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Incidence of a first venous thrombotic event in people with HIV in the Netherlands: a retrospective cohort study

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Summary

Background The risk of venous thrombotic events is elevated in people with HIV, but overall risk estimates and estimates specific to immune status and antiretroviral medication remain i mprecise. In this study, we aimed to estimate these parameters in a large cohort of people with HIV in the Netherlands.

Methods In this retrospective cohort study, we used the Dutch ATHENA cohort to estimate crude, age and sex standardised, and risk period-specific incidences of a first venous thrombotic event in people with HIV aged 18 years or older attending 12 HIV treatment centres in the Netherlands. Crude and standardised incidences were compared with European population-level studies of venous thrombotic events. We used time-updated Cox regression to estimate the risk of a first venous thrombotic event in association with HIV-specific factors (CD4 cell count, viral load, recent opportunistic infections, antiretroviral medication use) adjusted for traditional risk factors for venous thrombotic events.

Findings With data collected from Jan 1, 2003, to April 1, 2015, our study cohort included 14 389 people with HIV and 99 762 person-years of follow-up, with a median follow-up of 7·2 years (IQR 3·3–11·1). During this period, 232 first venous thrombotic events occurred, yielding a crude incidence of 2·33 events per 1000 person-years (95% CI 2·04–2·64) and an incidence standardised for age and sex of 2·50 events per 1000 (2·18–2·82). CD4 counts less than 200 cells per µL were independently associated with higher risk of a venous thrombotic event: adjusted hazard ratio (aHR) 3·40 (95% CI 2·28–5·08) relative to counts of 500 cells per µL. A high viral load (aHR 3·15, 95% CI 2·00–5·02; >100 000 copies per mL *vs* <50 copies per mL) and current or recent opportunistic adverse events (2·80, 1·77–4·44) were also independently associated with higher risk of a venous thrombotic event. There were no associations between any specific antiretroviral drugs and risk of a venous thrombotic event. Rates associated with pregnancy (9·4, 95% CI 4·6–17·3), malignancy (16·7, 10·6–25·1), and hospitalisation (24·4, 19·1–30·6) were lower than primary thromboprophylaxis thresholds suggested by the respective guidelines.

Interpretation Our findings support neither prescribing primary outpatient thromboprophylaxis nor avoiding any type of antiretroviral medication in people with HIV at high risk of a venous thrombotic event.

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Introduction

In various clinical settings, HIV infection has been associated with a two to ten times increased risk of venous thrombotic events.[1,2] This association is consistent with the epidemiology of these events in other infectious and inflammatory, or autoimmune, conditions.[3–6] Laboratory studies of coagulation in people with HIV have shown evidence of a hypercoagulable state,[7,8] further implicating HIV infection and its sequelae as a cause of venous thrombotic events. However, controversy remains about the magnitude to which the course of an HIV infection and its treatment can lead to venous thrombotic events.

The guidelines recommending treating people with HIV as soon as possible are built on the prevention of acquired immune deficiency, characterised by declining CD4 cell count, ongoing immune activation, and, consequently, HIV-related sequelae.[9,10] In view of the well established relation between immune activation and coagulation, the risk of a venous thrombotic event might decline with increasing CD4 cell count. However, data published thus far do not support this association: laboratory studies have shown only partial reversion of hypercoagulability in people with HIV who started combination antiretroviral therapy (ART).[11,12] Additionally, the largest cohort study[2] to date, of 4333 people with HIV in Denmark, showed an absolute incidence of 3·2 venous thrombotic events per 1000 person-years and a relative risk of 3·84 for people with HIV who did not use intravenous drugs compared with that of matched controls. However, the study[2] did not provide sufficient statistical evidence for a venous thrombotic event incidence difference when dichotomising the CD4 count at 200 cells per µL (adjusted rate ratio 1·53, 95% CI 0·83–2·84). However, in the aforementioned laboratory studies, people with HIV with full immune reconstitution were underrepresented. Also, the wide 95% CI in the Danish study could suggest low statistical power.

Research in context

Evidence before this study

HIV infection has been associated with an elevated risk of venous thrombotic events. We searched PubMed with the terms "('HIV'[Mesh] OR 'HIV'[tiab]) AND ('venous thrombosis'[Mesh] OR 'venous thromboembolism'[Mesh] OR 'pulmonary embolism'[Mesh] OR thrombo*[tiab])" as syntax, for papers published up to Nov 30, 2017, with no language restrictions. We found several studies assessing both coagulation parameters and the risk of a venous thrombotic event in people with HIV. These studies gave wide relative risk estimates (two to ten times) in people with HIV for the risk of venous thrombotic events and contradictory results on whether immune status (mainly represented by CD4 cell count) or antiretroviral medication use (particularly protease inhibitors) influenced coagulation parameters and the risk of venous thrombotic events. Many studies were limited because of their cross-sectional design, and one large-scale cohort study, analysing the risk of venous thrombotic events in 4333 ambulatory people with HIV, still seemed to have limited power. Additionally, data on risk of venous thrombotic events for people with HIV after 2008 are scarce. Therefore, the available data have important internal (methodological) and external (generalisability) validity issues, leaving room for improvement. Finally, whether the risk of a venous thrombotic event in people with HIV exposed to major risk factors for these events exceeds guideline thromboprophylaxis thresholds is unknown.

