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Venous thromboembolism among people with HIV: Design, implementation, and findings of a centralized adjudication system in clinical care sites across the United States

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Abstract

BACKGROUND—People with HIV (PWH) are at increased risk for venous thromboembolism (VTE). We conducted this study to characterize VTE including provoking factors among PWH in the current treatment era.

METHODS—We included PWH with VTE between 2010–2020 at six sites in the CFAR Network of Integrated Clinical Systems (CNICS) cohort. We ascertained for possible VTE using diagnosis, VTE-related imaging, and VTE-related procedure codes, followed by centralized adjudication of primary data by expert physician reviewers. We evaluated sensitivity and positive predictive value

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of VTE ascertainment approaches. VTEs were classified by type and anatomic location. Reviewers identified provoking factors such as hospitalizations, infections, and other potential predisposing factors such as smoking.

RESULTS—We identified 557 PWH with adjudicated VTE: 239 (43%) had pulmonary embolism (PE) with or without deep venous thrombosis (DVT), and 318 (57%) had DVT alone. Ascertainment with clinical diagnoses alone missed 6% of VTEs identified with multiple ascertainment approaches. DVTs not associated with intravenous lines were most often in the proximal lower extremities. Among PWH with VTE, common provoking factors included recent hospitalization (n=134, 42%), infection (n=133, 42%), and immobilization/bed rest (n=78, 25%). Only 57 (10%) PWH had no provoking factor identified. Smoking (46%), HIV viremia (27%) and injection drug use (22%) were also common.

CONCLUSION—We conducted a robust adjudication process that demonstrated the benefits of multiple ascertainment approaches followed by adjudication. Provoked VTEs were more common than unprovoked events. Non-traditional and modifiable potential predisposing factors such as viremia and smoking were common.

Keywords

venous thromboembolism; pulmonary embolism; deep venous thrombosis; HIV

Antiretroviral therapy (ART) has led to increased life expectancy for people with HIV (PWH)[1–6]. However, treated PWH remain at increased risk for age-associated conditions such as venous thromboembolism (VTE) including deep venous thrombosis (DVT) and pulmonary embolism (PE). VTE is frequently serious with an incidence of ~1–1.7/1000 person-years[7–10] among the general population. While data among PWH are more limited, particularly in the current era when many PWH start ART earlier, VTEs are likely 1.5–10 times more common in PWH than the general population[11–22]. Whether VTEs are provoked has implications for treatment decisions and long-term outcomes, including recurrence[23]. Questions remain regarding the proportion and causes of provoked VTEs among PWH. Prior studies that examined HIV-related factors such as CD4 count have had limited information on provoking factors such as surgery or estrogen[22], or focused on traditional provoking factors such as comorbidities but without information regarding HIV-related factors such as CD4 count[24]. The limited knowledge, including VTE risk factors, among PWH has been noted[25]. However, VTEs in PWH are clearly due to acquired and inherited factors resulting in a dynamic multifactorial disorder[26,27]. The pathogenesis of HIV contributing to a hypercoagulable state is likely associated with ongoing chronic inflammation and immune activation[26–28].

Many prior VTE studies among PWH were case reports, small case series, or otherwise limited by small numbers of outcomes[29–42]. Some have not included PEs[33,43] or DVTs[25,44] or were unable to examine differences between PEs and DVTs due to size[34]. Most were conducted before ART or before currently used agents such as integrase inhibitors were common[14,15,36–41,45–48]. Finally, VTE studies require clearly defined endpoints and accurate identification of events. Reliance on administrative diagnosis codes and other non-adjudicated outcomes misclassifies outcomes and overestimates VTE rates[45,49,50]. Medical

record review and verification to minimize misclassification has been rare in previous VTE studies among PWH[34,40,45].

A call has been made for multisite HIV cohort studies to characterize VTE risks[34] and thereby improve approaches to prevention and treatment. We therefore implemented a robust verification process with centralized VTE ascertainment and adjudication in the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort. The protocol addresses issues specific to HIV including collecting a comprehensive list of provoking and potentially predisposing factors, both traditional and HIV-related. We characterized VTEs in a large diverse cohort including types and locations. We also evaluated sensitivity and positive predictive value (PPV) of different criteria to ascertain potential VTE events, using adjudication as the gold standard.

