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ORIGINAL ARTICLE

# AIDS in the era of antiretroviral therapy: Changes in incidence rates and predictors of AIDS among people living with HIV under clinical care in Germany, a cohort study 1999–2018

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## Abstract

**Objectives:** This study examined the incidence rates and predictive utility of established prognostic factors for the progression to AIDS among people living with HIV under clinical care.

**Methods:** We used data from two observational cohorts of people living with HIV in Germany between 1999 and 2018. The outcome measure was the first AIDS-defining event that occurred during follow-up. Incidence rates (IRs) per 1000 person-years (PY) were calculated by years of follow-up and calendar periods. We used Cox models in our prediction analyses, including CD4 count, viral load, and age at baseline to estimate the predictive performance. Additionally, we included transmission mode to examine its predictive utility.

**Results:** A total of 23 299 people living with HIV were included in the analyses. Of these, 1832 developed a first AIDS event during follow-up, constituting an overall rate of 14.6/1000 PY (95% confidence interval [CI] 13.9–15.2). IRs were highest in the first year of follow-up (45.6/1000 PY, 95% CI 42.6–48.8) and then declined continuously. IRs were highest among people living with HIV who enrolled between 1999 and 2003 (36.1/1000 PY, 95% CI 32.6–40.0). A low CD4 count, high viral load, and older age at baseline increased the likelihood of progressing to AIDS. Adding transmission mode to the models did not improve the predictive performance.

**Conclusions:** The rates of a first AIDS event among people living with HIV have continuously declined in Germany. Health outcomes depend on a person's CD4 count, viral load, and age but not on transmission mode. To further

reduce the number of AIDS cases, the focus should be on groups more likely to present in progressed stages of their HIV infection.

KEYWORDS
AIDS, antiretroviral therapy, clinical surveillance, cohort study, HIV opportunistic infections, mode of transmission

## INTRODUCTION

Since its introduction in 1996, combination antiretroviral therapy (ART) has substantially improved the health outcomes of people living with HIV. It has led to a continuous decline in HIV-related morbidity and mortality worldwide [1, 2].

With the improvements in drug efficacy and safety, therapy recommendations were gradually amended over the years: until 2008, the European guidelines recommended treatment initiation generally not before a patient's CD4 cell count dropped below 200 cells/μL, which was then raised to 350 cells/μL [3, 4]. After the START and TEMPRANO trials demonstrated significant benefits of immediate initiation over deferred therapy in 2015 [5, 6], ART was recommended for all people living with HIV, irrespective of CD4 cell count [7]. As effective ART leads to viral suppression and eliminates the risk for onward sexual transmission [8], early treatment initiation is beneficial not only for individuals but also for populations at risk.

Even though HIV treatment has advanced considerably over time, is widely available in Germany and immune recovery can be achieved in most patients these days, AIDS-defining illnesses still occur in Germany [9, 10]. Around 15% of all new HIV infections are currently diagnosed at the stage of AIDS, and AIDS-defining conditions are also observed among people receiving treatment [9, 11, 12]. Several prognostic models to predict HIV-related morbidity and mortality have been developed and validated [13–17]. In a model derived from one of the largest data sources in the European and North American context by the ART Cohort Collaboration, predictors for AIDS and HIV-related mortality were a low CD4 cell count, high viral load (VL), older age, infection through drug use, and a previous AIDS-defining illness at therapy initiation [13, 14].

As the incidence of AIDS-defining illnesses has not been systematically examined in Germany, the objective of this study was to analyse the progression to AIDS among people living with HIV under clinical care in a large cohort study from 1999 to 2018. First, we aimed to examine changes in the rates of a first AIDS-defining event over time by years of follow-up and by calendar periods to assess how these relate to continuous clinical supervision and changes in ART and prescription guidelines. We also aimed to analyse predictors to identify people at higher risk. As the ART Cohort Collaboration model was developed more than a decade ago, we aimed to examine the predictive accuracy of these established contributors with current data. Moreover, we were interested in further analysing the predictive utility of transmission mode because it is a complex variable comprising a wide range of factors and findings about its role regarding HIV progression have repeatedly been conflicting [18, 19].

A better understanding of the rates and predictors and their changes over time can be used to inform clinicians and help to improve the public health response with regard to the goal of ending the AIDS epidemic as a public health threat by 2030 as postulated by the Joint United Nations Programme on HIV/AIDS [20].

