune activation in HIV-infected patients return to those of uninfected individuals within the first year after ART-induced viral suppression, several markers remain unusually high.[16] The future scale of the associated diseases and conditions and how this will affect HIV care remain unclear. Such an evaluation is important to address future challenges, develop evidence-based changes to clinical guidelines, and ensure continued high-quality care.

We constructed an individual-based model, which represented the onset of NCDs, ageing, polypharmacy, and drug–drug interactions, and parameterised it with data from the Dutch ATHENA cohort.[17] We used the model to project the future of the ageing HIV-infected population in the Netherlands and to identify the implications of the predictions and actions needed to address these coming trends.

## Methods

### Data source

We developed the model for the Netherlands using data from the ATHENA cohort. ATHENA is a national observational cohort that has collected data from all HIV-infected patients in clinical care in the Netherlands since 1996. The design of this cohort has been described previously.[17] Clinical, biological, and immunological data for HIV-infected patients are collected at entry and at each follow-up visit.

We included patients from the ATHENA cohort in the analysis if they were aged 18 or older, infected with HIV-1, antiretroviral drug naive, and diagnosed with HIV on or after Jan 1, 1996. We excluded women who were known to have been pregnant during follow-up because of the treatment changes that occur because of pregnancy and the effect this would have on the model's predictions of drug–drug interactions. In total, we excluded 1005 pregnant women (9·7%) from the analysis out of the total study population. We analysed the data up to and including Dec 31, 2010, with the data encompassing 10 278 individuals. All values for parameters were based on data from patients on ART.

Most of the study population used for model parameterisation were Dutch men who have sex with men (table 1). The three most prevalent NCDs were hypercholesterolaemia, hypertension, and chronic kidney disease. The epidemic in the Netherlands is well documented,[18,19] and in 2010, mortality was 0·8% and the number of AIDS diagnoses was 0·3%. Similar to most other countries in Europe and North America, the epidemic in the Netherlands is concentrated in men who have sex with men. The prevalence of HIV in the Netherlands is 0·2%, which is similar to that of the UK (0·2%) and lower than that of the USA (0·6%).[20]

| | ATHENA cohort population (n=10 278) |
|---|---|
| Sex | |
| Male | 8586 (84%) |
| Female | 1692 (16%) |
| Age in 2010, years | 44·5 (10·4) |
| Transmission | |
| Men who have sex with men | 6040 (59%) |
| Heterosexual | 3300 (32%) |
| Injecting drug user | 208 (2%) |
| Other or unknown | 730 (7%) |
| Region of origin | |
| Netherlands | 5967 (58%) |
| Sub-Saharan Africa | 1628 (16%) |
| Europe | 855 (8%) |
| Other | 1828 (18%) |
| Prevalence of NCD | |
| Diabetes | 578 (6%) |
| Hypertension | 2379 (23%) |
| Hypercholesterolaemia | 2502 (24%) |
| Malignancies* | 765 (7%) |
| Myocardial infarction* | 216 (2%) |
| Osteoporosis | 829 (8%) |
| Chronic kidney disease | 1399 (14%) |
| Stroke* | 156 (2%) |

Data are n (%) or median (SD). NCD=non-communicable disease. *Defined as the number of patients ever diagnosed with an NCD in the study population.

***Table 1:*** **Demographic characteristics of the ATHENA cohort used for model parameterisation**

### Model

We constructed an individual-based model of the ageing HIV-infected population in the Netherlands (figure 1). The appendix contains technical details of how the model was constructed. The model follows HIV-infected patients from the start of treatment until death or the end of the model simulation in 2030, as they age, develop NCDs, start co-medication for these disorders, and how co-medications affect HIV treatment. The model also captures the interactions between NCDs (figure 1). The choice of factors modelled was based on incorporation of the major age-related NCDs that will play an important part in future clinical care for HIV and for which the available data were sufficient for predictions to be made—ie, diabetes mellitus, hypertension, hypercholesterolaemia, osteoporosis, chronic kidney disease, strokes, myocardial infarctions, and non-AIDS malignancy. We validated model performance by use of out-of-sample prediction checks for the period of 2011–13 in the data, in which we set aside the most recent ATHENA data to compare with our predictions (appendix).