Added value of this study

We assessed the incidence of venous thrombotic events in a large, representative sample of people with HIV from the Dutch ATHENA cohort. To our knowledge, this was the largest study on venous thrombotic events in people with HIV to date, including both people with recently diagnosed HIV infections and people with HIV ageing stably with suppressed viral loads and reconstituted immune systems on antiretroviral medication. We took special care to adjust for known major risk factors of venous thrombotic events and tested our main findings in sensitivity analyses. Contrary to previous studies, our study showed clear associations between immune deficient states and virus activity and the risk of venous thrombotic events. Moreover, the risk of a venous thrombotic event in people with HIV who have normalised CD4 cell counts was close to that in the general population.

Implications of all the available evidence

The risk of a venous thrombotic event in people with HIV is elevated. Our study highlights a major influence of uncontrolled HIV infection, especially when cellular immunity is compromised, on the risk of a venous thrombotic event in people with HIV. This influence further emphasises the importance of adequately controlling HIV infection. Additionally, our results do not support the position that some antiretroviral drug classes are contraindicated for people with HIV with a high risk of venous thrombotic events. HIV infection, by itself, is not an indication to consider primary thromboprophylaxis in pregnancy, malignancy, or during or after hospitalisation. The observed venous thrombotic events in these subgroups were sparse and too infrequent to study the risk of a venous thrombotic event in people with HIV with both immune deficiency and exposure to these traditional risk periods for venous thrombotic events.

Studies have also shown striking inconsistencies concerning the effects of antiretroviral medication on the risk of a venous thrombotic event, particularly protease inhibitors.[2,13–15] Additionally, abacavir exposure has been associated with cardiovascular disease,[16] potentially by altering platelet adhesion,[17] and thus, might also influence the risk of venous thrombotic events. Indeed, some studies have associated ART in general with a higher risk of venous thrombotic events, whereas other studies have not. These inconsistencies might arise from confounding by indication: almost all studies took place in the first decade of ART, when starting ART was mainly driven by the clinical risk of developing AIDS-defining illnesses, which are, clinically speaking, venous thrombotic event risk periods. These associations have clear practical implications, because clinicians might perceive specific antiretroviral drugs to be contraindicated in people with HIV with high risk of venous thrombotic events.

The reported association between HIV and venous thrombotic events raises the question of whether HIV interacts with known risk factors to cause an exceedingly high risk of such events. Several clinical situations have been designated as settings in which physicians should consider outpatient primary thromboprophylaxis: pregnancy, malignant disease, and discharge after hospitalisation.[18–22] It is of clinical interest to estimate the risk of venous thrombotic events for people with HIV in these situations. We aimed to investigate these uncertainties in a cohort of people with HIV in the Netherlands.

Methods

Study design

We used the infrastructure of the ongoing, long-term ATHENA Dutch National HIV prospective cohort. Details of this cohort have been described elsewhere.[23] In short, clinical data for ATHENA are collected prospectively from consenting people with HIV in care in the Netherlands. These include information on both HIV-specific data (antiretroviral medication use, immunology markers, viral load, and active infections) and data on selected medications and medical complications.

For logistical reasons, our study was done in 12 of 26 HIV treatment centres in the Netherlands, which were visited by two data collectors specifically trained to validate venous thrombotic events. For efficiency reasons, we selected centres that cared for a large number of people with HIV, but we also ensured that these centres covered the Netherlands spatially. The selected centres care for about 70% of the total people with HIV in care in the Netherlands (a map displaying participating centres is shown in the appendix p 1).

Venous thrombotic events were not routinely captured as an adverse event in ATHENA. However, use of anticoagulants has been prospectively recorded in ATHENA since January, 2003. Therefore, we developed a case finding strategy for venous thrombotic events by use of the registered use of anticoagulants and stated cause of death. In ATHENA, a (probable) cause of death must be defined by a treating physician if an autopsy report is not available. In the absence of an autopsy report, pulmonary embolism was adjudicated if the treating physicians suspected it to be the leading cause of death. We also searched non-fatal venous thrombotic events by selecting for chart review people with HIV with registered anticoagulant use (designated Anatomical Therapeutic Chemical codes; appendix p 2) up to April 1, 2015, to determine the indication for anticoagulant use. A venous thrombotic event was counted as definite if a relevant radiology report was available (ultrasound, venography, CT scan, or ventilation-perfusion scan) or if a discharge letter cited such a radiology report mentioning a specific anatomical location (femoral vein thrombosis was considered specific, whereas deep venous thrombosis or leg thrombosis were not considered sufficiently specific). If records were not specific enough, a venous thrombotic event was counted as probable if anticoagulation use was documented at least 3 months after the event. In a pilot study, this case-finding strategy yielded a summarised 95% sensitivity compared with two reference data sources of people with HIV who had a venous thrombotic event from two participating centres. This strategy was thus deemed sufficiently reliable.

Procedures and participants

For the primary analyses, we estimated incidences of a first definite or probable venous thrombotic event diagnosis in the following locations: extremity deep venous thrombosis (popliteal, more proximal and subclavian veins, or more proximal), pulmonary embolism, and thrombosis of the jugular, splanchnic, caval, or cerebral veins. For the secondary analyses, we estimated incidences of unprovoked and provoked venous thrombotic events separately. A venous thrombotic event was counted as provoked if any of the following factors were present: cancer diagnosis, or active treatment thereof (basal and squamous skin cell carcinomas were excluded), in the 180 days before diagnosis of a venous thrombotic event; or surgery, pregnancy or puerperium (up to 90 days after childbirth), oestrogen use, fractures of extremities requiring a plaster cast, or immobilisation for longer than 3 days occurring in the 90 days before diagnosis of a venous thrombotic event.