## METHODS

### Study population and design

We used data from the HIV-1 Seroconverter Study and ClinSurv HIV Study, which are two multicentre, open, prospective long-term observational cohorts in Germany hosted at the Robert Koch Institute (RKI) [11, 12]. These were initiated in 1997 and 1999, respectively, as collaborations between HIV practitioners and the RKI for the clinical surveillance of people living with HIV. The datasets contain pseudonymised information on patient demographics, laboratory parameters, and clinical events from routine visits at the HIV practices. New information from the ClinSurv HIV and the HIV-1 Seroconverter cohorts is updated with the RKI every 6 and every 12 months, respectively. In the ClinSurv HIV cohort, people living with HIV with newly diagnosed or established HIV infections are eligible for inclusion. In the HIV-1 Seroconverter cohort, people living with HIV diagnosed during acute seroconversion or whose approximate time of infection is known on the basis of a negative HIV test within 3 years before diagnosis are eligible. The study designs have been described in detail elsewhere [11, 12]. In our analyses, we included people living with HIV aged

>18 years who enrolled in the cohorts between 1999 and 2018. To avoid immortal time bias, we excluded any available records prior to the HIV diagnosis or entry date in either of the two cohorts.

## Outcome

Our outcome was the progression to AIDS, which we defined as the first AIDS-defining event that occurred during follow-up. An AIDS-defining event was characterised by the occurrence of a clinical condition associated with AIDS according to the list of illnesses published by the Centers for Disease Control and Prevention [21]. As opposed to the expanded AIDS surveillance case definition [21], a CD4 cell count drop below 200 cells/μL was not defined as AIDS. Since data were recorded monthly, an AIDS-defining event can comprise a diagnosis of more than one AIDS-defining illness if these were recorded in the same month.

## Predictor selection

We selected predictors of the first AIDS-defining event based on the ART Cohort Collaboration prognostic model, which included CD4 cell count, VL, age, transmission through drug use, and a previous AIDS-defining illness at baseline [13, 14]. Where CD4 or VL values were missing, we used potentially available records within 3 months before or after the enrolment or diagnosis date. We categorised CD4 count into <50, 50–199, 200–499, and >500 cells/μL; VL into <50, 50–999, 1000–9999, 10 000–99 999, and >100 000 copies/mL; and transmission mode into men who have sex with men (MSM), people with heterosexual contact (HET), people who inject drugs (PWID), people from high-prevalence countries (PHPC), and other. PHPC comprise people living with HIV who migrated from countries with an HIV prevalence of >1% among adults aged 15–49 years. We treated age as a continuous variable. Since our endpoint was defined as the first AIDS-defining event developed under clinical care without prior progression to AIDS, we did not include AIDS at baseline as a predictor.

## Statistical analysis

Descriptive analyses of characteristics at baseline and at the first AIDS event during follow-up were performed. We computed person-time from baseline (month of cohort entry or month of HIV infection diagnosis for people living with HIV if diagnosis occurred after entry date) to the month of the first AIDS-defining event, loss-to-follow-up, death, or administrative censorship (31 December 2018). People living with HIV diagnosed with AIDS at baseline did not contribute person-time and were included in the descriptive analyses at baseline but excluded from the time-to-event analyses.

We calculated incidence rates (IRs) per 1000 person-years (PY) by years of follow-up in 5-year intervals to assess how these relate to continuous clinical care. We also calculated the IRs of the first year separately. To examine how potential changes over time relate to the changes in ART and prescription guidelines, we calculated IRs by calendar period (1999–2003, 2004–2008, 2009–2013, and 2014–2018), including only people living with HIV with entry or diagnosis dates during the respective period. For both IR calculations, we present transmission-mode-specific rates.

In our prediction analysis, we conducted complete case analyses using Cox proportional hazards regression models estimating regression coefficients and corresponding 95% confidence intervals (CIs). To evaluate the predictive utility of transmission mode, we examined whether adding transmission mode to a model consisting of CD4 count, VL, and age improved the predictive performance. Here, we split follow-up time into two separate 10-year follow-up periods (1999–2008 and 2009–2018) in which the models were run and assessed to account for the changes in drugs and prescription guidelines. We excluded the transmission groups "other" and "unknown" from the analyses due to sparse data and limited interpretability.

Predictive ability of the models was evaluated by several performance metrics: We assessed calibration by obtaining the calibration slopes to indicate the agreement between predicted and observed risks. As a measure of discrimination, we estimated Harrell's concordance index (C-index) to quantify how well the models discriminate between people living with HIV with different event times. In addition, we computed the Brier score at 5 years of follow-up as a measure of both discrimination and calibration. To account for potential overfitting, we selected bootstrap as our internal validation procedure and carried out bootstrapping at 500 replications. We calculated optimism-corrected estimates of performance ($p$) for each calibration slope, C-index, and Brier score using the formula $p_{\text{corrected}} = p_{\text{apparent}} - p_{\text{optimism}}$ [22].