Methods

Cohort.

This observational study was conducted in CNICS which includes >38,000 PWH in clinical care at eight sites across the United States[51]. We included potential VTEs from 1/1/2010–3/1/2020 (end date varies somewhat by site with no VTEs after 3/1/2020) at six sites with VTE adjudication. PWH provided written consent to be part of CNICS and sites received local Institutional Review Board approval for CNICS.

CNICS Data.

The CNICS data repository systematically captures comprehensive clinical data from all outpatient and inpatient encounters including demographic, clinical, medication, and laboratory data from electronic health records (EHR) and other institutional data systems[51]. Clinical diagnoses are recorded in the EHR by treating clinicians using standardized diagnosis and ICD-9/ICD-10 coding. Data quality assessment is conducted by sites prior to transmission and by the Data Management Core prior to insertion into the central repository.

CNICS VTE Protocol:

We developed our protocol based on the Longitudinal Investigation of Thromboembolism Etiology study[52] and the experience of VTE adjudication among PWH in a case-control study at Johns Hopkins University[45]. We incorporated lessons learned with adjudicating CNICS myocardial infarctions (MIs) where we found central adjudication is crucial to prevent misclassification and that diagnoses alone identify only ~half of MIs (positive predictive value 45%) and are therefore insufficient for MI ascertainment[53]. Specifically, we developed a three-step protocol consisting of event ascertainment, review packet assembly, and adjudication.

Ascertainment.

Potential VTEs were identified centrally based on a standard protocol applied to diagnosis, imaging, and procedure codes in the CNICS data repository (Supplement Figure 1). Multiple criteria were used to optimize sensitivity of ascertainment for potential VTEs. The presence of any of these three criteria types was sufficient for ascertainment.

VTE review packet assembly.

For each potential VTE, sites assembled a deidentified packet of standardized clinical information for central review (Supplement Figure 1).

Completed packets were uploaded to the web-based CNICS VTE platform, a securely operated information system that manages adjudication workflow. Sites were asked to document reasons for missing packets, such as potential events occurring outside the hospital system, and to make two attempts to obtain outside records before declaring information unavailable. Packets were reviewed centrally for completeness and appropriate redaction to ensure they were deidentified. In addition, as part of screening, a physician reviewed and then excluded all packets from the adjudication process whose only indication of a potential VTE was a code indicating a VTE-related imaging test was performed, such as a lower extremity doppler, and the results of that test were negative for a VTE.

VTE Adjudication.

Members of the adjudication committee were physicians with prior adjudication experience including the Multi-Ethnic Study of Atherosclerosis and other studies. All reviewers adjudicated the same initial group of events and discrepancies between reviewers were discussed. Two reviewers adjudicated each event, followed by a third reviewer in cases of discrepancy. Reviewers were blinded to specific antiretroviral medication use to minimize bias or preconceived notions of associations impacting reviews[53]. Reviewers entered standardized data required to define VTE into a web-based platform application facilitating centralized review with minimal administrative burden. Each Reviewer was unable to see the results of the other reviewers within the platform to avoid being influenced.

Each VTE was categorized by type: DVT, PE; as definite or probable; and by anatomic location (Supplement Figure 1). For confirmed VTEs, reviewers captured information from the packet regarding provoking factors previously identified in key VTE guidelines[23,54,55] such as trauma, surgery, family history, immobilization, autoimmune disease, intravenous lines, transfusions, hospitalizations, heart failure (right or left-sided), recent infections, cancers (excluding basal cell carcinoma), and chemotherapy within 90 days. Reviewers also captured potentially predisposing risk factors such as smoking status. Other comorbidities such as diabetes, myocardial infarction, and stroke were captured from the CNICS data repository as was HIV viremia[56,57].