Because the use of anticoagulants was registered in the ATHENA database from January, 2003, onwards, and anticoagulation therapy duration, at that time in the Netherlands, was generally 6 months for a first venous thrombotic event, the earliest theoretically detectable venous thrombotic event by our targeted case-finding strategy would have been on July 1, 2002. This was consequently defined as the index date for all people with HIV who were already enrolled in ATHENA before Jan 1, 2003. For people with HIV who enrolled in ATHENA after this date, the index date was set at 6 months before the date of their first visit to an HIV treatment centre.

See Online for appendix

Participants were censored at occurrence of a first definite or probable venous thrombotic event diagnosis (as previously described), death, loss to follow-up, emigration, date of last contact, or if they started anticoagulation in a therapeutic dose for reasons other than a venous thrombotic event. Additionally, participants with anticoagulant exposure were excluded if their chart review revealed a venous thrombotic event diagnosis before the index date. Observations done before participants were aged 18 years were also excluded; in other words, participants diagnosed with HIV before they were 18 years old participated in analyses once they turned 18 years.

For all participants with a venous thrombotic event, we extracted detailed information by on-site chart review. This focused on circumstances in which the events occurred (such as dates of malignancy diagnosis or treatment, surgery, hospitalisation, immobilisation for longer than 3 days, pregnancy and puerperal period, oestrogen use, or limb fractures in the preceding 90 days) and the occurrence of any infection. Case report form data were then linked with data from ATHENA.

Because no Dutch population study has reliable data on the incidence of a first venous thrombotic event, we selected three literature sources[24–26] presenting contemporary European population-level incidences as comparison cohorts.

The ATHENA cohort was approved by the institutional review board of all participating centres. People entering HIV care are informed of participation in the ATHENA cohort and the purpose of data collection, after which they can consent verbally or elect to opt out.[23]

Statistical analysis

We calculated crude and exposure-specific incidence of venous thrombotic events by dividing the number of events by person-years of exposure. Additionally, we

	Analysis dataset (n=14 389)	All participants in ATHENA (n=22 567)
Sex		
Men	11 448 (80%)	18 113 (80%)
Women	2941 (20%)	4454 (20%)
Age (years) at first visit	38 (31–45)	37 (30–45)
HIV transmission route		
MSM	7811 (54%)	13 107 (58%)
Heterosexual contact	4585 (32%)	7292 (32%)
Intravenous drug use	469 (3%)	662 (3%)
Other*	984 (7%)	491 (2%)
Unknown	540 (4%)	1015 (5%)
Region of birth		
Western Europe	8714 (61%)	13 815 (61%)
Americas	2256 (16%)	3304 (15%)
Sub-Saharan Africa	2341 (16%)	3229 (14%)
Other	1078 (7%)	2219 (10%)
Year of HIV diagnosis		
<1995	2220 (15%)	3227 (14%)
1996–2000	2470 (17%)	3536 (16%)
2001–05	3673 (26%)	5468 (24%)
2006–10	3971 (28%)	6155 (27%)
2011–14	2055 (14%)	4181 (19%)
Characteristics during follow-up		
Follow-up (years)	7·2 (3·3–11·1)	7·9 (3·8–12·8)
Age (years)	44 (37–51)	44 (37–52)
Time (years) since HIV diagnosis	7 (3–12)	7 (3–12)
Time (years) since starting ART	4 (1–9)	6 (3–10)
Time (days) from HIV diagnosis to start of ART	316 (51–1301)	263 (47–1213)
CD4 count (cells per μL)	510 (360–690)	519 (360–705)
CD4 count nadir (cells per μL)	220 (100–340)	210 (83–330)
HIV RNA viral load (copies per mL)	<50 (<50–424)	<50 (<50–319)
HIV RNA viral load zenith (copies per mL)	83 000 (16 000–236 400)	100 000 (31 900–320 000)
Lost to follow-up	894 (6%)	1563 (7%)
Emigration	745 (5%)	1305 (6%)
Death	1074 (7%)	2132 (9%)

Data are n (%) or median (IQR). MSM=men who have sex with men. ART=antiretroviral therapy. *Other routes include blood products, needle accidents, vertical transmission, and breastfeeding.

Table 1: **Characteristics of people with HIV enrolled in ATHENA 2002–15**

	HIV (ATHENA), Netherlands 2003–15	Nord-Trondelag, Norway 1995–2001*	Tromsø, Norway 1994–2012	West France, France 2013†
Crude incidence (95% CI)	2·33 (2·04–2·64)	1·43 (1·33–1·54)	1·88 (1·75–2·03)	1·57 (1·44–1·69)
Standardised incidence (95% CI)	2·50 (2·18–2·82)	0·94 (0·86–1·01)	0·86 (0·59–1·13)	1·33 (1·23–1·44)

*The standardised incidence was based on standardisation to the Segi standard,[27] giving more weight to younger age strata. †Standardised incidence was not presented in the original study; this rate was calculated from age stratum-specific rates for venous thrombotic events presented in a supplementary appendix of the original study.

Table 2: **Comparison of crude and standardised incidences of venous thrombotic events between cohorts**

calculated age and sex-standardised incidences (WHO standard population) to enhance comparability.[27]

We used a time-updated Cox regression for multivariable analysis. Fixed variables were sex, region of birth, and intravenous drug use, as recorded in ATHENA. General time-updated variables, updated every 3 months, were age, diagnosis of malignant disease within the preceding 12 months, admission to hospital in the preceding 3 months, and pregnancy. Pregnancy and puerperal period were defined as the 9 months preceding the expected date of delivery until 3 months after birth. Unfortunately, exposure to surgery or oral oestrogen use was not deemed to be collected reliably prospectively, thus we could not calculate a venous thrombotic event incidence for these risk factors. HIV-specific, time-updated variables were CD4 and CD8 cell counts, HIV RNA, antiretroviral medication use, use of specific antiretroviral medication, and occurrence of the US Centers for Disease Control and Prevention (CDC) category B and C adverse events within the preceding 12 months.

