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MAJOR ARTICLE

Associations Between Plasma Human Immunodeficiency Virus (HIV) Ribonucleic Acid Levels and Incidence of Invasive Cancer in People With HIV After Initiation of Combination Antiretroviral Therapy

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Background. Human immunodeficiency virus (HIV) viremia could be involved in the increased risk of cancer in people with HIV (PWH) receiving combination antiretroviral therapy (cART). We analyzed the association between plasma HIV ribonucleic acid levels in PWH starting cART and incident invasive cancer using the Swedish cohort InfCare HIV linked with national registers.

Methods. Adults starting cART in 1996–2017 were included if they had ≥1 viral load (VL) measurement before receiving any antiretroviral agent (pre-ART VL) and ≥2 VLs ≥6 months after start of cART. Viremia during cART was analyzed both as viremia-copy-years and categorized as suppression (<50 copies/mL), low-level viremia ([LLV] 50–999 copies/mL), and nonsuppression (≥1000 copies/mL). The main outcome was a composite of invasive malignancies with increased incidence among PWH. We fitted proportional subhazard models (including sex, age, pre-ART CD4 count, and injection drug use) for both pre-ART VL and viremia during cART.

Results. After 32 105 person-years, 3254 of 4931 participants (66%) were classified as suppressed, 438 (9%) were classified as LLV, and 1221 (25%) were classified as nonsuppressed. Neither viremia category nor cumulative viremia during cART had a statistically significant association with cancer. Higher pre-ART VL was associated with cancer (adjusted subhazard ratio, 1.4; 95% confidence interval, 1.0–1.8); this remained statistically significant with viremia during cART in the model. In subanalysis, the association with pre-ART VL was statistically significant for acquired immune deficiency syndrome (AIDS)-defining and infection-related non-AIDS-defining cancer, but not for other malignancies.

Conclusions. In this nationwide cohort, pre-ART VL was an independent predictor of invasive cancer, whereas viremia profile during cART was not associated with cancer incidence.

Keywords. acquired immunodeficiency syndrome; anti-retroviral agents; HIV infection; neoplasms; viremia.

The association between human immunodeficiency virus infection (HIV) and cancer has been evident from the early years of the epidemic. Apart from acquired immune deficiency syndrome (AIDS)-defining tumors (Kaposi sarcoma, non-Hodgkin lymphoma, and invasive cervical cancer), a range of non-AIDS-defining malignancies are more common among people with HIV (PWH) [1, 2]. Although cancer incidence has declined in the combination antiretroviral therapy (cART) era, overall cancer incidence remained 60% higher in HIV-positive US veterans compared with uninfected controls [3]. Although PWH have higher prevalence of established risk factors for cancer [4], HIV-specific factors likely contribute to this excess risk [5]. Low CD4 counts (reflecting cellular immunodeficiency) have been linked to both AIDS-defining and non-AIDS-defining cancer [6, 7]. Still, immediate compared with deferred cART initiation has been associated with reduced cancer incidence [8]. This effect was independent of CD4 counts but partly mediated by plasma HIV ribonucleic acid (RNA) (viral load [VL]), suggesting that the degree of viral replication could be involved in the development of cancer among PWH [8].

Virologic response during cART could also influence cancer incidence. Several observational studies report increased risk of different cancer types in individuals with incomplete viral suppression [9–19]. Although most cART recipients achieve viral suppression, approximately 3%–10% of individuals in European and North American cohorts have low-level viremia

Received 28 December 2020; editorial decision 11 March 2021; accepted 12 March 2021.

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Open Forum Infectious Diseases®2021

DOI: 10.1093/ofid/ofab131

(LLV), commonly defined as repeatedly detectable VL below the threshold of virologic failure [20]. We recently reported increased mortality and non-AIDS morbidity in Swedish PWH with LLV; among serious non-AIDS events in this cohort, 29% were non-AIDS malignancies [21]. The relationship between cancer and LLV has only been explored in 1 study restricted to non-Hodgkin lymphoma, showing increased incidence in persons with LLV compared with those with viral suppression [22].