All analyses were performed using Stata 17.0 (Stata Statistical Software: Release 17, USA).

## Sensitivity analyses

With regard to the IR calculations, we conducted sensitivity analyses to examine whether baseline characteristics of

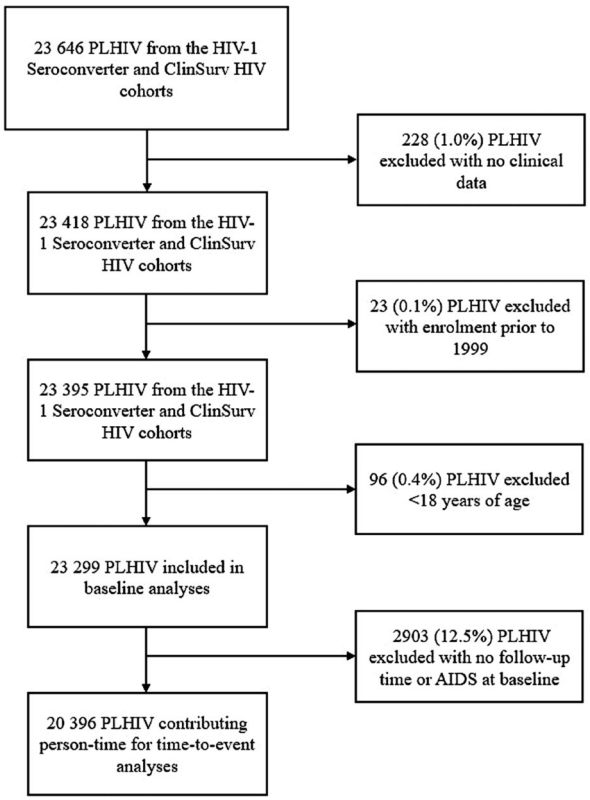


**FIGURE 1** Flowchart of people living with HIV (PLHIV) included in the analyses, selected from the German HIV-1 Seroconverter and ClinSurv HIV cohorts.

people living with HIV were comparable across the time periods. To check whether the models in our prediction analyses were affected by multicollinearity, we calculated the variance inflation factor to assess correlations between the predictor variables. We also repeated all time-to-event analyses with transmission mode stratified by gender (MSM, HET–male/female, PWID–male/female, PHPC–male/female) to examine potential gender differences and account for biases that might have been introduced by using a grouped variable.

## ETHICS STATEMENT

Ethical approval for the HIV-1 Seroconverter Study was granted by the ethics commission at the Charité – Universitätsmedizin Berlin (EA2/105/05). The ClinSurv HIV Study data from 1999 to 2018 were collected anonymously in compliance with the German Infection Protection Act (IfSG) as of 2001. As the data collection processes adhered to the legal requirements of the IfSG, no written informed consent was required. Approval was given by the data protection officer at the RKI and the Federal Commissioner for Data Protection and Freedom of Information.

**TABLE 1** Characteristics of people living with HIV at baseline.

| Characteristics | Result |
|---|---|
| Total | 23 299 (100.0%) |
| Age (years) | |
| Mean (SD) | 38.6 (10.9) |
| 18–29 | 5117 (22.0%) |
| 30–39 | 8263 (35.5%) |
| 40–49 | 6209 (26.6%) |
| 50–59 | 2647 (11.4%) |
| 60–69 | 866 (3.7%) |
| >69 | 197 (0.9%) |
| Gender | |
| Male | 18 407 (79.0%) |
| Female | 4892 (21.0%) |
| Transmission mode | |
| Men who have sex with men | 11 311 (48.6%) |
| People with heterosexual contact | 3230 (13.9%) |
| People who inject drugs | 1676 (7.2%) |
| People from high-prevalence countries | 3344 (14.4%) |
| Other | 193 (0.8%) |
| Unknown | 3545 (15.2%) |
| Origin | |
| Germany | 15 429 (66.2%) |
| Abroad | 7136 (30.6%) |
| Unknown | 734 (3.2%) |
| CD4 count (cells/μL) | |
| Mean (SD) | 365.0 (274.0) |
| <50 | 2423 (10.4%) |
| 50–199 | 4518 (19.4%) |
| 200–499 | 9027 (38.7%) |
| 500+ | 6036 (25.9%) |
| Missing | 1295 (5.6%) |
| Viral load (copies/mL) | |
| Mean (SD) | 229 963 (877 719) |
| <50 | 3258 (14.0%) |
| 50–999 | 1988 (8.5%) |
| 1000–9999 | 3271 (14.0%) |
| 10 000–99 999 | 6797 (29.2%) |
| 100 000+ | 6429 (27.6%) |
| Missing | 1556 (6.7%) |

*Note*: Numbers may not add up to 100% because of rounding.
Abbreviations: SD, standard deviation.