Sex, age, intravenous drug use,[2] and malignant disease were forced into a multivariable model as controlling variables on the basis of their known association with venous thrombotic events. Because of our prespecified interest in protease inhibitor and abacavir use, these were forced into the fully adjusted model. All other variables were introduced into a fully adjusted model if the covariate specific Wald test p value was lower than 0·10 after correction for the previously mentioned risk factors for venous thrombotic events. Because hospitalisation is a confounder for some variables, but only a mediator for other variables, separate models were assessed with and without hospitalisation as a covariate. Additionally, fully adjusted models were fitted considering only unprovoked and provoked venous thrombotic events as the outcome. Data were analysed with R, version 3.5.0. Handling of missing data is described in the appendix (p 2). We did not predefine any sensitivity analyses, which were done post hoc.

Role of the funding source

The funder 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 study data and final responsibility for the decision to submit for publication.

Results

With data collected from Jan 1, 2003, to April 1, 2015, our study's cohort included 14 389 people with HIV and 99 762 person-years of follow-up, with a median follow-up of 7·2 years (IQR 3·3–11·1). Participants were predominantly men, of median 38 years of age, and mostly born in western Europe (table 1). Only a small minority had a history of intravenous drug use. There were minimal differences in baseline characteristics between the ATHENA and the analysis cohorts (table 1).

We recorded 232 venous thrombotic events during follow-up, yielding a crude incidence of 2·33 events per 1000 person-years (95% CI 2·04–2·64). Of these, 212 venous thrombotic events were classified as definite, 16 events were classified as probable, and four events were registered as cause of death. Of these 232 events, 99 were deep venous thrombosis in the lower extremities, 105 were pulmonary embolisms with or without concomitant deep venous thrombosis elsewhere, and 28 were events located elsewhere (appendix p 3).

Venous thrombotic event incidence after standardisation for age and sex to the WHO population was 2·50 per 1000 person-years (95% CI 2·18–2·82). A comparison with several large-scale cohorts (table 2) showed that standardised incidence of venous thrombotic events in people with HIV is two to three times higher than in populations without HIV infection.

The crude incidence of venous thrombotic events associated with HIV-related and other risk factors (table 3) showed that incidences of events increased with decreasing CD4 cell counts, increasing HIV viral load, and occurrence of recent CDC category B and C events. Compared with the overall incidence of venous thrombotic events, there was no appreciable effect of antiretroviral medication in general, or of protease inhibitors or abacavir. However, we observed an increased incidence of venous thrombotic events associated with integrase inhibitor use (98% of which concerned raltegravir). The incidence of venous thrombotic events was high in pregnant women with HIV, in people with HIV with a diagnosis of malignant disease in the preceding year, and in people admitted to hospital.

The relations between venous thrombotic events and CD4 cell counts, viral load higher than 100 000 copies per mL, and recent CDC category B and C events observed in the univariate analyses persisted after full adjustment and after considering either unprovoked or provoked venous thrombotic events separately (table 4; appendix p 3). Fully adjusted models did not reveal an association between any antiretroviral medication, protease inhibitors (as a class), or abacavir use and venous thrombotic events, nor did the analysis of any specific protease inhibitor (appendix p 4). Statistical evidence for an association between integrase inhibitor use and overall risk of a venous thrombotic event remained present in the fully adjusted models but disappeared when the analysis considered only unprovoked venous thrombotic events (table 4)

We did several post-hoc sensitivity analyses to assess the robustness of the inverse relationship that we found between CD4 cell count and venous thrombotic event risk. First, our finding that the risk of a venous thrombotic event is low in people with HIV who have CD4 counts higher than 500 cells per µL might be partly because people with HIV with high CD4 cell counts have survived periods of immune deficiency and its sequelae free of thrombosis because of some favourable characteristic (eg, genetics) and might thus represent a selection of individuals with low venous thrombotic event risk. To assess this survivorship bias, we added time since HIV diagnosis as a covariate to our models. This new covariate did not change the results (appendix p 4). However, we subsequently found evidence suggestive of an interaction between time since diagnosis and the CD4 cell count (Wald test p=0·10 between nested models), showing larger hazard ratio (HR) in each stratum shortly after HIV diagnosis that diminished over time (figure, appendix p 4). An additional sensitivity analysis exploring reverse causation as an explanation for the association between CD4 cell count and venous thrombotic events overall found no evidence for reverse causation (appendix p 4).

	Events	Follow-up (years)	Rate (95% CI)
Overall	232	99762	2·3 (2·0–2·6)
Sex			
Men	191	78422	2·4 (2·1–2·8)
Women	41	21340	1·9 (1·4–2·6)
Specific risk periods			
Pregnancy or puerperium	9	954	9·4 (4·6–17·3)
Malignant disease (diagnosed <1 year previously)	21	1257	16·7 (10·6–25·1)
Hospitalisation plus 90 days after discharge	70	2867	24·4 (19·1–30·6)
CDC-C event (diagnosed <1 year previously)	30	2442	12·2 (8·4–17·3)
CDC-B event (diagnosed <1 year previously)	21	1275	16·5 (10·5–24·8)
CD4 count (cells per µL)			
<200	58	7225	8·0 (6·2–10·3)
200–349	53	15972	3·3 (2·5–4·3)
350–500	50	24769	2·0 (1·5–2·7)
>500	68	51474	1·3 (1·0–1·7)
Viral load (copies per mL)			
<50	85	40739	2·1 (1·7–2·6)
50–1000	79	35855	2·2 (1·8–2·7)
1000–100 000	31	18177	1·7 (1·2–2·4)
>100 000	37	4614	8·2 (5·7–10·9)
Treatment status			
No treatment	70	27374	2·6 (2·0–3·2)
On any antiretroviral medication	162	72388	2·2 (1·9–2·6)
On protease inhibitors	53	25247	2·1 (1·6–2·7)
On abacavir	32	12961	2·5 (1·7–3·4)
On integrase inhibitors	14	2909	4·8 (2·7–7·8)