In the current study, we aimed to investigate whether the amplitude of pre-ART VL and the degree of viral suppression during cART are linked to cancer incidence. For this purpose, we have analyzed associations between viremia status in persons initiating cART and incident invasive cancer (of types known to have increased incidence among PWH), based on a cohort encompassing all PWH in Sweden 1996–2017 with linkage to national registers.

METHODS

Study Population

Participants of this study were identified from InfCare HIV, a register with clinical and virologic data from >99.9% of PWH registered in Sweden. All adults (≥15 years old) with a complete Personal Identity Number in this register were eligible for inclusion if they started cART between 1996 and 2017 (see Supplementary Table S1 for a list of regimens), had ≥1 VL measurement before receiving any antiretroviral agent (pre-ART VL), and ≥2 VLs available ≥6 months after cART initiation. For this study, InfCare HIV was linked to the Cancer Register, which is administered by the National Board of Health and Welfare and contains data on malignancies since 1958 [23]. The Cancer Register also contains information on date of death and underlying cause of death. To find cases of hepatitis B and C virus (HBV, HCV) coinfection not registered in InfCare HIV, the cohort was also linked to the Patient Register.

Endpoint Definitions

The outcome of interest was a composite consisting of invasive cancer types shown to have increased incidence among PWH compared with uninfected persons in a large meta-analysis [1], termed "HIV-related cancer." This included malignancies for which infectious etiology has been reported (non-Hodgkin and Hodgkin lymphoma, cervix cancer, vulva and vagina cancer, penis cancer, anal cancer, oral cavity and pharynx [excluding nasopharynx] cancer, nonmelanoma skin cancer, lip cancer, esophagus cancer, larynx cancer, eye cancer, hepatocellular carcinoma, Kaposi sarcoma, and stomach cancer), as well as the following malignancies (for which no infectious etiology has been shown): trachea, bronchus, and lung cancer; kidney cancer; multiple myeloma; leukemia; malignant melanoma; brain cancer; and testis cancer. Cancer forms without increased incidence among PWH were not included in the composite endpoint (a list of these diagnoses is presented in Supplementary Table S2). For backward compatibility, malignancies were classified using topography and morphology codes from the *International Classification of Diseases Oncology, Second Edition* (ICD-O/2) together with ICD-10 [24] (complete list of codes used for classification in Supplementary Table S3).

Measures of Viremia During Combination Antiretroviral Therapy

We used 2 separate measures of viremia during cART. First, total cumulative exposure to viremia during cART was calculated, starting from the first recorded VL obtained ≥6 months after starting cART, using viremia copy-years [25]. We used the trapezoidal rule, and the copy-years variable was $\log_{10}$-transformed. Second, to specifically assess the impact of LLV, participants were grouped into 3 categories: viral suppression (<50 copies/mL), LLV 50–999 copies/mL (≥2 consecutive VLs in this range, ≥1 month apart), and nonsuppression (≥1000 copies/mL). Since the relationships between LLV and cancer are largely unexplored, we chose a broad definition of LLV with an upper cutoff of 1000 copies/mL. Participants with single VL measurements in the range of 50–999 copies/mL were categorized as virally suppressed if these measurements were preceded and followed by undetectable VLs. Viremia category was included as a time-varying covariate, so that participants could change category over time. Reclassification was only possible to a higher category.

Statistical Analysis

This study was based on a nationwide cohort of PWH; consequently, no sample size calculation was performed. All participants were followed from the first VL recorded ≥6 months after start of cART until the first of the following events: first diagnosis of any of the malignancies of interest, death from any cause, loss to follow-up (defined as ≥12 months with no recorded VL), or administrative censoring (June 2017). Incidence rates of specific cancer diagnoses were calculated for the entire cohort, and age-standardized incidence rates to the Segi's world standard population were compared with the general population in Sweden for men and women, respectively.