# RESULTS

## Study population characteristics

A total of 23 299 people living with HIV were included in the baseline analyses (Figure 1). Almost half of these were MSM (48.6%), followed by PHPC (14.4%), HET (13.9%), and PWID (7.2%). We present all baseline characteristics in Table 1. A first AIDS-defining event was recorded for 4475 people living with HIV, of whom 1832 developed the event during follow-up and 2643 were diagnosed at baseline. People living with HIV with AIDS at baseline were included in the descriptive baseline analyses (Table 1) but excluded from all further analyses. Mean age at the first AIDS event developed during follow-up was 42 years. Mean CD4 cell count and VL were 249.9 cells/μL and 162 855 copies/mL, respectively (Table S1, Additional file 1). At the time of the first AIDS-defining event during follow-up, 9.2% were not receiving ART, 16.0% had initiated ART within the month of the event, 23.9% had taken ART continuously for 1–6 months, 6.9% for 7–12 months, and 25.2% for more than a year. The AIDS-defining illnesses observed most often were oesophageal candidiasis (17.4%), pneumocystis-jirovecii-pneumonia (12.8%), and wasting syndrome (10.4%) (Table S1, Additional file 1).

## Incidence rates

A total of 20 396 people living with HIV contributed person-time (Figure 1) and were followed up for a median of 5.4 years (range 1 month to 19.9 years). In total, 1832 first AIDS-defining events were recorded during follow-up, constituting an overall rate of 14.6 (95% CI 13.9–15.2) AIDS events per 1000 PY between 1999 and 2018. The median time from baseline to AIDS progression was 17 months (range 1 month to 18.3 years).

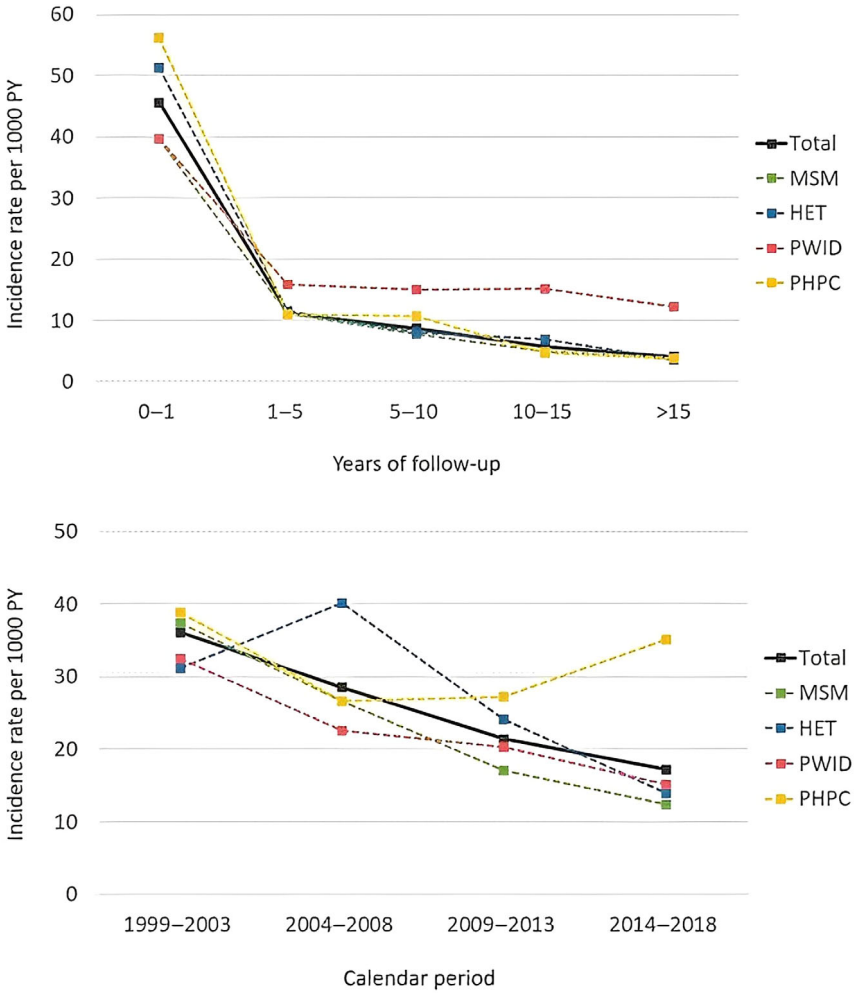


**FIGURE 2** Incidence rates of the first AIDS event per 1000 person-years (PY) by years of follow-up (upper chart) and by calendar period (lower chart). MSM, men who have sex with men; HET, people with heterosexual contact; PWID, people who inject drugs; PHPC, people from high-prevalence countries.

