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Short-Term and Long-Term Effects of Highly Active Antiretroviral Therapy on the Incidence of Herpes Zoster in HIV-Infected Children

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Abstract

Background—Highly active antiretroviral therapy (HAART) has reduced herpes zoster (HZ) incidence in HIV-infected children, yet it remains common.

Methods—We evaluated perinatally HIV-infected youth with varicella infection enrolled between 1993 and 2006 in a prospective cohort study. Incidence rates (IRs) and 95% confidence intervals of HZ were estimated by calendar year, age group, and HAART use. The effect of initiating HAART was also evaluated by fitting Cox survival models adjusted for potential confounders.

Results—Among 536 perinatally infected children with documented prior varicella (median follow-up = 6.8 years), 116 (22%) developed HZ (IR = 3.2 events/100 person-years, confidence interval: 2.6 to 3.8). IRs increased from 1993 to 1996 and then declined significantly through 2006 ($P < 0.001$). However, an IR of 1.4–3.1 HZ episodes per 100 person-years persisted from 2001 to 2006. The risk of HZ was higher for those with lower CD4% or in Centers for Disease Control and Prevention clinical class C. The IR of HZ was similar in the 90 days before or after initiation of HAART but declined significantly after more than 90 days of HAART.

Conclusions—Although HAART has markedly reduced the IR of HZ, it remains a frequent complication in HIV-infected children. The risk of HZ is similar in the 90 days before and after initiating HAART.

Keywords

herpes zoster; pediatric HIV; immune reconstitution; antiretroviral therapy

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INTRODUCTION

Herpes zoster (HZ), which is the clinical manifestation of reactivation of varicella zoster virus (VZV) latent in sensory ganglia after primary infection (varicella), commonly occurs in patients with deficits in T-cell mediated immunity (CMI).¹ It was recognized early in the HIV epidemic that HZ indicates the presence of significant immune deficiency.² This was subsequently confirmed by demonstrating a striking increase in age-specific rates of HZ in HIV-infected individuals and by recording HZ cases of unusual severity and duration.²⁻⁶

HZ in HIV-infected children is now less frequent and less severe as a consequence of the widespread utilization of highly active antiretroviral therapy (HAART).⁵⁻⁷ Because HZ rates in HIV-infected children have been correlated with CD4 percent and number,⁵⁻⁷⁻⁹ it is likely that the decline in HZ incidence rates (IRs) observed in recent years in HIV-infected children reflects the reconstitution of VZV-specific CMI that occurs, to a variable extent, after HAART.¹⁰⁻¹¹ An additional factor in reducing HZ in HIV-infected children in the United States may be universal varicella vaccination, which began shortly before HAART came into widespread use.¹² Although immunizing HIV-infected children is likely to prevent varicella and thereby prevent HZ,¹³ another important effect of universal vaccination is mediated by establishing herd immunity that reduces exposure to VZV.¹⁴⁻¹⁵ In contrast to the observed overall decline in HZ incidence that followed the introduction of HAART, there are observations and case series describing a transient increase in the incidence of HZ shortly after HAART initiation.¹⁶⁻¹⁹ It has been suggested, albeit based on relatively small numbers of patients, that HZ in this setting is analogous to the immune reconstitution inflammatory syndromes reported with many bacterial, mycobacterial, and fungal pathogens.¹⁷⁻¹⁹

A recently published retrospective analysis reported the IRs of HZ in a cohort of HIV-infected children that spanned the pre-HAART and post-HAART eras and included 24 fully evaluable first cases of HZ.⁷ The analysis we describe covered a similar period, but was based on 454 cases of HZ, thereby allowing more detailed evaluation of (1) past and recent IRs of HZ, (2) the impact of HAART on HZ incidence, including the immediate post-HAART initiation period, and (3) other risk factors for HZ.

METHODS

Study Population

The source population was Pediatric AIDS Clinical Trials Group (PACTG) protocol 219/219C. Enrollment into PACTG 219 of HIV-exposed and HIV-infected children participating in PACTG treatment trials began in 1993. PACTG 219C, which was a revision of PACTG 219 introduced in 2000, included HIV-infected children younger than 24 years regardless of their participation in a PACTG treatment trial. All versions of PACTG 219/219C were approved by institutional review boards at 89 participating sites across the United States and Puerto Rico. Informed written consent was obtained before participation from a parent or legal guardian or from the participants directly when age appropriate.

This analysis considered a subset of the perinatally HIV-infected children and adolescents enrolled before March 2006 who were deemed “at risk” of developing HZ because of prior infection with varicella as evidenced by (1) a documented diagnosis of varicella (n = 536) or (2) a documented diagnosis of HZ without documented varicella (n = 338).