Rates shown are per 1000 person-years of follow-up. CDC=US Centers for Disease Control and Prevention

Table 3: **Crude incidences of venous thrombotic events per variable of interest**

Discussion

In this study, incidence of venous thrombotic events in people with HIV was approximately two times

	Overall VTE				Unprovoked VTE	Provoked VTE
	Univariate	Adjusted*	Model 1	Model 2	Adjusted*	Adjusted†
CDC-C event <1 year previously	5·92 (4·03–8·69)	4·21 (2·54–6·99)	2·80 (1·77–4·44)	2·33 (1·51–3·64)	2·56 (1·36–4·80)	4·42 (2·50–7·85)
CDC-B event <1 year previously	7·68 (4·91–12·0)	5·66 (3·29–9·76)	3·01 (1·80–5·05)	1·51 (0·87–2·62)	3·61 (1·81–7·21)	3·28 (1·64–6·55)
HIV-RNA (copies per mL)						
Undetectable	1	1	1	1	1	1
50–1000	1·05 (0·78–1·43)	1·14 (0·84–1·55)	0·98 (0·71–1·36)	0·98 (0·71–1·35)	1·18 (0·79–1·76)	0·68 (0·40–1·17)
1000–100 000	0·82 (0·54–1·23)	1·13 (0·75–1·71)	1·02 (0·60–1·72)	1·00 (0·60–1·68)	1·38 (0·72–2·66)	0·59 (0·25–1·38)
>100 000	3·84 (2·61–5·66)	4·98 (3·37–7·37)	3·15 (2·00–5·02)	2·69 (1·69–4·29)	4·08 (2·29–7·27)	1·74 (0·83–3·66)
CD4 count (cells per µL)						
>500	1				1	1
350–500	1·53 (1·06–2·20)	1·52 (1·05–2·18)	1·45 (1·01–2·09)	1·44 (1·00–2·07)	1·23 (0·80–1·91)	2·47 (1·23–4·97)
200–349	2·51 (1·75–3·60)	2·37 (1·65–3·39)	2·10 (1·45–3·05)	2·00 (1·38–2·89)	1·38 (0·84–2·25)	5·37 (2·79–10·3)
<200	6·07 (4·28–8·63)	5·37 (3·73–7·72)	3·40 (2·28–5·08)	2·55 (1·66–3·91)	2·11 (1·24–3·61)	9·14 (4·54–18·4)
Antiretroviral medication						
Any ART use *vs* no use	0·88 (0·66–1·16)	0·69 (0·52–0·92)	1·23 (0·84–1·82)	1·29 (0·88–1·89)	1·57 (0·96–2·58)	0·83 (0·44–1·57)
Protease inhibitor use	0·87 (0·64–1·19)	0·77 (0·57–1·05)	0·75 (0·54–1·03)	0·70 (0·51–0·98)	0·71 (0·47–1·05)	0·89 (0·51–1·56)
Abacavir use	1·07 (0·74–1·56)	0·98 (0·67–1·43)	1·11 (0·75–1·65)	1·07 (0·72–1·59)	1·31 (0·83–2·07)	0·69 (0·31–1·54)
Integrase inhibitor use	2·14 (1·25–3·68)	1·72 (1·00–2·97)	1·98 (1·14–3·44)	1·79 (1·04–3·11)	1·32 (0·59–2·98)	3·10 (1·41–6·77)

Data are hazard ratio (95% CI). 95% CIs were calculated with robust SEs. Model 1 was adjusted for all variables presented here plus age, sex, malignancy, pregnancy, and intravenous drug use. Model 2 was adjusted as model 1, with additional adjustment for hospitalisation. VTE=venous thrombotic event. CDC=US Centers for Disease Control and Prevention. ART=antiretroviral therapy. *Hazard ratio adjusted for age, sex, malignancy, pregnancy, and intravenous drug use. †Hazard ratio adjusted for age, sex, intravenous drug use, and the variables presented here.

Table 4: **Time-updated Cox regression models of HIV-specific risk factors and venous thrombotic events**

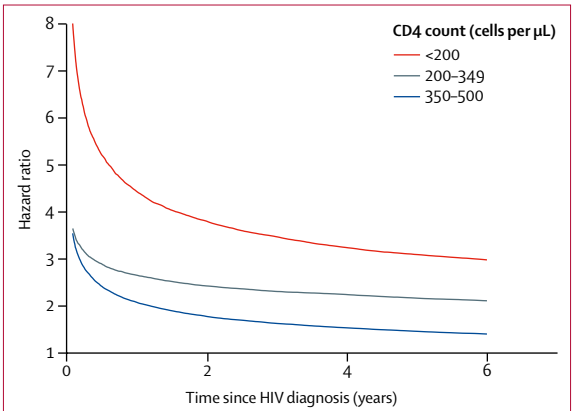

Figure: **Relation between CD4 cell count, time since diagnosis, and venous thrombotic events**
Fully adjusted association of CD4 cell count strata with overall venous thrombotic events by time since HIV diagnosis. Reference category is a CD4 count higher than 500 cells per µL.

higher than the generally cited incidence of 1 event per 1000 person-years in the general population.[28] This relative risk estimate is in the same range when comparing the standardised rate from our study with standardised rates from contemporary European population studies on venous thrombotic events.[24–26] Furthermore, our study showed a clear association between the risk of a venous thrombotic event and lower CD4 cell counts, supporting the role of viral load and opportunistic infections in venous thrombotic events, but not suggesting any association with drugs that were previously associated with venous thrombotic events.