See Online for appendix

We probabilistically assigned demographic factors to patients upon entry into the model in accordance with frequency distributions from ATHENA cohort data. We

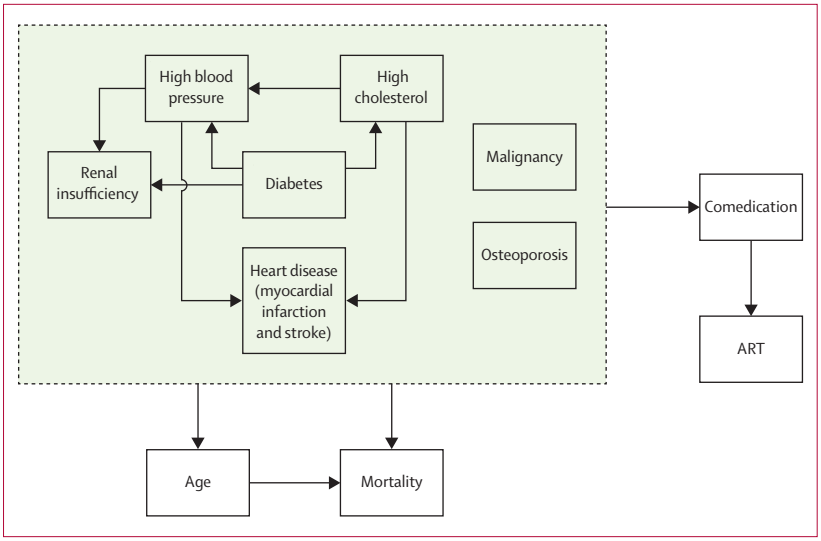


***Figure 1:*** **Schematic of the model of an ageing HIV-infected population**
The model follows HIV-infected patients from the start of treatment until death or last year of model (2030). The model simulates how, over time, HIV-infected patients age, develop comorbidities, start co-medication for these conditions, and how these co-medications affect HIV treatment. The dashed square shows the comorbidities and interactions included in the model. Patients developed comorbidities as a function of age and sex. Comedication is prescribed on the basis of the comorbidities a patient has, which in turn affect drug–drug interactions with HIV treatment (ART). Mortality risk is affected by both age and the number and type of comorbidity and is simulated for patients on ART. ART=antiretroviral therapy.

| | Incidence in men per 1000 person-years | Incidence in women per 1000 person-years |
|---|---|---|
| **Diabetes mellitus** | | |
| <30 years | 0·5 (0·1–2·0) | 3·0 (1·5–5·3) |
| 30–40 years | 2·5 (1·9–3·3) | 3·8 (2·6–5·3) |
| 40–50 years | 4·4 (3·7–5·2) | 5·7 (3·9–8·1) |
| 50–60 years | 7·2 (5·9–8·8) | 7·2 (3·6–12·9) |
| ≥60 years | 11·7 (9·0–15·1) | 13·6 (6·2–25·8) |
| **Hypercholesterolaemia** | | |
| <30 years | 25·8 (20·0–32·7) | 36·5 (25·8–50·1) |
| 30–40 years | 34·3 (31·1–37·7) | 38·0 (31·4–45·6) |
| 40–50 years | 59·2 (55·4–63·1) | 50·9 (42·4–60·6) |
| 50–60 years | 82·6 (76·0–89·5) | 116·4 (94·7–141·5) |
| ≥60 years | 117·3 (104·6–131·2) | 130·8 (98·9–170·0) |
| **Hypertension** | | |
| <30 years | 19·3 (14·3–25·4) | 20·1 (13·2–31·9) |
| 30–40 years | 25·8 (23·0–28·8) | 18·8 (14·2–24·5) |
| 40–50 years | 39·7 (36·5–43·0) | 43·4 (35·2–52·9) |
| 50–60 years | 57·8 (52·1–63·9) | 58·1 (41·3–79·5) |
| ≥60 years | 72·3 (61·8–84·1) | 69·5 (45·4–101·8) |
| **Malignancy** | | |
| <30 years | 1·4 (0·4–3·2) | 0·3 (0·0–1·5) |
| 30–40 years | 2·3 (1·7–3·1) | 1·9 (1·1–3·1) |
| 40–50 years | 5·1 (4·3–6·0) | 5·2 (3·5–7·5) |
| 50–60 years | 9·6 (8·1–11·3) | 6·5 (3·1–11·9) |
| ≥60 years | 18·5 (15·0–22·6) | 9·9 (4·0–20·4) |

(Table 2 continues on next page)

simulated the rate of future entry into care using a compartmental model of the HIV epidemic by extrapolating past trends in HIV diagnosis and ART initiation rates from observational data (appendix). The main results assume a medium incidence scenario whereby incidence decreases gradually in the coming years, but alternative analyses for different future trajectories in incidence are described in the appendix. The model makes an implicit assumption that time from infection to treatment initiation is constant. We took parameters to define cause-specific death rates by age and sex from a large multicohort study by the Data Collection on Adverse Events of Anti-HIV drugs study group.[21]