Data Collection

At enrollment in PACTG 219C, lifetime histories of antiretroviral therapy (ART) and major diagnoses were collected. Study visits were conducted every 3-6 months (depending on

protocol version and age of child), at which sociodemographic characteristics, diagnoses, ART, and CD4 measures were recorded.²⁰ PACTG 219C collected start and stop dates for all ART medications before study entry and during follow-up, whereas PACTG 219 only indicated whether individual ART drugs had been initiated or discontinued since the last visit. Thus, for those on PACTG 219 only, we assumed that the initiation of ART occurred at the midpoint between study visits. Similarly, HIV RNA viral load was routinely monitored in PACTG 219C, but was not widely available before 1999, and was not routinely measured in PACTG 219. However, viral load information was available from a subset of children who were coenrolled in other PACTG studies. HAART was defined as concurrent use of at least 3 antiretroviral drugs from at least 2 drug classes. Because some diagnoses of varicella and/or HZ occurred before study entry, participants of the current analysis could have contributed person-time before enrollment in PACTG 219/219C. Therefore, information on some study covariates other than ART (such as CD4%) was not available for some subjects before study entry. Our analysis thus combines retrospective data collection with prospective monitoring after study entry.

Statistical Analysis

The primary outcome for our analysis was diagnosis of incident HZ. Follow-up for each subject began 30 days after the date of varicella diagnosis. When the date of varicella diagnosis was not known, it was imputed as the period-specific mean age at varicella diagnosis (4.7 years, before 1996; 5.5 years, 1996-2000; 7.7 years, 2001-2006) calculated from study participants with documented varicella dates or at 219C enrollment, whichever occurred earlier. If a diagnosis of HZ among this subset occurred before the mean varicella age was reached and before study entry, follow-up was assumed to start 30 days before the diagnosis of HZ ($n = 54$). Thus, “baseline” for this study was defined as the date of known or estimated varicella infection, and baseline characteristics are those values measured at or before this date. Follow-up for primary analyses continued until the earliest event of a diagnosis of HZ, varicella vaccination, death, or the last documented study visit date on or before December 31, 2006. For the analysis of recurrent HZ, follow-up in person-time was considered to resume 30 days after the date of any diagnosis of HZ.

IRs and 95% confidence intervals (CIs) of HZ and P values for linear trend were computed based on a Poisson distribution. For covariates which could change during followup (time-varying covariates; eg, age, CD4%, HIV viral load, and HAART status), we calculated person-time of follow-up within each level of a covariate and attributed HZ events to the level corresponding to the most recent measure at the time of the HZ event. To evaluate whether effects of HAART initiation were confounded by disease severity at the time of initiation, we also evaluated the IR for HZ in the 90-day period before HAART initiation and compared it with the 90-day period after HAART initiation.

Cox proportional hazards regression models and extended Cox models including time-varying covariates were used to estimate associations of covariates with time to HZ, as reflected by hazard ratios (HRs) and their corresponding 95% CIs. Final reduced multivariate Cox models evaluated the effect of HAART as a time-dependent covariate adjusting for all other covariates with $P < 0.10$ as fixed baseline covariates.

A fundamental difficulty in evaluating IRs for HZ is that dates of varicella diagnoses are often not documented. Thus, inclusion of subjects with either a documented varicella diagnosis or an assumed varicella diagnosis based on reported HZ diagnosis will tend to yield overestimates of IRs. We therefore evaluated a second HZ cohort by including only those participants with documented varicella dates. Evaluation of this subcohort will tend to yield underestimates of IRs because many additional HZ cases were known to occur without information on prior varicella and could not be included in this latter analysis. We therefore

present IRs from both cohorts to provide a range of possible true IRs. In addition, all Cox models were repeated among the subset of study participants with known varicella dates to evaluate the sensitivity of model results. All reported *P* values and CIs are 2 sided, and analyses were conducted using SAS 9.1 (SAS Institute, Cary, NC) and Stata Version 8 (Stata Corporation, College Station, TX) based on data submitted to the data management center by February 2007.

RESULTS

A total of 874 children and adolescents from PACTG 219/219C were identified with VZV infection based on either (1) documented dates of varicella ($n = 536$; 61%) or (2) varicella implied by a verified HZ diagnosis ($n = 338$; 39%). The median duration of follow-up for all 874 subjects was 5.2 years. A summary of their characteristics is provided in Table 1 by HZ diagnosis status. At the time of varicella, most were relatively healthy; only 12% had CD4% <15. Participants who developed HZ were more likely to be born in earlier years; to have CD4% <15; and to not be on HAART, than those who did not develop HZ.

Incidence of HZ in HIV-Infected Children

Because estimating IRs for HZ is complicated by the fact that dates of varicella are often not documented, we present results based on the full HZ cohort (including those with either known or assumed prior varicella) and for the subset with known dates of varicella. There were 454 cases of HZ (52%) among 874 subjects in the full HZ cohort. Figure 1 indicates an almost 4-fold rise in the incidence of HZ in the total study population from before 1993 until 1996, after which the incidence declined by over half by 2000 and remained relatively stable at 4.1-6.6 cases of HZ per 100 person-years. When the study population was limited to the 536 subjects with documented varicella dates, 116 HZ cases (22%) were recorded, and the pattern of HZ incidence by calendar year was very similar (Fig. 1), but the IRs were lower. IRs in this subset since 2000 ranged from 1.4 to 3.1 cases per 100 person-years.