We observed the highest IRs during the first year of follow-up with a rate of 45.6/1000 PY (95% CI 42.6–48.8), which declined substantially to 11.2/1000 PY (95% CI 10.3–12.1) between 1 and 5 years and then further decreased to 4.1/1000 PY (95% CI 2.4–6.9) after 15 years of follow-up (Figure 2 and Table 2). This pattern was observed among all transmission groups except for PWID, whose IRs dropped after the first year but then stagnated and only declined again after 15 years of follow-up to a rate of 12.3/1000 PY (95% CI 4.6–32.8), remaining higher than all other groups (Figure 2 and Table 2). The results of the IRs stratified by calendar period showed that the rates decreased continuously from 36.1/1000 PY (95% CI 32.6–40.0) between 1999 and 2013 to 17.2/1000 PY (95% CI 14.6–20.4) in the latest period between 2014 and 2018 (Figure 2 and Table 3). With regard to the transmission-mode-specific IRs, this decline was observed among all groups except for PHPC, whose rates increased again to 35.1/1000 PY (95% CI 26.0–47.3) in the latest period (Figure 2 and Table 3).

Our sensitivity analyses showed that baseline characteristics were comparable across all time periods. We observed minor disparities in the proportion of people living with HIV with a VL of <50 copies/mL, which rose

**TABLE 2** Incidence rates of the first AIDS event per 1000 person-years by years of follow-up.

| Years of follow-up | Events | Person-years | Incidence rate (95% CI) |
|---|---|---|---|
| 0–1 | 828 | 18168.2 | 45.6 (42.6–48.8) |
| 1–5 | 583 | 52082.1 | 11.2 (10.3–12.1) |
| 5–10 | 315 | 36335.3 | 8.7 (7.8–9.7) |
| 10–15 | 92 | 15784.3 | 5.8 (4.8–7.2) |
| >15 | 14 | 3441.3 | 4.1 (2.4–6.9) |
| Transmission mode[a] | | | |
| Men who have sex with men | | | |
| 0–1 | 360 | 9090.7 | 39.6 (35.7–43.9) |
| 1–5 | 293 | 26405.9 | 11.1 (9.9–12.4) |
| 5–10 | 140 | 18268.7 | 7.7 (6.5–9.0) |
| 10–15 | 39 | 7765.8 | 5.0 (3.7–6.9) |
| >15 | 6 | 1639.5 | 3.7 (1.6–8.2) |
| People with heterosexual contact | | | |
| 0–1 | 128 | 2496.8 | 51.3 (43.1–61.0) |
| 1–5 | 85 | 7357.9 | 11.6 (9.3–14.3) |
| 5–10 | 43 | 5343.3 | 8.0 (6.0–10.9) |
| 10–15 | 16 | 2322.9 | 6.9 (4.2–11.1) |
| >15 | 2 | 549.1 | 3.6 (0.9–14.6) |
| People who inject drugs | | | |
| 0–1 | 53 | 1337.9 | 39.6 (30.3–51.9) |
| 1–5 | 62 | 3898.8 | 15.9 (13.0–20.4) |
| 5–10 | 43 | 2863.3 | 15.0 (11.1–20.3) |
| 10–15 | 20 | 1319.3 | 15.2 (9.8–23.5) |
| >15 | 4 | 324.7 | 12.3 (4.6–32.8) |
| People from high-prevalence countries | | | |
| 0–1 | 146 | 2600.1 | 56.2 (47.7–66.0) |
| 1–5 | 83 | 7571.2 | 11.0 (8.8–13.6) |
| 5–10 | 59 | 5492.5 | 10.7 (8.3–13.9) |
| 10–15 | 12 | 2537.4 | 4.7 (2.7–8.3) |
| >15 | 2 | 513.0 | 3.9 (1.0–15.6) |

Abbreviation: CI, confidence interval.

[a]Transmission groups "other" and "unknown" are not presented due to sparse data and limited interpretability.