Where possible, we defined all NCDs in accordance with European AIDS Clinical Society (EACS) clinical and laboratory guidelines for diagnosis.[22] We based definitions of myocardial infarction, stroke, osteoporosis, and non-AIDS malignancies on information registered in patients' files. We defined chronic kidney disease as glomerular filtration rate less than 60 mL/min per 1·73 m² using the Cockcroft-Gault equation, confirmed after 3 months or later,[23] hypertension, and hypercholesterolaemia on blood pressure measurements and laboratory results. For diabetes, we used both registry data and use of antidiabetic drugs to define diabetes status. Where possible, we used pathology reports to confirm diagnosis of any non-AIDS malignancy.[23] Malignancies included all cancers, except AIDS-defining cancers, precancerous stages of anal and cervical cancer, basal cell carcinoma, and squamous cell carcinoma of the skin.

We modelled age-and-sex-specific prevalence of existing NCDs among patients already in care in 2010 (when the model starts) using observational ATHENA data. We simulated incidence of new NCDs by using observational estimates of the age-and-sex-specific incidence per 1000 person-years of follow-up from the ATHENA cohort (table 2). The propensity for one disorder to be associated with increased risk for development of another, through common causal pathways, was incorporated into the model, with parameters to define these pathways based on both ATHENA data and an in-depth literature review (figure 1, table 3). Where patients had two or more NCDs that could affect the development of another NCD, we calculated parameters as the mean of the largest factor and the product of the factors. To simulate NCD burden in the age-and-sex-matched HIV-negative population, we reran the model with the relative reduced risk for chronic kidney disease and cardiovascular disease reported by the $AGE_hIV$ study.[6] The $AGE_hIV$ study has compared prevalence and incidence of a broad range of NCDs in HIV-infected individuals and age-matched uninfected controls since 2010.[6]

The choice of co-medication in the model was restricted to the most commonly prescribed co-medications in HIV-infected patients in the Netherlands, and excludes co-medication contraindicated for HIV-infected patients on

| | Incidence in men per 1000 person-years | Incidence in women per 1000 person-years |
|---|---|---|
| (Continued from previous page) | | |
| **Myocardial infarction** | | |
| <30 years | 0·0 (0·0–1·2) | 0·0 (0·0–1·1) |
| 30–40 years | 0·7 (0·4–1·3) | 0·5 (0·1–1·4) |
| 40–50 years | 2·8 (2·2–3·5) | 0·9 (0·3–2·2) |
| 50–60 years | 5·6 (4·4–7·0) | 0·0 (0·0–2·4) |
| ≥60 years | 8·9 (6·5–12·0) | 7·5 (2·4–17·5) |
| **Osteoporosis** | | |
| <30 years | 0·4 (0·0–2·2) | 0·7 (0·1–2·5) |
| 30–40 years | 0·8 (0·4–1·5) | 0·5 (0·1–1·3) |
| 40–50 years | 2·6 (2·0–3·4) | 2·9 (1·6–4·8) |
| 50–60 years | 3·7 (2·7–4·9) | 10·9 (6·1–17·9) |
| ≥60 years | 5·8 (3·8–8·3) | 16·5 (7·9–30·4) |
| **Chronic kidney disease** | | |
| <30 years | 2·8 (1·1–5·7) | 2·4 (1·0–5·0) |
| 30–40 years | 3·5 (2·6–4·7) | 2·1 (1·2–3·6) |
| 40–50 years | 4·7 (3·8–5·6) | 6·2 (4·2–8·9) |
| 50–60 years | 8·4 (6·8–10·1) | 14·8 (9·0–22·8) |
| ≥60 years | 17·7 (14·1–21·9) | 11·4 (4·6–23·4) |
| **Stroke** | | |
| <30 years | 1·0 (0·2–2·9) | 0·6 (0·1–2·1) |
| 30–40 years | 0·9 (0·5–1·5) | 1·2 (0·5–2·3) |
| 40–50 years | 1·4 (1·0–1·9) | 1·9 (0·9–3·5) |
| 50–60 years | 3·2 (2·4–4·3) | 2·7 (0·7–6·8) |
| ≥60 years | 7·4 (5·2–10·2) | 7·4 (2·4–17·3) |

Data are incidence (95% CI). Incidence data for all NCDs, except hypercholesterolaemia and hypertension, are from the Monitoring report 2011.[23] Hypercholesterolaemia and hypertension were calculated from the ATHENA data, with the same method as used in the report. NCD=non-communicable disease.