To analyze the association between viremia and the risk of invasive cancer in the presence of the competing risk of noncancer death, we used proportional subhazard models with viral suppression as the reference category [26]. We checked the proportional subhazard assumption by fitting a separate model including time interaction for all covariates and found no indication of violation. Multivariable analysis included the following variables: sex, time-updated age, CD4 count before start of any type of ART (surrogate for HIV disease stage at start of ART), and injection drug use (IDU). To determine whether a possible association between viremia during cART and cancer was dependent on pre-ART viremia, which per se is a risk factor for LLV [27, 28], we also included

pre-ART VL (defined as last VL before receiving any antiretroviral agent) on a logarithmic scale in these models. Separately, pre-ART VL was also analyzed as a risk factor for invasive cancer; in these models, viremia during cART was included as a potential mediator. To further explore whether the association between cancer and viremia was restricted to specific categories of cancer, we fitted 3 separate models with the following outcomes: (1) AIDS-defining cancer, (2) infection-related non-AIDS-defining cancer, and (3) non-AIDS-defining cancer not related to infectious agents. We handled missing data using a complete-case approach and report the number of missing values for each step. We defined statistical significance as 2-sided $P < .05$.

Patient Consent Statement

The regional ethics committee of Lund, Sweden approved the study (2017/1023). This study did not include factors necessitating patient consent.

RESULTS

Study Participants

Of 10 855 individuals in the InfCare HIV cohort, 4931 (45%) (1) started cART in 1996–2017, (2) were ≥15 years old, (3) had ≥1 pre-ART VL and ≥2 VLs available ≥6 months after start of treatment, and (4) were not diagnosed with HIV-related cancer or lost to follow-up before the first VL ≥ months after cART initiation (Figure 1). Background characteristics by viremia category are presented in Table 1. The 4931 participants were followed for a median of 5.3 years, corresponding to 32 105 person-years of follow-up. Of the 2137 participants excluded due to missing pre-ART VL, 784 had complete data for other variables. Most of these participants were diagnosed with HIV during the first decade of the epidemic and had received antiretroviral drugs before VL testing was introduced in clinical care (Supplementary Table S4).

Incidence of Invasive Cancer

In total, 111 participants accounted for 116 cases of HIV-related cancer during follow-up. The overall incidence of the composite endpoint HIV-related cancer was 346 cases per 100 000 person-years. The most common diagnosis was non-Hodgkin lymphoma, followed by cervix cancer and lung cancer (Table 2). Compared with the general population, we observed higher sex- and age-standardized incidence of non-Hodgkin lymphoma, Kaposi sarcoma, cervix cancer, Hodgkin lymphoma, and anal cancer, respectively (Table 2). The majority of participants (107 of 111; 96%) had only 1 registered cancer diagnosis.

Associations Between Viremia and Invasive Cancer

There was no statistically significant association between overall cumulative exposure to viremia from 6 months after starting cART and HIV-related cancer in unadjusted analysis, nor after adjustment for sex, age, pre-ART CD4 count, pre-ART VL, and IDU (adjusted subhazard ratio [aSHR], 0.99; 95% confidence interval [CI], 0.85–1.2).