**TABLE 3** Incidence rates of the first AIDS event per 1000 person-years by calendar period.

| Calendar period | Events[a] | Person-years[a] | Incidence rate (95% CI) |
|---|---|---|---|
| 1999–2003 | 369 | 10208.0 | 36.1 (32.6–40.0) |
| 2004–2008 | 335 | 11737.7 | 28.5 (25.6–31.8) |
| 2009–2013 | 251 | 11737.8 | 21.4 (18.9–24.2) |
| 2014–2018 | 139 | 8061.2 | 17.2 (14.6–20.4) |
| Transmission mode[b] | | | |
| Men who have sex with men | | | |
| 1999–2003 | 174 | 4654.8 | 37.4 (32.2–43.4) |
| 2004–2008 | 158 | 5941.9 | 26.6 (22.8–31.1) |
| 2009–2013 | 106 | 6230.9 | 17.0 (14.1–20.6) |
| 2014–2018 | 49 | 3953.8 | 12.4 (9.4–16.4) |
| People with heterosexual contact | | | |
| 1999–2003 | 44 | 1412.2 | 31.2 (23.2–41.9) |
| 2004–2008 | 66 | 1641.2 | 40.2 (31.6–51.2) |
| 2009–2013 | 41 | 1700.4 | 24.1 (17.8–32.8) |
| 2014–2018 | 14 | 1004.7 | 13.9 (8.3–23.5) |
| People who inject drugs | | | |
| 1999–2003 | 44 | 1354.2 | 32.5 (24.2–43.7) |
| 2004–2008 | 22 | 974.0 | 22.6 (14.9–34.3) |
| 2009–2013 | 13 | 640.7 | 20.3 (11.8–34.9) |
| 2014–2018 | 4 | 265.0 | 15.1 (5.7–40.2) |
| People from high-prevalence countries | | | |
| 1999–2003 | 61 | 1571.3 | 38.8 (30.2–49.9) |
| 2004–2008 | 49 | 1840.2 | 26.6 (20.1–35.2) |
| 2009–2013 | 41 | 1509.5 | 27.2 (20.0–36.9) |
| 2014–2018 | 43 | 1226.5 | 35.1 (26.0–47.3) |

Abbreviation: CI, confidence interval.

[a]Only events and person-years from people living with HIV with entry or HIV diagnosis dates during the respective calendar period were included in the incidence rate calculations.

[b]Transmission groups "other" and "unknown" are not presented due to sparse data and limited interpretability.

**TABLE 4** Apparent and optimism-corrected[a] model performance statistics for the comparison of $Model_{noTM}$ and $Model_{TM}$.

| | Calibration slope apparent/ corrected | C-index apparent/ corrected | Brier score[b] apparent/ corrected |
|---|---|---|---|
| Period 1999–2008 | | | |
| $Model_{noTM}$ (CD4, VL, age) | 1.00/0.923 | 0.649/0.641 | 0.114/0.138 |
| $Model_{TM}$ (CD4, VL, age, transmission mode) | 1.00/0.894 | 0.648 0.637 | 0.114/0.138 |
| Period 2009–2018 | | | |
| $Model_{noTM}$ (CD4, VL, age) | 1.00/0.946 | 0.736/0.725 | 0.040/0.053 |
| $Model_{TM}$ (CD4, VL, age, transmission mode) | 1.00/0.924 | 0.748/0.732 | 0.040/0.053 |

Abbreviations: VL, viral load.

[a]Optimism-corrected performance measures were calculated by subtracting the estimated average optimism after 500 bootstrap replications from the apparent performance statistic (i.e., the naïve performance metric derived from the original dataset).

[b]The Brier score was calculated at 5 years of follow-up.

from 9.3% between 1999 and 2003 to 25.3% between 2014 and 2018 (Tables S2–S5, Additional file 2). In our gender sensitivity analyses, we found higher rates after 15 years of follow-up mainly among female PWID, and higher rates in the latest calendar period between 2014 and 2018 mainly among male PHPC (Tables S6–S7, Additional file 3).

## Predictive performance

The performance measures of the multivariable Cox regression models to predict a first AIDS-defining event showed that in the first follow-up period (1999–2008), $Model_{noTM}$ (CD4, VL, age) and $Model_{TM}$ (CD4, VL, age, transmission mode) performed similarly in terms of calibration and discrimination (Table 4). Both models were well calibrated, with optimism-corrected calibration slopes close to 1, confirming agreement between predicted and observed risks. With regard to discrimination, we obtained modest optimism-corrected C-indices with values of 0.641 ($Model_{noTM}$) and 0.637 ($Model_{TM}$), showing that failure times until the first AIDS event were correctly ordered for pairs of people living with HIV 64.1% and 63.7% of the time. Furthermore, we obtained optimism-corrected Brier scores of 0.138 in both models, which showed that the average squared distances between the observed event status and predicted risks were under 0.25, indicating satisfactory overall predictive accuracy.