***Table 2:*** **Incidence of newly diagnosed, routinely collected serious comorbidities by age group and sex**

ART in accordance with European guidelines.[22] Co-medications include diabetes drugs (metformin, insulin, and the sulfonylurea derivatives glibenclamide, gliclazide, glipizide, and tolbutamide); alendronic acid, vitamin D, and calcium supplements for osteoporosis; and angiotensin-converting enzyme inhibitors (captopril, enalapril, and lisinopril), β blockers (atenolol and metoprolol), calcium channel blockers (amlodipine, nifedipine, and verapamil), diuretics (bumetanide, furosemide, and hydrochlorothiazide), and statins (atorvastatin, pravastatin, and rosuvastatin) for cardiovascular disease.

The model incorporated the fact that existing guidelines in the Netherlands do not recommend any specific treatment for chronic kidney disease, except renal replacement therapy for end stage chronic kidney disease (not modelled).[22] To capture long-term burden of polypharmacy and drug–drug interactions, we modelled only long-term treatment of NCDs. Consequently, we did not include the treatment of malignancies. Model parameters for co-medication accounted for the fact that not all patients with each NCD received treatment, and were based on current prescribing practices in the Netherlands in accordance with the ATHENA data. The model assumed that current prescribing practices would remain the same in the future.

We quantified drug–drug interactions with the HIV Drug Interaction chart from the University of Liverpool, and contraindications between recommended first-line ART and NCDs were based on EACS guidelines.[22] The EACS-recommended regimens (as of October, 2013) consisted of a backbone of tenofovir/emtricitabine or abacavir/lamivudine combined with either efavirenz, rilpivirine, raltegravir or ritonavir-boosted atzanavir, darunavir, or lopinavir.[22]

For the **HIV Drug Interaction chart** see http://www.hiv-druginteractions.org

### Role of funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

The model predicts that the median age of patients receiving treatment for HIV will increase from 43·9 years in 2010 to 56·6 years in 2030. The proportion of patients older than 50 years is predicted to increase from 28% in 2010 to 73% in 2030, while the proportion of patients aged 60 years or older will increase from 8% to 39% and the proportion aged 70 years or older will increase from 8% to 12% (figure 2). Even if patients starting ART had exactly the same average age as those in 2010, the median age in 2030 would still be 55·7 years. If incidence declined more rapidly or slowly than expected, the median age in 2030 would vary between 55·3 and 56·9 years (appendix).

As a result of the ageing HIV-infected population, the number of HIV-infected patients in the Netherlands with at least one NCD is projected to increase from 29% in 2010 to 84% in 2030 (figure 3). The number of patients with three or more NCDs is expected to increase from 0·3% in 2010 to 28% of patients in clinical care in 2030. In 2030, only 16% of HIV-infected patients will not have any of the NCDs investigated (figure 3). Sensitivity analysis that varied the incidence rates of NCDs did not materially affect the overall patterns of increasing burden of NCDs in patients on ART, with lower rates tending to result in a slightly reduced burden of NCDs in 2030 and increased rates resulting in increased burden of NCDs compared with the projections presented here.

The profile of NCD burden is higher than is expected for the HIV-uninfected population with the same age structure and sex ratio (figure 3). Simulations for both populations show that in 2030, 27% of HIV-infected patients are expected to have three or more NCDs, compared with 19% of HIV-uninfected individuals (figure 3).

The increasing burden of NCDs will be driven by a steep increase in prevalence of cardiovascular disease, diabetes, and malignancies. In 2010, 19% of HIV-

| | Hazard ratio (95% CI) | Source |
|---|---|---|
| Myocardial infarction or stroke if diabetes | 2·31 (1·83–2·92) | Worm and colleagues 2009[24] |
| Myocardial infarction or stroke if hypertension | 1·26 (0·98–1·62) | Worm and colleagues 2009[24] |
| Myocardial infarction or stroke if hypercholesterolaemia | 1·41 (1·12–1·76) | Worm and colleagues 2009[24] |
| Chronic kidney disease if diabetes | 1·50 (1·05–2·16) | Mocroft and colleagues 2010[25] |
| Chronic kidney disease if hypertension | 1·69 (1·26–2·27) | Mocroft and colleagues 2010[25] |
| Hypertension if diabetes | 1·40 (1·19–1·64) | ATHENA data |
| Hypercholesterolaemia if diabetes | 1·12 (0·968–1·295) | ATHENA data |
| Hypertension if hypercholesterolaemia | 1·277 (1·16–1·397) | ATHENA data |

Hazard ratio gives ratio of risk for an individual developing a disorder in view of another underlying disorder compared with patients without another underlying disorder.