Analyses:

Analyses were limited to initial VTE for those with recurrent events. We calculated the positive predictive value (PPV): the proportion of VTEs identified by each ascertainment method (clinical diagnoses, imaging/procedures) that were verified by adjudication; and sensitivity: proportion of true VTEs verified by adjudication that were identified as positive by each ascertainment method[58]. We combined probable and definite VTEs and VTE types (PE, DVT) for these analyses. To further evaluate our approach, we also reviewed EHR documentation including provider notes and imaging reports looking for VTEs from a random sample of 100 PWH from one site who did not meet any ascertainment criteria. We conducted chi square tests and t-tests to compare demographic and clinical characteristics by

VTE type (PE vs. DVT; categorizing those with both as PE). Descriptive analyses including prevalence were used to characterize provoking and other potential predisposing factors and the distribution of anatomic locations.

RESULTS

We identified 1,625 potential VTEs which met at least one ascertainment criteria during the study period (Figure 1). Of these, 56% (905/1,625) were excluded before full review due to meeting ascertainment criteria only by imaging codes and imaging results were negative. Of the remaining 720 potential events, adjudication confirmed 557 PWH with VTE (90% definite and 10% probable). We found 163 events out of 720 (23%) that met ascertainment criteria and passed initial screening but did not have an adjudicated VTE on full review. Thus, the positive predictive value for a VTE among the 1625 who met ascertainment criteria was 34% however this increased to 77% among the 720 that passed initial screening.

Adjudicated events could have been identified by more than one ascertainment/identification criterion. Of the 557 adjudicated VTEs, sensitivity for ascertainment was highest for clinical diagnoses with 94% of adjudicated VTEs ascertained by diagnosis codes either alone or in combination with imaging/procedures, and 6% identified by imaging/procedures codes alone. Of 100 randomly selected individuals who did not meet any VTE ascertainment criteria, no events were detected (0%, 95%CI: 0–3.6%).

PWH with VTE were predominantly male (78%); median age was 50 years (interquartile range [IQR]: 42,57) with 19% 60 or older; 223 (40%) were non-Hispanic White, 264 (47%) non-Hispanic Black, and 55 (10%) Hispanic. The median CD4 count was 347 cells/μL (IQR: 166,567) and 73% had an HIV viral load <400 copies/ml (Table 1).

Among 557 PWH with adjudicated VTE, 239 (43%) had PEs of whom 77 also had a concurrent DVT identified. In addition, there were 318 (57%) DVTs without a PE (Table 1). Demographic and clinical characteristics of PWH by VTE type are described in Table 1. Overall, PWH who had a PE (with or without a DVT) were generally similar to those who only had a DVT although those who had a PE were more likely to be Black and to be obese (BMI≥30 kg/m^2).

Anatomic Locations

PEs were often segmental (49%), followed by sub-segmental (35%) and lobar (29%) with many having multiple locations. DVTs that were not associated with intravenous lines were most commonly in the lower extremities (194, 73%), and lower extremity DVTs were most often proximal (75%). In contrast, among the 53 DVTs that were associated with intravenous lines, 70% were in the upper extremities with 81% related to central venous access catheters vs. 13% dialysis/graft/shunt/fistulas. In addition, 18% of DVTs were not in an extremity, such as portal, mesenteric or splenic thromboses.

Provoking and potential predisposing factors

Only 57 (10%) VTEs had no provoking factor identified. The most common provoking factors included recent hospitalization (210, 38%), infection (207, 37%), or

immobilization/bed rest (114, 20%) within the prior 90 days (Table 2). Among those with infections, pneumonia (38% of infections), sepsis/bacteremia (35%), and cellulitis (21%) were common. Among 78 PWH with pneumonia, many had community acquired pneumonia without an identified organism. Among those with known organisms, 8 had *Staphylococcus aureus*; 8 *Pneumocystis jirovecii*; 6 respiratory viruses such as Respiratory Syncytial Virus (RSV); 5 gram-negative infections such as *Escherichia coli*; 3 *Streptococcus pneumoniae*; and 3 each had *Mycobacterium tuberculosis* and other *Mycobacterium* species. Many provoking factors overlapped, for example, 125 (22%) had both hospitalization and infection in the past 90 days; 80 (14%) had both immobilization/bed rest and hospitalization. Other common provoking factors included cancer (100, 18%) and recent surgery (58, 10%) with Kaposi's sarcoma and anal cancer the most common cancers (18% and 15% of cancers, respectively). In addition, intravenous lines were a common provoking factor for VTE (61, 11%). Factors such as plane rides were uncommon (Table 2).