Table 2 presents a summary of IRs for the full HZ cohort by risk factors of interest. There were no significant differences in rates of HZ by race/ethnicity, gender, or Centers for Disease Control and Prevention (CDC) class. However, there were significant trends of higher IRs with lower CD4 percent levels, either nadir CD4% or the current CD4%. Higher HZ IRs were also associated with higher HIV RNA levels, either peak HIV RNA level or the current HIV RNA level. IRs tended to be higher for children 0-2 or 3-5 years old as compared with children aged 6 or older (trend test $P = 0.04$). IRs for HZ were significantly lower while subjects were on HAART than while off HAART (7.4 vs. 10.6 cases/100 person-years, $P < 0.001$). Although the IR was greater within the 90 days immediately after initiation of HAART as compared with HAART 90 days or more after initiation (21.4 vs. 6.9 cases/100 person-years, $P < 0.001$), it was no different from the IR in the 90-day pre-HAART period (21.4 vs. 26.8, $P = 0.48$).

When the above analyses were repeated evaluating all risk factors for the subset of HZ cases with known dates of varicella (Table 3), the IRs were lower, but comparisons were similar to those of the full cohort, except that there was no significant difference in IRs by age group ($P = 0.56$) and those designated as CDC clinical class C had significantly higher IRs (IR = 4.0 vs. 2.7, $P = 0.05$). The IR of HZ in the 90-day pre-HAART period was again almost identical to the IR during the immediate 90-day post-HAART period.

Risk Factors for HZ

The Cox proportional hazards models for univariate associations for time to HZ are summarized in Table 4. Among the full HZ cohort, univariate factors associated with

increased risk of HZ included lower CD4% at the time of varicella and lower time-varying nadir CD4%; HIV RNA >10,000 copies per milliliter or missing relative to <10,000 copies; classification with AIDS at entry or during follow-up as reflected by CDC clinical class C; and being less than 90 days after initiation of HAART. There was also a significant reduction in risk of HZ over calendar time based on the year in which varicella infection was diagnosed and for those aged ≥ 6 years at VZV diagnosis. In addition, initiation of HAART before varicella or during follow-up after varicella was associated with a significant protective effect. Among the restricted HZ cohort with known dates of varicella (also Table 4), the results were generally similar except that initiation of HAART before varicella or during follow-up after varicella was no longer significantly protective (although the estimated HR = 0.82 was similar to that of the full HZ cohort), and age at varicella was no longer associated with risk of HZ, in parallel with the results of the incidence analyses in Tables 2 and 3.

In multivariate adjusted Cox models (Table 5), no effect of year of varicella infection, race/ethnicity, or gender was detected. After reducing the multivariate model to a final model, an increased risk of HZ was identified for those with lower CD4% or designation as CDC clinical class C at the time of varicella or during follow-up after varicella, whereas reduced risk of HZ was observed for children who were at least 6 years of age at the time of varicella infection or who had initiated HAART more than 90 days previously. In this analysis, there was also an increased risk of HZ (HR = 1.47) within the first 90 days after initiation of HAART compared with those who had not initiated HAART, although this analysis does not distinguish between the 90-day pre-HAART period vs. more than 90 days before HAART initiation.

Sensitivity analyses conducted using the subset with known dates of varicella infection provided similar results (Table 6), except that age was not significant. In the final multivariate Cox model, for this subgroup, parameter estimates were generally in the same direction and of a similar magnitude but no longer statistically significant due to the smaller sample size. In particular, those who had initiated HAART more than 90 days previously had a 49% reduction in risk of HZ, whereas the risk of HZ was slightly (although not significantly) increased in the first 90 days after HAART initiation, as compared with those who had not initiated HAART.

Recurrent HZ in HIV-Infected Children

Of the 454 subjects who developed HZ, 2 were subsequently lost to follow-up within 30 days. One hundred nineteen (26%) of the remaining 452 had 1 or more subsequent recurrences, for a total of 182 subsequent cases of HZ. Twenty-three children had 3 cases of HZ, and 16 had 4 or more cases. The incidence of recurrent HZ over the study period had a pattern similar to that observed for the incidence of first cases of HZ (Fig. 2), declining from a peak in 1995-1996 and stabilizing after 1999. Among the subset of those 119 subjects with recurrent HZ, the median time to first recurrence was 22 months. Of the 187 subjects who were on HAART at the time of first diagnosis of HZ, 27 subjects (14%) had a recurrence, as compared with 92 subjects (35%) with a recurrence among the 265 not on HAART at the time of first HZ.