When run in the second follow-up period (2009–2018), both models demonstrated better predictive performance than in the first follow-up period (Table 4). Optimism-corrected C-indices of 0.725 in $Model_{noTM}$ and 0.732 in $Model_{TM}$, calibration slopes close to 1 and Brier scores of 0.053 in each model were obtained, showing that the predictive performance was again almost identical in both models. Overall, we observed little model overfitting, which was reflected in the similar apparent and optimism-corrected performance metrics (Table 4). Similar results were obtained in our sensitivity analyses in which transmission mode was further stratified by gender (Table S8, Additional file 3).

## Predictors

In all models, we observed significant predictive associations of CD4 count, VL, and age with the outcome: The lower the CD4 cell count at baseline, the higher the likelihood of developing a first AIDS event, with CD4 counts below 50 cells/μL contributing the most (Tables S11–S14, Additional file 4). Similarly, each additional year of age at baseline was associated with an increased likelihood of progression to AIDS. With regard to VL, values of more than 100 000 copies/mL at baseline contributed the most to an increased likelihood in both 10-year follow-up periods. Although we observed a significant individual predictive association of the transmission group PHPC in the second follow-up period (Table S14, Additional file 4), this did not translate into an overall better predictive performance of $Model_{TM}$ compared with $Model_{noTM}$.

We observed comparable results in the sensitivity analyses on gender (Tables S9–S10, Additional file 3). In our analyses on multicollinearity, we obtained variance inflation factors near 1 for all models, indicating only very weak correlations between the predictor variables with hence no substantial effect on the precision of the estimated coefficients (Table S15, Additional file 5).

# DISCUSSION

This study investigated the IRs and predictors of the progression to AIDS among people living with HIV under clinical care in Germany between 1999 and 2018. We found that the IRs of a first AIDS-defining event were highest in the first year of follow-up, then dropped substantially and continued to decline. With regard to calendar periods, the rates during the first years of follow-up were highest among people living with HIV who enrolled between 1999 to 2003 and then decreased continuously over time, with the lowest rates between 2014 and 2018. Our prediction analyses showed that the established predictors of disease progression, i.e., a low CD4 count, high VL, and older age at baseline, were predictive in both 10-year follow-up periods, with better predictive performance in the later period. However, the inclusion of transmission mode did not improve predictive accuracy, suggesting that when CD4 count, VL, and age are available, knowledge about a person's transmission mode does not confer any additional predictive benefit. This finding has important implications for the clinical setting, suggesting that – in the presence of these three variables – information on transmission mode might not be necessary for clinicians to prognosticate disease progression.

Our main findings with regard to the IRs are consistent with other studies in the Western European and North American context, which showed that the rates of AIDS-defining opportunistic infections among people living with HIV have continuously declined since the advent of effective ART [23–25]. As we observed this decline over the course of both follow-up and calendar periods, our findings also build on existing evidence that the decreasing rates can be attributed to both consistent clinical supervision and improved ART regimens,

together with adapted guidelines recommending earlier treatment [26–29].

When comparing IRs between transmission groups, our analyses of the unadjusted rates showed that PWID had a slower and less pronounced decline over the entire course of clinical care, and PHPC who enrolled in the latest calendar period had substantially higher rates during their first years than those in the other groups. The higher rates among PWID could be related to poorer therapy access and adherence as well as generally worse health conditions among people in this group, which has also been reported by previous studies [29–32]. Similarly, it was found that PHPC are more often diagnosed in advanced stages and also present with higher rates of comorbid illnesses [33, 34], potentially resulting from obstacles such as limited access to healthcare and socioeconomic challenges, rendering PHPC more vulnerable to disease progression [35]. The fact that an increasing number of migrants from high-prevalence countries was registered in Germany after 2013 [36] might explain the higher IRs between 2014 and 2018 in this group. During this time, HIV screenings and medical care were increased especially for PHPC [36].

Across all transmission groups, the rates in the initial year of follow-up were highest. This may reflect that the risk for opportunistic infections is not immediately lower but only decreases with continuous ART and the achievement of a durably undetectable VL [37]. Another explanation might be the development of the immune reconstitution inflammatory syndrome (IRIS), a hyperinflammatory reaction that usually manifests within the first 4–8 weeks after starting ART and that can give rise to opportunistic infections [38, 39]. Even though the exact overall incidence and pathogenesis of IRIS remains elusive, our findings are reconcilable with this phenomenon.