***Table 3*: Association between risk of an individual developing a new disorder, in view of current disorders**

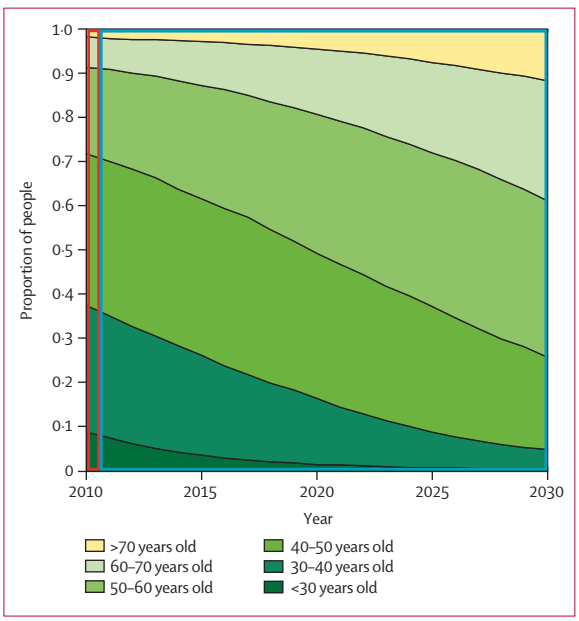


***Figure 2*: Projected age distribution of HIV-infected patients**
The red box shows the age distribution of patients on antiretroviral therapy in clinical care in the Netherlands in 2010, which matches the data exactly, and the blue box shows model output from 2011–30.

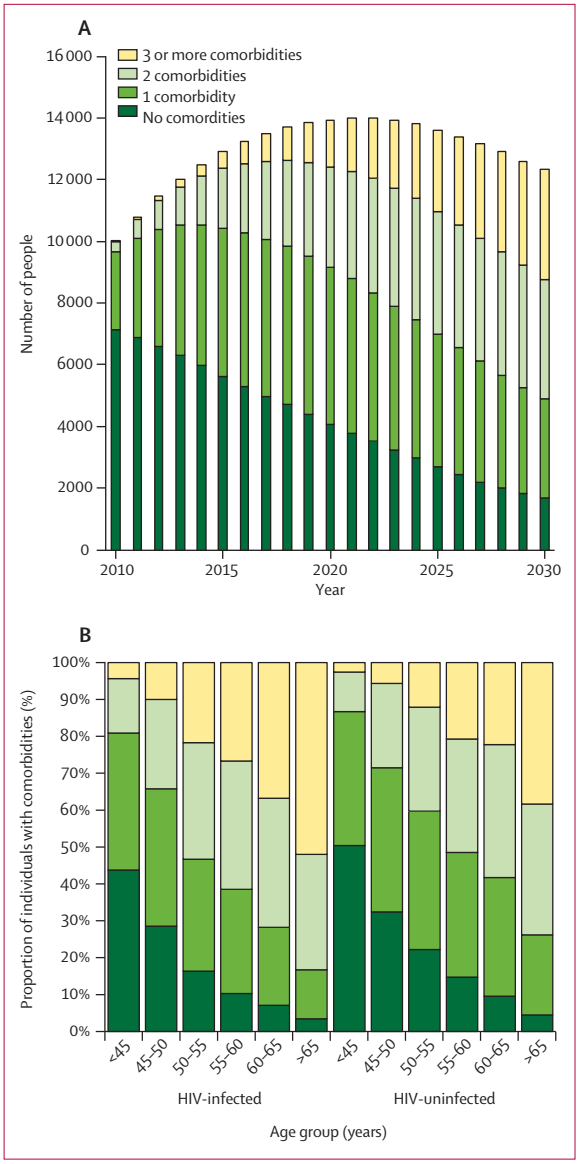


***Figure 3*: Predicted comorbitities**
(A) Predicted burden of NCDs in HIV-infected patients between 2010 and 2030 as simulated by the model. (B) Distribution of the number of NCDs by age group for HIV-infected and HIV-uninfected patients in 2030. NCD=non-communicable disease.

infected patients had been diagnosed with at least one cardiovascular disease, 4% with diabetes, and 2% with a non-AIDS disease, 4% had diabetes, and 2% had a non-AIDS malignancy. The model predicts that in 2030, 78% of patients will have been diagnosed with cardiovascular disease, 17% with diabetes, and 17% with malignancies.

One of the many consequences of an ageing population and increasing burden of NCDs will be an increase in polypharmacy. The model projects that in 2030, 54% of HIV-infected patients in clinical care will be taking at least one other long-term drug aside from their HIV drugs (up from 13% in 2010), and 20% of patients will be prescribed three or more co-medications (up from 5% in 2010; figure 4).

The increasing burden of polypharmacy will mainly be driven by cardiovascular drugs, in turn driven by the increasing burden of cardiovascular disease (figure 4). In the ATHENA cohort in 2010, 9% of HIV-infected patients were prescribed cardiovascular drugs. This proportion is predicted to increase to 50% in 2030, with patients prescribed both antidiabetic drugs and cardiovascular drugs expected to increase from 2% in 2010 to 7% in 2030.