DISCUSSION

During an extended follow-up of HIV-infected children who had prior varicella, the annual IR of HZ rose steadily during the early 1990s (pre-HAART era) to a peak in 1995 (Fig. 1, VZV cohort). This peak, greater than 9 cases per 100 patient-years, is probably an underestimate because the occurrence of prior varicella was not known or recorded for some subjects who developed HZ. The increase in incidence from the beginning of our

observation period probably reflects the aging of subjects and the progression of their HIV infection during the long follow-up interval. This peak HZ incidence is 3-fold higher than reported in a summary of opportunistic infections occurring in HIV-infected children participating in treatment trials,⁴ although that analysis only included events that occurred during the treatment period of each trial and was based on treatment trials that often involved limited age groups and ART that was not optimal. In addition, this and other studies did not limit their consideration to subjects with prior varicella.^{4,8} The peak incidence we observed was also 3-fold higher than that reported by Wood et al,⁷ who used methods comparable to ours. After the peak observed in 1995, the incidence of HZ declined from 1996 to 1999 and thereafter remained at 2.0-2.5 cases per 100 patient-years in subjects with known dates of varicella. This decline is inversely related to the increasing proportion of HIV-infected children who received HAART during this time (Fig. 1), most of whom subsequently achieved significant return of immune responses.²¹ When the incidence of HZ was calculated on the basis of follow-up of all subjects with presumed latent VZV (ie, those with known varicella or known HZ), the shape of the incidence-by-year curve was very similar, although the IRs were 2- to 3-fold higher. Because this is likely an overestimate of the incidence of HZ, the curve of actual incidence likely lies between these 2 curves.

An additional contributor to the decline in HZ incidence in HIV-infected children might be the universal application of varicella vaccine to young children. However, this decline was observed in children with known prior varicella, and Wood et al⁷ observed the same decline in children with known varicella. Thus, it is likely that recovery of immune responses with HAART is the primary factor in the decline of HZ incidence. We excluded or censored 30 vaccine recipients from our analysis.

The IRs of HZ was significantly more likely to occur in subjects with lower CD4% and higher HIV RNA viral load. These factors are all direct or indirect measures of immune responsiveness in HIV-infected people. It is well established that VZV-specific CMI is necessary to maintain VZV latent in sensory ganglia and to prevent HZ.^{22,23} The magnitude of HIV RNA viral load has been established as an independent marker for immunological dysfunction.^{24,25} The lowest CD4% and highest HIV viral load at any point in the history of a child also correlated with the likelihood of HZ, indicating that all aspects of maximal immune suppression are not readily reversed by HAART. The univariate and multivariate Cox models for time to HZ reinforced the strong association of low CD4% with the incidence of HZ. In the univariate models, we also observed a significant reduction in risk of HZ over calendar time and as a function of the age at which varicella occurred. This probably reflects the likelihood of being on HAART at the time of varicella, and also the fact that early in the epidemic, the older children represented a selective cohort with relatively long-term survival and therefore a bias toward greater immune competence.

Lower CD4% and higher HIV viral load at the time of varicella constituted another risk factor for HZ. This confirms the observations of Gershon et al²⁶ that related the occurrence of HZ in HIV-infected children to their CD4 count at the time of varicella and suggests the failure to establish adequate VZV-specific T-cell memory. This failure is similar to that observed in HIV-uninfected infants who develop varicella in the first year of life. These children have diminished VZV-specific CMI responses after varicella, compared with older children who develop varicella, and are more likely to develop HZ in early childhood.^{27,28} Such an explanation is consistent with our finding that being on HAART at the time of varicella significantly decreases the likelihood of subsequent HZ.

As expected by the relationship between immune measures and the incidence of HZ, the analysis of risk factors for the full study cohort indicated that the incidence of HZ was significantly greater in subjects not on HAART than in those on HAART. This effect of the

timing of HAART on the incidence of HZ, which confirms the findings of Wood et al,⁷ was readily apparent in the univariate and multivariate Cox models consistent with the importance of adequate VZV-specific immunity in preventing HZ. Although the incidence of HZ was significantly greater within the first 90 days after instituting HAART than in the extended period after this interval, this early post-HAART effect on HZ incidence is not explained by the occurrence of an immune reconstitution phenomenon because the 90-day pre-HAART and the 90-day post-HAART IRs were very similar. The high IR in the early post-HAART period is most likely explained by the depressed level of VZV-specific CMI in many patients just before embarking on HAART. Given the pathophysiology of HZ, it is difficult to devise a mechanism whereby reactivation of VZV would be enhanced by immune reconstitution because depression of VZV-specific immune responses, and not increased responses, is believed to be the final path for VZV reactivation.²² Moreover, there is no known reservoir of VZV antigens accumulating in ganglia of untreated patients that would be the target of a reconstitution syndrome, by analogy with the mechanism invoked, when bacterial, mycobacterial, and fungal antigens stimulate an immune reconstitution syndrome.²⁹

We did not observe an association of African American ethnicity with a reduced risk for HZ, unlike that reported by previous epidemiologic studies in immunocompetent adults.³⁰⁻³² These studies were quite different from ours in design, examined immune competent populations, and reported results from adult populations.

Our analysis also documented a high proportion of subjects with HZ who had 1 or more subsequent episodes of HZ, with an incidence-by-year pattern similar to that for first episodes. Almost one third of these subjects had 3 or more episodes.