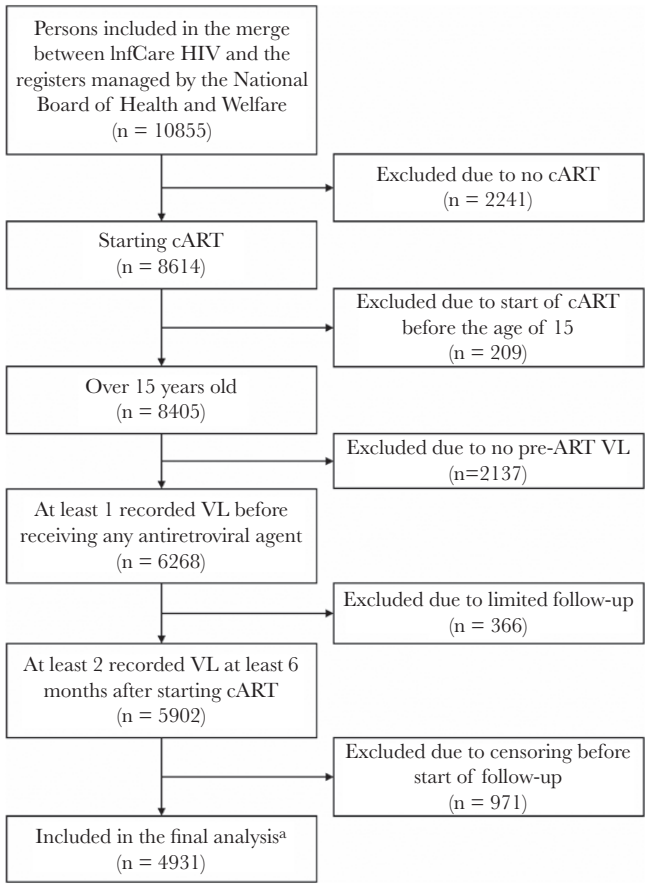

Figure 1. Exclusion flowchart. [a]Depending on the outcome, this number is slightly different in the different models (since participants are excluded if reaching the outcome during the 6 months between combination antiretroviral therapy [cART] initiation and start of follow-up). For the composite outcome of invasive cancer, the number is 4931. ART, antiretroviral therapy; VL, viral load.

In the analysis of 3 viremia categories, neither LLV nor nonsuppressed viremia had statistically significant association to HIV-related cancer compared with virological suppression (aSHR for LLV, 0.67; 95% CI, 0.30–1.5; aSHR for nonsuppression, 1.4; 95% CI, 0.89–2.4) (Table 3). In subanalysis, participants with nonsuppression had higher risk of AIDS-defining cancer compared with virologic suppression, but the difference was not statistically significant (aSHR, 2.0; 95% CI, 0.92–4.2). There was no association between viremia category and infection-related non-AIDS-defining cancer or non-AIDS-defining cancer not related to infectious agents (Table 4).

Higher pre-ART VL was associated with HIV-related cancer (SHR for VL $\log_{10}$, 1.4 (95% CI, 1.0–1.8). This effect remained after adjustment for age, sex, pre-ART CD4 count, and IDU (aSHR, 1.4; 95% CI, 1.0–1.8). Inclusion of viremia category during cART as a potential mediator did not change this effect (aSHR, 1.4; 95% CI 1.0–1.9), which remained statistically significant

Table 1. Characteristics of Study Participants Identified From the Swedish InfCare HIV Cohort

	Overall (*N* = 4931)	Virologic Suppression[a] (*n* = 3272; 66%)	Low-Level Viremia[b] (*n* = 438; 9%)	Nonsuppression[c] (*n* = 1221; 25%)
Age at start of cART, year	38 (31–46)	38 (31–46)	40 (33–49)	36 (30–43)
Male sex (%)	3064 (62%)	2105 (64%)	303 (69%)	656 (54%)
Median year of HIV diagnosis	2007	2009	2006	2001
Median year of start of cART	2009	2010	2007	2003
Transmission Group (%)				
Heterosexual contact	2658 (54%)	1729 (53%)	231 (53%)	698 (57%)
Male-to-male sexual contact	1520 (31%)	1112 (34%)	130 (30%)	278 (23%)
Injection drug use	278 (6%)	124 (4%)	27 (6%)	127 (11%)
Other	387 (8%)	234 (7%)	46 (11%)	107 (9%)
Transmission group missing	88 (2%)	73 (2%)	4 (1%)	11 (1%)
Born in Sweden (%)	1872 (38%)	1254 (38%)	177 (40%)	441 (36%)
Pre-ART VL, $\log_{10}$ copies/mL[d]	4.9 (4.3–5.4)	4.8 (4.2–5.3)	5.3 (4.8–5.8)	4.9 (4.3–5.4)
Pre-ART CD4 count, cells/μL[d]	247 (140–360)	257 (150–370)	180 (80–280)	250 (140–360)
HBsAg positive (%)	244 (5%)	139 (4%)	25 (6%)	80 (7%)
HBV status missing	2412 (49%)	1619 (49%)	202 (46%)	591 (48%)
Anti-HCV positive (%)	524 (11%)	269 (8%)	54 (12%)	201 (16%)
HCV status missing	557 (11%)	394 (12%)	46 (11%)	117 (10%)

Abbreviations: cART, combination antiretroviral therapy; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LLV, low-level viremia; VL, viral load.

NOTE: Data are presented as No. (%) or median (interquartile range).

[a]<50 copies/mL.

[b]50–999 copies/mL.

[c]≥1000 copies/mL.

[d]Refers to the last measurement before receiving any antiretroviral agent.