Our overall incidence was lower than that reported in previous studies, including in the study most comparable with ours, the Danish cohort study (3·2 events per 1000 person-years, HR 3·42; for people with no intravenous drug use).[2] This difference can probably be explained by the general characteristics of our cohort compared with those from cohorts of older published data: our cohort represents people with HIV from a resource-rich setting who are clinically stable and have well suppressed viral replication with antiretroviral medication. This is best illustrated by the fact that, in more than 50% of the follow-up time, participants in our cohort had CD4 counts higher than 500 cells per µL.

We found a relation between CD4 cell counts and the risk of a venous thrombotic event, which is biologically plausible because of the elevated coagulation parameters observed in people with HIV who have high levels of HIV replication and advanced cellular immunodeficiency. However, given the ambiguity of earlier clinical data, the size of the association was unexpected. Therefore, we did several sensitivity analyses, excluding that the association could be (partly) explained by reversed causation or survivorship bias. On the contrary, the sensitivity analyses with time since HIV diagnosis as a covariate showed evidence suggestive of effect modification: the shorter the time from initial HIV diagnosis, the higher the overall effect of CD4 cell count was on the risk of a venous thrombotic event. These

results constitute indirect evidence suggesting that preventing CD4 cell count decline through timely institution of antiretroviral medication might prevent venous thrombotic events.

We also aimed to assess whether there is an association between venous thrombotic events and antiretroviral medication, in particular protease inhibitors and abacavir, and we found no evidence of any such association. As stated, we suspected that previously reported associations concerning venous thrombotic events and protease inhibitors were prone to confounding by indication. Our analysis was probably less prone to this because of the evolution of treatment guidelines with time: in our modern cohort, starting ART would have been more frequently independent of opportunistic infections and severe immune deficiency than it was during studies of venous thrombotic events done in the first decade of ART.

We did find an association between integrase inhibitor use (most of which was raltegravir) and venous thrombotic events overall, which raised suspicion as to whether raltegravir might increase the risk of a venous thrombotic event. However, we consider such a causal relation to be unlikely for two reasons. On one hand, raltegravir use was part of an exploratory analysis of risk factors for venous thrombotic event, one of many risk factors that we tested, raising the possibility that the association resulted from a type 1 error due to testing multiplicity. On the other hand, raltegravir was preferentially used in patients who needed ART with a favourable drug–drug interaction profile (ie, because of treatment of malignancy or mycobacterial infections) during the timeframe of our study, therefore the association we found might be confounded by specific indications. This second reason is illustrated by the stronger association of integrase inhibitor use with provoked venous thrombotic events and weak association with unprovoked events. Therefore, we concluded that there are no clear associations between the risk of a venous thrombotic event and any type of antiretroviral medication.

The venous thrombotic event rates observed during the investigated risk periods in our study did not support the use of outpatient thromboprophylaxis: during pregnancy, the venous thrombotic event rate showed an upper limit of the 95% CI of 17·3 per 1000 person-years, which does not surpass a threshold rate designated as low risk (20 per 1000) in the American College of Chest Physicians Guidelines on thrombosis in pregnancy.[18] The same holds true for the upper 95% CI limit found in people with HIV with a diagnosis of malignant disease (25·1 per 1000 person-years) and the threshold rate of oncological guidelines (about 10% 1-year rate or 100 per 1000).[29] Finally, the rate associated with hospitalisations translated to a 90-day risk lower than 1%, which was lower than venous thrombotic event rates found in active treatment arms of trials investigating thromboprophylaxis during and after hospitalisation (1–1·5%).[22] This lower risk was also the case if only hospitalisations longer than 3 days were considered (data not shown).

The strengths of our study include its size (to our knowledge, the largest to date) and the inclusion of all people with HIV in care in the participating hospitals during the study, maximising generalisability and statistical power. Another strength of our study is that the use of the ATHENA infrastructure enabled us to adjudicate venous thrombotic events with greater precision than that of previous studies, relying on administrative coding as a proxy for the outcome of interest (venous thrombotic event).

The main limitation of this study was that we did not have an HIV-negative control group. We partly mediated this by presenting an age-standardised and sex-standardised incidence and comparing it with standardised incidences from population studies done in countries in close geographical proximity and with comparable health standards to the Netherlands. However, our case-finding method differs from these other studies, making comparisons difficult. Because we found absolute and relative risk estimates of venous thrombotic events in people with HIV that were generally lower than those of previous reports, our findings would be problematic if our study had potential to greatly underestimate venous thrombotic event incidence. Indeed, several factors could have led to underestimation of incidence. A simple error in registration of anticoagulation seems minimal, as the high sensitivity of our case-finding strategy has shown. Regardless, it is conceivable that we would miss venous thrombotic events when deaths unrelated to such an event occurred shortly after a diagnosis of a venous thrombotic event. However, records of participants enrolled in ATHENA who died are scrutinised for missed data (including medication) up to a year before death. Nevertheless, we explored the potential effect of this source of measurement error by comparing cumulative mortality after venous thrombotic event in our cohort with those in a Norwegian population cohort.[30] Cumulative mortality after 3 months was 7% in our study and 16% in the Norwegian cohort, which suggests that we might have missed about 10% of venous thrombotic events because of non-registration of anticoagulant use when a patient died shortly after an event. However, cumulative mortality is probably lower in our cohort than in the Norwegian cohort because the median age of patients having a venous thrombotic event in our cohort (47 years) was lower than that in the Norwegian cohort (67 years). Therefore, we consider a 10% underestimation to be a worst-case scenario, and adding 10% to our indicence estimates would not change our conclusions.