The model predicts that the increasing burden of polypharmacy and NCDs could cause an increase in complications with first-line ART. We predict that the proportion of HIV-infected patients on ART who will

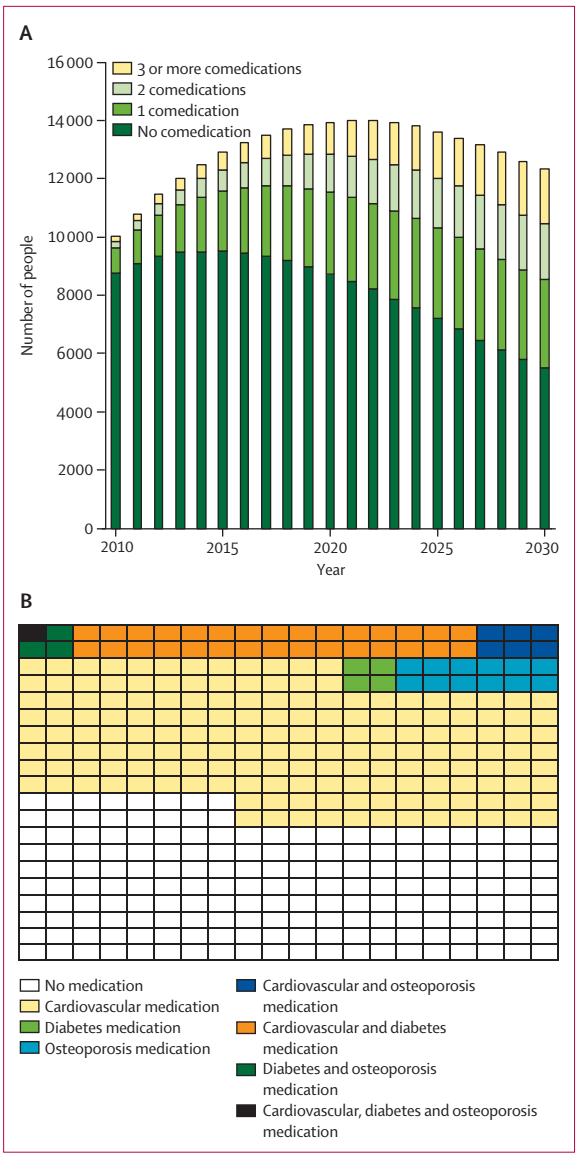


***Figure 4:*** **Predicted co-medications**
(A) Predicted burden of co-medications in HIV-infected patients between 2010 and 2030. (B) Predicted prevalence of comedication in 2030 as cross-section of number of patients on the different types of co-medications, based on a representative 400 patients (each square represents a patient). NCD=non-communicable disease.

experience drug–drug interactions or contraindications with any of the currently recommended first-line regimens will increase from 12% in 2010 to 53% in 2030. Additionally, 3% of patients in 2030 will be prescribed co-medication with as yet unknown drug–drug interactions, compared with 1% in 2010. Consequently, 40% of HIV-infected patients in clinical care in the Netherlands could experience some form of long-term complication with at least one of the currently recommended first-line ART regimens, and might need to switch to alternative ART regimens. Furthermore, 11% of HIV-infected patients in 2030 are projected to have potential problems with all of the currently recommended ART regimens. These complications will mainly be driven by an increase in the number of patients with chronic kidney disease (where tenofovir is contraindicated) and severe cardiovascular disease (where abacavir is contraindicated) and increased use of alendronic acid to treat osteoporosis.

## Discussion

The profile of patients in Europe infected with HIV is changing and this will have major implications for clinical care. In the Netherlands in 2030, almost three-quarters of patients on ART will be aged 50 years or older. This distribution will result in an increased burden of age-related NCDs (higher than that of uninfected individuals), increased burden of polypharmacy, and an increasing proportion of patients who might have potential complications with their HIV treatment. Improvements achieved in clinical care so far, in terms of mortality,[2,26] better tolerability of antiretroviral drugs and immunological and virological recovery of patients on ART,[1] could potentially be offset by an ageing HIV-infected population. We expect other European countries with HIV epidemics concentrated in men who have sex with men to face broadly similar trends to those we have projected for the Netherlands, although these will be modified by underlying lifestyle and other factors.