This large long-term follow-up of HIV-infected children indicates that HZ remains a common infectious complication in the post-HAART era, where the HZ IR is at least 10 times greater than reported from uninfected children.³³⁻³⁴ The high prevalence of HZ represents a significant burden for HIV-infected children, their caretakers, and their medical providers and has the potential to temporarily interfere with specific therapy for HIV and temporarily increase the quantity of circulating HIV. This persistent high IR is partially explained by children who have a failed response to HAART as indicated by the correlation of HZ incidence with CD4%. This is probably especially true of the patients who had multiple episodes of HZ. It is also likely that some patients who developed HZ had an incomplete response to HAART. There is some evidence that VZV-specific CMI, which is essential for maintaining latency of VZV in ganglia, may fail to recover in many HIV-infected patients despite a vigorous increase in CD4 count and CD4%.³⁵ That evidence suggests that in some patients, certain specific antigens must be presented anew to the immune system to stimulate adequate functional immune responses and to develop adequate and persisting specific immune memory. This is not a problem with ubiquitous antigens (eg, *Candida*) to which specific immune responses are readily reestablished, whereas VZV-specific immunologic memory cannot be reestablished without either subclinical reactivation of VZV or an attack of HZ.³⁴ This is also consistent with our observation that the CD4% at the time of HZ has increased substantially since HAART was introduced. Thus, comparing CD4 lymphocytes at the time of HZ (<15%; 15%-24%; 25%), we found that before 1996 these categories contained 56%, 27%, and 16% of HZ cases, respectively; from 1996 to 2000, the distribution was 44%, 24%, and 31% and from 2001 to 2006, the distribution was 28%, 35%, and 35%. This indicates that an increasing proportion of HZ in HIV-infected children is occurring at higher CD4%, consistent with our argument that immune reconstitution is not "functionally" complete. This suggests that a VZV vaccine could be used to boost immune responses in these children, as it does in normal adults with declining VZV-specific CMI,²² and thereby further reduce the incidence of HZ. Phases 1

and 2 pilot studies of this concept have been undertaken by administering the licensed varicella vaccine to HIV-infected children and adults who previously had varicella (Gershon AA, MD, Levin MJ, MD, Weinberg A, MD, unpublished data, 2008; Weinberg A, MD, Brady K, MD, Lavin M, MD, MacGregor R, MD, unpublished data, 2005). A better candidate to test this concept is the more potent VZV-containing vaccine that is being administered to elderly people to prevent and/or attenuate HZ.³⁶

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FIGURE 1.

Incidence of HZ by year for the full HZ cohort and for the subset with known varicella dates, with percent receiving HAART by year.

FIGURE 2.

Incidence of first HZ and subsequent recurrence rates for HZ by year for the full HZ cohort, with percent initiating HAART by year.

TABLE 1

Baseline Demographic and Health Characteristics for HZ Study Participants

	Total (N = 874), n (%)	HZ Status		P
		Noncase (n = 420), n (%)	HZ Case (n = 454), n (%)	
Sex				
Male	429 (49)	209 (50)	220 (48)	0.735 *
Female	445 (51)	211 (50)	234 (52)	
Race/ethnicity				
White non-Hispanic	130 (15)	62 (15)	68 (15)	0.690 ‡
Black non-Hispanic	494 (57)	245 (58)	249 (55)	
Hispanic	235 (27)	107 (25)	128 (28)	
More than 1 race	15 (2)	6 (1)	9 (2)	
Birth cohort				
Median	1990	1992	1989	<0.001 ‡
pre-1985	107 (12)	26 (6)	81 (18)	
1986-1990	362 (41)	136 (32)	226 (50)	
1991-1995	351 (40)	213 (51)	138 (30)	
1996-2000	52 (6)	43 (10)	9 (2)	
2001-2006	2 (0)	2 (0)	0 (0)	
Varicella date				
Imputed	338 (39)	0 (0)	338 (74)	<0.001 *
Known	536 (61)	420 (100)	116 (26)	
Age at varicella (yrs)				
Median	5	5	5	0.508 ‡
<6	622 (71)	260 (62)	362 (80)	
6	252 (29)	160 (38)	92 (20)	
Year of varicella				
Median	1995	1997	1994	<0.001 ‡
pre-1990	82 (9)	15 (4)	67 (15)	
1991-1995	375 (43)	121 (29)	254 (56)	
1996-2000	364 (42)	242 (58)	122 (27)	
2001-2006	53 (6)	42 (10)	11 (2)	
CDC class at varicella onset				
CDC class C	193 (22)	109 (26)	84 (19)	0.009 *
Not class C	681 (78)	311 (74)	370 (81)	
CD4% at varicella onset				
Median	27	31	21	<0.001 ‡
<15	101 (12)	31 (8)	70 (15)	
15-25	110 (13)	57 (14)	53 (12)	
>25	275 (31)	200 (48)	75 (17)	

	Total (N = 874), n (%)	HZ Status		P
		Noncase (n = 420), n (%)	HZ Case (n = 454), n (%)	
Missing/unknown	388 (44)	132 (31)	256 (56)	
Viral Load at varicella onset				
Median	17878	9175	43066	<0.001 [‡]
<10,000 copies/mL	80 (9)	64 (15)	16 (4)	
>10,000 copies/mL	111 (13)	60 (14)	51 (11)	
Missing/unknown	683 (78)	296 (70)	387 (85)	
HAART				
Never on HAART	364 (42)	97 (23)	267 (59)	<0.001 [‡]
HAART at varicella onset [§]	156 (18)	110 (26)	46 (10)	
HAART after varicella onset	354 (41)	213 (51)	141 (31)	

* Fisher exact test.