Potential predisposing factors such as low (<350 cells/ml^3) CD4 cell count (51%) and injection drug use (22%), were common. Approximately one-fourth of PWH with a VTE had detectable viral loads (27%) and almost half (46%) were actively smoking. One-fifth of PWH with a VTE were obese (24%) or had diabetes (20%) (Table 2).

DISCUSSION

We implemented a robust verification process with centralized ascertainment and adjudication to characterize VTE including types, locations, and provoking factors in a large multi-site HIV cohort. Clinical diagnoses identified the majority of adjudicated VTEs. However, the need for multiple ascertainment approaches including imaging was demonstrated by the 6% of VTEs identified by imaging codes alone. The importance of adjudication to exclude individuals who met ascertainment criteria but did not have a VTE was demonstrated by the 163 events that passed initial screening, underwent full review, but did not have a VTE (positive predictive value 77%). Among 557 PWH with adjudicated VTE, we identified more DVTs than PEs with lower extremity, particularly proximal DVTs most common. Provoking factors such as hospitalizations and infections were common with only 10% having no provoking factors.

Adjudication/ascertainment

We used multiple ascertainment criteria including diagnoses, procedures, and imaging codes to be comprehensive. Although we are not the first to use multiple ascertainment approaches to avoid missing events (e.g., one study used prescribed anticoagulants or causes of death[22]), our approach is the most comprehensive we could find in a large HIV cohort study. While clinical diagnoses had the greatest sensitivity, other ascertainment criteria identified additional VTEs that would otherwise have been missed. Examples of imaging codes included venous doppler testing and chest CTs. We limited ascertainment using chest CTs to those done with a PE protocol because preliminary evaluation demonstrated including all chest CTs would result in the need to review thousands of extra potential events without identifying additional VTEs.

Because we included only potential events, negative results were not included and thus, we did not calculate specificity and negative predictive value. However, no events were identified among 100 randomly sampled PWH from one site with neither clinical VTE diagnoses nor imaging/procedure codes suggesting that given the low prevalence of the outcome, the estimated specificity for each ascertainment criteria would be >97%.

In addition to missing VTE events, using diagnoses without VTE adjudication is misleading, as some non-events will be misclassified as VTEs. Several general population studies have identified issues with relying solely on medical diagnoses including inaccuracy, missed events, and low PPV[59,60]. We found diagnoses mis-identified potential VTEs when the documentation was referencing VTE prophylaxis not VTE. Diagnoses also were sometimes inaccurate in the setting of superficial phlebitis. Reviewers adjudicated these events as non-VTEs. Many previous studies in PWH lacked central adjudication of clinical events and occurred in earlier treatment eras using diagnosis or discharge codes[11–14,25,61]. One of the best prior studies that validated VTE was a case-control study at Johns Hopkins University[45]. This study used adjudicated outcomes as a gold standard and demonstrated the poor specificity of diagnosis codes without additional validation among PWH with a positive predictive value of 71%; thus 29% with a VTE diagnosis code had no indication of a VTE upon medical record review[45]. This is consistent with our findings in which 23% of PWH who were ascertained and met criteria for full review were adjudicated as not having a VTE even after excluding those who met criteria only due to imaging studies which were negative. These findings highlight the need for adjudication as using diagnoses without adjudication would have resulted in including many false positive events.

Types and locations of VTEs

DVTs not associated with intravenous lines were most often proximal lower extremity DVTs. These findings contrast with a study of PWH from the Netherlands which identified slightly more PEs than DVTs[22]. However, that study focused on anticoagulant medications and death certificate cause-of-death diagnoses to identify VTEs and therefore may have captured predominantly more severe VTEs. Furthermore, differences in clinical practice settings, particularly the likelihood of performing chest CTs or lower extremity testing, may contribute to some differences across studies. Our findings are consistent with a review that identified 129 VTEs from the pre- and early ART era and found lower extremity DVTs were more common than PEs, upper extremity DVTs, or other locations[19]. Similarly, the aforementioned Johns Hopkins University study found that among 145 PWH with a VTE, there were 109 DVTs, more of which occurred in the lower extremities than other locations[45]. Our findings build on prior studies that predominantly did not parse DVT locations or parsed only to the level of lower vs. upper extremity vs. other location. Understanding VTE types and locations among PWH is important. For example, in the general population, it is clear there are outcome differences such as rates of extension or PE among those with proximal vs. distal lower extremity DVT[62,63].