(Table 3). Apart from pre-ART VL, only age had a statistically significant relationship to invasive cancer (Supplementary Table S5). When dividing the composite endpoint HIV-related cancer into 3 groups, higher pre-ART VL had a statistically significant association with increased risk of AIDS-defining cancer and infection-related non-AIDS-defining cancer, but not with non-AIDS-defining cancer not related to infectious agents (Table 4).

DISCUSSION

In this long-term follow-up of a nationwide cohort of PWH starting cART, longitudinal viremia profiles during treatment were not associated with cancer incidence. However, the risk of cancer was independently associated with higher pre-ART VL, driven by increased incidence of AIDS-defining and infection-related non-AIDS-defining malignancies.

Although an effect of viremia during cART on cancer risk cannot be ruled out from our study, these results do not support the hypothesis that unsuppressed viremia during cART is associated with invasive cancer. In particular, LLV did not show associations with cancer (despite our comparatively high threshold level to define LLV, <1000 copies/mL).

Several observational studies have reported higher cancer incidence in persons with nonsuppressed viremia (using different thresholds, and in persons both with and without cART) for both AIDS-defining cancers [9–12, 15, 16, 22] and virus-related non-AIDS-defining cancer [11, 13, 14, 16, 17]. However, only 2 of these studies have clearly separated the effects of viremia before and after initiation of cART; in these, pre-ART VL was considered as a potential variable, but this was not included in the final model [9, 22]. Our findings are in agreement with those from a US-based multicenter clinical cohort, in which viral suppression at 6 months after start of cART had no statistically significant association with the risk of invasive cancer after adjustment for pre-ART VL [29].

Complex interactions may exist between viremia levels before and during cART and the risk of cancer. The increased cancer incidence associated with deferred ART initiation is partly mediated by higher pre-ART VL [8], which is also linked to lower likelihood of viral suppression during ART [27, 28]. Therefore, "pre-ART viremia" could be considered a confounder in the relationship between "viremia during cART" and cancer, and "viremia during cART" may be a mediator in the relationship between "pre-ART viremia" and cancer. It is interesting to note that the association between pre-ART VL and cancer did not change when including viremia during cART in the model, which suggests that this effect is mainly mediated by other factors. This type of mediation analysis could lead to bias, however, because it introduces the potential of mediator-outcome confounding in addition to exposure-outcome confounding [30]. With the possibility of residual confounding arising from unmeasured factors, such as socioeconomic condition [31], the results from this mediation analysis should be interpreted with caution.

Table 2. Incidence Rates of Invasive Cancer in the Study Cohort

	Incidence per 100 000 Person-Years (95% CI)	Number of Cases	Age-Standardized Incidence per 100 000 Person-Years (95% CI)		Age-Standardized Incidence in the Swedish General Population[a]	
			Men	Women	Men	Women
Composite endpoint	346 (287–416)	111				
AIDS-Defining Cancer						
Non-Hodgkin lymphoma	73 (49–109)	24	83 (17–149)	18 (0–40)	14	9
Kaposi sarcoma	18 (8–41)	6	21 (4–39)	0	1	0
Cervix cancer[b]	121 (73–201)	15	-	309 (0–683)	-	10
Infection-Related Non-AIDS-Defining Cancer						
Hodgkin lymphoma	30 (16–56)	10	28 (8–47)	4 (0–12)	3	2
Hepatocellular carcinoma	6 (2–24)	2	2 (0–5)	5 (0–15)	10	8
Stomach cancer	6 (2–24)	2	4 (0–10)	0	8	5
Vulva and vagina cancer[b]	8 (1–57)	1	-	3 (0–9)	-	2
Penis cancer[c]	10 (2–39)	2	4 (0–10)	-	2	-
Anal cancer	24 (12–48)	8	19 (4–34)	3 (0–9)	1	1
Oral cavity and pharynx SCC[d]	9 (3–28)	3	8 (0–16)	0	8	4
Nonmelanoma skin cancer	36 (21–64)	12	27 (11–42)	0	33	21
Lip cancer	-	0	0	0	1	1
Esophagus cancer	6 (2–24)	2	4 (0–10)	0	5	2
Larynx cancer	3 (0.4–21)	1	2 (0–5)	0	2	1
Eye cancer	3 (0.4–21)	1	0	4 (0–12)	1	1
Non-AIDS-Defining Cancer Not Related to Infectious Agents						
Trachea, bronchus, or lung cancer	42 (25–71)	14	26 (12–41)	10 (0–28)	30	29
Kidney cancer	6 (2–24)	2	2 (0–5)	8 (0–24)	11	7
Multiple myeloma	3 (0.4–21)	1	2 (0–5)	0	5	4
Leukemia	9 (3–28)	3	9 (0–20)	0	14	10
Malignant melanoma	21 (10–44)	7	16 (2–30)	4 (0–11)	26	27
Brain cancer	3 (0.4–21)	1	2 (0–7)	0	12	13
Testis cancer[c]	5 (0.7–35)	1	4 (0–12)	-	10	-