The ageing HIV-infected population will put new demands on the health-care systems, which will have important implications for the health of HIV-infected patients in clinical care.[3–5,27] Care management for HIV-infected individuals will increasingly need to draw on a wide range of medical disciplines, including geriatric medicine, cardiology, and oncology. Evidence-based changes to screening and monitoring protocols for NCDs in HIV-infected patients will be important to ensure continued high-quality care. HIV treatment and other guidelines are continuously evolving, and future guidelines will have to account for the changing demographics and complex changes in patient profiles and needs identified here.

Until recently, the ageing HIV-infected population has been largely ignored, with most randomised trials of ART excluding older patients or people with comorbid disease.[3] Consequently, many questions remain,[28] including those regarding the clinical care of ageing HIV-infected patients, tolerability of ART in patients with multiple morbidities, the effect of large pill burden on adherence and treatment outcome, pharmacodynamics and pharmacokinetics in older patients, and interactions between ART and coadministered drugs. Quantification of the scale and overall effect of this changing demography is an important step to tackle this challenge.

New drugs will be needed to fulfil the demand for increased numbers of antiretroviral drugs that can safely be given alongside co-medications, while maintaining high efficacy. Antiretroviral drugs with no drug–drug interactions with co-medications for the NCDs that will increase in prevalence during the next 20 years, including

drugs for osteoporosis, cardiovascular diseases, and diabetes, will be particularly important. For example, nucleoside reverse-transcriptase inhibitors are needed that can be used safely in first-line regimens for individuals with serious cardiovascular disease and chronic kidney disease, such as tenofovir alafenamide, which showed significantly reduced toxic effects in the liver and bone compared with tenofovir disoproxil fumarate in phase 2 clinical trials.[29] In terms of antiretroviral drugs that can be used as a third component in combination therapy, need is increasing for more antiretroviral drugs with high efficacy and good safety profiles—such as raltegravir and dolutegravir—that can safely be coadministered with co-medication such as osteoporosis drugs, cardiovascular drugs, and sulfonylurea derivatives to treat diabetes. New drug development will become increasingly important in view of the increasing burden of polypharmacy and a falling number of recommended highly effective first-line HIV-treatment regimen options that can be safely given to patients with multiple morbidities.

Our results comparing HIV-infected and HIV-uninfected individuals in 2030 mostly accord with those of the AGE$_h$IV study,[6] largely reproducing the different patterns of NCD burden reported for these two populations. However, the NCDs studied and diagnostic definitions used do differ somewhat between our study and theirs.[6] Our predictions about age structure are similar in outlook to those reported by Jansson and colleagues[30] in Australia, who constructed an individual-based stochastic geographically referenced model of HIV-infected people. They predicted that by 2020, 44% of HIV-infected people will be aged 55 years or older. By contrast, Cysique and colleagues[31] estimated that the proportion of HIV-infected individuals aged 60 years and older in Australia would only increase from 7% to 19% between 2009 and 2030. Because of different incidence projections, these estimates are lower than were those generated by our model (38%), despite similar age distributions at the start of the models.[31]

We believe that our results can be generalised to other high-income countries with mature epidemics predominantly in male populations and a history of good access to HIV care. The exclusion of pregnant women restricts the extent to which the results can be extrapolated to other populations, especially those in sub-Saharan Africa, which have large generalised epidemics. However, the trends towards an ageing HIV-infected population that are emerging in Australia and Europe, can broadly be expected to occur in Africa in the future: Hontelez and colleagues[32] have predicted that by 2040, the proportion of HIV-infected patients aged 50 years or older will be 25% in sub-Saharan Africa compared with 73% predicted in the Netherlands. The challenges in an African setting will vary substantially, especially where health-care systems are mainly providing episodic care for acute symptomatic conditions or services for maternal and infant health.[33,34]

The model captures the key factors that affect HIV clinical care, including major age-related NCDs, their common physiological pathways, and treatment. We based the parameterisation on the national ATHENA cohort, a non-selective dataset of all HIV-infected patients in clinical care in the Netherlands. Where the data were insufficient, we did an in-depth literature review, selecting, where possible, data from recent large international studies. The incorporation of common causal pathways allows us to model the natural aggregation of NCDs in patients. We did out-of-sample model checks that showed that the projections made by the model concurred with the ATHENA data, at least in the short term (appendix).