Provoking and predisposing VTE risk factors

Definitions and categorizations of VTE risk factors have varied[23,54,55] including acquired or environmental; major and minor; transient and chronic; etc. The role of comorbidities in the

general population is also unclear. Some, such as cancer, are important provoking factors, others are less established[23]. The roles of various comorbidities among PWH are even less clear. We therefore categorized risk factors into provoking and potential predisposing risk factors with comorbidities such as cancer being categorized as provoking while other comorbidities were categorized as potential predisposing risk factors. As VTE continues to be better understood among PWH, categorization of factors as provoking or predisposing may change and additional risk factors may be identified. In addition, an argument has been made that terms such as provoking may be misleading and should also evolve[55].

We found high hospitalization, immobilization, and infection rates. Only 10% of VTEs were without provoking risk factors, lower than in general population studies where about half of VTEs are provoked by immobilization, trauma, surgery, or hospitalization; 20% are associated with cancer; and 30% are unprovoked[64]. We found infections were a common VTE provoking factor (37%), most often associated with pneumonia, sepsis/bacteremia, and cellulitis. This contrasts with studies particularly in the pre and early ART era that identified increased risk among those with opportunistic infections such as Cytomegalovirus[46,65,66], as well as other factors less relevant currently such as indinavir use[46]. We found 18% of VTEs occurred among PWH with cancer, which is not surprising given the large increase in VTE risk associated with cancer in the general population as well as the higher prevalence of cancer among PWH[66]. Expanding on findings from earlier case series which linked thrombotic events among PWH with Kaposi's sarcoma[38], we found the most common types of cancers were Kaposi's sarcoma and anal cancer. We also found a high percentage of other potentially predisposing characteristics such as 46% of VTEs occurred among PWH who smoked, 51% had a low CD4 cell count (<350 cells/mm^3), and 22% had used injection drugs, highlighting that in addition to provoking factors, there may be additional important modifiable pro-thrombotic factors however more research is needed to confirm these roles.

Strengths

CNICS includes comprehensive clinical information including detailed laboratory and medication information as well as other potential predisposing risk factors. It is strengthened by the large size and demographic, clinical and geographic diversity. Simple, yet sophisticated health informatics platforms supported efficient adjudication. Adjudication including central review allows capture of additional information such as locations and provoking factors as well as greatly reducing measurement error due to outcome misclassification. To our knowledge, in addition to having a more comprehensive assessment of provoking factors than most studies, this study included the largest number of adjudicated VTEs to assess provoking risk factors among PWH in the current treatment era.

Limitations

While our adjudication methods are applicable to any VTE, the focus on incident or first VTE does not provide information on follow-up VTEs, which may be higher among PWH than those without HIV[67]. This limits the ability to evaluate prior VTE as a risk factor. Testing for VTEs was done as part of clinical care so we did not control who did and did not get testing or whether they received testing for both PEs and DVTs or just one or the other. VTEs with subtle clinical symptoms that PWH and providers failed to recognize or

evaluate would be missed as would VTEs that resulted in death before hospitalization. We captured provoking risk factors from clinical information so if not addressed as part of care, such as a cancer not yet identified or diagnosed, it would not be captured. In addition, we included PWH in care. While this increases the likelihood of capturing VTEs, it decreases generalizability to PWH not in care or with undiagnosed HIV.

Future studies

We provide insights into understanding VTEs among PWH, particularly related to the high proportion of provoked events and types of provoking factors compared to the general population, and reduce misclassification allowing for robust studies of risk and progression. This provides a resource to address additional VTE-related questions among PWH in the future including impacts of COVID-19. Furthermore, VTEs including both PE and DVT are increasing in incidence in the US[64] and how this will impact PWH is unknown. VTEs appear highly heritable in the general population[64]; but the extent genetic vs. other risk factors account for greater disease burden among PWH is unanswered as is whether HIV interacts with other provoking and predisposing risk factors to further increase VTE risk. Finally, while the impact of VTEs on subsequent mortality, hospitalization, stroke and myocardial infarction risk and other outcomes are being addressed in the general population[68], questions remain regarding impacts as the population of PWH continue to become older.