Abbreviations: AIDS, acquired immune deficiency syndrome; CI, confidence interval; SCC, squamous cell carcinoma.

NOTE: Age-standardization was made to Segi's world standard population.

[a] Calculated for the Swedish population ≥15 years old. The year 2009 (the median year of diagnosis for cancer cases among persons with human immunodeficiency virus in this cohort) is chosen for comparison. Data from the Statistics Database for Cancer, Swedish Cancer Register (https://sdb.socialstyrelsen.se/if_can/val.aspx. Accessed May 6, 2020).

[b]Only calculated for females.

[c]Only calculated for males.

[d]Excluding nasopharynx cancer.

Table 3. Proportional Subhazard Models for the Risk of Invasive Cancer Accounting for the Competing Risk of Noncancer Death

	Unadjusted	Adjusted for Sex, Age, Pre-ART CD4 Cell Count, and IDU	Full Model[a]
Viremia during cART	(*n* = 4931)	(*n* = 4474)	(*n* = 4474)
Virologic suppression[b]	1 (Ref)	1 (Ref)	1 (Ref)
Low-level viremia[c]	0.84 (0.40–1.8)	0.74 (0.34–1.7)	0.67 (0.30–1.5)
Nonsuppression[d]	1.2 (0.77–1.9)	1.5 (0.91–2.4)	1.4 (0.89–2.4)
Pre-ART VL (per $\log_{10}$ copies/mL)[e]	1.4 (1.0–1.8)	1.4 (1.0–1.8)	1.4 (1.0–1.9)

Abbreviations: cART, combination antiretroviral therapy; IDU, injection drug use; Ref, reference category; LLV, low-level viremia; VL, viral load.

NOTE: Results are subhazard ratios with 95% confidence interval.

[a]Fully adjusted model includes both viremia category during cART and pre-ART viral load.

[b]<50 copies/mL.

[c]50–999 copies/mL.

[d]≥1000 copies/mL.

[e]Refers to the last measurement before receiving any antiretroviral agent.

Table 4. Proportional Subhazard Models for the Risk of HIV-Related Cancer Grouped Into (1) AIDS-Defining Cancer, (2) Infection-Related Non-AIDS-Defining Cancer, and (3) Non-AIDS-Defining Cancer Not Related to Infectious Agents

	Unadjusted	Adjusted for Sex, Age, Pre-ART CD4 Cell Count, and IDU	Full Model[a]
AIDS-Defining Cancer[b]			
Viremia during cART	(*n* = 4949)	(*n* = 4489)	(*n* = 4489)
Virologic suppression[c]	1 (Ref)	1 (Ref)	1 (Ref)
Low-level viremia[d]	0.96 (0.29–3.2)	0.72 (0.16–3.2)	0.61 (0.14–2.7)
Nonsuppression[e]	2.0 (0.97–4.1)	2.0 (0.93–4.4)	2.0 (0.92–4.2)
Pre-ART VL (per $\log_{10}$ copies/mL)[f]	1.3 (0.77–2.2)	1.8 (1.0–3.0)	1.8 (1.0–3.2)
Infection-Related Non-AIDS-Defining Cancer[g]			
Viremia during cART	(*n* = 4997)	(*n* = 4531)	(*n* = 4531)
Virologic suppression[c]	1 (Ref)	1 (Ref)	1 (Ref)
Low-level viremia[d]	0.46 (0.11–2.0)	0.44 (0.10–1.9)	0.37 (0.08–1.7)
Nonsuppression[e]	0.86 (0.42–1.8)	1.3 (0.62–2.6)	1.2 (0.60–2.5)
Pre-ART VL (per $\log_{10}$ copies/mL)[f]	1.8 (1.3–2.5)	1.6 (1.1–2.3)	1.7 (1.1–2.5)
Non-AIDS-Defining Cancer Not Related to Infectious Agents[h]			
Viremia during cART	(*n* = 5001)	(*n* = 4536)	(*n* = 4536)
Virologic suppression[c]	1 (Ref)	1 (Ref)	1 (Ref)
Low-level viremia[d]	1.2 (0.34–4.0)	1.1 (0.33–3.9)	1.2 (0.33–4.2)
Nonsuppression[e]	1.1 (0.44–2.7)	1.4 (0.50–3.8)	1.4 (0.50–4.0)
Pre-ART VL (per $\log_{10}$ copies/mL)[f]	1.1 (0.72–1.6)	0.87 (0.54–1.4)	0.86 (0.53–1.4)