Another potential source of bias was the fact that we did not cover all people with HIV in care in the Netherlands. There were only minimal differences in baseline characteristics between the study cohort and the ATHENA cohort, which is reassuring. However, because large centres participated, we might be selecting

participants who are slightly sicker than average who might preferentially be referred to large tertiary referral centres, which can provide a wider range of health services. This might have slightly inflated our incidence estimates.

We could not estimate rates of venous thrombotic events for two traditional risk factors, surgery and oestrogen use, and thus model parameters were not adjusted for these factors. However, the effects of surgery are partly captured by adjusting for hospitalisation. Additionally, the analysis of unprovoked venous thrombotic events disaggregates independent of provoking risk factors and is generally in line with our conclusions. Another limitation is that our follow-up duration could be considered low for the traditional risk factors that we assessed (about 1000 person-years for malignant disease and pregnancy each). Despite this, upper limits of the CIs of these rates were lower than the recommended thromboprophylaxis threshold rates, rendering our analysis sufficient. The duration of follow-up for these risk factors precluded assessing for interaction between them because of power issues; it might be that people with HIV with low CD4 cell counts and malignant disease have a venous thrombotic event rate closer to the thromboprophylaxis thresholds. Multicohort studies are needed to investigate these issues.

In conclusion, the risk of a venous thrombotic event in people with HIV is elevated compared with that of the general population. This can be mainly, but not completely, attributable to periods in which HIV infection is uncontrolled and cellular immunity is impaired. There was no evidence of an elevated risk of a venous thrombotic event with any antiretroviral drug or drug class, thus none should be considered contraindicated in people with HIV with perceived high risk of venous thrombotic events. Finally, HIV infection should not prompt standard initiation of primary thromboprophylaxis in combination with classic risk factors for venous thrombotic events. If any concern exists about prevention of primary venous thrombotic events in people with HIV, our results reaffirm what should be considered in any case: the start of effective ART early on and the support for people with HIV to continue ART.

Contributors

CR, KM, BR, WFWB, and YIGVT were responsible for the study idea. JFBH, CR, KM, BR, WFWB, and YIGVT were responsible for the study design. JFBH and CR did the literature search. CS was responsible for linkage of data with ATHENA. EDP was responsible for data collection. JFBH and CR supervised data collection. JFBH analysed the data. CS and FWNMW supervised the data analysis. JFBH and CR wrote the manuscript. CS, FWNMW, EDP, KM, BR, WFWB, and YIGVT critically reviewed the manuscript.

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Declaration of interests

YIGVT works for the Dutch National Health Institute as a medical advisor. CS reports grants from the Netherlands Ministry of Health, Welfare and Sport, National Institute for Public Health and the Environment, and Centre for Infectious Disease Control, during the conduct of the study. FWNMW reports personal fees from Gilead Sciences and ViiV Healthcare, outside the submitted work. BR reports grants from Gilead and MSD, non-financial support from MSD, Gilead, BMS, Janssen-Cilag, ViiV, and AbbVie, personal fees from Gilead, ViiV, and Great-Lakes Pharmaceuticals, and financial compensation payed to institution for advisory board participation organised by Gilead, ViiV, BMS, Janssen-Cilag, and MSD, outside the submitted work. KM reports grants and other support from Bayer and Sanquin, grants from Pfizer, other support from Boehringer Ingelheim, BMS, Aspen, and Uniqure, outside the submitted work. WFWB reports reimbursement payed to institution for investigator-initiated study from Janssen-Cilag, financial compensation payed to institution for a multicentre study by GlaxoSmithKline, and catering of a symposium by Janssen-Cilag, all outside the submitted work. CR reports grants from Merck, Erasmus MC, and Gilead, personal fees from the advisory board of ViiV Gilead Virology Education, and speaker fees from ViiV Gilead Virology Education, outside the submitted work. JFBH and EDP declare no competing interests.

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References

1 Klein SK, Slim EJ, de Kruijf MD, et al. Is chronic HIV infection associated with venous thrombotic disease? A systematic review. *Neth J Med* 2005; **63:** 129–36.

2 Rasmussen LD, Dybdal M, Gerstoft J, et al. HIV and risk of venous thromboembolism: a Danish nationwide population-based cohort study. *HIV Med* 2011; **12:** 202–10.

3 Schmidt M, Horvath-Puho E, Thomsen RW, Smeeth L, Sorensen HT. Acute infections and venous thromboembolism. *J Intern Med* 2012; **271:** 608–18.

4 Borjas-Howard JF, Bierman WFW, Meijer K, van der Werf TS, Tichelaar YIGV. Venous thrombotic events in patients admitted to a tuberculosis centre. *QJM* 2017; **110:** 215–18.

5 Dentan C, Epaulard O, Seynaeve D, Genty C, Bosson JL. Active tuberculosis and venous thromboembolism: association according to international classification of diseases, ninth revision hospital discharge diagnosis codes. *Clin Infect Dis* 2014; **58:** 495–501.