Conclusions

VTE studies among PWH have been limited by small sizes and low numbers of VTEs, differences in endpoint definitions, and lack of information on key provoking factors. Large multicenter VTE studies are needed. CNICS is ideally situated to increase knowledge and shape future VTE management among PWH. We conducted a robust adjudication process and examined provoking factors. Provoked VTEs such as due to hospitalization and/or infections were much more common than unprovoked events. Differences in the role of HIV-related and non-HIV-related provoking factors underscore the need for continued VTE research among PWH. Understanding causes of provoked VTEs will provide insight into the need for prophylaxis. As the PWH population continues to age, VTEs may become increasingly common and it is important for providers to be aware of VTE risk factors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of Interest:

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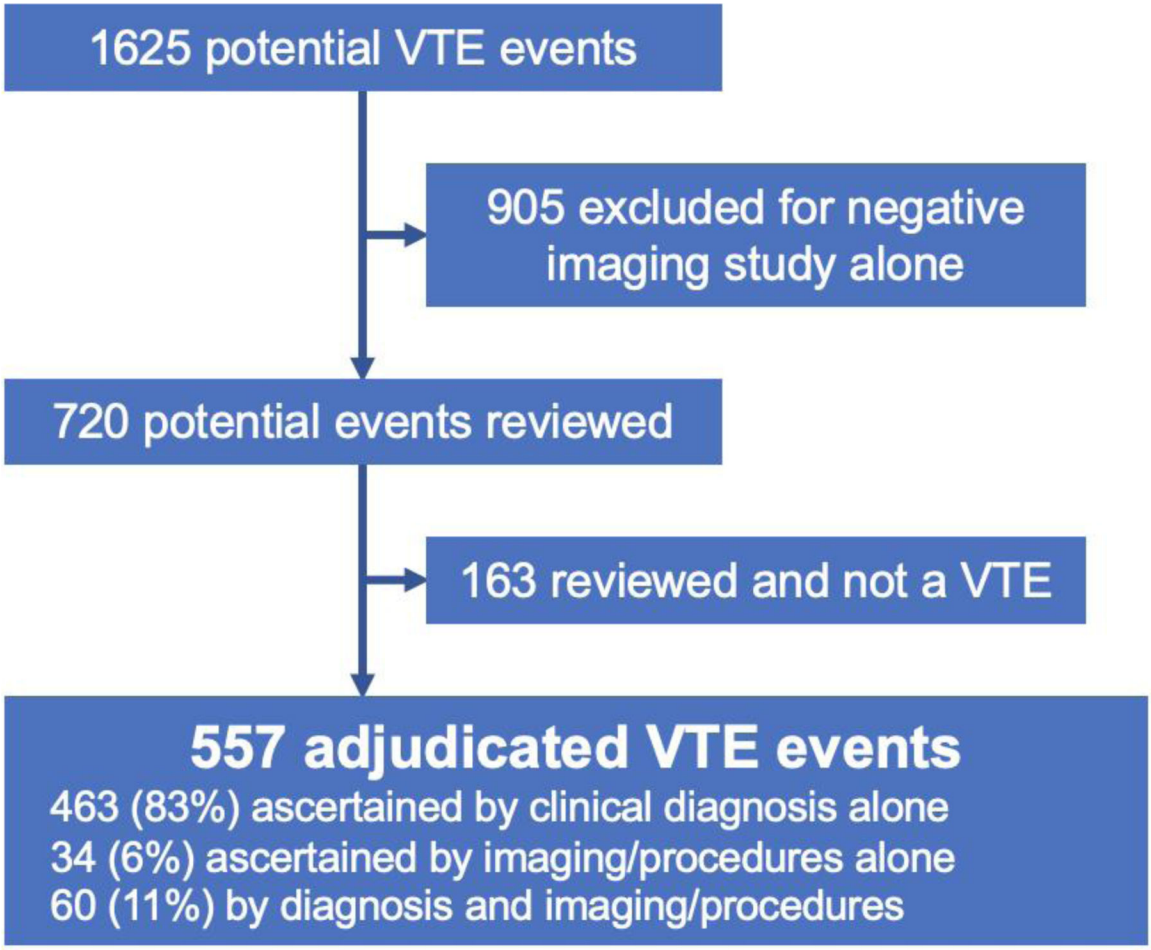

FIGURE 1.
Flowchart of potential VTEs

Table 1.