Abbreviations: AIDS, acquired immune deficiency syndrome; cART, combination antiretroviral therapy; IDU, injection drug use; LLV, low-level viremia; Ref, reference category; VL, viral load.

NOTE: Results are subhazard ratios with 95% confidence interval. Proportional subhazard models are used to account for the competing risk of noncancer death.

[a]Fully adjusted model includes both viremia category during cART and pre-ART viral load.

[b]Non-Hodgkin lymphoma, Kaposi sarcoma, cervix cancer.

[c]<50 copies/mL.

[d]50–999 copies/mL.

[e]≥1000 copies/mL.

[f]Refers to the last measurement before receiving any antiretroviral agent.

[g]Hodgkin-lymphoma, hepatocellular carcinoma, stomach cancer, vulva and vagina cancer, penis cancer, anal cancer, oral cavity and pharynx squamous cell carcinoma (excluding nasopharynx cancer), nonmelanoma skin cancer, lip cancer, esophagus cancer, larynx cancer, and eye cancer.

[h]Trachea, bronchus, or lung cancer, kidney cancer, multiple myeloma, leukemia, malignant melanoma, brain cancer, and testis cancer.

The association between high pre-ART VL and incident cancer in this cohort supports results from the Strategic Timing of Antiretroviral Therapy (START) trial and from a recent North American multicenter cohort study, showing an effect of early ART initiation on the incidence of HIV-related cancer [8, 32]. In START, the median VL at time of ART initiation was 13 462 and 41 525 copies/mL in the 2 study arms, respectively [33]. The importance of VL could vary for different cancer types, however, as demonstrated in 2 recent North American cohort studies. Whereas VL measures between 8.5 and 4.5 years in the past were the most predictive for risk of anal cancer (entirely mediated by lowering of CD4) [19], viremia levels during the preceding 3.5–0.5 years were the most predictive of non-Hodgkin lymphoma [18]. Viremia levels were not separated with regard to ART status in either of these studies. Because the individual numbers of these cancer diagnoses were low in our material (8 and 24, respectively), we were not able to reproduce these analyses with regard to VL before and during cART. In our study, the previously reported association between non-Hodgkin lymphoma and LLV was not corroborated (Supplementary Table S6) [22]. Our material includes 24 cases of non-Hodgkin lymphoma (compared with 37 in [22]), none of which occurred in a person with LLV.

Previous reports on HIV viremia and cancer have focused on separate cancer forms or different composite outcomes. These discrepancies make comparisons between studies difficult. For this study, we based our composite endpoint on a large meta-analysis that identified cancer forms with increased prevalence among PWH [1]. This list is highly consistent with a more recent register-based study on 448 258 PWH [2]. In this latter report, stomach, brain, and kidney cancers did not have increased prevalence among PWH; our endpoint could hence be slightly overinclusive (these diagnoses constituted 5% of cases in our material) [2]. Because our composite outcome is heterogenous, it is possible that viremia only affects some components, and that this could be obscured by a neutral or opposite effect on other diagnoses. To investigate this, we separated the outcome into 3 groups. In subanalyses, higher pre-ART VL was only associated with increased risk of AIDS-cancer and infection-related non-AIDS-defining cancer. This finding is in accordance with previous studies [8, 16, 18, 19, 32], supporting the link between HIV replication and tumors with microbial etiology.