The results of our prediction analyses are partially consistent with the findings of the ART Cohort Collaboration [13, 14]. Although our results confirmed that the combination of CD4 count, VL, and age at baseline was predictive of disease progression, transmission mode did not improve predictive performance in our analyses, suggesting that the observed differences across the transmission groups hinged on these variables. We assume that this inconsistent finding can mostly be attributed to methodological differences. In addition to longer follow-up periods, we did not include AIDS at baseline as a predictor, which might have changed the combination of independent predictors and overall model performance. As transmission mode is a proxy for a wide range of associated factors, we presume that the generally observed inconsistent findings across previous literature result from different variables included in the analyses as well as different methodological frameworks, i.e., whether a predictive or causal approach was chosen for the analyses.

Our results provide new insights into the changes in predictive utility of the established predictors over time. The predictive performance of the models was better in the latter period (2009–2018), showing that CD4 count, VL, and age at baseline have become better predictive factors for the further course of treatment. This allows for the assumption that with improved ART efficacy, treatment initiation irrespective of CD4 cell count, and fewer side effects, health outcomes depend even more on a person's condition at baseline than they did in the early days of ART.

Overall, our findings suggest that the public health response working towards the goal of 'ending the AIDS epidemic' [20] should mainly focus on people living with HIV who present late. Seeing that more than half of all AIDS-defining events were diagnosed at baseline, early detection of HIV and timely therapy commencement are pivotal to reducing the number of AIDS cases. This is corroborated by the finding that low CD4 counts and high VLs at therapy initiation, both indicators of advanced HIV infections [40], together with older age were predictive of disease progression. Here, public health efforts should continue to address various barriers to testing, especially among populations who are more often diagnosed in progressed stages, focusing on increasing HIV awareness and reducing stigma-related fears and misconceptions about HIV [34, 41–43]. Moreover, we recommend that support structures to strengthen therapy adherence and general health are increased for people living with HIV presenting in advanced stages.

## Strengths and limitations

Strengths of our study include the large number of people living with HIV and the long observation time, capturing almost the entire period of treatment with ART since its introduction in Germany. Our findings can therefore be regarded as informative for Germany and other countries with similar demographics in terms of HIV prevalence and ART coverage.

Some limitations of our study should also be considered. These include the common limitations of cohort studies, such as loss to follow-up. Dropouts could have switched practitioners or stopped therapy during that time, potentially resulting in missed outcomes and attrition bias. As our data were derived from routine consultations at the practices, another limitation is that the frequency depended on the patients' decision to seek medical care. Some people living with HIV therefore had

more extensive follow-ups than others. In addition, the HIV practices participating in the data collection are mostly specialised centres with a higher proportion of people living with HIV presenting in progressed stages than the overall population of people living with HIV [11]. Our calculated IRs might therefore be somewhat higher than those that would have been observed in the entire population of people living with HIV in Germany.

## CONCLUSIONS

Our study found that the IRs of a first AIDS-defining condition among people living with HIV under clinical care have continuously decreased in Germany between 1999 and 2018. People with low CD4 counts, high VLs, and older age had an increased likelihood of progressing to AIDS. These predictors showed better predictive utility in the later study period. Information on transmission mode did not improve the predictive ability and may therefore not be an additionally useful variable in the clinical context. Our findings suggest that the German public health response working towards the goal of ending AIDS should mainly focus on groups more likely to present in progressed stages of their HIV infection.

### AUTHOR CONTRIBUTIONS

Annemarie Pantke, Uwe Koppe, Barbara Gunsenheimer-Bartmeyer, and Viviane Bremer designed the study. Christian Kollan merged the cohort data and assisted in the preparation and interpretation of the data. Tobias Kurth provided guidance with regard to the methodological conception of the study and supported the data analyses. Annemarie Pantke and Uwe Koppe coordinated the study and performed the analyses. Björn-Erik Ole Jensen, Christoph Stephan, Olaf Degen, and Dirk Schürmann are HIV clinicians who contributed to the data collection and assisted in the interpretation of the results. Annemarie Pantke drafted the manuscript, and all authors contributed to discussing and revising the draft. All authors read and approved the final manuscript.

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## CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests with the specific matter of the manuscript. Outside the submitted work, Tobias Kurth reports having received research grants from the Gemeinsamer Bundesausschuss (G-BA–Federal Joint Committee, Germany) and from the Bundesministerium für Gesundheit (BMG–Federal Ministry of Health, Germany). He has also received personal compensation from Eli Lilly & Company, Teva Pharmaceuticals, TotalEnergies S.E., the BMJ, and Frontiers. Outside the submitted work, Uwe Koppe reports having received research grants from the Bundesministerium für Gesundheit (BMG–Federal Ministry of Health, Germany) and from the Gemeinsamer Bundesausschuss (G-BA–Federal Joint Committee, Germany).

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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