Despite these strengths, the model is limited by the fact that it does not represent all diseases that affect these populations. To the extent that NCDs have not been included, the model results will be conservative in its predictions of multimorbidity and polypharmacy. In particular, the model does not include neurocognitive disorders. We expect age-related neurocognitive disorders, such as late-onset Alzheimer's disease and Parkinson's disease to have little effect on model projections because they are rare, with a mean age of onset of about 74 and 61 years, respectively.[35,36] However, depression is the most prevalent neuropsychiatric complication in HIV-infected patients.[37] Depression has been reported[37,38] to reduce drug adherence and quality of life while increasing pill burden, drug–drug interactions, and mortality. Data for neurocognitive impairment are poorly collected in cohort studies but have important consequences for treatment outcome. Collection of these

***Panel:* Research in Context**

**Systematic review**

We searched PubMed for studies up to Aug 14, 2014, with the terms "HIV" and "ageing" or "aging", and "co-morbidity" or "non-communicable disease", and "model" or "modelling" or "modeling", in addition to "HIV" and "ageing" or "aging" and "model" or "modelling" or "modeling" with no language or date restrictions. We identified no studies that predicted the burden of non-communicable diseases, polypharmacy, or drug–drug interactions in HIV-infected patients in the future using any of these search terms. We identified several studies that predicted the age structure of patients infected with HIV beyond 2010.

In Australia, Jansson and colleagues[28] constructed an agent-based stochastic geographically referenced model of HIV-infected people, which predicted that by 2020, 44% of HIV-infected people will be aged 55 years or older. Hontelez and colleagues[30] predicted that in sub-Saharan Africa, this proportion will increase to about 25% by 2040. Additionally, Cysique and colleagues[29] predicted that the number of HIV-infected patients aged 60 years or older in Australia would increase from 7% in 2009 to 19% in 2030, paralleled by an increase in the number of patients who will have HIV-associated neurocognitive disorders and non-HIV dementia.[29]

**Interpretation**

To our knowledge, this is the first model that has quantified burden of disease and polypharmacy, in addition to demographic projections for a developed country with an ageing epidemic. The model captures the key factors affecting clinical care of HIV-infected patients, including the major age-related non-communicable diseases, their common physiological pathways, and their treatment.

data should be a priority in the context of the ageing HIV-infected population. In their model, Cysique and colleagues[31] further estimated that the number of HIV-infected individuals with HIV-associated neurocognitive disease would increase to 8·5%. Some other NCDs might remain undiagnosed or under-reported in observational cohorts and have therefore not been entered into the model. Furthermore, we did not explicitly model recurrent events of myocardial infarction or stroke.

In the absence of detailed data for heterogeneity of lifestyle factors (eg, diet, smoking, and exercise) or credible projections for how the prevalence of these factors will change with time, we assumed that their effect would be uniform in the population and constant with time, as already shown in the estimates from ATHENA data. A potential consequence of this assumption could be overestimation of the proportion of patients who have one or more NCDs if risk factors are confined to a small proportion of the population or the proportion of individuals with such risk factors would decline in the future. The model does not simulate the effect of individual antiretroviral drug use on the development of NCDs—eg, the reported association of abacavir with cardiovascular disease[39–41] or the association between specific protease inhibitors and tenofovir and osteoporosis.[13,42] Although disease caused by historical use of antiretroviral drugs will have been captured in the parameter estimates, we saw no evidence that the risk for development of NCDs differed between cohorts who started ART early (1996–2000) compared with those who started more recently (2006–10).

Finally, another aspect of clinical care that is difficult to represent in a model is the complex, multifactorial nature of prescribing practices. Treatment depends on a large number of factors, such as patient characteristics, compliance, and medical judgments made by clinicians, including those based on information and perceptions not recorded in patients' records. By necessity, the model had to make several assumptions (for example that prescribing co-medication is independent of age), but these should not prevent conclusions from being drawn about the long-term effect of polypharmacy. Our model projections rely on the assumption that clinical and demographic patterns will remain constant in the future. Any changes in clinical care, including guidelines recommending earlier treatment initiation, new first-line ART with reduced toxic effect and drug interaction profiles, or aggressive screening and monitoring protocols for NCDs and their risk factors, could reduce the burden of NCDs. If the future of clinical care changes the drivers of increased risk of NCDs in HIV-positive individuals (ie, inflammation, immune activation, and toxic antiretroviral drugs), the disease burden in future cohorts of HIV-infected populations will be more similar to that of the HIV-uninfected populations than these projections suggest. The model results can be updated if new data becomes available on some of these factors.

To our knowledge, this is the first modelling study quantifying the burden of age-related NCDs and polypharmacy, in addition to demographic projections, for a developed country with an ageing epidemic (panel).

#### Contributors

MS formulated the research question, did the data analysis for model parameterisation, constructed the model, interpreted the results and wrote the first draft of the manuscript. KB and SG advised on the medical aspects of the model construction and interpretation of the results. CS assisted with the data analysis of the ATHENA cohort. KT did a literature review to parameterise the common causal pathways of the model. AvS, FdW, and TBH contributed to the formulation of the research question and the interpretation of the data. All authors contributed to the redrafting of the manuscript and in the process of approving the final draft.

#### Declaration of interests

We declare no competing interests.

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