The mechanisms involved in this association likely reflect the impact of immune function for control of infection-related tumors. Cellular immunosuppression is a well established risk factor for both AIDS-defining [6] and virus-related non-AIDS-defining cancer [7]. Both current and previous immunosuppression (which can be estimated through nadir CD4 count or cumulative time below a certain CD4 threshold level) have been shown to have predictive capacity for the development of cancer [34, 35]. It is interesting to note that we found an effect of HIV viremia independent of pre-ART CD4 counts. Because complex relationships between CD4 trajectories and different types of cancer may exist, the effect between viremia and invasive cancer could also be influenced by CD4 counts during ART. Another potential mechanism could be chronic immune activation accompanying HIV replication, which has been linked to incident cancer in PWH [36]. In addition, a direct lymphomagenic role of HIV has been proposed [37].

Our study has certain limitations inherent to its observational design. First, exclusion of participants without recorded pre-ART VL could lead to selection bias. This group mainly consisted of individuals diagnosed before introduction of cART, and exclusion of these participants likely make our results more generalizable to current settings (Supplementary Table S4). Second, we used pre-ART VL as a proxy for total exposure to viremia before start of cART. Other studies have used viremia-copy years to estimate total viremia exposure; however, this model is highly dependent on assumptions, because time of HIV acquisition is seldom known, and prone to bias due to differences in sampling frequency [38]. Furthermore, we lack information on some factors that may be involved in development of HIV-related cancer, such as smoking and alcohol use [4]. We performed a separate analysis excluding outcomes with known link to HBV and HCV (hepatocellular carcinoma and non-Hodgkin lymphoma), which showed similar associations between cancer and viremia during cART and pre-ART VL, respectively (Supplementary Table S7). Moreover, differences in cancer incidence could be due to diagnostic bias, for example, because of targeted screening or care-seeking behavior patterns [39]. To address this issue, we compared cancer stage at diagnosis between the 3 different viremia categories for diagnoses with available and relevant TNM (tumor, lymph nodes, metastasis) classification, with no statistically significant differences in distribution observed (data not shown). Finally, even though we analyzed a nationwide cohort, the low number of outcomes did not allow us to assess the relationship of viremia and specific cancer forms.

This study represents long-term follow-up of a national cohort in a setting with relatively equal access to care [40] and is based on data from the Swedish Cancer Register, which has high overall completeness with 99% of cases verified morphologically [23]. To our knowledge, this is the first study to specifically address the impact of LLV during cART on the risk of cancer. Furthermore, by entering pre-ART VL in the final model, we have been able to delineate the effects of pre-ART viremia and viremia during cART. Finally, although most other studies have right-censored deaths, we used a competing risk approach, which leads to less biased results [26].

CONCLUSIONS

In conclusion, in this nationwide cohort of PWH initiating cART, pre-ART VL was independently associated with cancer incidence, whereas no such association was observed for longitudinal HIV RNA profiles during cART. These findings support early start of cART as the major HIV-specific intervention for reducing cancer incidence among PWH.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases online*. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

This study benefitted from data provided by the InfCare HIV Quality Assurance register.

Disclaimer. The funders had no impact on the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Financial support. This work was funded by Department of Research and Development, Region Kronoberg, Växjö (0825-001 8298; to O. E.); the Swedish State under the agreement between Swedish government and the county councils, the ALF-Agreement (ALFGBG-717531; to M. G.); Gilead Nordic Fellowship (2018004132; to P. B.); and Region Skåne (REGSKANE821541; to P. B.).

Potential conflicts of interest. O. E. reports grants from Pfizer, outside the submitted work. M. G. reports personal fees from Gilead, personal fees from GSK/ViiV, personal fees from MSD, other from Gilead, other from GSK/ViiV, personal fees from Biogen, personal fees from Novocure, personal fees from Amgen, and personal fees from Novo Nordic, outside the submitted work. P. B. reports grants from Swedish State, grants from Region Skåne, grants from Gilead Nordic Fellowship during the conduct of the study, and personal fees from Gilead, outside the submitted work. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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