6 Tichelaar YIGV, Kluin-Nelemans HJC, Meijer K. Infections and inflammatory diseases as risk factors for venous thrombosis: a systematic review. *Thromb Haemost* 2012; **107:** 827–37.

7 Lijfering WM, Sprenger HG, Georg RR, van der Meulen PA, van der Meer J. Relationship between progression to AIDS and thrombophilic abnormalitities in HIV infection. *Clin Chem* 2008; **54:** 1226–33.

8 Van den Dries LW, Gruter RA, Hövels-van der Borden SB, de Maat MP, van Gorp EC, van der Ende ME. Von Willebrand factor is elevated in HIV patients with a history of thrombosis. *Front Microbiol* 2015; **11:** 180.

9 Opportunistic Infections Project Team of the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) in EuroCoord, Young J, Psichogiou M, et al. CD4 cell count and the risk of AIDS or death in HIV-infected adults on combination antiretroviral therapy with a suppressed viral load: a longitudinal cohort study from COHERE. *PLoS Med* 2012; **9:** e1001194.

10 The INSIGHT START Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med* 2015; **373:** 795–807.

11 Jong E, Louw S, Meijers JC, et al. The hemostatic balance in HIV-infected patients with and without antiretroviral therapy: partial restoration with antiretroviral therapy. *AIDS Patient Care STDS* 2009; **23:** 1001–07.

12 Jong E, Louw S, van Gorp EC, Meijers JC, ten Cate H, Jacobson BF. The effect of initiating combined antiretroviral therapy on endothelial cell activation and coagulation markers in South African HIV-infected individuals. *Thromb Haemost* 2010; **104:** 1228–34.

13 Crum-Cianflone NF, Weekes J, Bavaro M. Review: thromboses among HIV-infected patients during the highly active antiretroviral therapy era. *AIDS Patient Care STDS* 2008; **22:** 771–78.

14 Sullivan PS, Dworkin MS,Jones JL, Hooper WC. Epidemiology of thrombosis in HIV-infected individuals. The adult/adolescent spectrum of HIV disease project. *AIDS* 2000; **14:** 321–24.

15 Lijfering WM, Ten Kate MK, Sprenger HG, van der Meer J. Absolute risk of venous and arterial thrombosis in HIV-infected patients and effects of combination antiretroviral therapy. *J Thromb Haemost* 2006; **4:** 1928–30.

16 Sabin CA, Reiss P, Ryom L, et al. Is there continued evidence for an association between abacavir usage and myocardial infarction risk in individuals with HIV? A cohort collaboration. *BMC Med* 2016; **14:** 61.

17 Alvarez A, Rios-Navarro C, Blanch-Ruiz MA, et al. Abacavir induces platelet-endothelium interactions by interfering with purinergic signalling: a step from inflammation to thrombosis. *Antiviral Res* 2017; **141:** 179–85.

18 Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO. VTE, thrombophilia, antithrombotic therapy, and pregnancy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012; **141** (suppl 2)**:** e691S–736.

19 Kahn SR, Lim W, Dunn AS, Cushman M, et al. Prevention of VTE in non-surgical patients. Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012; **141** (suppl 2)**:** e195S–226.

20 Timp JF, Braekkan SK, Versteeg HH, Cannegieter SC. Epidemiology of cancer-associated venous thrombosis. *Blood* 2013; **122:** 1712–23.

21 Ay C, Posch F, Kaider A, Zielinski C, Pabinger I. Estimating risk of venous thromboembolism in patients with cancer in the presence of competing mortality. *J Thromb Haemost* 2015; **13:** 390–97.

22 Cohen AT, Harrington RA, Goldhaber SZ, et al, for the APEX Investigators. Extended thromboprophylaxis with betrixaban in acutely ill medical patients. *N Engl J Med* 2016; **375:** 534–44.

23 Boender TS, Smit C, Sighem AV, et al. AIDS therapy evaluation in the Netherlands (ATHENA) national observational HIV cohort: cohort profile. *BMJ Open* 2018; **8:** e022516.

24 Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrom J. Incidence and mortality of venous thrombosis: a population-based study. *J Thromb Haemost* 2007; **5:** 692–99.

25 Arshad N, Isaksen T, Hansen JB, Braekkan SK. Time trends in incidence rates of venous thromboembolism in a large cohort recruited from the general population. *Eur J Epidemiol*. 2017; **32:** 299–305.

26 Delluc A, Tromeur C, Le Ven F. Current incidence of venous thromboembolism and comparison with 1998: a community-based study in Western France. *Thromb Haemost* 2016; **166:** 967–74.

27 WHO. Ahmad OB, Boschi-Pinto C, Lopez AD, Murray CJL, Lozano R, Inoue M. Age standardization of rates: a new WHO standard. Geneva: World Health Organization, 2001.

28 Heit JA, Ashrani AA, Crusan DJ, McBane RD, Petterson TM, Bailey KR. Reasons for the persistent incidence of venous thromboembolism. *Thromb Haemost* 2017; **117:** 390–400.

29 Khorana AA, Otten HM, Zwicker JI, Connoly GC, Bancel DF, Pabinger I, for the Subcommittee on Haemostasis and Malignancy. Prevention of venous thromboembolism in cancer outpatients: guidance from the SSC of the ISTH. *J Thromb Haemost* 2014; **12:** 1928–31.

30 Arshad N, Bjøri E, Hindberg K, Isaksen T, Hansen J-B, Brækkan SK. Recurrence and mortality after first venous thromboembolism in a large population-based cohort. *J Thromb Haemost* 2017; **15:** 295–303.