[†] Pearson χ^2 test.

[‡] Kruskal-Wallis test.

[§] Initiation of HAART before the date of known or imputed varicella diagnosis.

TABLE 2

IRs for HZ in Full HZ Cohort by Demographic Characteristics, Health Status, and HAART Exposure

Characteristics*	No. Events	No. at Risk	Person-Years	IR (per 100 Person-Years)	95% CI	P†
Overall	454	874	4921.6	9.2	8.4 to 10.1	—
Race/ethnicity						
White	68	130	763.9	8.9	6.9 to 11.3	0.662
Black	249	494	2774.2	9.0	7.9 to 10.2	
Hispanic	128	235	1317.0	9.7	8.1 to 11.6	
Other/unknown	9	15	66.6	13.5	6.2 to 25.7	
Gender						
Female	234	445	2521.0	9.3	8.1 to 10.6	0.892
Male	220	429	2400.7	9.2	8.0 to 10.5	
Age (yrs)						
0-2	21	166	182.4	11.5	7.1 to 17.6	0.041
3-5	100	596	835.3	12.0	9.7 to 14.6	
6-10	193	700	2351.4	8.2	7.1 to 9.5	
11+	140	433	1552.6	9.0	7.6 to 10.6	
CD4%						
<15	137	309	543.6	25.2	21.2 to 29.8	<0.001
15 to <25	91	406	806.5	11.3	9.1 to 13.9	
25	96	551	2323.2	4.1	3.3 to 5.0	
Missing	130	410	1248.3	10.4	8.7 to 12.4	
Nadir CD4%						
<15	207	347	1306.9	15.8	13.8 to 18.2	<0.001
15 to <25	78	327	1328.6	5.9	4.6 to 7.3	
25	39	265	1038.3	3.8	2.7 to 5.1	
Missing	130	410	1247.9	10.4	8.7 to 12.4	
HIV RNA						
400	28	330	883.5	3.2	2.1 to 4.6	<0.001
401-5000	29	325	493.8	5.9	3.9 to 8.4	
5001-10,000	12	242	182.3	6.6	3.4 to 11.5	

Characteristics*	No. Events	No. at Risk	Person-Years	IR (per 100 Person-Years)	95% CI	P [†]
10,001-100,000	80	341	602.3	13.3	10.5 to 16.5	
>100,000	40	191	275.4	14.5	10.4 to 19.8	
Missing	265	695	2484.3	10.7	9.4 to 12.0	
Peak HIV RNA						
400	6	84	204.0	2.9	1.1 to 6.4	<0.001
401-5000	6	108	232.2	2.6	0.9 to 5.6	
5001-10,000	9	78	148.8	6.0	2.8 to 11.5	
10,001-100,000	68	248	793.5	8.6	6.7 to 10.9	
>100,000	100	235	1058.7	9.4	7.7 to 11.5	
Missing	265	695	2484.3	10.7	9.4 to 12.0	
CDC clinical class						
C	148	319	1469.6	10.1	8.5 to 11.8	0.203
Non-C	306	681	3452.0	8.9	7.9 to 9.9	
HAART						
On HAART	157	502	2110.2	7.4	6.3 to 8.7	<0.001 [‡]
<90 days after	18	373	84.0	21.4	12.7 to 33.9	
>90 days after	139	480	2026.2	6.9	5.8 to 8.1	
Non-HAART	297	772	2811.5	10.6	9.4 to 11.8	
<90 days before	23	377	85.8	26.8	17.0 to 34.2	
>90 days before	199	546	1607.3	12.4	10.7 to 14.2	

* All characteristics, other than race/ethnicity and gender, are time varying; person-time of follow-up was attributed within each level of a covariate based on the amount of time spent in each category and HZ events were attributed to the level corresponding to the most recent measure before HZ.

[†] The *P* value from Poisson regression comparing categories or from Poisson regression model of trend for characteristics with ordered levels (age, CD4%, HIV RNA).

[‡] Comparing HAART with non-HAART. Additional comparisons include the following: 90 days after HAART initiation vs. >90 days after HAART initiation, *P* < 0.001; >90 days after HAART initiation vs. non-HAART, *P* < 0.001; 90 days after HAART initiation vs. 90 days before HAART initiation, *P* = 0.48; 90 days after HAART initiation vs. >90 days before HAART initiation, *P* = 0.03.