Demographic and clinical characteristics of people with HIV with VTE overall and by VTE type (DVT vs. PE) (N=557)

Characteristic	All VTEs N=557	DVT N=318 (57)	PE* N=239 (43)	P-value (comparing those with DVT vs. PE)
Sex				0.3
Female	120 (22)	64 (20)	56 (23)	
Age				0.5
<40	109 (20)	69 (22)	40 (17)	
40–49	164 (29)	95 (30)	69 (29)	
50–59	178 (32)	94 (30)	84 (35)	
60–69	86 (15)	48 (15)	38 (16)	
≥70	20 (4)	12 (4)	8 (3)	
Race/Ethnicity				0.03
White	223 (40)	138 (43)	85 (36)	
Black	264 (47)	136 (43)	128 (54)	
Hispanic	55 (10)	32 (10)	23 (10)	
Other/unknown	15 (3)	12 (4)	3 (1)	
HIV Transmission Risk Factor				0.2
Heterosexual	185 (33)	100 (31)	85 (36)	
MSM	226 (41)	130 (41)	96 (40)	
IDU	121 (22)	77 (24)	44 (18)	
Other/unknown	25 (4)	11 (3)	14 (6)	
CD4 count closest to event (cells/mm^3)				0.06
0–200	152 (30)	98 (34)	54 (25)	
201–350	107 (21)	61 (21)	46 (21)	
>350	253 (49)	133 (46)	120 (55)	
HIV-1 RNA closest to event				0.8
<400	371 (73)	211 (73)	160 (74)	
BMI kg/m^2				0.002
<18.5	32 (7)	25 (9)	7 (3)	
18.5–25	161 (34)	101 (38)	60 (30)	
25–30	164 (35)	89 (34)	75 (37)	
≥30	110 (24)	50 (19)	60 (30)	
Smoking status				1.0
Never	183 (33)	103 (32)	80 (33)	
Former	120 (22)	69 (22)	51 (21)	
Current	254 (46)	146 (46)	108 (45)	

*PWH with both PE and DVT are included in PE column

**BMI based on 467 PWH (84%)

DVT: deep venous thrombosis; PWH: people with HIV; VTE: venous thromboembolism

Table 2.

Prevalence of provoking factors and other potential predisposing characteristics among people with HIV with VTE (N=557)

Provoking risk factors	**Number**	**Percentage**
Hospitalization in the past 90 days	210	38%
Infection in the past 90 days	207	37%
Immobilization/bed rest in the past 90 days	114	20%
Malignancy, active in the past year	100	18%
Catheter associated thrombosis	61	11%
Surgery in past 90 days	58	10%
Chemotherapy in the past 90 days	43	8%
Family history of VTE	34	6%
Estrogen and/or progestin or anabolic steroid use in last 30 days	30	5%
Major trauma including fracture in past 90 days	29	5%
Inherited or acquired thrombophilia (other than malignancy)	27	5%
Transfusion in past 30 days	18	3%
Long plane ride/prolonged sitting in the past 30 days	15	3%
Current pregnancy or within 3 months post-partum	3	1%
Other potentially predisposing patient characteristics		
CD4 cell count <350 cells/mm^3	259	51%
Smoking	254	46%
Viral Load >400 copies/mL	136	27%
Injection drug use	122	22%
Obesity (BMI≥30 kg/m^2)	110	24%
Diabetes	109	20%
Older age (>60 years)	80	14%
COPD	57	10%
MI	38	7%
Dialysis	36	6%
Heart failure	33	6%
Stroke	22	4%
Pulmonary hypertension	19	3%
Nephrotic syndrome	7	1%

COPD: chronic obstructive pulmonary disease; MI: myocardial infarction