TABLE 3

IRs of HZ in Cohort With Known Varicella Dates by Demographic Characteristics, Health Status Measures, and HAART Exposure

Characteristics*	No. Events	No. at Risk	Person-Years	IR (per 100 Person-Years)	95% CI	P†
Overall	116	536	3666.2	3.2	2.6 to 3.8	—
Race/ethnicity						
White	17	79	550.0	3.1	1.8 to 4.9	0.383
Black	59	304	2117.1	2.8	2.1 to 3.6	
Hispanic	38	145	948.1	4.0	2.8 to 5.5	
Other/unknown	2	8	51.0	3.9	0.5 to 14.2	
Gender						
Female	55	266	1838.7	3.0	2.3 to 3.9	0.555
Male	61	270	1827.5	3.3	2.6 to 4.3	
Age (yrs)						
0-2	2	123	156.6	1.3	0.2 to 4.6	0.564
3-5	19	322	598.4	3.2	1.9 to 5.0	
6-10	55	462	1623.9	3.4	2.6 to 4.4	
11+	40	333	1287.4	3.1	2.2 to 4.2	
CD4%						
<15	36	173	322.3	11.2	7.8 to 15.5	<0.001
15 to <25	27	275	598.0	4.5	3.0 to 6.6	
25	24	424	2050.0	1.2	0.8 to 1.7	
Missing	29	194	695.9	4.2	2.8 to 6.0	
Nadir CD4%						
<15	59	203	949.5	6.2	4.7 to 8.0	<0.001
15 to <25	20	230	1110.0	1.8	1.1 to 2.8	
25	8	210	911.2	0.9	0.4 to 1.7	
Missing	29	194	695.5	4.2	2.8 to 6.0	
HIV RNA						
400	4	287	834.0	0.5	0.1 to 1.2	<0.001
401-5000	9	261	434.6	2.1	0.9 to 3.9	
5001-10,000	5	192	152.4	3.3	1.1 to 7.7	

Characteristics*	No. Events	No. at Risk	Person-Years	IR (per 100 Person-Years)	95% CI	P [†]
10,001-100,000	26	248	434.8	6.0	3.9 to 8.8	
>100,000	12	130	207.3	5.8	3.0 to 10.1	
Missing	60	394	1603.1	3.7	2.9 to 4.8	
Peak HIV RNA						
400	0	73	193.9	0	0 to 1.9	<0.001
401-5000	1	92	213.3	0.5	0.0 to 2.6	
5001-10,000	2	59	129.7	1.5	0.2 to 5.6	
10,001-100,000	20	181	637.2	3.1	1.9 to 4.8	
>100,000	33	169	889.1	3.7	2.6 to 5.2	
Missing	60	394	1603.1	3.7	2.9 to 4.8	
CDC clinical class						
C	50	221	1256.1	4.0	3.0 to 5.2	0.046
Non-C	66	391	2410.1	2.7	2.1 to 3.5	
HAART						
On HAART	49	376	1820.3	2.7	2.0 to 3.6	0.112 [‡]
<90 days after	5	268	62.0	8.1	2.6 to 18.8	
>90 days after	44	368	1758.3	2.5	1.8 to 3.4	
Non-HAART	67	453	1845.9	3.6	2.8 to 4.6	
<90 days before	5	263	60.8	8.2	2.7 to 19.2	
>90 days before	44	284	839.3	5.2	3.8 to 7.0	

* All characteristics other than race/ethnicity and gender are time-varying; person-time of follow-up attributed within each level of a covariate based on the amount of time spent in each category, and HZ events were attributed to the level corresponding to the most recent measure prior to HZ.

[†] The P value from Poisson regression comparing categories, or from Poisson regression model of trend for characteristics with ordered levels (age, CD4%, HIV RNA).

[‡] Comparing HAART to non-HAART. Additional comparisons include: 90 days after HAART initiation vs. >90 days after HAART initiation, $P = 0.01$; >90 days after HAART initiation vs. non-HAART, $P = 0.06$; 90 days after HAART initiation vs. 90 days before HAART initiation, $P = 0.98$.

TABLE 4

Univariate Cox Models for Predictors of Time to HZ

Characteristics	Full HZ Cohort (N = 874)			HZ Cohort With Known Varicella Dates (n = 536)		
	HR	95% CI	P	HR	95% CI	P
Year at varicella	0.93	0.91 to 0.96	<0.001	0.91	0.86 to 0.96	0.002
Race/ethnicity						
White/other	Ref	—	—	Ref	—	—
Black	0.96	0.75 to 1.24	0.775	0.87	0.52 to 1.45	0.584
Hispanic	1.05	0.79 to 1.39	0.753	1.26	0.73 to 2.19	0.405
Male gender	0.98	0.82 to 1.18	0.838	1.11	0.77 to 1.59	0.592
Age 6 years at varicella	0.55	0.44 to 0.69	<0.001	1.23	0.85 to 1.79	0.273
CD4% at varicella						
25	Ref	—	—	Ref	—	—
15 to <25	1.65	1.16 to 2.34	0.005	1.53	0.84 to 2.78	0.167
<15	3.98	2.87 to 5.51	<0.001	4.44	2.57 to 7.68	<0.001
Missing	2.39	1.85 to 3.10	<0.001	1.66	1.04 to 2.64	0.033
Nadir CD4% during follow-up after varicella *						
25	Ref	—	—	Ref	—	—
15 to <25	1.59	1.08 to 2.33	0.019	2.08	0.92 to 4.73	0.080
<15	4.29	3.05 to 6.05	<0.001	7.35	3.51 to 15.40	<0.001
Missing	2.58	1.80 to 3.70	<0.001	4.49	2.05 to 9.86	<0.001
Viral Load at varicella						
10,000 copies/mL	Ref	—	—	Ref	—	—
>10,000 copies/mL	2.20	1.26 to 3.86	0.006	3.29	1.24 to 8.73	0.017
Missing	2.57	1.56 to 4.24	<0.001	2.57	1.04 to 6.33	0.040
CDC clinical class C at varicella	0.92	0.72 to 1.16	0.481	1.41	0.95 to 2.10	0.086
CDC clinical class C during follow-up after varicella *	1.35	1.11 to 1.63	0.003	1.53	1.06 to 2.21	0.023
HAART at varicella	0.62	0.45 to 0.84	0.002	0.54	0.30 to 0.96	0.037
HAART initiation during follow-up *	0.78	0.64 to 0.96	0.018	0.82	0.56 to 1.20	0.309
HAART initiation: HZ within 90 days *						

Characteristics	Full HZ Cohort (N = 874)			HZ Cohort With Known Varicella Dates (n = 536)		
	HR	95% CI	P	HR	95% CI	P
Never on HAART	Ref	—	—	Ref	—	—
<90 days after HAART	1.56	1.04 to 2.33	0.031	1.79	0.74 to 4.32	0.193
>90 days after HAART	0.69	0.55 to 0.85	<0.001	0.75	0.51 to 1.12	0.162

* Time-varying measure updated throughout follow-up.

TABLE 5

Multivariate Cox Models for Predictors of Time to HZ in Full HZ Cohort

Characteristics	Full Multivariate Model			Final Reduced Model		
	HR	95% CI	P	HR	95% CI	P
Year at Varicella	0.97	0.93 to 1.01	0.087	—	—	—
Race/ethnicity						
White/other	Ref	—	—	—	—	—
Black	1.03	0.79 to 1.33	0.849	—	—	—
Hispanic	1.12	0.84 to 1.48	0.447	—	—	—
Male gender	0.98	0.81 to 1.17	0.793	—	—	—
Age 6 years at varicella	0.56	0.44 to 0.72	<0.001	0.54	0.43 to 0.68	<0.001
Nadir CD4% during follow-up*						
25	Ref	—	—	Ref	—	—
15 to <25	1.75	1.18 to 2.59	0.005	1.84	1.25 to 2.71	0.002
<15	4.49	3.15 to 6.42	<0.001	4.80	3.39 to 6.79	<0.001
Missing	2.21	1.49 to 3.28	<0.001	2.51	1.75 to 3.61	<0.001
CDC Class C during follow-up*	1.37	1.11 to 1.68	0.003	1.33	1.09 to 1.63	0.005
HAART initiation: HZ within 90 days*						
Never on HAART	Ref	—	—	Ref	—	—
<90 days after HAART	1.58	1.05 to 2.40	0.030	1.47	0.98 to 2.21	0.064
>90 days after HAART	0.70	0.53 to 0.91	0.009	0.62	0.49 to 0.79	<0.001

* Time-varying measure updated throughout follow-up.

TABLE 6
Multivariate Cox Models for Time to HZ in HZ Cohort With Known Varicella Dates

Characteristic	Full Multivariate Model			Final Reduced Model		
	HR	95% CI	P	HR	95% CI	P
Year at VZV	0.94	0.86 to 1.02	0.107	—	—	—
Race/ethnicity						
White/other	Ref	—	—	—	—	—
Black	0.97	0.57 to 1.63	0.893	—	—	—
Hispanic	1.46	0.84 to 2.56	0.181	—	—	—
Male gender	1.10	0.76 to 1.58	0.631	—	—	—
Age 6 years at varicella	1.24	0.83 to 1.84	0.293	1.18	0.80 to 1.73	0.414
Nadir CD4% during follow-up*						
25	Ref	—	—	Ref	—	—
15 to <25	1.98	0.86 to 4.58	0.109	2.16	0.94 to 4.96	0.069
<15	7.33	3.38 to 15.87	<0.001	8.00	3.75 to 17.1	<0.001
Missing	3.49	1.51 to 8.05	0.003	4.22	1.92 to 9.28	<0.001
CDC Class C during follow-up*	1.41	0.96 to 2.07	0.077	1.37	0.94 to 2.01	0.101
HAART initiation: HZ within 90 days*						
Never on HAART	Ref	—	—	Ref	—	—
<90 days after HAART	1.51	0.62 to 3.66	0.367	1.35	0.56 to 3.27	0.508
>90 days after HAART	0.64	0.39 to 1.05	0.079	0.51	0.33 to 0.80	0.003

* Time-varying measure updated throughout follow-up.